HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Olanzapine and Fluoxetine Capsules USP safely and effectively. See full prescribing information for Olanzapine and Fluoxetine Capsules USP.

Olanzapine and Fluoxetine Capsules USP for oral use

Initial U.S. Approval: 2003

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

See full prescribing information for complete boxed warning.

- **Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for Major Depressive Disorder (MDD) and other psychiatric disorders. Olanzapine and Fluoxetine Capsules are not approved for use in children and adolescents (5.1, 8.4, 17.2).**
- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Olanzapine and Fluoxetine Capsules are not approved for the treatment of patients with dementia-related psychosis (5.2, 5.19, 17.3).**

RECENT MAJOR CHANGES

Dosage and Administration:
Specific Populations (**2.3**) 01/2013
Switching a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders (**2.4**) 01/2013
Use of Olanzapine and Fluoxetine Capsules with other MAOIs such as Linezolid or Methylene Blue (**2.5**) 01/2013
Contraindications:
Monoamine Oxidase Inhibitors (MAOIs) (**4.1**) 01/2013
Other Contraindications (**4.2**) 01/2013
Warnings and Precautions:
Serotonin Syndrome (**5.7**) 01/2013

INDICATIONS AND USAGE

Olanzapine and fluoxetine capsules combines olanzapine, an atypical antipsychotic and fluoxetine, a selective serotonin reuptake inhibitor, indicated for acute treatment of:
- Depressive Episodes Associated with Bipolar I Disorder in adults (**1.1**)

DOSAGE AND ADMINISTRATION

- Once daily in the evening, generally beginning with 6 mg/25 mg (**2.1**)
- The starting dose of Olanzapine and Fluoxetine Capsules 3 mg/25 mg – 6 mg/25 mg should be used in patients predisposed to hypotensive reactions, hepatic impairment, or with potential for slowed metabolism. Escalate dose cautiously (**2.3**)
- Consider tapering the dose of fluoxetine for pregnant women during the third trimester (**2.3**)
- Discontinue gradually (**2.4**)
- The safety of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated in clinical trials (**2.1**)

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

- Serotonin Syndrome and MAOIs: Do not use MAOIs intended to treat psychiatric disorders with Olanzapine and Fluoxetine Capsules or within 5 weeks of stopping treatment with Olanzapine and Fluoxetine Capsules. Do not use Olanzapine and Fluoxetine Capsules within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start Olanzapine and Fluoxetine Capsules in a patient who is being treated with linezolid or intravenous methylene blue. (**4.1**)
- Do not use with pimozide due to risk of drug interaction or QTc prolongation (**4, 7.7**)
- Do not use with thioridazine due to QTc interval prolongation or potential for elevated thioridazine plasma levels. Do not use thioridazine within 5 weeks of discontinuing olanzapine and fluoxetine capsules (**4, 7.7**)

WARNINGS AND PRECAUTIONS

- *Clinical Worsening and Suicide Risk:* Monitor for clinical worsening and suicidal thinking and behavior (**5.1**)
- *Elderly Patients with Dementia-Related Psychosis:* Increased risk of death and increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) (**5.2**)
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation and close monitoring (**5.3**)
- *Hyperglycemia:* In some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients taking olanzapine. Patients taking olanzapine and fluoxetine should be monitored for symptoms of hyperglycemia and undergo fasting blood glucose testing at the beginning of, and periodically during, treatment. (**5.4**)
- *Hyperlipidemia:* Undesirable alterations in lipids have been observed. Appropriate clinical monitoring is recommended, including fasting blood lipid testing at the beginning of, and periodically during, treatment (**5.5**)
- *Weight gain:* Potential consequences of weight gain should be considered. Patients should receive regular monitoring of weight (**5.6**)
- *Serotonin Syndrome* – Serotonin Syndrome has been reported with SSRIs and SNRIs, including Olanzapine and fluoxetine capsules, both when taken alone, but especially when coadministered with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone and St. John's Wort). If such symptoms occur, discontinue Olanzapine and fluoxetine capsules and initiate supportive treatment. If concomitant use of Olanzapine and fluoxetine capsules with other serotonergic drugs is clinically warranted, patients should be made aware of a potential increased risk of serotonin syndrome, particularly during treatment initiation and dose increases (**5.7**).
- *Allergic Reactions and Rash:* Discontinue upon appearance of rash or allergic phenomena (**5.8**)
- *Activation of Mania/Hypomania:* Screen for Bipolar Disorder and monitor for activation of mania/hypomania (**5.9**)
- *Tardive Dyskinesia:* Discontinue if clinically appropriate (**5.10**)
- *Orthostatic Hypotension:* Orthostatic hypotension associated with dizziness, tachycardia, bradycardia and, in some patients, syncope, may occur especially during initial dose titration. Use caution in patients with cardiovascular disease or cerebrovascular disease, and those conditions that could affect hemodynamic responses (**5.11**)
- *Leukopenia, Neutropenia, and Agranulocytosis:* Has been reported with antipsychotics, including olanzapine and fluoxetine. Patients with a history of a clinically significant low white blood cell count (WBC) or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of olanzapine and fluoxetine should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors (**5.12**)
- *Seizures:* Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold (**5.14**)
- *Abnormal Bleeding:* May increase the risk of bleeding. Use with NSAIDs, aspirin, warfarin, or drugs that affect coagulation may potentiate the risk of gastrointestinal or other bleeding (**5.15**)
- *Hyponatremia:* Has been reported with olanzapine and fluoxetine in association with syndrome of inappropriate antidiuretic hormone (SIADH) (**5.16**)
- *Potential for Cognitive and Motor Impairment:* Has potential to impair judgment, thinking, and motor skills. Use caution when operating machinery (**5.17**)
- *Hyperprolactinemia:* May elevate prolactin levels (**5.20**)
- *Long Elimination Half-Life of Fluoxetine:* Changes in dose will not be fully reflected in plasma for several weeks (**5.22**)
- *Laboratory Tests:* Monitor fasting blood glucose and lipid profiles at the beginning of, and periodically during, treatment (**5.24**)

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical Companies, Inc. 1-800-828-9393 or FDA at 1-800- FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- *Monoamine Oxidase Inhibitor (MAOI):* (**2.4, 2.5, 4.1, 5.7, 7.1**)
- *Pimozide:* Olanzapine and fluoxetine is contraindicated for use with pimozide due to risk of drug interaction or QT_c prolongation (**4, 7.7**)
- *Thioridazine:* Olanzapine and fluoxetine is contraindicated for use with thioridazine due to QT_c interval prolongation or potential for elevated thioridazine plasma levels. Do not use thioridazine within 5 weeks of discontinuing olanzapine and fluoxetine capsules (**4, 7.7**)
- *Drugs Metabolized by CYP2D6:* Fluoxetine is a potent inhibitor of CYP2D6 enzyme pathway (**7.7**)
- *Tricyclic Antidepressants (TCAs):* Monitor TCA levels during coadministration with olanzapine and fluoxetine or when olanzapine and fluoxetine capsules has been recently discontinued (**5.7, 7.7**)
- *CNS Acting Drugs:* Caution is advised if the concomitant administration of olanzapine and fluoxetine and other CNS-active drugs is required (**7.2**)
- *Antihypertensive Agent:* Enhanced antihypertensive effect (**7.7**)
- *Levodopa and Dopamine Agonists:* May antagonize levodopa/dopamine agonists (**7.7**)
- *Benzodiazepines:* May potentiate orthostatic hypotension and sedation (**7.6, 7.7**)
- *Clozapine:* May elevate clozapine levels (**7.7**)
- *Haloperidol:* Elevated haloperidol levels have been observed (**7.7**)
- *Carbamazepine:* Potential for elevated carbamazepine levels and clinical anticonvulsant toxicity (**7.7**)
- *Phenytoin:* Potential for elevated phenytoin levels and clinical anticonvulsant toxicity (**7.7**)
- *Alcohol:* May potentiate sedation and orthostatic hypotension (**7.7**)
- *Serotonergic Drugs:* (**2.4, 2.5, 4.1, 5.7**)
- *Fluvoxamine:* May increase olanzapine levels; a lower dose of the olanzapine component of olanzapine and fluoxetine capsules should be considered (**7.6**)
- *Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, Warfarin, etc.):* May potentiate the risk of bleeding (**7.4**)
- *Drugs Tightly Bound to Plasma Proteins:* Fluoxetine may cause shift in plasma concentrations (**7.7**)

USE IN SPECIFIC POPULATIONS

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

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

Revised: 02/2013

FULL PRESCRIBING INFORMATION: CONTENTS *

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

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

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

Increased Mortality in Elderly Patients with Dementia-Related Psychosis — Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Olanzapine and fluoxetine is not approved for the treatment of patients with dementia-related psychosis *[see WARNINGS AND PRECAUTIONS (5.2, 5.19) and PATIENT COUNSELING INFORMATION (17.3)].*

1 INDICATIONS AND USAGE

1.1 Depressive Episodes Associated with Bipolar I Disorder

Olanzapine and fluoxetine is indicated for the acute treatment of depressive episodes associated with Bipolar I Disorder in adults *[see* **CLINICAL STUDIES (14.1)***]*.

2 DOSAGE AND ADMINISTRATION

2.1 Depressive Episodes Associated with Bipolar I Disorder

Olanzapine and Fluoxetine Capsules 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 olanzapine and fluoxetine has not been studied. Dosage adjustments, if indicated, can be made according to efficacy and tolerability. Antidepressant efficacy was demonstrated with olanzapine and fluoxetine in a dose range of olanzapine 6 to 12 mg and fluoxetine 25 to 50 mg *[see* **Clinical Studies (14.1)***]*. The safety of doses above 18 mg per 75 mg has not been evaluated in clinical studies.

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

2.3 Specific Populations

The starting dose of Olanzapine and Fluoxetine Capsules 3 mg/25 mg to 6 mg/25 mg should be used for patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of olanzapine and fluoxetine (female gender, geriatric age, nonsmoking status) or those patients who may be pharmacodynamically sensitive to olanzapine. Dosing modification may be necessary in patients who exhibit a combination of factors that may slow metabolism. When indicated, dose escalation should be performed with caution in these patients. Olanzapine and fluoxetine has not been systematically studied in patients >65 years of age or in patients <18 years of age *[see* **Warnings and Precautions (5.19)**, **Use in Specific Populations (8.5)**, *and* **Clinical Pharmacology (12.3, 12.4)***]*.

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

2.4 Switching a Patient To or From a Monamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders

At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders, and initiation of therapy with olanzapine and fluoxetine. Conversely, at least 5 weeks should be allowed after stopping olanzapine and fluoxetine before starting an MAOI intended to treat psychiatric disorders *[see* **Contraindications (4.1)***]*.

2.5 Use of Olanzapine and Fluoxetine Capsules with Other MAOIs such as Linezolid or Methylene Blue

Do not start olanzapine and fluoxetine in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered *[see* **Contraindications (4.1)***]*.

In some cases, a patient already receiving olanzapine and fluoxetine therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue are judged to outweigh the risks of serotonin syndrome in a particular patient, olanzapine and fluoxetine should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for five weeks or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with Olanzapine and Fluoxetine Capsules may be resumed 24 hours after the last dose of linezolid and intravenous methylene blue *[see* **Warning and Precautions (5.7)***]*.

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1mg/kg with olanzapine and fluoxetine in unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use *[see* **Warnings and Precautions (5.7)***]*.

2.6 Discontinuation of Treatment with Olanzapine and Fluoxetine Capsules

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

4.1 Monoamine Oxidase Inhibitors (MAOIs)

The use of MAOIs intended to treat psychiatric disorders with olanzapine and fluoxetine or within 5 weeks of stopping treatment with olanzapine and fluoxetine is contraindicated because of an increased risk of serotonin syndrome. The use of olanzapine and fluoxetine within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated. *[see* **Dosage and Administration (2.4)** *and* **Warnings and Precautions (5.7)***]*.

Starting olanzapine and fluoxetine in a patient who is being treated with MAOIs such and linezolid and intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome. *[see* **Dosage and Administration (2.5)** *and* **Warnings and Precautions (5.7)***]*.

4.2 Other Contraindications

The use of olanzapine and fluoxetine is contraindicated with the following:
- Pimozide — *[see* **Drug Interactions (7.7)***]*
- Thioridazine — *[see* **Drug Interactions (7.7)***]*

5 WARNINGS AND PRECAUTIONS

5.1 Clinical Worsening and Suicide Risk

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

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

Table 1: Suicidality per 1000 Patients Treated

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18 to 24	5 additional cases
	Decreases Compared to Placebo
25 to 64	1 fewer case
≥65	6 fewer cases

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

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

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

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

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

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms *[see* **Warnings and Precautions (5.23)***]*.

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

It should be noted that olanzapine and fluoxetine capsules are not approved for use in treating any indications in the pediatric population *[see* **USE IN SPECIFIC POPULATIONS (8.4)***]*.

5.2 Elderly Patients with Dementia-Related Psychosis

Increased Mortality— **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Olanzapine and fluoxetine capsules are not approved for the treatment of patients with dementia-related psychosis** *[see* **BOXED WARNING, Warnings and Precautions (5.19),** *and* **Patient Counseling Information (17.3)***]*.

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

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

5.3 Neuroleptic Malignant Syndrome (NMS)

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

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

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

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

5.4 Hyperglycemia

Physicians should consider the risks and benefits when prescribing olanzapine and fluoxetine capsule to patients with an established diagnosis of diabetes mellitus, or having borderline increased blood glucose level (fasting 100 to 126 mg/dL, nonfasting 140 to 200 mg/dL). Patients taking olanzapine and fluoxetine capsules should be monitored regularly for worsening of glucose control. Patients starting treatment with olanzapine and fluoxetine should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug *[see* **Patient Counseling Information (17.5)***]*.

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

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

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

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

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

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

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

Table 2: Changes in Random Glucose Levels from Adult Olanzapine and Fluoxetine Studies

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

[a] Not Applicable

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

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

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine and fluoxetine in combination have not been established in patients under the age of 18 years. The safety and efficacy of olanzapine have not been established in patients under the age of 13 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with Schizophrenia (6 weeks) or Bipolar I Disorder (manic or mixed episodes) (3 weeks), olanzapine was associated with a greater mean change from baseline in fasting glucose levels compared to placebo (2.68 mg/dL vs -2.59 mg/dL). The mean change in fasting glucose for adolescents exposed at least 24 weeks was 3.1 mg/dL (N=121). **Table 3** shows short-term and long-term changes in fasting blood glucose from adolescent olanzapine monotherapy studies.

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

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

[a] Not Applicable

5.5 Hyperlipidemia

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

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

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

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

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

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

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

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

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

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

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

[a] Not Applicable

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

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine and fluoxetine in combination have not been established in patients under the age of 18 years. The safety and efficacy of olanzapine have not been established in patients under the age of 13 years.

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

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

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

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	Up to 6 weeks exposure N	Up to 6 weeks exposure Patients	At least 24 weeks exposure N	At least 24 weeks exposure Patients
Fasting Triglycerides	Increase by ≥ 50 mg/dL	Olanzapine	138	37.0%	122	45.9%
		Placebo	66	15.2%	NA[a]	NA[a]
	Normal to High (<90 mg/dL to >130 mg/dL)	Olanzapine	67	26.9%	66	36.4%
		Placebo	28	10.7%	NA[a]	NA[a]
	Borderline to High (≥90 mg/dL and ≤130 mg/dL to >130 mg/dL)	Olanzapine	37	59.5%	31	64.5%
		Placebo	17	35.3%	NA[a]	NA[a]
Fasting Total Cholesterol	Increase by ≥ 40 mg/dL	Olanzapine	138	14.5%	122	14.8%
		Placebo	66	4.5%	NA[a]	NA[a]
	Normal to High (<170 mg/dL to ≥200 mg/dL)	Olanzapine	87	6.9%	78	7.7%
		Placebo	43	2.3%	NA[a]	NA[a]
	Borderline to High (≥170 mg/dL and <200 mg/dL to ≥200 mg/dL)	Olanzapine	36	38.9%	33	57.6%
		Placebo	13	7.7%	NA[a]	NA[a]
Fasting LDL Cholesterol	Increase by ≥30 mg/dL	Olanzapine	137	17.5%	121	22.3%
		Placebo	63	11.1%	NA[a]	NA[a]
	Normal to High (<110 mg/dL to ≥130 mg/dL)	Olanzapine	98	5.1%	92	10.9%
		Placebo	44	4.5%	NA[a]	NA[a]
	Borderline to High (≥110 mg/dL and <130 mg/dL to ≥130 mg/dL)	Olanzapine	29	48.3%	21	47.6%
		Placebo	9	0%	NA[a]	NA[a]

[a] Not Applicable

5.6 Weight Gain

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

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

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

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

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

Table 7: Weight Gain with Olanzapine Use in Adults

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

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine and fluoxetine in combination have not been established in patients under the age of 18 years. The safety and efficacy of olanzapine have not been established in patients under the age of 13 years. Mean increase in weight in adolescents was greater than in adults. In 4 placebo-controlled trials, discontinuation due to weight gain occurred in 1% of olanzapine-treated patients, compared to 0% of placebo-treated patients.

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

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

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

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

Table 9: Weight Gain with Olanzapine Use in Adolescents

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

5.7 Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs including olanzapine and fluoxetine, alone but particularly with concomitant use of serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl,lithium,tramadol, tryptophan, buspirone, and St. John's Wort) and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination)seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of olanzapine and fluoxetine with MAOIs intended to treat psychiatric disorders is contraindicated. Olanzapine and fluoxetine should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided informations on the route of administration involved intravenous administration in the dose range of 1mg/kg to 8mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking olanzapine and fluoxetine. Olanzapine and fluoxetine should be discontinued before initiating treatment with the MAOI *[see* **Dosage and Adminstration (2.4, and 2.5) and Contraindications (4.1)***]*.

If concomitant use of olanzapine and fluoxetine with other serotonergic drugs including triptans, tricyclic anitdepressants, fentanyl, lithium, tramadol, buspirone, tryptophan and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initation and dose increases.

Treatment with olanzapine and fluoxetine and any concomitant serotonergic agents should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

5.8 Allergic Reactions and Rash

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

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

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

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

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

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

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

5.9 Activation of Mania/Hypomania

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

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

5.10 Tardive Dyskinesia

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

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

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

The incidence of dyskinetic movement in olanzapine and fluoxetine-treated patients was infrequent. The mean score on the Abnormal Involuntary Movement Scale (AIMS) in the olanzapine and fluoxetine-controlled database across clinical studies involving olanzapine and fluoxetine -treated patients decreased from baseline. Nonetheless, olanzapine and fluoxetine 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 olanzapine and fluoxetine capsules, drug discontinuation should be considered. However, some patients may require treatment with olanzapine and fluoxetine despite the presence of the syndrome. The need for continued treatment should be reassessed periodically.

5.11 Orthostatic Hypotension

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

In the olanzapine and fluoxetine-controlled clinical trials across all indications, there were no significant differences between olanzapine and fluoxetine-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 olanzapine and fluoxetine, olanzapine, fluoxetine, and placebo groups, respectively. In this group of studies, the incidence of syncope-related adverse reactions (i.e., syncope and/or loss of consciousness) in olanzapine and fluoxetine-treated patients was 0.4% (3/771) compared to placebo 0.2% (1/477).

In a clinical pharmacology study of olanzapine and fluoxetine, 3 healthy subjects were discontinued from the trial after experiencing severe, but self-limited, hypotension and bradycardia that occurred 2 to 9 hours following a single 12 mg/50 mg dose of olanzapine and fluoxetine capsules. Reactions consisting of this combination of hypotension and bradycardia (and also accompanied by sinus pause) have been observed in at least 3 other healthy subjects treated with various formulations of olanzapine (1 oral, 2 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 olanzapine and fluoxetine 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.

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

5.12 Leukopenia, Neutropenia, and Agranulocytosis

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

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

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

5.13 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 fluoxetine capsules are not approved for the treatment of patients with Alzheimer's disease.

5.14 Seizures

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

5.15 Abnormal Bleeding

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

Patients should be cautioned about the risk of bleeding associated with the concomitant use of olanzapine and fluoxetine and NSAIDs, aspirin, or other drugs that affect coagulation *[see* **Drug Interactions (7.4)** *and* **Patient Counseling Information (17.11)***]*.

5.16 Hyponatremia

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

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

5.17 Potential for Cognitive and Motor Impairment

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

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 olanzapine and fluoxetine capsules for patients who will be experiencing conditions which may contribute to an elevation in core body temperature (e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration). *[See* **Patient Counseling Information (17.13)***]*.

5.19 Use in Patients with Concomitant Illness

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

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

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

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

Olanzapine and fluoxetine 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 olanzapine and fluoxetine in cardiac patients and in patients with diseases or conditions that could affect hemodynamic responses *[see* **Warnings and Precautions (5.11)***]*.

5.20 Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, olanzapine and fluoxetine elevates prolactin levels, and the elevation persists during administration. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and erectile dysfunction have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

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

In controlled clinical studies of olanzapine and fluoxetine (up to 12 weeks), changes from normal to high in prolactin concentrations were observed in 28% of adults treated with olanzapine and fluoxetine as compared to 5% of placebo-treated patients. The elevations persisted throughout administration of olanzapine and fluoxetine. In a pooled analysis from clinical studies including 2929 adults treated with olanzapine and fluoxetine, potentially associated clinical manifestations included menstrual-related events[1] (1% [20/1946] of females), sexual function-related events[2] (7% [192/2929] of females and males), and breast-related events[3] (0.8% [16/1946] of females, 0.2% [2/983] of males).

In placebo-controlled olanzapine clinical studies (up to 12 weeks), changes from normal to high in prolactin concentrations were observed in 30% of adults treated with olanzapine as compared to 10.5% of adults treated with placebo. In a pooled analysis from clinical studies including 8136 adults treated with olanzapine, potentially associated clinical manifestations included menstrual-related events[1] (2% [49/3240] of females), sexual function-related events[2] (2% [150/8136] of females and males), and breast-related events[3] (0.7% [23/3240] of females, 0.2% [9/4896] of males).

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

1. Based on a search of the following terms: amenorrhea, hypomenorrhea, menstruation delayed, and oligomenorrhea.
2. Based on a search of the following terms: anorgasmia, delayed ejaculation, erectile dysfunction, decreased libido, loss of libido, abnormal orgasm, and sexual dysfunction.
3. Based on a search of the following terms: breast discharge, enlargement or swelling, galactorrhea, gynecomastia, and lactation disorder.

5.21 Concomitant Use of Olanzapine and Fluoxetine Products

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

5.22 Long Elimination Half-Life of Fluoxetine

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

5.23 Discontinuation of Treatment with Olanzapine and Fluoxetine Capsules

During marketing of fluoxetine, a component of olanzapine and fluoxetine, SNRIs, and SSRIs, there have been spontaneous reports of adverse reactions occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these reactions are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with fluoxetine. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate. Plasma fluoxetine and norfluoxetine concentration decrease gradually at the conclusion of therapy, which may minimize the risk of discontinuation symptoms with this drug *[see* **Dosage and Administration (2.4)** *and* **Patient Counseling Information (17.16)***]*.

5.24 Laboratory Tests

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

6 ADVERSE REACTIONS

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

6.1 Clinical Trials Experience

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

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

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

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

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

Commonly Observed Adverse Reactions in Short-Term, Controlled Studies Including Depressive Episodes Associated with Bipolar 1 Disorder — The most commonly observed adverse reactions associated with the use of olanzapine and fluoxetine (incidence ≥5% and at least twice that for placebo in the olanzapine and fluoxetine-controlled database) using MedDRA Dictionary coding were: disturbance in attention, dry mouth, fatigue, hypersomnia, increased appetite, peripheral edema, sedation, somnolence, tremor, vision blurred, and weight increased. Adverse reactions reported in clinical trials of olanzapine and fluoxetine in combination are generally consistent with treatment-emergent adverse reactions during olanzapine or fluoxetine monotherapy.

Adverse Reactions Occurring at an Incidence of 2% or More in Short-Term Controlled Studies Including Depressive Episodes Associated with Bipolar 1 Disorder — **Table 10** enumerates the treatment-emergent adverse reactions associated with the use of olanzapine and fluoxetine (incidence of at least 2% for olanzapine and fluoxetine and twice or more than for placebo). The olanzapine and fluoxetine-controlled column includes patients with various diagnoses while the placebo column includes only patients with bipolar depression and major depression with psychotic features.

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

System Organ Class	Adverse Reaction	Percentage of Patients Reporting Event: Olanzapine and Fluoxetine-Controlled (N=771)	Percentage of Patients Reporting Event: Placebo (N-477)
Eye disorders	Vision blurred	5	2
Gastrointestinal disorders	Dry mouth	15	6
	Flatulence	3	1
	Abdominal distension	2	0
General disorders and administration site conditions	Fatigue	12	2
	Edema peripheral	9	0
	Edema	3	0
	Asthenia	3	1
	Pain	2	1
	Pyrexia	2	1
Infections and infestations	Sinusitis	2	1
Investigations	Weight increased	25	3
Metabolism and nutrition disorders	Increased appetite	20	4
Musculoskeletal and connective tissue disorders	Arthralgia	4	1
	Pain in extremity	3	1
	Musculoskeletal stiffnes	2	1
Nervous system disorders	Somnolence	14	6
	Tremor	9	3
	Sedation	8	4
	Hypersomnia	5	1
	Distrubance in attention	5	1
	Lethargy	3	1
Psychiatric disorders	Restlessness	4	1
	Thinking abnormal	2	1
	Nervousness	2	1
Reproductive system and breast disorders	Erectile dysfunction	2	1

Extrapyramidal Symptoms

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

Additional Findings Observed in Clinical Studies

Sexual Dysfunction — In the pool of controlled olanzapine and fluoxetine studies in patients with bipolar depression, there were higher rates of the treatment-emergent adverse reactions decreased libido, anorgasmia, erectile dysfunction and abnormal ejaculation in the olanzapine and fluoxetine group than in the placebo group. One case of decreased libido led to discontinuation in the olanzapine and fluoxetine group. In the controlled studies that contained a fluoxetine arm, the rates of decreased libido and abnormal ejaculation in the olanzapine and fluoxetine 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.

There are no adequate and well-controlled studies examining dysfunction with olanzapine and fluoxetine or fluoxetine treatment. Symptoms of sexual dysfunction occasionally persist after discontinuation of fluoxetine treatment.

Difference Among Dose Levels Observed in Other Olanzapine Clinical Trials

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

Other Adverse Reactions Observed in Clinical Studies

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

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

Body as a Whole — *Frequent:* chills, neck rigidity, photosensitivity reaction; *Rare:* death[1].
Cardiovascular System — *Frequent:* vasodilatation; *Infrequent:* QT-interval prolonged.
Digestive System — *Frequent:* diarrhea; *Infrequent:* gastritis, gastroenteritis, nausea and vomiting, peptic ulcer; *Rare:* gastrointestinal hemorrhage, intestinal obstruction, liver fatty deposit, pancreatitis.
Hemic and Lymphatic System — *Frequent:* ecchymosis; *Infrequent:* anemia, thrombocytopenia; *Rare:* leukopenia, purpura.
Metabolic and Nutritional — *Frequent:* generalized edema, weight loss; *Rare:* bilirubinemia, creatinine increased, gout.
Musculoskeletal System — *Rare:* osteoporosis.
Nervous System — *Frequent:* amnesia; *Infrequent:* ataxia, buccoglossal syndrome, coma, depersonalization, dysarthria, emotional lability, euphoria, hypokinesia, movement disorder, myoclonus; *Rare:* hyperkinesia, libido increased, withdrawal syndrome.
Respiratory System — *Infrequent:* epistaxis, yawn; *Rare:* laryngismus.
Skin and Appendages — *Infrequent:* alopecia, dry skin, pruritis; *Rare:* exfoliative dermatitis.
Special Senses — *Frequent:* taste perversion; *Infrequent:* abnormality of accommodation, dry eyes.
Urogenital System — *Frequent:* breast pain, menorrhagia[2], urinary frequency, urinary incontinence; *Infrequent:* amenorrhea[2], female lactation[2], hypomenorrhea[2], metrorrhagia[2], urinary retention, urinary urgency, urination impaired; *Rare:* breast engorgement[2].

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

Other Adverse Reactions Observed with Olanzapine or Fluoxetine Monotherapy

The following adverse reactions were not observed in olanzapine and fluoxetine-treated patients during premarketing clinical studies but have been reported with olanzapine or fluoxetine monotherapy: aplastic anemia, bruxism, cholestatic jaundice, diabetic coma, dysuria, eosinophilic pneumonia[3], erythema multiforme, esophageal ulcer, gynecological bleeding, headache, hypotension, jaundice, neutropenia, sudden unexpected death[3], sweating, and violent behaviors[3]. Random triglyceride levels of ≥1000 mg/dL have been reported.

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

6.2 Vital Signs and Laboratory Studies

Vital Signs — Tachycardia, bradycardia, and orthostatic hypotension have occurred in olanzapine and fluoxetine-treated patients *[see* **Warnings and Precautions (5.11)***]*. The mean standing pulse rate of olanzapine and fluoxetine-treated patients was reduced by 0.7 beats/min.

Laboratory Changes — In olanzapine and fluoxetine clinical studies, olanzapine and fluoxetine was associated with statistically significantly greater frequencies for the following treatment-emergent findings in laboratory analytes (normal at baseline to abnormal at any time during the trial) compared to placebo: elevated prolactin (28% vs 5%); elevated urea nitrogen (3% vs 0.8%); elevated uric acid (3% vs 0.5%); low albumin (3% vs 0.3%); low bicarbonate (14% vs 9%); low hemoglobin (3% vs 0%); low inorganic phosphorus (2% vs 0.3%); low lymphocytes (2% vs 0%); and low total bilirubin (15% vs 4%).

As with olanzapine, asymptomatic elevations of hepatic aminotransferases [ALT, AST, and GGT] and alkaline phosphatase have been observed with olanzapine and fluoxetine. In the olanzapine and fluoxetine-controlled database, clinically significant ALT elevations (change from <3 times the upper limit of normal [ULN] at baseline to ≥3 times ULN) were observed in 5% (38/698) of patients exposed to olanzapine and fluoxetine compared with 0.5% (2/378) of placebo-treated patients and 4% (33/751) of olanzapine-treated patients. ALT elevations ≥5 times ULN were observed in 2% (11/701 of olanzapine and fluoxetine-treated patients, compared to 0.3% (1/379) of placebo-treated patients and 1% (11/760) of olanzapine-treated patients. No patient with elevated ALT values experienced jaundice or liver failure, or met the criteria for Hy's Rule. ALT values returned to normal, or were decreasing, at last follow-up in the majority of patients who either continued treatment with olanzapine and fluoxetine or discontinued olanzapine and fluoxetine.

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

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

An increase in creatine phosphokinase has been reported very rarely in olanzapine and fluoxetine-treated patients and infrequently in clinical trials of olanzapine-treated patients.

Effect on Cardiac Repolarization — The mean increase in QT_c interval for olanzapine and fluoxetine-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 olanzapine and fluoxetine, placebo, olanzapine, or fluoxetine in the incidence of QT_c outliers (>500 msec).

6.3 Postmarketing Experience

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

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

7 DRUG INTERACTIONS

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

7.1 Monoamine Oxidase Inhibitors (MAOI)

[See **Dosage and Administration (2.4), (2.5), Contraindications (4.1)** *and* **Warnings and Precautions (5.7)***]*.

7.2 CNS Acting Drugs

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

7.3 Serotonergic Drugs

[See **Dosage and Administration (2.4), (2.5), Contraindications (4.1)** *and* **Warnings and Precautions (5.7)***]*.

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

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SNRIs or SSRIs are coadministered with warfarin *[see* **Warnings and Precautions (5.15)***]*. Warfarin (20 mg single dose) did not affect olanzapine pharmacokinetics. Single doses of olanzapine did not affect the pharmacokinetics of warfarin. Patients receiving warfarin therapy should be carefully monitored when olanzapine and fluoxetine is initiated or discontinued.

7.5 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 (5.14)***]*.

7.6 Potential for Other Drugs to Affect Olanzapine and Fluoxetine

Benzodiazepines — Coadministration of diazepam with olanzapine potentiated the orthostatic hypotension observed with olanzapine *[see* **DRUG INTERACTIONS (7.7)***]*.

Inducers of 1A2 — Carbamazepine therapy (200 mg BID) causes an approximate 50% increase in the clearance of olanzapine. This increase is likely due to the fact that carbamazepine is a potent inducer of CYP1A2 activity. Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance *[see* **Drug Interactions (7.7)***]*.

Alcohol — Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics *[see* **Drug Interactions (7.7)***]*.

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

The Effect of Other Drugs on Olanzapine — Fluoxetine, an inhibitor of CYP2D6, decreases olanzapine clearance a small amount *[see* **Clinical Pharmacology (12.3)***]*. Agents that induce CYP1A2 or glucuronyl transferase enzymes, such as omeprazole and rifampin, may cause an increase in olanzapine clearance. The effect of CYP1A2 inhibitors, such as fluvoxamine and some fluoroquinolone antibiotics, on olanzapine and fluoxetine 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.

7.7 Potential for Olanzapine and Fluoxetine to Affect Other Drugs

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

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

Alcohol — The coadministration of ethanol with olanzapine and fluoxetine may potentiate sedation and orthostatic hypotension *[see* **Drug Interactions (7.6)***]*.

Thioridazine — Thioridazine should not be administered with olanzapine and fluoxetine or administered within a minimum of 5 weeks after discontinuation of olanzapine and fluoxetine capsules.

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

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

Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated thioridazine plasma levels, thioridazine should not be administered with fluoxetine or within a minimum of 5 weeks after fluoxetine has been discontinued *[see* **Contraindications (4)***]*.

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

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

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

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

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

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

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

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

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

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

Fluoxetine inhibits the activity of CYP2D6 and may make individuals with normal CYP2D6 metabolic activity resemble a poor metabolizer. Coadministration of fluoxetine with other drugs that are metabolized by CYP2D6, including certain antidepressants (e.g., TCAs), antipsychotics (e.g., phenothiazines and most atypicals), and antiarrhythmics (e.g., propafenone, flecainide, and others) should be approached with caution. Therapy with medications that are predominantly metabolized by the CYP2D6 system and that have a relatively narrow therapeutic index should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the previous 5 weeks. If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need for a decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (including but not limited to, flecainide, propafenone, vinblastine, and TCAs).

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

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Olanzapine and Fluoxetine - Olanzapine and fluoxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, taking into account the risk of untreated Bipolar I Depression. *[See fluoxetine safety information under Treatment of Pregnant Women during the First Trimester and Clinical Considerations below.]*

Teratogenic Effects

Animal Data — Embryo fetal development studies were conducted in rats and rabbits with olanzapine and fluoxetine in low-dose and high-dose combinations. In rats, the doses were: 2 and 4 mg/kg/day (low-dose) [1 and 0.5 times the maximum recommended human dose (MRHD) for olanzapine (20 mg) and fluoxetine (80 mg), respectively, on a mg/m^2 body surface area], and 4 and 8 mg/kg/day (high-dose) [2 and 1 times the MRHD on a mg/m^2 body surface area, 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 orally administered during pregnancy and throughout lactation in combination at dose levels up to 2 (olanzapine) plus 4 (fluoxetine) mg/kg/day (1 and 0.5 times the MRHD on a mg/m^2 body surface area. An elevation of early postnatal mortality (survival through postnatal day 4 was 69% per litter) and reduced bodyweight (approximately 8% in females) occurred among offspring at the highest dose: the no-effect dose was 0.5 (olanzapine) plus 1 (floxetine) mg/kg/day (0.25 and 0.13 times the MRHD on a mg/m^2 body surface area). Among the surviving progeny, there were no adverse effects on physical or neurobehavioral development and reproductive performance at any dose.

Olanzapine — In oral reproduction studies in rats at doses up to 18 mg/kg/day and in rabbits at doses up to 30 mg/kg/day (9 and 30 times the MRHD on a mg/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). Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Placental transfer of olanzapine occurs in rat pups.

There are no adequate and well-controlled clinical studies with olanzapine in pregnant women. Seven pregnancies were observed during premarketing clinical studies with olanzapine, including 2 resulting in normal births, 1 resulting in neonatal death due to a cardiovascular defect, 3 therapeutic abortions, and 1 spontaneous abortion.

Fluoxetine — *Treatment of Pregnant Women during the First Trimester* - There are no adequate and well-controlled clinical studies on the use of fluoxetine in pregnant women. Results of a number of published epidemiological studies assessing the risk of fluoxetine exposure during the first trimester of pregnancy have demonstrated inconsistent results. More than 10 cohort studies and case-control studies failed to demonstrate an increased risk for congenital malformations overall. However, one prospective cohort study conducted by the European Network of Teratology Information Services reported an increased risk of cardiovascular malformations in infants born to women (N - 253) exposed to fluoxetine during the first trimester of pregnancy compared to infants of women (N = 1359) who were not exposed to fluoxetine. There was no specific pattern of cardiovascular malformations. Overall, however, a causal relationship has not been established.

Animal Data — In embryo-fetal development studies in rats and rabbits, there was no evidence of teratogenicity following administration of fluoxetine at doses up to 12.5 and 15 mg/kg/day, respectively (1.5 and 3.6 times, respectively, the maximum recommended human dose (MRHD) of 80 mg on a mg/m2 basis) 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).

Nonteratogenic Effects

Neonates exposed to fluoxetine, a component of olanzapine and fluoxetine, and other SSRIs or serotonin and norepinphrine reuptake inhibitors (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* **Dosage and Administration (2.3)** *and* **Warnings and Precautions (5.7)***]*.

Infants exposed to SSRIs in pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 to 2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. Several recent epidemiologic studies suggest a positive statistical association between SSRI (including fluoxetine) use in pregnancy and PPHN. Other studies do not show a significant statistical association.

Physicians should also note the results of a prospective longitudinal study of 201 pregnant women with a history of major depression, who were either on antidepressants or had received antidepressants less than 12 weeks prior to their last menstrual period, and were in remission. Women who discontinued antidepressant medication during pregnancy showed a significant increase in relapse of their major depression compared to those women who remained on antidepressant medication throughout pregnancy.

Neonates exposed to antipsychotic drugs (including olanzapine), during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

When treating a pregnant woman with olanzapine and fluoxetine, the physician should carefully consider both the potential risks of taking an SSRI, along with established benefits of treating depression with an antidepressant. This decision can only be made on a case by case basis *[see* **Dosage and Administration (2.3)***]*.

8.2 Labor and Delivery

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

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

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

8.3 Nursing Mothers

Olanzapine and Fluoxetine — Studies evaluating the individual components of olanzapine and fluoxetine in nursing mothers are described below. Because of the potential for serious adverse reactions in nursing infants from olanzapine and fluoxetine, 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 olanzapine and fluoxetine.

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

Fluoxetine — Fluoxetine is excreted in human breast milk. In 1 breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/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/mL of norfluoxetine on the 2nd day of feeding.

8.4 Pediatric Use

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

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

Olanzapine – Safety and effectiveness of olanzapine in children <13 years of age have not been established.

Compared to patients from adult clinical trials, adolescents treated with oral olanzapine were likely to gain more weight, experience increased sedation, and have greater increases in total cholesterol, triglycerides, LDL cholesterol, prolactin and hepatic aminotransferase levels.

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 to 0.2, 1 to 2, and 5 to 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 to 0.8, 1 to 8, and 3 to 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

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

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

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

Fluoxetine — U.S. fluoxetine clinical studies included 687 patients ≥65 years of age and 93 patients ≥75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. SNRIs and SSRIs, including olanzapine and fluoxetine, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse reaction *[see* **Warnings and Precautions (5.16)***]*.

8.6 Hepatic Impairment

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

9 DRUG ABUSE AND DEPENDENCE

9.3 Dependence

Olanzapine and fluoxetine, 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 olanzapine and fluoxetine (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

Olanzapine and Fluoxetine — During premarketing clinical studies of olanzapine and fluoxetine in combination, overdose of both fluoxetine and olanzapine were reported in 5 study subjects. Four of the 5 subjects experienced loss of consciousness (3) or coma (1). No fatalities occurred.

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

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

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

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

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

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

10.1 Management of Overdose

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

A specific precaution involves patients who are taking or have recently taken olanzapine and fluoxetine 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.

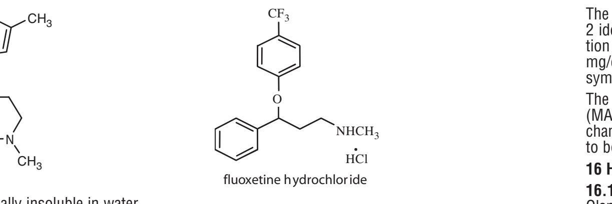
The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*.

11 DESCRIPTION

Olanzapine and Fluoxetine Capsules USP combines an atypical antipsychotic and a selective serotonin reuptake inhibitor, olanzapine (the active ingredient in Zyprexa®*, and Zyprexa Zydis®*) and fluoxetine hydrochloride (the active ingredient in Prozac®*, Prozac® Weekly™*, and Sarafem®*).

Olanzapine belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-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 $C_{17}H_{18}F_3NO{\bullet}HCl$, 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.

Olanzapine and Fluoxetine Capsules USP are available for oral administration in the following strength combinations:

	3 mg/25 mg	6 mg/25 mg	6 mg/50 mg	12 mg/25 mg	12 mg/50 mg
Olanzapine equivalent	3	6	6	12	12
Fluoxetine base equivalent	25	25	50	25	50

Each capsule consists of gelatin, magnesium stearate, partially pregelatinized starch, titanium dioxide, and yellow iron oxide. In addition, the 3 mg/25 mg capsule also contains red iron oxide; the 6 mg/50 mg capsule also contains FD&C blue No. 2, FD&C red No. 3, and FD&C yellow No. 6; the 12 mg/25 mg capsule also contains D&C red No. 28, FD&C blue No. 1, FD&C red No. 40, and red iron oxide; and the 12 mg/50 mg capsule also contains D&C red No. 28, FD&C blue No. 1 FD&C blue No. 2, FD&C red No. 3, FD&C red No. 40, and FD&C yellow No. 6. The capsules also have printing in edible black ink which contains the following ingredients: D&C yellow No. 10, ethanol, FD&C blue No. 1, FD&C blue No. 2, FD&C red No. 40, iron oxide black, methanol, n-Butyl alcohol, propylene glycol, and shellac glaze in alcohol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

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

12.3 Pharmacokinetics

Olanzapine and Fluoxetine — 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

Olanzapine and Fluoxetine — Following a single oral 12 mg/50 mg dose of olanzapine and fluoxetine, 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 olanzapine and fluoxetine 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 olanzapine and fluoxetine.

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

Olanzapine and Fluoxetine — The *in vitro* binding to human plasma proteins of olanzapine and fluoxetine in 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 (7.7)***]*.

Metabolism and Elimination

Olanzapine and Fluoxetine — Olanzapine and fluoxetine 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 olanzapine and fluoxetine.

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 (7.7)***]*.

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.

12.4 Specific Populations

Geriatric — Based on the individual pharmacokinetic profiles of olanzapine and fluoxetine, the pharmacokinetics of olanzapine and fluoxetine 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 reactions was observed in those elderly patients.

Renal Impairment — The pharmacokinetics of olanzapine and fluoxetine has not been studied in patients with renal impairment. However, olanzapine and fluoxetine individual pharmacokinetics do not differ significantly in patients with renal impairment. Olanzapine and fluoxetine 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 olanzapine and fluoxetine may be altered in patients with hepatic impairment. The lowest starting dose should be considered for patients with hepatic impairment *[see* **Dosage and Administration (2.3)** *and* **Warnings and Precautions (5.19)***]*.

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 olanzapine and fluoxetine pharmacokinetic study was conducted to investigate the effects of race. *In vivo* studies have shown that exposures to olanzapine are similar among Japanese, Chinese and Caucasians, especially after normalization for body weight differences. Dosage modifications for race, therefore, are not routinely required.

Combined Effects — The combined effects of age, smoking, and gender could lead to substantial pharmacokinetic differences in populations. The clearance of olanzapine in young smoking males, for example, may be 3 times higher than that in elderly nonsmoking females. Olanzapine and fluoxetine 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 olanzapine and fluoxetine. The following data are based on findings in studies performed with the individual components, therefore all dose multiples (based on body surface area) reflect the maximum recommended human dose (MRHD) of 20 mg olanzapine, or 80 mg fluoxetine, when each drug is administered separately.

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 1 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* **Warnings and Precautions (5.20)***]*.

Fluoxetine — The dietary administration of fluoxetine to rats and mice for 2 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 genotoxic potential for olanzapine was found in the Ames reverse mutation test, *in vivo* micronucleus test in mice, the chromosomal aberration test in Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of forward mutation test in mouse lymphoma cells, or *in vivo* sister chromatid exchange test in bone marrow of Chinese hamsters.

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

Impairment of Fertility

Olanzapine and Fluoxetine — Fertility studies were not conducted with olanzapine and fluoxetine. However, in a repeat-dose rat toxicology study of 3 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 luteal depletion and uterine atrophy were observed to a greater extent in the females receiving the high-dose combination than in females receiving either olanzapine or fluoxetine alone. In a 3-month repeat-dose dog toxicology study, reduced epididymal sperm and reduced testicular and prostate weights were observed with the high-dose combination of olanzapine and fluoxetine [5 and 5 mg/kg/day (9 and 2 times the MRHD on a mg/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 an oral fertility and reproductive performance study in rats, male mating performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female fertility was decreased at a dose of 3 mg/kg/day (11 and 1.5 times the MRHD on a mg/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. However, adverse effects on fertility were seen when juvenile rats were treated with fluoxetine at a high dose (30 mg/kg) associated with significant toxicity *[see* **Use in Specific Populations (8.4)***]*.

14 CLINICAL STUDIES

14.1 Depressive Episodes Associated with Bipolar I Disorder

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Olanzapine and Fluoxetine Capsules USP are supplied in 3/25 mg, 6/25 mg, 6/50 mg, 12/25 mg, and 12/50 mg (mg equivalent olanzapine/mg equivalent fluoxetine[a]) strengths.

Olanzapine and Fluoxetine Capsules	CAPSULE STRENGTH				
	3 mg/25 mg	6 mg/25 mg	6 mg/50 mg	12 mg/25 mg	12 mg/50 mg
Color	white opaque body & orange opaque cap	rich yellow opaque body and cap	light grey opaque body & rich yellow opaque cap	dark tan opaque body & red opaque cap	light grey opaque body & red opaque cap
Imprintings	'277' on body and 'par' on cap in black ink	'par' on body and '250' on cap in black ink	'251' on body and 'par' on cap in black ink	'252' on body and 'par' on cap in black ink	'253' on body and 'par' on cap in black ink
NDC Codes					
Bottle of 30	49884-277-11	49884-250-11	49884-251-11	49884-252-11	49884-253-11
Bottle of 100	49884-277-01	49884-250-01	49884-251-01	49884-252-01	49884-253-01
Bottle of 1000	49884-277-10	49884-250-10	49884-251-10	49884-252-10	49884-253-10

[a] Fluoxetine base equivalent

16.2 Storage and Handling

Store olanzapine and fluoxetine capsules at room temperature, between 20° to 25°C (68° to 77°F) with excursions permitted between 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Protect from light. Keep container tightly closed and protect from moisture.

*Zyprexa®, Zyprexa Zydis®, Prozac®, Prozac Weekly™, and Sarafem® are registered trademarks of Eli Lilly and Company.

17 PATIENT COUNSELING INFORMATION

See **FDA-approved Medication Guide**.

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

17.1 Information on Medication Guide

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

17.2 Clinical Worsening and Suicide Risk

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

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

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

17.4 Neuroleptic Malignant Syndrome (NMS)

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

17.5 Hyperglycemia

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

17.6 Hyperlipidemia

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

17.7 Weight Gain

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

17.8 Serotonin Syndrome

Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of olanzapine and fluoxetine and other serotonergic agents including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort *[see* **Contraindications (4.1) Warnings and Precautions (5.7)** *and* **Drug Interactions (7.3)***]*.

Patients should be advised of the signs and symptoms associated with serotonin syndrome that may include mental status changes (e.g., agitation, hallucinations, delirium, coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular aberrations (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination) seizures and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be cautioned to seek medical care immediately if they experience these symptoms.

17.9 Allergic Reactions and Rash

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

17.10 Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration and in association with the use of concomitant drugs that may potentiate the orthostatic effect of olanzapine, e.g., diazepam or alcohol *[see* **Warnings and Precautions (5.11)** *and* **Drug Interactions (7.6, 7.7)***]*. Patients should be advised to change positions carefully to help prevent orthostatic hypotension, and to lie down if they feel dizzy or faint, until they feel better. Patients should be advised to call their doctor if they experience any of the following signs and symptoms associated with orthostatic hypotension: dizziness, fast or slow heart beat, or fainting.

17.11 Abnormal Bleeding

Patients should be cautioned about the concomitant use of olanzapine and fluoxetine and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents have been associated with an increased risk of bleeding *[see* **Warnings and Precautions (5.15)***]*. Patients should be advised to call their doctor if they experience any increased or unusual bruising or bleeding while taking olanzapine and fluoxetine capsules.

17.12 Hyponatremia

Patients should be advised that hyponatremia has been reported during treatment with SNRIs and SSRIs, including olanzapine and fluoxetine. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. More severe and/or acute cases have been associated with hallucination, syncope, seizure, coma, respiratory arrest, and death *[see* **Warnings and Precautions (5.16)***]*.

17.13 Potential for Cognitive and Motor Impairment

As with any CNS-active drug, olanzapine and fluoxetine has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that olanzapine and fluoxetine therapy does not affect them adversely *[see* **Warnings and Precautions (5.17)***]*.

17.14 Body Temperature Regulation

Patients should be advised regarding appropriate care in avoiding overheating and dehydration. Patients should be advised to call their doctor right away if they become severely ill and have some or all of these symptoms of dehydration: sweating too much or not at all, dry mouth, feeling very hot, feeling thirsty, not able to produce urine *[see* **Warnings and Precautions (5.18)***]*.

17.15 Concomitant Medication

Patients should be advised to inform their physician if they are taking Prozac, Prozac Weekly, Sarafem, fluoxetine, Zyprexa, or Zyprexa Zydis. Patients should be advised to inform their physicians if they are taking, plan to take, or have stopped taking any prescription or over-the-counter drugs, including herbal supplements, since there is a potential for interactions. Patients should also be advised to inform their physicians if they plan to discontinue any medications they are taking while taking olanzapine and fluoxetine capsules, as stopping a medication may also impact the overall blood level of olanzapine and fluoxetine *[see* **Warnings and Precautions (5.21)***]*.

17.16 Discontinuation of Treatment with Olanzapine and Fluoxetine

Patients should be advised to take olanzapine and fluoxetine capsules exactly as prescribed, and to continue taking olanzapine and fluoxetine capsules as prescribed even after their mood symptoms improve. Patients should be advised that they should not alter their dosing regimen, or stop taking olanzapine and fluoxetine capsules, without consulting their physician *[see* **Warnings and Precautions (5.23)***]*.

17.17 Alcohol

Patients should be advised to avoid alcohol while taking olanzapine and fluoxetine capsules *[see* **Drug Interactions (7.6, 7.7)***]*.

17.18 Use in Specific Populations

Pregnancy -Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during olanzapine and fluoxetine therapy. Olanzapine and fluoxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus *[see* **Use in Specific Populations (8.1)***]*.

Nursing Mothers - Patients, if taking olanzapine and fluoxetine, should be advised not to breast-feed *[see* **Use in Specific Populations (8.1)***]*.

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Medication Guide

Olanzapine and Fluoxetine Capsules USP

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

What is the most important information I should know about Olanzapine and Fluoxetine Capsules?

Olanzapine and Fluoxetine Capsules may cause serious side effects, including:

1. **Suicidal thoughts or actions.**
2. **Increased risk of death in elderly people who are confused, have memory loss and have lost touch with reality (dementia-related psychosis).**
3. **High blood sugar (hyperglycemia).**
4. **High fat levels in your blood (increased cholesterol and triglycerides), especially in teenagers age 13 to 17.**
5. **Weight gain, especially in teenagers age 13 to 17.**

These serious side effects are described below.

1. **Suicidal thoughts or actions.**

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

Talk to your, or your family member's, healthcare provider about:
- all risks and benefits of treatment with antidepressant medicines.
- all treatment choices for depression or other serious mental illness.
    - **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
    - **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
    - **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
- Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
- Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
- Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

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

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

What else do I need to know about antidepressant medicines?

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

2. **Increased risk of death in elderly people who are confused, have memory loss and have lost touch with reality (dementia-related psychosis).** Olanzapine and fluoxetine capsules are not approved for treating psychosis in elderly people with dementia.

3. **High blood sugar (hyperglycemia):** High blood sugar can happen if you have diabetes already or if you have never had diabetes. High blood sugar could lead to:

- build up of acid in your blood due to ketones (ketoacidosis)
- coma
- death

Your doctor should do tests to check your blood sugar before you start taking olanzapine and fluoxetine capsules and during treatment. In people who do not have diabetes, sometimes high blood sugar goes away when olanzapine and fluoxetine capsules are stopped. People with diabetes and some people who did not have diabetes before taking olanzapine and fluoxetine capsules need to take medicine for high blood sugar even after they stop taking olanzapine and fluoxetine capsules.

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

Call your doctor if you have any of these symptoms of high blood sugar (hyperglycemia) while taking olanzapine and fluoxetine capsules:
- feel very thirsty
- need to urinate more than usual
- feel very hungry
- feel weak or tired
- feel sick to your stomach
- feel confused, or your breath smells fruity.

4. **High fat levels in the blood (increased cholesterol and triglyceride).** High fat levels may happen in people treated with olanzapine and fluoxetine capsules, especially in teenagers (13 to 17 years old) who received olanzapine, one of the drugs in olanzapine and fluoxetine capsules. Olanzapine and fluoxetine capsules are not approved for use in patients less than 18 years old. You may not have any symptoms, so your doctor should do blood tests to check your cholesterol and triglyceride levels before you start taking olanzapine and fluoxetine capsules and during treatment.

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

What is Olanzapine and Fluoxetine Capsules?

Olanzapine and fluoxetine capsules are a prescription medicine approved for use in adults:
- for short-term treatment of episodes of depression that happen with Bipolar I Disorder.

Olanzapine and fluoxetine capsules contain two medicines, olanzapine and fluoxetine hydrochloride.

It is not known if olanzapine and fluoxetine capsules are safe and effective in children under the age of 18.

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

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

Who should not take Olanzapine and Fluoxetine Capsules?

- Do not take olanzapine and fluoxetine capsules if you take a Monoamine Oxidase Inhibitor (MAOI).
  Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI, including the antibiotic linezolid.
- Do not take an MAOI **within 5 weeks of stopping olanzapine and fluoxetine capsule** unless directed to do so by your physician.
- Do not start Olanzapine and fluoxetine capsules if you stopped taking an MAOI in the last 2 weeks unless directed to do so by your physician.
- People who take olanzapine and fluoxetine capsules close in time to an MAOI can have serious and life-threatening side effects, with symptoms including:
    - high fever
    - continued muscle spasms that you cannot control
    - rigid muscles
    - changes in heart rate and blood pressure that happen fast
    - confusion
    - unconsciousness.

Ask your doctor or pharmacist if you are not sure if your medicine is an MAOI.

- Do not take olanzapine and fluoxetine capsules if you take Mellaril® (thioridazine). Do not take Mellaril **within 5 weeks of stopping olanzapine and fluoxetine capsules. Mellaril can cause serious heart rhythm problems and you could die suddenly**.
- Do not take olanzapine and fluoxetine capsules if you take the antipsychotic medicine pimozide (Orap®).

What should I tell my doctor before taking Olanzapine and Fluoxetine Capsules?

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

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

Before starting olanzapine and fluoxetine capsules **tell your doctor about all the medicines that you take,** including:
- Prescription and non-prescription medicines
- Vitamins, and herbal supplements
- Triptans used to treat migraine headache
- Medicines used to treat mood, anxiety, psychotic or thought disorders, including tricyclics, lithium, buspirone, SSRIs, SNRIs, MAOIs, or antipsychotics
- Tramadol and fentanyl
- Over-the- counter supplements such as tryptophan or St. John's Wort
- Electroconvulsive therapy (ECT)

Olanzapine and fluoxetine capsules and some medicines may interact with each other and may not work as well, or cause possible serious side effects. Your doctor can tell you if it is safe to take olanzapine and fluoxetine capsules with your other medicines. Do not start or stop any medicine while taking olanzapine and fluoxetine capsules without talking to your doctor first.

If you take olanzapine and fluoxetine capsules, you should not take any other medicines that contain:
- olanzapine (the active ingredient in Zyprexa® and Zyprexa® Zydis®) or
- fluoxetine hydrochloride (the active ingredient in Prozac®, Prozac Weekly™, and Sarafem®).

You could take too much medicine (overdose).

How should I take Olanzapine and Fluoxetine Capsules?

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

What should I avoid while taking Olanzapine and Fluoxetine Capsules?

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

What are the possible side effects of Olanzapine and Fluoxetine Capsules?
Other possible serious risks:

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

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

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

These are not all the possible side effects with olanzapine and fluoxetine capsules. For more information, ask your doctor or pharmacist.

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

How should I store Olanzapine and Fluoxetine Capsules?
- Store olanzapine and fluoxetine capsules at room temperature, between 20° to 25°C (68° to 77°F) with excursions permitted between 15° to 30°C (59° to 86°F).
- Keep olanzapine and fluoxetine capsules away from light.
- Keep olanzapine and fluoxetine capsules dry and away from moisture. Keep the bottle closed tightly.

Keep Olanzapine and Fluoxetine Capsules and all medicines out of the reach of children.

General information about Olanzapine and Fluoxetine Capsules

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

This Medication Guide summarizes the most important information about olanzapine and fluoxetine capsules. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about olanzapine and fluoxetine capsules that was written for healthcare professionals.

What are the ingredients in Olanzapine and Fluoxetine Capsules?
Active ingredients: olanzapine and fluoxetine hydrochloride
Inactive ingredients: gelatin, magnesium stearate, partially pregelatinized starch, titanium dioxide, and yellow iron oxide. In addition, the 3 mg/25 mg capsule also contains red iron oxide; the 6 mg/50 mg capsule also contains FD&C blue No. 2, FD&C red No. 3, and FD&C yellow No. 6; the 12 mg/25 mg capsule also contains D&C red No. 28, FD&C blue No. 1, FD&C red No. 40, and red iron oxide; and the 12 mg/50 mg capsule also contains D&C red No. 28, FD&C blue No. 1 FD&C blue No. 2, FD&C red No. 3, FD&C red No. 40, and FD&C yellow No. 6. The capsules also have printing in edible black ink which contains the following ingredients: D&C yellow No. 10, ethanol, FD&C blue No. 1, FD&C blue No. 2, FD&C red No. 40, iron oxide black, methanol, n-Butyl alcohol, propylene glycol, and shellac glaze in alcohol.

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

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