DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-520/S-012

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

Dear Ms. Wojcieszek:

Please refer to your supplemental new drug application dated September 28, 2006, received September 29, 2006 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Symbyax (olanzapine/fluoxetine) 3 mg/25 mg, 6 mg/25 mg, 6 mg/50 mg, 12 mg/25 mg, and 12 mg/50 mg (mg equivalent olanzapine/mg equivalent fluoxetine) capsules.

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

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

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

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

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

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

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

Regarding data displays, an overall strategy will be to subgroup patients on the basis of their status at baseline so that clinicians can better understand the risks associated with treatment of patients falling into different risk categories. For example, we note that your proposed Symbyax label includes information only on proportions of patients who are relatively normal at baseline with regard to random blood glucose (< 140 mg/dL), i.e., 2.9% of such patients receiving OFC had on-treatment levels ≥ 200 mg/dL compared to 0.3% of placebo-treated patients. However, we note that 46% of patients who were borderline to high at baseline (140 to 200) had such on-treatment levels compared to only 5% of placebo-treated patients. This latter finding was based on a small number of patients in the OFC program, and for this reason, we would like to see such data for the entire olanzapine program. In addition, we were troubled that this important finding was not included in your proposed label. We will want you to provide similar information based on subgroupings of patients on the basis of weight and BMI (for weight change), and lipid findings for the lipid data. We will want you to provide data both on proportions of patients meeting certain on-treatment criteria and also for mean change from baseline.

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

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

Post Marketing Commitments

Long-Term Efficacy Studies

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

Labeling

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

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

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

Foreign Regulatory Update/Labeling

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

Request for Safety Update and World Literature Update

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

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Prior to an approval action, we require an updated report on the world's archival literature pertaining to the safety of Symbyax. Please provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries. This report should include only literature not covered in your previous submissions. We will need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of Symbyax. The report should also detail how the literature search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of

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

Promotional Materials

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

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

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

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

Sincerely,

(See appended electronic signature page)

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

Enclosure

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[This version of labeling is based up on the version submitted with the application. We have used track changes to indicate our additions and deletions. We have added bracketed comments to explain our actions where needed.]

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

SYMBYAX® (olanzapine and fluoxetine HCl capsules) for oral administration
Initial U.S. Approval: 2003

WARNING

See full prescribing information for complete boxed warning.

SUICIDALITY IN CHILDREN AND ADOLESCENTS:

- Increased risk of suicidal thinking and behavior in children and adolescents taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders. Not approved for use in children and adolescents.

INCREASED MORTALITY IN ELDERLY PATIENTS:

- Increased mortality in elderly patients with dementia-related psychosis compared to placebo. Not approved for the treatment of patients with dementia-related psychosis.

~~SUICIDALITY IN CHILDREN AND ADOLESCENTS:~~
~~Increased risk of suicidal thinking and behavior in children and adolescents taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders. Not approved for use in children and adolescents.~~

RECENT MAJOR CHANGES

~~Warnings and Precautions, Mortality in patients with dementia-related psychosis (5.1)~~	~~10/2006~~
Contraindications, Pimozide (4)	3/2006
Warnings and Precautions, Hepatobiliary events (5.14)	4/2006
Warnings and Precautions, Serotonin Syndrome (5.6)	8/2006
Warnings and Precautions, Weight Gain	
Warnings and Precautions, Risk of Glucose Dysregulation	
Warnings and Precautions, Hyperlipidemia	

INDICATIONS AND USAGE

SYMBYAX combines olanzapine, a psychotropic agent belonging to the thienobenzodiazepine class, and fluoxetine, a selective serotonin reuptake inhibitor, indicated for treatment of:

- Depressive episodes associated with bipolar disorder (1.1)
- Treatment Resistant Depression (major depressive disorder in patients who do not respond to 2 antidepressants of adequate dose and duration in the current episode) (1.2)

DOSAGE AND ADMINISTRATION

- Once daily in the evening, generally beginning with 6 mg/25 mg (2)
- Escalate dose cautiously in patients predisposed to hypotensive reactions, hepatic impairment, or with potential for slowed metabolism (2.3)
- Discontinue gradually (2.4)
- The safety of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated in clinical trials.

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

- Do not use with an MAOI or within 14 days of discontinuing an MAOI. At least 5 weeks should be allowed after stopping SYMBYAX before starting treatment with an MAOI (4, 7.13)
- Do not use with Pimozide (4, 7.15)
- Do not use with Thioridazine. Do not use Thioridazine within 5 weeks of discontinuing SYMBYAX (4, 7.15)

WARNINGS AND PRECAUTIONS

- Patients should be monitored for clinical worsening and suicidal thinking and behavior (5.2)
- Cerebrovascular adverse events including fatalities were reported more commonly with olanzapine than placebo in trials of elderly patients with dementia-related psychosis (5.3)
- Neuroleptic Malignant Syndrome has been reported with atypical antipsychotics (5.4)
  [See Approvable Letter for information requested for hyperglycemia section.]
- Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients taking atypical antipsychotics, including olanzapine alone as well as olanzapine taken concomitantly with fluoxetine. Diabetic patients should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes should undergo fasting blood glucose testing at the beginning of and periodically during treatment. Monitor all patients for symptoms of hyperglycemia. (5.5)
- Hypercholesterolemia [insert appropriate wording here, see Approvable Letter.]
- Clinically significant weight gain may occur.
- Serotonin Syndrome may occur with SYMBYAX (5.6)
- Discontinue upon appearance of rash or allergic phenomena (5.7)
- Screen for bipolar disorder and monitor for mania/hypomania (5.8)
- Tardive Dyskinesia may develop acutely or chronically (5.9)
- 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 (5.10)
- Use cautiously in patients at risk for aspiration pneumonia due to esophageal dysmotility (5.11)
- Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold (5.12)
- ~~Clinically significant weight gain may occur (5.13)~~
- Asymptomatic elevations of hepatic transaminases and alkaline phosphatase have been observed with olanzapine. Periodic assessment recommended in patients with hepatic disease (5.14)
- May increase the risk of bleeding. Use with NSAIDs or drugs that affect coagulation may potentiate the risk of gastrointestinal or other bleeding (5.15)
- Hyponatremia (some cases with serum sodium lower than 110 mmol/L) possibly associated with the syndrome of inappropriate antidiuretic hormone (SIADH) have been reported with fluoxetine (5.16)
- Has potential to impair judgment, thinking, and motor skills (5.17)
- May disrupt temperature regulation (5.18)
- Due to anticholinergic activity, use with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, or a history of paralytic ileus or related conditions (5.19)
- Use a lower dose in patients with cirrhosis (5.19)
- May elevate prolactin levels (5.20)
- Use caution when prescribing with other products containing olanzapine, and/or fluoxetine as active ingredients (i.e., Zyprexa, Prozac, Sarafem) (5.21)
- Fluoxetine has a long elimination half-life (5.22)
- Monitor when discontinuing treatment since discontinuation symptoms may occur (5.23)

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Lilly at 1-800-545-5979 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Antihypertensives – enhanced antihypertensive effect (7.1)
- Anti-Parkinsonian – may antagonize levodopa/dopamine agonists (7.2)

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- Benzodiazepines – may potentiate orthostatic hypotension and sedation (7.3)
- Carbamazepine – potential for elevated carbamazepine levels (7.5)
- Clozapine – may elevate Clozapine levels (7.6).
- CNS Acting Drugs – caution should be used when taken in combination with other centrally acting drugs and alcohol (7.7)
- Ethanol – may potentiate sedation and orthostatic hypotension (7.9)
- Fluvoxamine – may double olanzapine levels (7.10)
- Haloperidol – elevated haloperidol levels have been observed (7.11)
- Lithium – monitor lithium levels (7.12)
- Phenytoin – potential for elevated phenytoin levels (7.14)
- Serotonergic drugs – potential for Serotonin Syndrome (5.6, 7.16, 7.20)
- Tricyclic antidepressants (TCAs) – monitor TCA levels (7.19)
- Warfarin – increase monitoring with SYMBYAX dose change (7.23)
- Drugs that interfere with hemostasis (NSAIDs, aspirin, warfarin, etc.) may potentiate the risk of bleeding (7.24)
- Fluoxetine is an inhibitor of CYP450 2D6 enzyme pathway (7.25)
- Drugs tightly bound to plasma proteins, may cause shift in plasma concentrations (7.29)

USE IN SPECIFIC POPULATIONS

- Pregnancy: SYMBYAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (8.1)
- Nursing mothers, breast feeding is not recommended (8.3)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling.

Revised: [9/2006]

(BNL561JAMP)

FULL PRESCRIBING INFORMATION: CONTENTS*

[Section reference numbers must be re-ordered to reflect changes, both here and in the body of the document.]

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

4
FULL PRESCRIBING INFORMATION

WARNING

Suicidality in Children and Adolescents — Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of SYMBYAX or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SYMBYAX is not approved for use in pediatric patients. *(See Warnings and Precautions (5.2) and Use in Specific Populations (8.4)).*

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials. *(See Warnings and Precautions (5.2)).*

Increased Mortality in Elderly Patients — Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen 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 infections (e.g., pneumonia) in nature. SYMBYAX (olanzapine and fluoxetine HCl) is not approved for the treatment of patients with dementia-related psychosis *(see Warnings and Precautions (5.1))*.

~~Suicidality in Children and Adolescents — Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of SYMBYAX or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SYMBYAX is not approved for use in pediatric patients. *(See Warnings and Precautions (5.2) and Use in Specific Populations (8.4))*.~~

~~Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials. *(See Warnings and Precautions (5.2))*.~~

1 INDICATIONS AND USAGE

1.1 Bipolar Depression

SYMBYAX is indicated for the treatment of depressive episodes associated with bipolar disorder.

Unlike with unipolar depression, there are no established guidelines for the length of time patients with bipolar disorder experiencing a major depressive episode should be treated with agents containing antidepressant drugs.

The effectiveness of SYMBYAX for maintaining antidepressant response in this patient population beyond 8 weeks has not been established in controlled clinical studies. Physicians who elect to use SYMBYAX for extended periods should periodically reevaluate the benefits and long-term risks of the drug for the individual patient.

1.2 Treatment Resistant Depression

SYMBYAX is indicated for treatment resistant depression (major depressive disorder in patients who do not respond to 2 antidepressants of adequate dose and duration in the current episode) *(see Clinical Studies (14.2))*.

The effectiveness of SYMBYAX for maintaining antidepressant response in this patient population beyond 8 weeks has not been established in controlled clinical studies. Physicians who elect to use SYMBYAX for extended periods should periodically reevaluate the benefits and long-term risks of the drug for the individual patient.

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2 DOSAGE AND ADMINISTRATION

2.1 Bipolar Depression

SYMBYAX should be administered once daily in the evening, generally beginning with the 6-mg/25-mg capsule. While food has no appreciable effect on the absorption of olanzapine and fluoxetine given individually, the effect of food on the absorption of SYMBYAX has not been studied. Dosage adjustments, if indicated, can be made according to efficacy and tolerability. Antidepressant efficacy was demonstrated with SYMBYAX in a dose range of olanzapine 6 to 12 mg and fluoxetine 25 to 50 mg *[see Clinical Studies (14)]*.

The safety of doses above 18 mg/75 mg has not been evaluated in clinical studies.

2.2 Treatment Resistant Depression

SYMBYAX should be administered once daily in the evening, generally beginning with the 6-mg/25-mg capsule. While food has no appreciable effect on the absorption of olanzapine and fluoxetine given individually, the effect of food on the absorption of SYMBYAX has not been studied. Dosage adjustments, if indicated, can be made according to efficacy and tolerability. Antidepressant efficacy was demonstrated with SYMBYAX in a dose range of olanzapine 6 to 18 mg and fluoxetine 25 to 50 mg *[see Clinical Studies (14)]*. The safety of doses above 18 mg/75 mg has not been evaluated in clinical studies.

2.3 Special Populations

The starting dose of SYMBYAX 3 mg/25 - 6 mg/25 mg should be used for patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of SYMBYAX (female gender, geriatric age, nonsmoking status) or those patients who may be pharmacodynamically sensitive to olanzapine. When indicated, dose escalation should be performed with caution in these patients. SYMBYAX has not been systematically studied in patients over 65 years of age or in patients <18 years of age *[see Warnings and Precautions (5.19), Use in Specific Populations (8.4 and 8.5), and Clinical Pharmacology (12.3)]*.

2.4 Discontinuation of Treatment with SYMBYAX

Symptoms associated with discontinuation of fluoxetine, a component of SYMBYAX, and other SSRIs and SNRIs, have been reported *[see Warnings and Precautions (5.23)]*.

3 DOSAGE FORM AND STRENGTHS

Capsules (mg equivalent olanzapine/mg equivalent fluoxetine):

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

4 CONTRAINDICATIONS

The use of SYMBYAX is contraindicated with the following:

- Monoamine Oxidase Inhibitors (MAOI) — *[see Drug Interactions (7.13)]*
- Pimozide — *[see Drug Interactions (7.15)]*
- Thioridazine — *[see Drug Interactions (7.18)]*

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. SYMBYAX is not approved for the treatment of patients with dementia-related psychosis *(see Box Warning)*.

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

5.2 Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that

antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in any of these trials. It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

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

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

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms *(see Warnings and Precautions (5.23) and Dosage and Administration (2.4)*, for a description of the risks of discontinuation of SYMBYAX*)*.

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

It should be noted that SYMBYAX is not approved for use in treating any indications in the pediatric population.

5.3 Cerebrovascular Adverse Events (CVAE), Including Stroke, in Elderly Patients with Dementia-Related Psychosis

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine and SYMBYAX are not approved for the treatment of patients with dementia-related psychosis.

5.4 Neuroleptic Malignant Syndrome (NMS)

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

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or

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S. Brophy

inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

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

If after recovering from NMS, a patient requires treatment with an antipsychotic, the patient should be carefully monitored, since recurrences of NMS have been reported.

[As noted above, we have requested additional information on treating patients with hyperglycemia in the Approvable Letter. Section 5.5 will be modified when we have reviewed the requested information. We have also grouped hyperglycemia, hyperlipidemia, and weight gain together (see Full Prescribing Contents section and order the appropriate sections below to correspond to those changes.)]

5.5 Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including olanzapine alone, as well as olanzapine taken concomitantly with fluoxetine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics 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.

5.6 Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome may occur with SYMBYAX, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of SYMBYAX with MAOIs intended to treat depression is contraindicated *[see Contraindications (4) and Drug Interactions (7.13)]*.

If concomitant treatment of SYMBYAX with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases *[see Drug Interactions (7.19)]*.

The concomitant use of SYMBYAX with serotonin precursors (such as tryptophan) is not recommended *[see Drug Interactions (7.20)]*.

5.7 Allergic Events and Rash

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

In fluoxetine US clinical studies, 7% of 10,782 fluoxetine-treated patients developed various types of rashes and/or urticaria. Among the cases of rash and/or urticaria reported in premarketing clinical studies, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

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

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

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

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

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

5.8 Screening Patients for Bipolar Disorder and Monitor for Mania/Hypomania

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

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

5.9 Tardive Dyskinesia

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

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

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

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

5.10 Orthostatic Hypotension

SYMBYAX may induce orthostatic hypotension associated with dizziness, tachycardia, bradycardia, and in some patients, syncope, especially during the initial dose-titration period.

In the SYMBYAX-controlled clinical trials across all indications, there were no significant differences between SYMBYAX-treated patients and olanzapine, fluoxetine or placebo-treated patients in exposure adjusted rates of orthostatic systolic blood pressure

decreases of at least 30 mm Hg. Orthostatic systolic blood pressure decreases of at least 30 mm Hg occurred in 4.0% (28/705), 2.3% (19/831), 4.5% (18/399), and 1.8% (8/442) of the SYMBYAX, olanzapine, fluoxetine, and placebo groups, respectively. In this group of studies, the incidence of syncope-related adverse events (i.e., syncope and/or loss of consciousness) in SYMBYAX-treated patients was 0.4% (3/771) compared to placebo 0.2% (1/477).

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

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

5.11 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 and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

5.12 Seizures

Seizures occurred in 0.2% (4/2547) of SYMBYAX-treated patients during open-label clinical studies. No seizures occurred in the controlled SYMBYAX studies. Seizures have also been reported with both olanzapine and fluoxetine monotherapy. SYMBYAX should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of ≥65 years of age.

[As noted, we will want the Weight Section revised with new requested information and moved to be adjacent to the hyperglycemia and hyperlipidemia sections.]

5.13 Weight Gain

In clinical studies, the mean weight increase for SYMBYAX-treated patients after 8 weeks of treatment was statistically significantly greater than placebo-treated (4.3 kg vs -0.5 kg) and fluoxetine-treated (4.3 kg vs -0.2 kg) patients, but was not statistically significantly different from olanzapine-treated patients (4.3 kg vs 4.1 kg). Thirty-five percent of SYMBYAX-treated patients met criterion for having gained >7% of their baseline weight. This was statistically significantly greater than placebo-treated (3%) and fluoxetine-treated patients (3%) but was not statistically significantly different than olanzapine-treated patients (31%).

5.14 Transaminase Elevations

As with olanzapine, asymptomatic elevations of hepatic transaminases [ALT (SGPT), AST (SGOT), and GGT] and alkaline phosphatase have been observed with SYMBYAX. In the SYMBYAX-controlled database, ALT (SGPT) elevations (normal baseline and ≥3 times the upper limit of the normal range post-baseline) were observed in 3.4% (20/586) of patients exposed to SYMBYAX compared with none of the 342 placebo patients and 3.5% (23/665) of olanzapine-treated patients. The difference between SYMBYAX and placebo was statistically significant. Of the SYMBYAX patients who started normal at baseline and had increases in ALT ≥5 times the upper limit of normal range, none experienced jaundice and four had transient elevations >200 IU/L. ~~In the premarketing SYMBYAX controlled database, ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 6.3% (31/495) of patients exposed to SYMBYAX compared with 0.5% (3/584) of the placebo patients and 1.5% (25/560) of olanzapine-treated patients-[see *Adverse Reactions (6.1)*].~~

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

Within the larger olanzapine premarketing database of about 2400 patients with baseline SGPT ≤90 IU/L, the incidence of SGPT elevation to >200 IU/L was 2% (50/2381). Again, none of these patients experienced jaundice or other symptoms attributable to liver impairment and most had transient changes that tended to normalize while olanzapine treatment was continued. Among all 2500 patients in olanzapine clinical studies, approximately 1% (23/2500) discontinued treatment due to transaminase increases.

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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. Periodic assessment of transaminases is recommended in patients with significant hepatic disease *[see Warnings and Precautions (5.24)]*.

5.15 Abnormal Bleeding

Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding *[see Drug Interactions (7.23, 7.24)]*. Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of SYMBYAX with NSAIDs, aspirin, or other drugs that affect coagulation.

5.16 Hyponatremia

Hyponatremia has been observed in SYMBYAX premarketing clinical studies. In controlled trials, no SYMBYAX-treated patients had a treatment-emergent serum sodium below 129 mmol/L; however, a lowering of serum sodium below the reference range occurred at an incidence of 1.6% (11/693) of SYMBYAX-treated patients compared with 0.5% (2/380) of placebo patients. This difference was not statistically significant. In open label studies, 0.0% (1/2376) of these SYMBYAX-treated patients had a treatment-emergent serum sodium below 129 mmol/L.

Cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported with fluoxetine. The hyponatremia appeared to be reversible when fluoxetine was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted. In two 6-week controlled studies in patients ≥60 years of age, 10 of 323 fluoxetine patients and 6 of 327 placebo recipients had a lowering of serum sodium below the reference range; this difference was not statistically significant. The lowest observed concentration was 129 mmol/L. The observed decreases were not clinically significant.

5.17 Cognitive and Motor Impairment

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

5.18 Body Temperature Regulation

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

5.19 Use in Patients with Concomitant Illness

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

Olanzapine exhibits in vitro muscarinic receptor affinity. In premarketing clinical studies, SYMBYAX was associated with constipation, dry mouth, and tachycardia, all adverse events possibly related to cholinergic antagonism. Such adverse events were not often the basis for study discontinuations; SYMBYAX should be used with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, a history of paralytic ileus, or related conditions.

In five placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis (n=1184), the following treatment-emergent adverse events 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 events was significantly greater with olanzapine than placebo (13% vs 7%). Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis.

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If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised *[see Box Warning and Warnings and Precautions (5.1)]*.

As with other CNS-active drugs, SYMBYAX should be used with caution in elderly patients with dementia. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised *[see Box Warning and Warnings and Precautions(5.1)]*.

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

Caution is advised when using SYMBYAX in cardiac patients and in patients with diseases or conditions that could affect hemodynamic responses *[see Warnings and Precautions (5.10)]*.

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

Olanzapine and fluoxetine individual pharmacokinetics do not differ significantly in patients with renal impairment. SYMBYAX dosing adjustment based upon renal impairment is not routinely required *[see Clinical Pharmacology (12.4)]*.

5.20 Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, SYMBYAX elevates prolactin levels, and a modest elevation persists during administration; however, possibly associated clinical manifestations (e.g., galactorrhea and breast enlargement) were infrequently observed.

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 of this type. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds that increase prolactin release, an increase in mammary gland neoplasia was observed in the olanzapine carcinogenicity studies conducted in mice and rats *[see Nonclinical Toxicology (13.1)]*. However, neither clinical studies nor epidemiologic studies 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.

5.21 Concomitant Use of Olanzapine and Fluoxetine Products

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

5.22 Long Half-Life of Fluoxetine

Because of the long elimination half-lives of fluoxetine and its major active metabolite, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment *[see Clinical Pharmacology (12.3)]*.

5.23 Discontinuation of Treatment with SYMBYAX

During marketing of fluoxetine, a component of SYMBYAX, and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with fluoxetine. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate. Plasma fluoxetine and norfluoxetine concentration decrease gradually at the conclusion of therapy, which may minimize the risk of discontinuation symptoms with this drug *[see Dosage and Administration (2.4)]*.

5.24 Laboratory Tests

Periodic assessment of transaminases is recommended in patients with significant hepatic disease *[see Warnings and Precautions, 5.14)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

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

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

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

Incidence in Controlled Clinical Studies

The following findings are based on the short-term, controlled studies including bipolar depression and treatment resistant depression.

Adverse events associated with discontinuation of treatment — Overall, 11.3% of the 771 patients in the SYMBYAX group discontinued due to adverse events compared with 4.4% of the 477 patients for placebo. Adverse events leading to discontinuation associated with the use of SYMBYAX (incidence of at least 1% for SYMBYAX and greater than that for placebo) using MedDRA Dictionary coding were weight increased (2%) and sedation (1%) versus placebo patients which had 0% incidence of weight increased and sedation.

Commonly observed adverse events in controlled clinical studies — The most commonly observed adverse events associated with the use of SYMBYAX (incidence ≥5% and at least twice that for placebo in the SYMBYAX-controlled database) using MedDRA Dictionary coding were: disturbance in attention, dry mouth, fatigue, hypersomnia, increased appetite, peripheral edema, sedation, somnolence, tremor, vision blurred and weight increased. Adverse events reported in clinical trials of olanzapine/fluoxetine in combination are generally consistent with treatment-emergent adverse events during olanzapine or fluoxetine monotherapy.

Adverse events occurring at an incidence of 2% or more in short-term controlled clinical studies — Table 1 enumerates the treatment-emergent adverse events associated with the use of SYMBYAX (incidence of at least 2% for SYMBYAX and twice or more than for placebo). The SYMBYAX-controlled column includes patients with various diagnoses while the placebo column includes only patients with bipolar depression and major depression with psychotic features.

Table 1: Treatment-Emergent Adverse Events: Incidence in Controlled Clinical Studies

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

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

Additional Findings Observed in Clinical Studies

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

[As discussed above, we intend to move and group together data relevant to treatment-emergent hyperglycemia, hyperlipidemia, and weight gain to Warnings/Precautions. In addition, the information in these sections will need to be revised to include new information based on requested new data searches and analyses.]

Laboratory changes — In SYMBYAX clinical studies, (including treatment resistant depression, bipolar depression, major depressive disorder with psychosis, or sexual dysfunction) SYMBYAX was associated with statistically significantly greater frequencies for the following treatment-emergent findings in laboratory analytes (normal at baseline to abnormal at any time during the trial) compared to placebo: elevated random blood glucose levels of ≥200 mg/dL in patients with levels of <140 mg/dL at baseline (2.9% vs. 0.3%); elevated random cholesterol ≥240 mg/dL in patients with levels of <200 mg/dL at baseline (9.7% vs. 1.9%); elevated prolactin (27.6% vs. 4.8%); elevated urea nitrogen (2.8% vs. 0.8%); elevated uric acid (2.9% vs. 0.5%); low albumin (2.7% vs. 0.3%); low bicarbonate (14.1% vs. 8.8%); low hemoglobin (2.6% vs. 0%); low inorganic phosphorus (1.9% vs. 0.3%); low lymphocytes (1.9% vs. 0%); and low total bilirubin (15.3% vs. 3.9%).

In olanzapine clinical studies among olanzapine-treated patients with random triglyceride levels of <150 mg/dL at baseline (N=659), 0.5% of patients experienced triglyceride levels of ≥500 mg/dL anytime during the trials. In these same trials, olanzapine-treated patients (N=1185) had a mean increase of 20 mg/dL in triglycerides from a mean baseline value of 175 mg/dL.

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

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

Vital signs — Tachycardia, bradycardia, and orthostatic hypotension have occurred in SYMBYAX-treated patients *[see Warnings and Precautions (5.10)]*. The mean standing pulse rate of SYMBYAX-treated patients was reduced by 0.7 beats/min.

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Other Events Observed in Clinical Studies

Following is a list of treatment-emergent adverse events reported by patients treated with SYMBYAX in clinical trials. This listing is not intended to include events (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.

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

[Provide your justification for modifying the listings of events below from currently approved labeling.]

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

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

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

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

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

Musculoskeletal System — *Rare:* osteoporosis.

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

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

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

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

Urogenital System — *Frequent:* breast pain, menorrhagia[1], urinary frequency, urinary incontinence; *Infrequent:* amenorrhea[1], female lactation[1], hypomenorrhea[1], metrorrhagia[1], urinary retention, urinary urgency, urination impaired; *Rare:* breast engorgement[1].

[1] Adjusted for gender.

Other Events Observed with Olanzapine or Fluoxetine Monotherapy

The following adverse events were not observed in SYMBYAX-treated patients during premarketing clinical studies but have been reported with olanzapine or fluoxetine monotherapy: aplastic anemia, cholestatic jaundice, diabetic coma, dyskinesia, eosinophilic pneumonia, erythema multiforme, jaundice, rhabdomyolysis, serotonin syndrome, vasculitis, venous thromboembolic events (including pulmonary embolism and deep venous thrombosis), violent behaviors. Random triglyceride levels of ≥1000 mg/dL have been rarely reported.

7 DRUG INTERACTIONS

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

7.1 Antihypertensive agents

Because of the potential for olanzapine to induce hypotension, SYMBYAX may enhance the effects of certain antihypertensive agents *[see Warnings and Precautions (5.10)]*.

7.2 Anti-Parkinsonians

The olanzapine component of SYMBYAX may antagonize the effects of levodopa and dopamine agonists.

7.3 Benzodiazepines

Multiple doses of olanzapine did not influence the pharmacokinetics of diazepam and its active metabolite N-desmethyldiazepam. However, the coadministration of diazepam with olanzapine potentiated the orthostatic hypotension observed with olanzapine.

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When concurrently administered with fluoxetine, the half-life of diazepam may be prolonged in some patients *[see Clinical Pharmacology (7.29, 12.3)]*. Coadministration of alprazolam and fluoxetine has resulted in increased alprazolam plasma concentrations and in further psychomotor performance decrement due to increased alprazolam levels.

7.4 Biperiden

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

7.5 Carbamazepine

Carbamazepine therapy (200 mg BID) causes an approximate 50% increase in the clearance of olanzapine. This increase is likely due to the fact that carbamazepine is a potent inducer of CYP1A2 activity. Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance.

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

7.6 Clozapine

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

7.7 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.

7.8 Electroconvulsive therapy (ECT)

There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment *[see Warnings and Precautions (5.12)]*.

7.9 Ethanol

Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics. The coadministration of ethanol with SYMBYAX may potentiate sedation and orthostatic hypotension.

7.10 Fluvoxamine

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

7.11 Haloperidol

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

7.12 Lithium

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

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

7.13 Monoamine oxidase inhibitors

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

7.14 Phenytoin

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

7.15 Pimozide

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

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7.16 Serotonergic Drugs

Based on the mechanism of action of SYMBYAX and the potential for serotonin syndrome, caution is advised when SYMBYAX is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort *[see Warnings and Precautions (5.6)]*. The concomitant use of SYMBYAX with other SSRIs, SNRIs or tryptophan is not recommended *[see Drug Interactions (7.21)]*.

7.17 Theophylline

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

7.18 Thioridazine

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

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

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

7.19 Tricyclic antidepressants (TCAs)

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

In two fluoxetine studies, previously stable plasma levels of imipramine and desipramine have increased >2- to 10-fold when fluoxetine has been administered in combination. This influence may persist for three weeks or longer after fluoxetine is discontinued. Thus, the dose of TCA may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when SYMBYAX is coadministered or has been recently discontinued *[see Drug Interactions (7.25) and Clinical Pharmacology (12.3)]*.

7.20 Triptans

There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of SYMBYAX with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases *[see Warnings and Precautions (5.6)]*.

7.21 Tryptophan

Five patients receiving fluoxetine in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress. Concomitant use with tryptophan is not recommended.

7.22 Valproate

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

7.23 Warfarin

Warfarin (20-mg single dose) did not affect olanzapine pharmacokinetics. Single doses of olanzapine did not affect the pharmacokinetics of warfarin.

Altered anticoagulant effects, including increased bleeding, have been reported when fluoxetine is coadministered with warfarin *[see Warnings and Precautions (5.15)]*. Patients receiving warfarin therapy should receive careful coagulation monitoring when SYMBYAX is initiated or stopped.

7.24 Drugs that Interfere with Hemostasis (NSAIDs, aspirin, warfarin, etc.)

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentiated the risk of bleeding *[see Warnings and Precautions (5.15)]*. Thus, patients should be cautioned about the use of such drugs concurrently with SYMBYAX.

7.25 Drugs metabolized by CYP2D6

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

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Approximately 7% of the normal population has a genetic variation that leads to reduced levels of activity of CYP2D6. Such individuals have been referred to as poor metabolizers of drugs such as debrisoquin, dextromethorphan, and TCAs. Many drugs, such as most antidepressants, including fluoxetine and other selective uptake inhibitors of serotonin, are metabolized by this isoenzyme; thus, both the pharmacokinetic properties and relative proportion of metabolites are altered in poor metabolizers. However, for fluoxetine and its metabolite, the sum of the plasma concentrations of the 4 enantiomers is comparable between poor and extensive metabolizers *[see Clinical Pharmacology (12.3)]*.

Fluoxetine, like other agents that are metabolized by CYP2D6, inhibits the activity of this isoenzyme, and thus may make normal metabolizers resemble poor metabolizers. Therapy with medications that are predominantly metabolized by the CYP2D6 system and that have a relatively narrow therapeutic index should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the previous five weeks. If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need for a decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (including but not limited to, flecainide, vinblastine, and TCAs). Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated thioridazine plasma levels, thioridazine should not be administered with fluoxetine or within a minimum of five weeks after fluoxetine has been discontinued *[see Contraindications, (4) and Drug Interactions (7.18)]*.

7.26 Drugs metabolized by CYP3A

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

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

7.27 Effect of olanzapine on drugs metabolized by other CYP enzymes

In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP1A2, CYP2C9, and CYP2C19. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

7.28 The effect of other drugs on olanzapine

Fluoxetine, an inhibitor of CYP2D6, decreases olanzapine clearance a small amount *[see Clinical Pharmacology (12.3)]*.. Agents that induce CYP1A2 or glucuronyl transferase enzymes, such as omeprazole and rifampin, may cause an increase in olanzapine clearance. Fluvoxamine, an inhibitor of CYP1A2, decreases olanzapine clearance *[see Drug Interactions (7.10)]*. The effect of CYP1A2 inhibitors, such as fluvoxamine and some fluoroquinolone antibiotics, on SYMBYAX has not been evaluated. Although olanzapine is metabolized by multiple enzyme systems, induction or inhibition of a single enzyme may appreciably alter olanzapine clearance. Therefore, a dosage increase (for induction) or a dosage decrease (for inhibition) may need to be considered with specific drugs.

7.29 Drugs tightly bound to plasma proteins

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects — Pregnancy Category C

[We have removed inaccurate and redundant information in the following section.]

SYMBYAX ~~—SYMBYAX has been shown to be teratogenic (or to have an embryocidal effect or other adverse effect) in rats when given in doses of olanzapine and fluoxetine in combination at 2 and 1 times the human dose, respectively. There are no adequate and well-controlled studies in pregnant women. SYMBYAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.~~ Embryo fetal development studies were conducted in rats and rabbits with olanzapine and fluoxetine in low-dose and high-dose combinations. In rats, the doses were: 2 and 4 mg/kg/day (low-dose) [1 and 0.5 times the MRHD on a mg/m^2 basis, respectively], and 4 and 8 mg/kg/day (high-dose) [2 and 1 times the MRHD on a mg/m^2 basis, respectively]. In rabbits, the doses were 4 and 4 mg/kg/day (low-dose) [4 and 1 times the MRHD on a mg/m^2 basis, respectively], and 8 and 8 mg/kg/day (high-dose) [9 and 2 times the MRHD on a mg/m^2 basis, respectively). In these studies, olanzapine and fluoxetine were

also administered alone at the high-doses (4 and 8 mg/kg/day, respectively, in the rat; 8 and 8 mg/kg/day, respectively, in the rabbit). In the rabbit, there was no evidence of teratogenicity; however, the high-dose combination produced decreases in fetal weight and retarded skeletal ossification in conjunction with maternal toxicity. Similarly, in the rat there was no evidence of teratogenicity; however, a decrease in fetal weight was observed with the high-dose combination.

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

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

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

Olanzapine — In reproduction studies in rats at doses up to 18 mg/kg/day and in rabbits at doses up to 30 mg/kg/day (9 and 30 times the MRHD on a mg/m^2 basis, respectively), no evidence of teratogenicity was observed. In a rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the MRHD on a mg/m^2 basis). Gestation was prolonged at 10 mg/kg/day (5 times the MRHD on a mg/m^2 basis). In a rabbit teratology study, fetal toxicity (manifested as increased resorptions and decreased fetal weight) occurred at a maternally toxic dose of 30 mg/kg/day (30 times the MRHD on a mg/m^2 basis).

Placental transfer of olanzapine occurs in rat pups.

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

Fluoxetine — In embryo fetal development studies in rats and rabbits, there was no evidence of teratogenicity following administration of up to 12.5 and 15 mg/kg/day, respectively (1.5 and 3.6 times the MRHD on a mg/m^2 basis, respectively) throughout organogenesis. However, in rat reproduction studies, an increase in stillborn pups, a decrease in pup weight, and an increase in pup deaths during the first 7 days postpartum occurred following maternal exposure to 12 mg/kg/day (1.5 times the MRHD on a mg/m^2 basis) during gestation or 7.5 mg/kg/day (0.9 times the MRHD on a mg/m^2 basis) during gestation and lactation. There was no evidence of developmental neurotoxicity in the surviving offspring of rats treated with 12 mg/kg/day during gestation. The no-effect dose for rat pup mortality was 5 mg/kg/day (0.6 times the MRHD on a mg/m^2 basis).

Treatment of Pregnant Women During the Third Trimester — Neonates exposed to fluoxetine, a component of ~~SYNBYAX~~SYMBYAX, and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome *[see Contraindications (4) and Drug Interactions (7.16)]*. When treating pregnant women with fluoxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering fluoxetine in the third trimester.

8.2 Labor and Delivery

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

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

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

8.3 Nursing Mothers

SYMBYAX — There are no adequate and well-controlled studies with SYMBYAX in nursing mothers or infants. Studies evaluating the individual components of SYMBYAX (olanzapine and fluoxetine) in nursing mothers are described below. It is not known whether SYMBYAX is excreted in human milk and because of the potential for serious adverse reactions in nursing infants

from SYMBYAX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. It is recommended that women not breast-feed when receiving SYMBYAX.

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

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

8.4 Pediatric Use

SYMBYAX — Safety and effectiveness in the pediatric population have not been established *[see Box Warning and Warnings and Precautions (5.3)]*. Anyone considering the use of SYMBYAX in a child or adolescent must balance the potential risks with the clinical need.

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

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

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

In another mouse study, administration of fluoxetine (10 mg/kg intraperitoneal) during early postnatal development (Postnatal Days 4 to 21) produced abnormal emotional behaviors (decreased exploratory behavior in elevated plus-maze, increased shock avoidance latency) in adulthood (12 weeks of age). The dose used in this study is approximately equal to the pediatric MRD on a mg/m^2 basis. Because of the early dosing period in this study, the significance of these findings to the approved pediatric use in humans is uncertain.

8.5 Geriatric Use

SYMBYAX — Clinical studies of SYMBYAX did not include sufficient numbers of patients ≥65 years of age to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Dosage and Administration (2.1)]*.

Olanzapine — Of the 2500 patients in premarketing clinical studies with olanzapine, 11% (263 patients) were ≥65 years of age. In patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared with younger patients. Studies in patients with dementia-related psychosis have suggested that there may be a different tolerability profile in this population compared with younger patients with schizophrenia. In placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis, there was a significantly 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

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treatment of patients with dementia-related psychosis. If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised [see Box Warning, Warnings and Precautions (5.19) and Dosage and Administration (2.3)].

As with other CNS-active drugs, olanzapine should be used with caution in elderly patients with dementia. Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric patient.

Fluoxetine — US fluoxetine clinical studies (10,782 patients) included 687 patients ≥65 years of age and 93 patients ≥75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other SSRIs, fluoxetine has been associated with cases of clinically significant hyponatremia in elderly patients.

9 DRUG ABUSE AND DEPENDENCE

9.3 Dependence

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

In studies in rats and rhesus monkeys designed to assess abuse and dependence potential, olanzapine alone was shown to have acute depressive CNS effects but little or no potential of abuse or physical dependence at oral doses up to 15 (rat) and 8 (monkey) times the MRHD (20 mg) on a mg/m^2 basis.

10 OVERDOSAGE

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

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

Olanzapine — In postmarketing reports of overdose with olanzapine alone, symptoms have been reported in the majority of cases. In symptomatic patients, symptoms with ≥10% incidence included agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma. Among less commonly reported symptoms were the following potentially medically serious events: aspiration, cardiopulmonary arrest, cardiac arrhythmias (such as supraventricular tachycardia as well as a patient that experienced sinus pause with spontaneous resumption of normal rhythm), delirium, possible neuroleptic malignant syndrome, respiratory depression/arrest, convulsion, hypertension, and hypotension. Eli Lilly and Company has received reports of fatality in association with overdose of olanzapine alone. In 1 case of death, the amount of acutely ingested olanzapine was reported to be possibly as low as 450 mg; however, in another case, a patient was reported to survive an acute olanzapine ingestion of 1500 mg.

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

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

Among pediatric patients (ages 3 months to 17 years), there were 156 cases of overdose involving fluoxetine alone or in combination with other drugs. Six patients died. 127 patients completely recovered, 1 patient experienced renal failure, and 22 patients

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had an unknown outcome. One of the 6 fatalities was a 9-year-old boy who had a history of OCD, Tourette's Syndrome with tics, attention deficit disorder, and fetal alcohol syndrome. He had been receiving 100 mg of fluoxetine daily for 6 months in addition to clonidine, methylphenidate, and promethazine. Mixed-drug ingestion or other methods of suicide complicated all 6 overdoses in children that resulted in fatalities. The largest ingestion in pediatric patients was 3 grams, which was non-lethal.

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

10.1 Management of Overdose

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

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

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

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

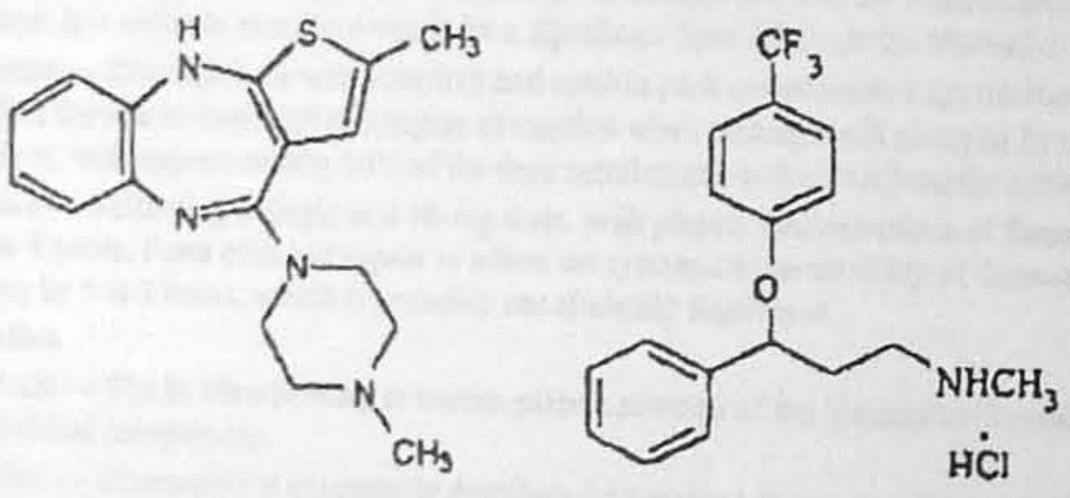
11 DESCRIPTION

SYMBYAX® (olanzapine and fluoxetine HCl capsules) combines 2 psychotropic agents, olanzapine (the active ingredient in Zyprexa®, and Zyprexa Zydis®) and fluoxetine hydrochloride (the active ingredient in Prozac®, Prozac Weekly™, and Sarafem®).

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

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

The chemical structures are:



Olanzapine fluoxetine hydrochloride

Olanzapine is a yellow crystalline solid, which is practically insoluble in water.
Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility of 14 mg/mL in water.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

Olanzapine is a psychotropic agent with high affinity binding to the following receptors: serotonin $5HT_{2A/2C}$ (K_i=4 and 11 nM, respectively), dopamine D_{1-4} (K_i=11 to 31 nM), muscarinic M_{1-5} (K_i=1.9 to 25 nM), histamine H_1 (K_i=7 nM), and adrenergic α_1 receptors (K_i=19 nM). Olanzapine binds weakly to $GABA_A$, BZD, and β-adrenergic receptors (K_i>10 μM). Fluoxetine is an inhibitor of the serotonin transporter and is a weak inhibitor of the norepinephrine and dopamine transporters.

Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities 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 effects. The antagonism of histamine H_1 receptors by olanzapine may explain the somnolence observed with this drug. The antagonism of α_1-adrenergic receptors by olanzapine may explain the orthostatic hypotension observed with this drug. Fluoxetine has relatively low affinity for muscarinic, α_1-adrenergic, and histamine H_1 receptors.

12.3 Pharmacokinetics

SYMBYAX — Fluoxetine (administered as a 60-mg single dose or 60 mg daily for 8 days) caused a small increase in the mean maximum concentration of olanzapine (16%) following a 5-mg dose, an increase in the mean area under the curve (17%) and a small decrease in mean apparent clearance of olanzapine (16%). In another study, a similar decrease in apparent clearance of olanzapine of 14% was observed following olanzapine doses of 6 or 12 mg with concomitant fluoxetine doses of 25 mg or more. The decrease in clearance reflects an increase in bioavailability. The terminal half-life is not affected, and therefore the time to reach steady state should not be altered. The overall steady-state plasma concentrations of olanzapine and fluoxetine when given as the combination in the therapeutic dose ranges were comparable with those typically attained with each of the monotherapies. The small change in olanzapine clearance, observed in both studies, likely reflects the inhibition of a minor metabolic pathway for olanzapine via CYP2D6 by fluoxetine, a potent CYP2D6 inhibitor, and was not deemed clinically significant. Therefore, the pharmacokinetics of the individual components is expected to reasonably characterize the overall pharmacokinetics of the combination.

Absorption and Bioavailability

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

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

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

Distribution

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

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

Fluoxetine — Over the concentration range from 200 to 1000 ng/mL, approximately 94.5% of fluoxetine is bound in vitro to human serum proteins, including albumin and α_1-glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has not been fully evaluated *[see Drug Interactions (7.29)]*.

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Metabolism and Elimination

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

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

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

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

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

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

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

Clinical Issues Related to Metabolism and Elimination

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

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

Because the metabolism of fluoxetine, like that of a number of other compounds including TCAs and other selective serotonin antidepressants, involves the CYP2D6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the TCAs) may lead to drug interactions *[see Drug Interactions (7.19 and 7.25)]*.

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

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

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12.4 **Special Populations**

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

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

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

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

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

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

Hepatic Impairment — Based on the individual pharmacokinetic profiles of olanzapine and fluoxetine, the pharmacokinetics of SYMBYAX may be altered in patients with hepatic impairment. The lowest starting dose should be considered for patients with hepatic impairment *[see Warnings and Precautions (5.19) and Dosage and Administration (2.3)]*.

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

As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of cirrhotic patients, with a mean of 7.6 days compared with the range of 2 to 3 days seen in subjects without liver disease: norfluoxetine elimination was also delayed, with a mean duration of 12 days for cirrhotic patients compared with the range of 7 to 9 days in normal subjects.

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

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

Race — No SYMBYAX pharmacokinetic study was conducted to investigate the effects of race. Results from an olanzapine cross-study comparison between data obtained in Japan and data obtained in the US suggest that exposure to olanzapine may be about 2-fold greater in the Japanese when equivalent doses are administered. Olanzapine clinical study safety and efficacy data, however, did not suggest clinically significant differences among Caucasian patients, patients of African descent, and a 3rd pooled category including Asian and Hispanic patients. Dosage modifications for race, therefore, are not routinely required.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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Carcinogenesis

Olanzapine — Oral carcinogenicity studies were conducted in mice and rats. Olanzapine was administered to mice in two 78-week studies at doses of 3, 10, and 30/20 mg/kg/day [equivalent to 0.8 to 5 times the maximum recommended human daily dose (MRHD) on a mg/m^2 basis] and 0.25, 2, and 8 mg/kg/day (equivalent to 0.06 to 2 times the MRHD on a mg/m^2 basis). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, and 4 mg/kg/day (males) and 0.25, 1, 4, and 8 mg/kg/day (females) (equivalent to 0.1 to 2 and 0.1 to 4 times the MRHD on a mg/m^2 basis, respectively). The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in one mouse study in females dosed at 8 mg/kg/day (2 times the MRHD on a mg/m^2 basis). These tumors were not increased in another mouse study in females dosed at 10 or 30/20 mg/kg/day (2 to 5 times the MRHD on a mg/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 MRHD 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 Warning and Precautions (5.20)]*.

Fluoxetine — The dietary administration of fluoxetine to rats and mice for two years at doses of up to 10 and 12 mg/kg/day, respectively (approximately 1.2 and 0.7 times, respectively, the MRHD on a mg/m^2 basis), produced no evidence of carcinogenicity.

Mutagenesis

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

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

Impairment of Fertility

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

Olanzapine — In a fertility and reproductive performance study in rats, male mating performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female fertility was decreased at a dose of 3 mg/kg/day (11 and 1.5 times the MRHD on a mg/m^2 basis, respectively). Discontinuance of olanzapine treatment reversed the effects on male-mating performance. In female rats, the precoital period was increased and the mating index reduced at 5 mg/kg/day (2.5 times the MRHD on a mg/m^2 basis). Diestrous was prolonged and estrous was delayed at 1.1 mg/kg/day (0.6 times the MRHD on a mg/m^2 basis); therefore, olanzapine may produce a delay in ovulation.

Fluoxetine — Two fertility studies conducted in adult rats at doses of up to 7.5 and 12.5 mg/kg/day (approximately 0.9 and 1.5 times the MRHD on a mg/m^2 basis) indicated that fluoxetine had no adverse effects on fertility *[see Use in Specific Populations (8.4)]*.

14 CLINICAL STUDIES

14.1 Bipolar Depression

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

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The primary rating instrument used to assess depressive symptoms in these studies was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale with total scores ranging from 0 to 60. The primary outcome measure of these studies was the change from baseline to endpoint in the MADRS total score. In both studies, SYMBYAX was statistically significantly superior to both olanzapine monotherapy and placebo in reduction of the MADRS total score. ~~The results of the studies are summarized below (Table 3).~~

~~Table 2: MADRS Total Score~~

~~Mean Change from Baseline to Endpoint~~

	~~Treatment Group~~	~~Baseline Mean~~	~~Change to Endpoint Mean*~~
~~Study 1~~	~~SYMBYAX (N=40)~~	~~30~~	~~-16~~
	~~Olanzapine (N=183)~~	~~33~~	~~-12~~
	~~Placebo (N=181)~~	~~31~~	~~-10~~
~~Study 3~~	~~SYMBYAX (N=42)~~	~~32~~	~~-18~~
	~~Olanzapine (N=169)~~	~~33~~	~~-14~~
	~~Placebo (N=174)~~	~~31~~	~~-9~~

~~* Negative number denotes improvement from baseline.~~

~~Statistically significant compared to both olanzapine and placebo.~~

14.2 Treatment Resistant Depression

[We have revised the following section to more accurately reflect the data used to assess efficacy.]

The efficacy of SYMBYAX in treatment resistant depression was demonstrated with data from ~~5~~ 3 clinical studies (n=579) ~~(Table 3)~~. Doses evaluated in these studies ranged from ~~6/25~~ 18/20 mg for olanzapine and ~~25~~20/~~50~~50/60 mg for fluoxetine.

~~Two identically designed~~An 8-week randomized, double-blind controlled study~~ies (Study 1 and 5) w~~ ~~was~~ere conducted to evaluate the efficacy of SYMBYAX in patients (n = 300) who met DSM-IV criteria for major depressive disorder and did not respond to 2 antidepressants of adequate dose and duration in their current episode ~~(N=605)~~. Patients who were not responding to an antidepressant in their current episode entered an 8-week open-label fluoxetine lead-in; non-responders were randomized (1:1:1) to receive SYMBYAX, olanzapine, or fluoxetine, and were treated for 8 weeks. SYMBYAX was flexibly dosed between 6/50 mg, 12/50 mg, and 18/50 mg. Results from ~~one (Study 1) of these 2 studies~~this study yielded statistically significant greater reduction ~~(p<0.001)~~ in mean total MADRS scores from baseline to endpoint for SYMBYAX ~~(-14.6)~~ versus fluoxetine ~~(-9.0)~~ and olanzapine ~~(-7.7)~~. A second study with the same treatment-resistant patient population (n=28), when analyzed with change in MADRS as the primary outcome measure, demonstrated statistically significantly greater reduction in MADRS scores for SYMBYAX versus fluoxetine and olanzapine. ~~Additionally~~A third study~~, 3 similarly designed studies (Study 2, 3, and 4) of 8-12 weeks duration (n=28, 251, 269, respectively)~~ demonstrated statistically significantly greater reduction in total MADRS scores for SYMBYAX versus fluoxetine ~~(p=0.012, 0.021, 0.106)~~ ~~and~~/or olanzapine ~~alone (p=0.035, 0.003, 0.007) respectively~~, when analyzed ~~for the same~~in a subpopulation of depressed patients (n=251) who met the definition of treatment resistance (patients who ~~were~~had not ~~responding~~responded to 2 antidepressants of adequate dose and duration~~, both~~ during in the current episode).

~~An integrated analysis of the 5 studies yielded statistically significant greater reduction in mean total MADRS scores from baseline to endpoint in the defined population (p=0.015, p=0.007 versus fluoxetine and olanzapine, respectively) for SYMBYAX (-12.2) versus fluoxetine (-8.5) and olanzapine (-7.7).~~

~~Table 3: MADRS Total Score~~

~~Mean Change from Baseline to Endpoint in~~

~~Treatment Resistant Depression~~

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	Treatment Group	Baseline Mean	Change to Endpoint Mean[1]
Study 1	SYMBYAX (N=97)	30.6	-14.6
	Fluoxetine (N=101)	30.1	-9.0[2]
	Olanzapine (N=103)	30.1	-7.7[2]
Study 2	SYMBYAX (N=10)	29.5	-17.6
	Fluoxetine (N=10)	27.8	-1.3[2]
	Olanzapine (N=8)	25.0	-2.8[2]
Study 3	SYMBYAX (N=163)	30.1	-13.3
	Fluoxetine (N=41)	31.1	-10.0[2]
	Olanzapine (N=47)	31.5	-8.8[2]
Study 4	SYMBYAX (N=91)	29.4	-9.0
	Fluoxetine (N=88)	28.9	-7.0[2,3]
	Olanzapine (N=90)	28.4	-5.1[2]
Study 5	SYMBYAX (N=101)	29.5	-10.8
	Fluoxetine (N=102)	29.7	-9.4[2,3]
	Olanzapine (N=95)	29.7	-10.1[2,3]
Integrated analysis of 5 studies	SYMBYAX (N=462)	29.9	-12.0
	Fluoxetine (N=342)	29.6	-8.5[2]
	Olanzapine (N=342)	29.6	-7.7[2]

[1] Negative number denotes improvement from baseline.
[2] SYMBYAX statistically significant ($p<0.05$) compared to fluoxetine and olanzapine.
[3] SYMBYAX demonstrated a greater reduction in total MADRS score, however did not reach statistical significance ($p<0.05$)

16 HOW SUPPLIED/STORAGE AND HANDLING

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

SYMBYAX	CAPSULE STRENGTH				
	3 mg/25 mg	6 mg/25 mg	6 mg/50 mg	12 mg/25 mg	12 mg/50 mg
Color	Peach & Light Yellow	Mustard Yellow & Light Yellow	Mustard Yellow & Light Grey	Red & Light Yellow	Red & Light Grey
Capsule No.	PU3230	PU3231	PU3233	PU3232	PU3234
Identification	Lilly 3230 3/25	Lilly 3231 6/25	Lilly 3233 6/50	Lilly 3232 12/25	Lilly 3234 12/50
NDC Codes					
Bottles 30	0002-3230-30	0002-3231-30	0002-3233-30	0002-3232-30	0002-3234-30
Bottles 100		0002-3231-02	0002-3233-02	0002-3232-02	0002-3234-02
Bottles 1000		0002-3231-04	0002-3233-04	0002-3232-04	0002-3234-04
Blisters ID† 100		0002-3231-33	0002-3233-33	0002-3232-33	0002-3234-33

* Fluoxetine base equivalent.
† IDENTI-DOSE®, Unit Dose Medication, Lilly.

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Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Keep tightly closed and protect from moisture.

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with SYMBYAX and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for SYMBYAX. The prescriber or health professional 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. The complete text of the Medication Guide is reprinted at the end of this document.

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

Patients should be cautioned about the concomitant use of SYMBYAX and NSAIDs, aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding *[see Warnings and Precautions (5.15)]*.

Patients should be advised to avoid alcohol while taking SYMBYAX.

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

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

Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Patients, if taking SYMBYAX, should be advised not to breast-feed.

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration and in association with the use of concomitant drugs that may potentiate the orthostatic effect of olanzapine, e.g., diazepam or alcohol *[see Warnings and Precautions (5.10) and Drug Interactions (7)]*.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during SYMBYAX therapy.

Patients should be advised to notify their physician if they develop a rash or hives while taking SYMBYAX.

Patients should be advised to take SYMBYAX exactly as prescribed, and to continue taking SYMBYAX as prescribed even after their mood symptoms improve. Patients should be advised that they should not alter their dosing regimen, or stop taking SYMBYAX, without consulting their physician.

Patient information is printed at the end of this insert. Physicians should discuss this information with their patients and instruct them to read the Medication Guide before starting therapy with SYMBYAX and each time their prescription is refilled.

17.2 Clinical Worsening and Suicide Risk

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

17.3 Serotonin Syndrome

Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of SYMBYAX and triptans, tramadol or other serotonergic agents.

17.4 FDA Approved Medication Guide

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Medication Guide

About Using Antidepressants in Children and Teenagers

What is the most important information I should know if my child is being prescribed an antidepressant?

Parents or guardians need to think about 4 important things when their child is prescribed an antidepressant:

1. There is a risk of suicidal thoughts or actions
2. How to try to prevent suicidal thoughts or actions in your child
3. You should watch for certain signs if your child is taking an antidepressant
4. There are benefits and risks when using antidepressants

1. There is a Risk of Suicidal Thoughts or Actions

Children and teenagers sometimes think about suicide, and many report trying to kill themselves.

Antidepressants increase suicidal thoughts and actions in some children and teenagers. But suicidal thoughts and actions can also be caused by depression, a serious medical condition that is commonly treated with antidepressants. Thinking about killing yourself or trying to kill yourself is called *suicidality* or *being suicidal*.

A large study combined the results of 24 different studies of children and teenagers with depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an antidepressant for 1 to 4 months. ***No one committed suicide in these studies,*** but some patients became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4 out of every 100 patients became suicidal.

For some children and teenagers, the risks of suicidal actions may be especially high. These include patients with

- Bipolar illness (sometimes called manic-depressive illness)
- A family history of bipolar illness
- A personal or family history of attempting suicide

If any of these are present, make sure you tell your health care provider before your child takes an antidepressant.

2. How to Try to Prevent Suicidal Thoughts and Actions

To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her or his moods or actions, especially if the changes occur suddenly. Other important people in your child's life can help by paying attention as well (e.g., your child, brothers and sisters, teachers, and other important people). The changes to look out for are listed in Section 3, on what to watch for.

Whenever an antidepressant is started or its dose is changed, pay close attention to your child.

After starting an antidepressant, your child should generally see his or her health care provider

- Once a week for the first 4 weeks
- Every 2 weeks for the next 4 weeks
- After taking the antidepressant for 12 weeks
- After 12 weeks, follow your health care provider's advice about how often to come back
- More often if problems or questions arise (see Section 3)

You should call your child's health care provider between visits if needed.

3. You Should Watch for Certain Signs if Your Child is Taking an Antidepressant

Contact your child's health care provider *right away* if your child exhibits any of the following signs for the first time, or if they seem worse, or worry you, your child, or your child's teacher:

- Thoughts about suicide or dying
- Attempts to commit suicide
- New or worse depression
- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Difficulty sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry, or violent
- Acting on dangerous impulses
- An extreme increase in activity and talking
- Other unusual changes in behavior or mood

Never let your child stop taking an antidepressant without first talking to his or her health care provider. Stopping an antidepressant suddenly can cause other symptoms.

4. There are Benefits and Risks When Using Antidepressants

Antidepressants are used to treat depression and other illnesses. Depression and other illnesses can lead to suicide. In some children and teenagers, treatment with an antidepressant increases suicidal thinking or actions. It is important to discuss all the risks of treating depression and also the risks of not treating it. You and your child should discuss all treatment choices with your health care provider, not just the use of antidepressants.

Other side effects can occur with antidepressants (see section below).

Of all the antidepressants, only fluoxetine (Prozac®) has been FDA approved to treat pediatric depression.

For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine (Prozac®), sertraline (Zoloft®), fluvoxamine, and clomipramine (Anafranil®).

Your health care provider may suggest other antidepressants based on the past experience of your child or other family members.

Is this all I need to know if my child is being prescribed an antidepressant?

No. This is a warning about the risk for suicidality. Other side effects can occur with antidepressants. Be sure to ask your health care provider to explain all the side effects of the particular drug he or she is prescribing. Also ask about drugs to avoid when taking an antidepressant. Ask your health care provider or pharmacist where to find more information.

Prozac® is a registered trademark of Eli Lilly and Company.
Zoloft® is a registered trademark of Pfizer Pharmaceuticals.
Anafranil® is a registered trademark of Mallinckrodt Inc.

This Medication Guide has been approved by the US Food and Drug Administration for all antidepressants.

Rx only

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Thomas Laughren
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AND DEVELOPMENTS