

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

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	X
Labeling	X
Summary Review	
Officer/Employee List	X
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	X
Chemistry Review(s)	X
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	X
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	X
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

**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



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 Effectuated” (CBE)

NDA 020592 S-053, S-055

NDA 021086 S-032, S-034

NDA 021253 S-039, S-043

Page 2

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/

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/

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(I)] 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>.

NDA 020592/S-040/S-041

Page 4

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/

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).

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

page 3

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/

THOMAS P LAUGHREN
08/31/2009



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(1)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling (text for the package insert and Medication Guide). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, “**SPL for approved NDA 21-520/S-012, NDA 20-592/S-039, & NDA 21-086/S-021.**”

CARTON AND IMMEDIATE CONTAINER LABELS

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

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

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

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

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

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

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

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

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

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

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

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

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

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

1. Long-Term Efficacy Studies

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

FINAL REPORT SUBMISSION: March 31, 2015

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

LETTERS TO HEALTH CARE PROFESSIONALS

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

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

INTRODUCTORY PROMOTIONAL MATERIALS

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

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

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

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

Page 5

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

/s/

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)

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)
Page 2

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.

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)

Page 3

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 Zydys 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:

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)

Page 4

- 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

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

/s/

Thomas Laughren
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)

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

/s/

Thomas Laughren
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) 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 ($\geq 5\%$ 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

FULL PRESCRIBING INFORMATION: CONTENTS*

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

1 INDICATIONS AND USAGE

- 1.1 Schizophrenia
- 1.2 Bipolar I Disorder (Manic or Mixed Episodes)
- 1.3 Special Considerations in Treating Pediatric Schizophrenia and Bipolar I Disorder
- 1.4 ZYPREXA IntraMuscular: Agitation Associated with Schizophrenia and Bipolar I Mania
- 1.5 ZYPREXA and Fluoxetine in Combination: Depressive Episodes Associated with Bipolar I Disorder
- 1.6 ZYPREXA and Fluoxetine in Combination: Treatment Resistant Depression

2 DOSAGE AND ADMINISTRATION

- 2.1 Schizophrenia
- 2.2 Bipolar I Disorder (Manic or Mixed Episodes)
- 2.3 Administration of ZYPREXA ZYDIS (olanzapine orally disintegrating tablets)
- 2.4 ZYPREXA IntraMuscular: Agitation Associated with Schizophrenia and Bipolar I Mania
- 2.5 ZYPREXA and Fluoxetine in Combination: Depressive Episodes Associated with Bipolar I Disorder
- 2.6 ZYPREXA and Fluoxetine in Combination: Treatment Resistant Depression

- 2.7 ZYPREXA and Fluoxetine in Combination: Dosing in Special Populations

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Elderly Patients with Dementia-Related Psychosis
- 5.2 Suicide
- 5.3 Neuroleptic Malignant Syndrome (NMS)
- 5.4 Hyperglycemia
- 5.5 Hyperlipidemia
- 5.6 Weight Gain
- 5.7 Tardive Dyskinesia
- 5.8 Orthostatic Hypotension
- 5.9 Leukopenia, Neutropenia, and Agranulocytosis
- 5.10 Dysphagia
- 5.11 Seizures
- 5.12 Potential for Cognitive and Motor Impairment
- 5.13 Body Temperature Regulation
- 5.14 Use in Patients with Concomitant Illness
- 5.15 Hyperprolactinemia
- 5.16 Use in Combination with Fluoxetine, Lithium, or Valproate
- 5.17 Laboratory Tests

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Vital Signs and Laboratory Studies

- 6.3 Postmarketing Experience
- 7 DRUG INTERACTIONS**
- 7.1 Potential for Other Drugs to Affect Olanzapine
- 7.2 Potential for Olanzapine to Affect Other Drugs
- 8 USE IN SPECIFIC POPULATIONS**
- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 9 DRUG ABUSE AND DEPENDENCE**
- 9.3 Dependence
- 10 OVERDOSAGE**
- 10.1 Human Experience
- 10.2 Management of Overdose
- 11 DESCRIPTION**
- 12 CLINICAL PHARMACOLOGY**
- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 13 NONCLINICAL TOXICOLOGY**
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology
- 14 CLINICAL STUDIES**
- 14.1 Schizophrenia
- 14.2 Bipolar I Disorder (Manic or Mixed Episodes)
- 14.3 Agitation Associated with Schizophrenia and Bipolar I Mania
- 16 HOW SUPPLIED/STORAGE AND HANDLING**
- 16.1 How Supplied
- 16.2 Storage and Handling
- 17 PATIENT COUNSELING INFORMATION**
- 17.1 Information on Medication Guide
- 17.2 Elderly Patients with Dementia-Related Psychosis: Increased Mortality and Cerebrovascular Adverse Events (CVAE), Including Stroke
- 17.3 Neuroleptic Malignant Syndrome (NMS)
- 17.4 Hyperglycemia
- 17.5 Hyperlipidemia
- 17.6 Weight Gain
- 17.7 Orthostatic Hypotension
- 17.8 Potential for Cognitive and Motor Impairment
- 17.9 Body Temperature Regulation
- 17.10 Concomitant Medication
- 17.11 Alcohol
- 17.12 Phenylketonurics
- 17.13 Use in Specific Populations
- 17.14 Need for Comprehensive Treatment Program in Pediatric Patients

*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.

<u>Dose, mg Olanzapine</u>	<u>Volume of Injection, mL</u>
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 4112	LILLY 4115	LILLY 4116	LILLY 4117	LILLY 4415	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:

ZYPREXA ZYDIS Tablets	TABLET STRENGTH			
	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

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	exposure		exposure	
			N	Patients	N	Patients
Fasting Glucose	Normal to High (<100 mg/dL to ≥ 126 mg/dL)	Olanzapine	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

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

^a Not Applicable.

5.5 Hyperlipidemia

Undesirable alterations in lipids have been observed with 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

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	Up to 12 weeks exposure		At least 48 weeks exposure	
			N	Patients	N	Patients
Fasting	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 (≥ 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

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	Up to 6 weeks exposure		At least 24 weeks exposure	
			N	Patients	N	Patients
Fasting Triglycerides	Increase by ≥ 50 mg/dL	Olanzapine	138	37.0%	122	45.9%
		Placebo	66	15.2%	NA ^a	NA ^a
	Normal to High (<90 mg/dL to >130 mg/dL)	Olanzapine	67	26.9%	66	36.4%
		Placebo	28	10.7%	NA ^a	NA ^a
Borderline to High (≥ 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 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 α_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 $<1000/\text{mm}^3$) 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 D₂ 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 events¹ (2% [49/3240] of females), sexual function-related events² (2% [150/8136] of females and males), and breast-related events³ (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 events¹ (1% [2/168] of females), sexual function-related events² (0.7% [3/454] of females and males), and breast-related events³ (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 $\geq 5\%$ 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	Percentage of Patients Reporting Event	
	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

Categories ^a	Percentage of Patients Reporting Event	
	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

Adverse Reaction	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)
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 attempt¹; *Rare*: chills and fever, hangover effect, sudden death¹.

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*: amenorrhea², breast pain, decreased menstruation, impotence², increased menstruation², menorrhagia², metrorrhagia², polyuria², 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 $\geq 5\%$ Incidence among Adolescents (13-17 Years Old) with Schizophrenia or Bipolar I Disorder (Manic or Mixed Episodes)

Adverse Reactions	Percentage of Patients Reporting Event			
	6 Week Trial		3 Week Trial	
	% Schizophrenia Patients		% Bipolar Patients	
	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 $\geq 2\%$ 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])

Adverse Reaction	Percentage of Patients Reporting Event	
	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 (≥ 3 X ULN in patients with ALT at baseline < 3 X 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 C_{max} 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 C_{max} 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/m² 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/m² basis). Gestation was prolonged at 10 mg/kg/day (5 times the maximum recommended human daily oral dose on a mg/m² 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/m² basis). Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Placental transfer of olanzapine occurs in rat pups.

There are no adequate and well-controlled 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/m² 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 $\geq 10\%$ 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 C_{max} 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.

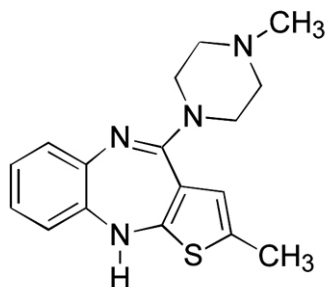
The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

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 C₁₇H₂₀N₄S, 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}, 5HT₆ (K_i=4, 11, and 5 nM, respectively), dopamine D₁₋₄ (K_i=11-31 nM), histamine H₁ (K_i=7 nM), and adrenergic α₁ receptors (K_i=19 nM). Olanzapine is an antagonist with moderate affinity binding for serotonin 5HT₃ (K_i=57 nM) and muscarinic M₁₋₅ (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 5HT₂ 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 H₁ receptors may explain the somnolence observed with this drug. Olanzapine's antagonism of adrenergic α₁ 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 α₁-acid glycoprotein.

Metabolism and Elimination — Following a single oral dose of ¹⁴C 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/m² basis, respectively). Discontinuance of olanzapine treatment reversed the effects on male mating performance. In female rats, the precoital period was increased and the mating index reduced at 5 mg/kg/day (2.5 times the maximum recommended human daily oral dose on a mg/m² basis). Diestrus was prolonged and estrus delayed at 1.1 mg/kg/day (0.6 times the maximum recommended human daily oral dose on a mg/m² 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/m² 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/m² 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/m² basis) for 3 months or 16 mg/kg (8 times the maximum recommended human daily oral dose on a mg/m² 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 $\mu\text{g/mL}$ to 125 $\mu\text{g/mL}$, 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 $\mu\text{g/mL}$ to 125 $\mu\text{g/mL}$, 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

FULL PRESCRIBING INFORMATION: CONTENTS*

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

1 INDICATIONS AND USAGE

- 1.1 Schizophrenia
- 1.2 Bipolar I Disorder (Manic or Mixed Episodes)
- 1.3 Special Considerations in Treating Pediatric Schizophrenia and Bipolar I Disorder
- 1.4 ZYPREXA IntraMuscular: Agitation Associated with Schizophrenia and Bipolar I Mania
- 1.5 ZYPREXA and Fluoxetine in Combination: Depressive Episodes Associated with Bipolar I Disorder
- 1.6 ZYPREXA and Fluoxetine in Combination: Treatment Resistant Depression

2 DOSAGE AND ADMINISTRATION

- 2.1 Schizophrenia

- 2.2 Bipolar I Disorder (Manic or Mixed Episodes)
- 2.3 Administration of ZYPREXA ZYDIS (olanzapine orally disintegrating tablets)
- 2.4 ZYPREXA IntraMuscular: Agitation Associated with Schizophrenia and Bipolar I Mania
- 2.5 ZYPREXA and Fluoxetine in Combination: Depressive Episodes Associated with Bipolar I Disorder
- 2.6 ZYPREXA and Fluoxetine in Combination: Treatment Resistant Depression
- 2.7 ZYPREXA and Fluoxetine in Combination: Dosing in Special Populations

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Elderly Patients with Dementia-Related Psychosis
- 5.2 Suicide

- 5.3 Neuroleptic Malignant Syndrome (NMS)
- 5.4 Hyperglycemia
- 5.5 Hyperlipidemia
- 5.6 Weight Gain
- 5.7 Tardive Dyskinesia
- 5.8 Orthostatic Hypotension
- 5.9 Leukopenia, Neutropenia, and Agranulocytosis
- 5.10 Dysphagia
- 5.11 Seizures
- 5.12 Potential for Cognitive and Motor Impairment
- 5.13 Body Temperature Regulation
- 5.14 Use in Patients with Concomitant Illness
- 5.15 Hyperprolactinemia
- 5.16 Use in Combination with Fluoxetine, Lithium, or Valproate
- 5.17 Laboratory Tests
- 6 ADVERSE REACTIONS**
 - 6.1 Clinical Trials Experience
 - 6.2 Vital Signs and Laboratory Studies
 - 6.3 Postmarketing Experience
- 7 DRUG INTERACTIONS**
 - 7.1 Potential for Other Drugs to Affect Olanzapine
 - 7.2 Potential for Olanzapine to Affect Other Drugs
- 8 USE IN SPECIFIC POPULATIONS**
 - 8.1 Pregnancy
 - 8.2 Labor and Delivery
 - 8.3 Nursing Mothers
 - 8.4 Pediatric Use
 - 8.5 Geriatric Use
- 9 DRUG ABUSE AND DEPENDENCE**
 - 9.3 Dependence
- 10 OVERDOSAGE**
 - 10.1 Human Experience
 - 10.2 Management of Overdose
- 11 DESCRIPTION**
- 12 CLINICAL PHARMACOLOGY**
 - 12.1 Mechanism of Action

- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 13 NONCLINICAL TOXICOLOGY**
 - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
 - 13.2 Animal Toxicology and/or Pharmacology
- 14 CLINICAL STUDIES**
 - 14.1 Schizophrenia
 - 14.2 Bipolar I Disorder (Manic or Mixed Episodes)
 - 14.3 Agitation Associated with Schizophrenia and Bipolar I Mania
- 16 HOW SUPPLIED/STORAGE AND HANDLING**
 - 16.1 How Supplied
 - 16.2 Storage and Handling
- 17 PATIENT COUNSELING INFORMATION**
 - 17.1 Information on Medication Guide
 - 17.2 Elderly Patients with Dementia-Related Psychosis: Increased Mortality and Cerebrovascular Adverse Events (CVAE), Including Stroke
 - 17.3 Neuroleptic Malignant Syndrome (NMS)
 - 17.4 Hyperglycemia
 - 17.5 Hyperlipidemia
 - 17.6 Weight Gain
 - 17.7 Orthostatic Hypotension
 - 17.8 Potential for Cognitive and Motor Impairment
 - 17.9 Body Temperature Regulation
 - 17.10 Concomitant Medication
 - 17.11 Alcohol
 - 17.12 Phenylketonurics
 - 17.13 Use in Specific Populations
 - 17.14 Need for Comprehensive Treatment Program in Pediatric Patients

*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.

<u>Dose, mg Olanzapine</u>	<u>Volume of Injection, mL</u>
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	LILLY	LILLY	LILLY	LILLY	LILLY
	4112	4115	4116	4117	4415	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:

ZYPREXA ZYDIS Tablets	TABLET STRENGTH			
	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

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	Up to 12 weeks exposure		At least 48 weeks exposure	
			N	Patients	N	Patients
Fasting 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

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

^a Not Applicable.

5.5 Hyperlipidemia

Undesirable alterations in lipids have been observed with 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

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	Up to 12 weeks exposure		At least 48 weeks exposure	
			N	Patients	N	Patients
Fasting Triglycerides	Increase by ≥ 50 mg/dL	Olanzapine	745	39.6%	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

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	Up to 6 weeks exposure		At least 24 weeks exposure	
			N	Patients	N	Patients
Fasting Triglycerides	Increase by ≥ 50 mg/dL	Olanzapine	138	37.0%	122	45.9%
		Placebo	66	15.2%	NA ^a	NA ^a
	Normal to High (<90 mg/dL to >130 mg/dL)	Olanzapine	67	26.9%	66	36.4%
		Placebo	28	10.7%	NA ^a	NA ^a
	Borderline to High (≥ 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 α_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 $<1000/\text{mm}^3$) 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 D₂ 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 events¹ (2% [49/3240] of females), sexual function-related events² (2% [150/8136] of females and males), and breast-related events³ (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 events¹ (1% [2/168] of females), sexual function-related events² (0.7% [3/454] of females and males), and breast-related events³ (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, galactorrhea, 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

Adverse Reaction	Percentage of Patients Reporting Event	
	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 $\geq 5\%$ 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

Body System/Adverse Reaction	Percentage of Patients Reporting Event	
	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

Categories ^a	Percentage of Patients Reporting Event	
	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

Adverse Reaction	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)
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 attempt¹; *Rare*: chills and fever, hangover effect, sudden death¹.

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*: amenorrhea², breast pain, decreased menstruation, impotence², increased menstruation², menorrhagia², metrorrhagia², polyuria², 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 $\geq 5\%$ Incidence among Adolescents (13-17 Years Old) with Schizophrenia or Bipolar I Disorder (Manic or Mixed Episodes)

Adverse Reactions	Percentage of Patients Reporting Event			
	6 Week Trial % Schizophrenia Patients		3 Week Trial % Bipolar Patients	
	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 $\geq 2\%$ 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])

Adverse Reaction	Percentage of Patients Reporting Event	
	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 $\leq$ 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 $\geq$ 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 ($\geq$ 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 $\geq$ 240 mg/dL and random triglyceride levels of $\geq$ 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 C_{max} 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 C_{max} 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 (TM) — 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/m² 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/m² basis). Gestation was prolonged at 10 mg/kg/day (5 times the maximum recommended human daily oral dose on a mg/m² 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/m² basis). Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Placental transfer of olanzapine occurs in rat pups.

There are no adequate and well-controlled 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/m² 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 overdose 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 overdose, 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 C_{max} 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.

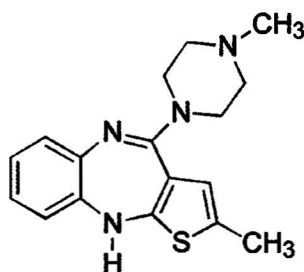
The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

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 C₁₇H₂₀N₄S, 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}, 5HT₆ (K_i=4, 11, and 5 nM, respectively), dopamine D₁₋₄ (K_i=11-31 nM), histamine H₁ (K_i=7 nM), and adrenergic α₁ receptors (K_i=19 nM). Olanzapine is an antagonist with moderate affinity binding for serotonin 5HT₃ (K_i=57 nM) and muscarinic M₁₋₅ (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 5HT₂ may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic M₁₋₅ receptors may explain its anticholinergic-like effects. Olanzapine's antagonism of histamine H₁ receptors may explain the somnolence observed with this drug. Olanzapine's antagonism of adrenergic α₁ 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 α_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/m² 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/m² 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/m² 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/m² 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/m² basis); in this study, there was a high incidence of early mortalities in males of the 30/20 mg/kg/day group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice dosed at ≥2 mg/kg/day and in female rats dosed at ≥4 mg/kg/day (0.5 and 2 times the maximum recommended human daily oral dose on a mg/m² basis, respectively). Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the olanzapine carcinogenicity studies; however, measurements during subchronic toxicity studies showed that olanzapine elevated serum prolactin levels up to 4-fold in rats at the same doses used in the carcinogenicity study. An increase in mammary gland neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance for human risk of the finding of prolactin mediated endocrine tumors in rodents is unknown [see *Warnings and Precautions (5.15)*].

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/m² basis, respectively). Discontinuance of olanzapine treatment reversed the effects on male mating performance. In female rats, the pre-coital 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/m² basis). Diestrus was prolonged and estrus delayed at 1.1 mg/kg/day (0.6 times the maximum recommended human daily oral dose on a mg/m² 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/m² 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/m² 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/m² basis) for 3 months or 16 mg/kg (8 times the maximum recommended human daily oral dose on a mg/m² 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 μ g/mL to 125 μ g/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

	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:

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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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

FULL PRESCRIBING INFORMATION: CONTENTS*

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

1 INDICATIONS AND USAGE

- 1.1 Schizophrenia
- 1.2 Bipolar I Disorder (Manic or Mixed Episodes)
- 1.3 Special Considerations in Treating Pediatric Schizophrenia and Bipolar I Disorder
- 1.4 ZYPREXA IntraMuscular: Agitation Associated with Schizophrenia and Bipolar I Mania
- 1.5 ZYPREXA and Fluoxetine in Combination: Depressive Episodes Associated with Bipolar I Disorder
- 1.6 ZYPREXA and Fluoxetine in Combination: Treatment Resistant Depression

2 DOSAGE AND ADMINISTRATION

- 2.1 Schizophrenia

- 2.2 Bipolar I Disorder (Manic or Mixed Episodes)
- 2.3 Administration of ZYPREXA ZYDIS (olanzapine orally disintegrating tablets)
- 2.4 ZYPREXA IntraMuscular: Agitation Associated with Schizophrenia and Bipolar I Mania
- 2.5 ZYPREXA and Fluoxetine in Combination: Depressive Episodes Associated with Bipolar I Disorder
- 2.6 ZYPREXA and Fluoxetine in Combination: Treatment Resistant Depression
- 2.7 ZYPREXA and Fluoxetine in Combination: Dosing in Special Populations

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Elderly Patients with Dementia-Related Psychosis
- 5.2 Suicide

3

- 5.3 Neuroleptic Malignant Syndrome (NMS)
- 5.4 Hyperglycemia
- 5.5 Hyperlipidemia
- 5.6 Weight Gain
- 5.7 Tardive Dyskinesia
- 5.8 Orthostatic Hypotension
- 5.9 Leukopenia, Neutropenia, and Agranulocytosis
- 5.10 Dysphagia
- 5.11 Seizures
- 5.12 Potential for Cognitive and Motor Impairment
- 5.13 Body Temperature Regulation
- 5.14 Use in Patients with Concomitant Illness
- 5.15 Hyperprolactinemia
- 5.16 Use in Combination with Fluoxetine, Lithium, or Valproate
- 5.17 Laboratory Tests
- 6 ADVERSE REACTIONS
 - 6.1 Clinical Trials Experience
 - 6.2 Vital Signs and Laboratory Studies
 - 6.3 Postmarketing Experience
- 7 DRUG INTERACTIONS
 - 7.1 Potential for Other Drugs to Affect Olanzapine
 - 7.2 Potential for Olanzapine to Affect Other Drugs
- 8 USE IN SPECIFIC POPULATIONS
 - 8.1 Pregnancy
 - 8.2 Labor and Delivery
 - 8.3 Nursing Mothers
 - 8.4 Pediatric Use
 - 8.5 Geriatric Use
- 9 DRUG ABUSE AND DEPENDENCE
 - 9.3 Dependence
- 10 OVERDOSAGE
 - 10.1 Human Experience
 - 10.2 Management of Overdose
- 11 DESCRIPTION
- 12 CLINICAL PHARMACOLOGY
 - 12.1 Mechanism of Action

- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 13 NONCLINICAL TOXICOLOGY
 - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
 - 13.2 Animal Toxicology and/or Pharmacology
- 14 CLINICAL STUDIES
 - 14.1 Schizophrenia
 - 14.2 Bipolar I Disorder (Manic or Mixed Episodes)
 - 14.3 Agitation Associated with Schizophrenia and Bipolar I Mania
- 16 HOW SUPPLIED/STORAGE AND HANDLING
 - 16.1 How Supplied
 - 16.2 Storage and Handling
- 17 PATIENT COUNSELING INFORMATION
 - 17.1 Information on Medication Guide
 - 17.2 Elderly Patients with Dementia-Related Psychosis: Increased Mortality and Cerebrovascular Adverse Events (CVAE), Including Stroke
 - 17.3 Neuroleptic Malignant Syndrome (NMS)
 - 17.4 Hyperglycemia
 - 17.5 Hyperlipidemia
 - 17.6 Weight Gain
 - 17.7 Orthostatic Hypotension
 - 17.8 Potential for Cognitive and Motor Impairment
 - 17.9 Body Temperature Regulation
 - 17.10 Concomitant Medication
 - 17.11 Alcohol
 - 17.12 Phenylketonurics
 - 17.13 Use in Specific Populations
 - 17.14 Need for Comprehensive Treatment Program in Pediatric Patients

*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)*].