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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OLANZAPINE ORALLY DISINTEGRATING TABLETS safely and effectively. See full prescribing information for OLANZAPINE ORALLY DISINTEGRATING TABLETS.

OLANZAPINE orally disintegrating tablets

Initial U.S. Approval: 1996

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

See full prescribing information for complete boxed warning.

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. (5.1, 5.14, 17.2)**

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

----RECENT MAJOR CHANGES----

Warnings and Precautions:

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (5.4) 10/2016

Falls (5.8) 02/2017

----INDICATIONS AND USAGE----

Olanzapine orally disintegrating tablets are atypical antipsychotic indicated:

As oral formulation for the:

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

As Olanzapine Orally Disintegrating Tablets and Fluoxetine in Combination for the:

- Treatment of depressive episodes associated with bipolar I disorder. (1.5)
  - Efficacy was established with Symbyax* (olanzapine and fluoxetine in combination); refer to the product label for Symbyax*.

----DOSAGE AND ADMINISTRATION----

Schizophrenia in adults (2.1)	Oral: Start at 5 to 10 mg once daily; Target: 10 mg/day within several days
Schizophrenia in adolescents (2.1)	Oral: Start at 2.5 to 5 mg once daily; Target: 10 mg/day
Bipolar I Disorder (manic or mixed episodes) in adults (2.2)	Oral: Start at 10 or 15 mg once daily
Bipolar I Disorder (manic or mixed episodes) in adolescents (2.2)	Oral: Start at 2.5 to 5 mg once daily; Target: 10 mg/day
Bipolar I Disorder (manic or mixed episodes) with lithium or valproate in adults (2.2)	Oral: Start at 10 mg once daily
Depressive Episodes associated with Bipolar I Disorder in adults (2.5)	Oral in combination with fluoxetine: Start at 5 mg of oral olanzapine and 20 mg of fluoxetine once daily
Depressive Episodes associated with Bipolar I Disorder in children and adolescents (2.5)	Oral in combination with fluoxetine: Start at 2.5 mg of oral olanzapine and 20 mg of fluoxetine once daily

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

Olanzapine Orally Disintegrating Tablets and Fluoxetine in Combination:

- Dosage adjustments, if indicated, should be made with the individual components according to efficacy and tolerability. (2.5)
- Olanzapine monotherapy is not indicated for the treatment of depressive episodes associated with bipolar I disorder. (2.5)
- Safety of co-administration of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated in adults. (2.5)
- Safety of co-administration of doses above 12 mg olanzapine with 50 mg fluoxetine has not been evaluated in children and adolescents ages 10 to 17. (2.5)

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

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

----CONTRAINDICATIONS----

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

----WARNINGS AND PRECAUTIONS----

- *Elderly Patients with Dementia-Related Psychosis:* Increased risk of death and increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack). (5.1)
- *Suicide:* The possibility of a suicide attempt is inherent in schizophrenia and in bipolar I disorder, and close supervision of high-risk patients should accompany drug therapy; when using in combination with fluoxetine, also refer to the Boxed Warning and Warnings and Precautions sections of the package insert for Symbyax*. (5.2)
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation and close monitoring. (5.3)
- *Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS):* Discontinue if DRESS is suspected. (5.4)
- *Metabolic Changes:* Atypical antipsychotic drugs have been associated with metabolic changes including hyperglycemia, dyslipidemia, and weight gain. (5.5)
  - *Hyperglycemia and Diabetes Mellitus:* In some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients taking olanzapine. Patients taking olanzapine should be monitored for symptoms of hyperglycemia and undergo fasting blood glucose testing at the beginning of, and periodically during, treatment. (5.5)
  - *Dyslipidemia:* 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. (5.5)
- *Tardive Dyskinesia:* Discontinue if clinically appropriate. (5.6)
- *Orthostatic Hypotension:* Orthostatic hypotension associated with dizziness, tachycardia, bradycardia and, in some patients, syncope, may occur especially during initial dose titration. Use caution in patients with cardiovascular disease, cerebrovascular disease, and those conditions that could affect hemodynamic responses. (5.7)
- *Leukopenia, Neutropenia, and Agranulocytosis:* Has been reported with antipsychotics, including olanzapine. 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 should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. (5.9)
- *Seizures:* Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. (5.11)
- *Potential for Cognitive and Motor Impairment:* Has potential to impair judgment, thinking, and motor skills. Use caution when operating machinery. (5.12)
- *Hyperprolactinemia:* May elevate prolactin levels. (5.15)
- *Use in Combination with Fluoxetine, Lithium or Valproate:* Also refer to the package inserts for Symbyax*, lithium, or valproate. (5.16)
- *Laboratory Tests:* Monitor fasting blood glucose and lipid profiles at the beginning of, and periodically during, treatment. (5.17)

----ADVERSE REACTIONS----

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

Oral Olanzapine Monotherapy:

- Schizophrenia (Adults) – postural hypotension, constipation, weight gain, dizziness, personality disorder, akathisia (6.1)
- Schizophrenia (Adolescents) – sedation, weight increased, headache, increased appetite, dizziness, abdominal pain, pain in extremity, fatigue, dry mouth (6.3)
- Manic or Mixed Episodes, Bipolar I Disorder (Adults) – asthenia, dry mouth, constipation, increased appetite, somnolence, dizziness, tremor (6.1)
- Manic or Mixed Episodes, Bipolar I Disorder (Adolescents) – sedation, weight increased, increased appetite, headache, fatigue, dizziness, dry mouth, abdominal pain, pain in extremity (6.3)

Combination of Olanzapine and Lithium or Valproate:

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

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

To report SUSPECTED ADVERSE REACTIONS, contact Jubilant Cadista Pharmaceuticals Inc., at 1-800-313-4623 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----DRUG INTERACTIONS----

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

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

- *Pregnancy:* Olanzapine 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 in children <13 years of age have not been established. Safety and effectiveness of olanzapine and fluoxetine in combination in children < 10 years of age have not been established. (8.4)

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

Revised: 05/2017

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FULL PRESCRIBING INFORMATION

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

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

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

1 INDICATIONS AND USAGE

1.1 Schizophrenia

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

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

1.2 Bipolar I Disorder (Manic or Mixed Episodes)

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

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

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

1.3 Special Considerations in Treating Pediatric Schizophrenia and Bipolar I Disorder

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

1.5 Olanzapine Orally Disintegrating Tablets and Fluoxetine in Combination: Depressive Episodes Associated with Bipolar I Disorder

Olanzapine orally disintegrating tablets and fluoxetine in combination are indicated for the treatment of depressive episodes associated with bipolar I disorder, based on clinical studies. When using olanzapine orally disintegrating tablets and fluoxetine in combination, refer to the Clinical Studies section of the package insert for Symbyax*.

Olanzapine orally disintegrating tablets monotherapy is not indicated for the treatment of depressive episodes associated with bipolar I disorder.

2 DOSAGE AND ADMINISTRATION

2.1 Schizophrenia

Adults

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

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

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

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

Adolescents

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

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

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

2.2 Bipolar I Disorder (Manic or Mixed Episodes)

Adults

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

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

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

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

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

Adolescents

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

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

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

2.3 Administration of Olanzapine Orally Disintegrating Tablets

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

2.5 Olanzapine Orally Disintegrating Tablets and Fluoxetine in Combination: Depressive Episodes Associated with Bipolar I Disorder

When using olanzapine orally disintegrating tablets and fluoxetine in combination, also refer to the Clinical Studies section of the package insert for Symbyax*.

Adults

Oral olanzapine should be administered in combination with fluoxetine once daily in the evening, without regard to meals, generally beginning with 5 mg of oral olanzapine and 20 mg of fluoxetine. Dosage adjustments, if indicated, can be made according to efficacy and tolerability within dose ranges of oral olanzapine 5 to 12.5 mg and fluoxetine 20 to 50 mg. Antidepressant efficacy was demonstrated with olanzapine orally disintegrating tablets and fluoxetine in combination in adult patients with a dose range of olanzapine 6 to 12 mg and fluoxetine 25 to 50 mg. Safety of co-administration of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated in clinical studies.

Children and Adolescents (10 to 17 years of age)

Oral olanzapine should be administered in combination with fluoxetine once daily in the evening, without regard to meals, generally beginning with 2.5 mg of oral olanzapine and 20 mg of fluoxetine. Dosage adjustments, if indicated, can be made according to efficacy and tolerability. Safety of co-administration of doses above 12 mg olanzapine with 50 mg fluoxetine has not been evaluated in pediatric clinical studies.

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

Table 1: Approximate Dose Correspondence Between Symbyax*[a] and the Combination of Olanzapine Orally Disintegrating Tablets and Fluoxetine

For Symbyax* (mg/day)	Use in Combination: Olanzapine Orally Disintegrating Tablets (mg/day)	Use in Combination: Fluoxetine (mg/day)
3 mg olanzapine/25 mg fluoxetine	2.5	20
6 mg olanzapine/25 mg fluoxetine	5	20
12 mg olanzapine/25 mg fluoxetine	10+2.5	20
6 mg olanzapine/50 mg fluoxetine	5	40+10
12 mg olanzapine/50 mg fluoxetine	10+2.5	40+10

[a] Symbyax* (olanzapine/fluoxetine HCl) is a fixed-dose combination of olanzapine orally disintegrating tablets and fluoxetine.

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

Olanzapine orally disintegrating tablets monotherapy is not indicated for the treatment of depressive episodes associated with bipolar I disorder.

2.7 Olanzapine Orally Disintegrating Tablets and Fluoxetine in Combination: Dosing in Special Populations

The starting dose of oral olanzapine 2.5 to 5 mg with fluoxetine 20 mg should be used for patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of olanzapine or fluoxetine in combination (female gender, geriatric age, nonsmoking status), or those patients who may be pharmacodynamically sensitive to olanzapine. Dosing modification may be necessary in patients who exhibit a combination of factors that may slow metabolism. When indicated, dose escalation should be performed with caution in these patients. Olanzapine orally disintegrating tablets and fluoxetine in combination have not been systematically studied in patients over 65 years of age or in patients under 10 years of age *[see Warnings and Precautions (5.14), Drug Interactions (7), and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Olanzapine orally disintegrating tablets, USP are yellow colored, round, flat face beveled edge, debossed tablets with characteristic flavour. Tablets are not scored. The tablets are available as follows:

	TABLET STRENGTH			
Olanzapine Orally Disintegrating Tablets	5 mg	10 mg	15 mg	20 mg
Debossed	D5;CO	D10;CO	D15;CO	D20;CO

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

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

5.1 Elderly Patients with Dementia-Related Psychosis

Increased Mortality — Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Olanzapine is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.14), and Patient Counseling Information (17.2)]*.

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

Cerebrovascular Adverse Events (CVAE), Including Stroke — Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning and Patient Counseling Information (17.2)]*.

5.2 Suicide

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

5.3 Neuroleptic Malignant Syndrome (NMS)

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

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

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

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported *[see Patient Counseling Information (17.3)]*.

5.4 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported with olanzapine exposure. DRESS may present with a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. DRESS is sometimes fatal. Discontinue olanzapine if DRESS is suspected *[see Patient Counseling Information (17.4)]*.

5.5 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes including hyperglycemia, dyslipidemia, and weight gain. Metabolic changes may be associated with increased cardiovascular/cerebrovascular risk. Olanzapine's specific metabolic profile is presented below.

Hyperglycemia and Diabetes Mellitus

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

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. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics.

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

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

Olanzapine Monotherapy in Adults — In an analysis of 5 placebo-controlled adult olanzapine monotherapy studies with a median treatment duration of approximately 3 weeks, olanzapine was associated with a greater mean change in fasting glucose levels compared to placebo (2.76 mg/dL versus 0.17 mg/dL). The difference in mean changes between olanzapine and placebo was greater in patients with evidence of glucose dysregulation at baseline (patients diagnosed with diabetes mellitus or related adverse reactions, patients treated with anti-diabetic agents, patients with a baseline random glucose level ≥200 mg/dL, and/or a baseline fasting glucose level ≥126 mg/dL). Olanzapine-treated patients had a greater mean HbA_{1c} increase from baseline of 0.04% (median exposure 21 days), compared to a mean HbA_{1c} decrease of 0.06% in placebo-treated subjects (median exposure 17 days).

In an analysis of 8 placebo-controlled studies (median treatment exposure 4-5 weeks), 6.1% of olanzapine-treated subjects (N=855) had treatment-emergent glycosuria compared to 2.8% of placebo-treated subjects (N=599). Table 2 shows short-term and long-term changes in fasting glucose levels from adult olanzapine monotherapy studies.

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

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	Up to 12 weeks exposure: N	Up to 12 weeks exposure: Patients	At least 48 weeks exposure: N	At least 48 weeks exposure: Patients
Fasting Glucose	Normal to High (<100 mg/dL to ≥126 mg/dL)	Olanzapine	543	2.2%	345	12.8%
		Placebo	293	3.4%	NA[a]	NA[a]
	Borderline to High (≥100 mg/dL and < 126 mg/dL to ≥126 mg/dL)	Olanzapine	178	17.4%	127	26.0%
		Placebo	96	11.5%	NA[a]	NA[a]

[a] Not Applicable.

The mean change in fasting glucose for patients exposed at least 48 weeks was 4.2 mg/dL (N=487). In analyses of patients who completed 9 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 have not been established in patients under the age of 13 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar I disorder (manic or mixed episodes) (3 weeks), olanzapine was associated with a greater mean change from baseline in fasting glucose levels compared to placebo (2.68 mg/dL versus -2.59 mg/dL). The mean change in fasting glucose for adolescents exposed at least 24 weeks was 3.1 mg/dL (N=121). Table 3 shows short-term and long-term changes in fasting blood glucose from adolescent olanzapine monotherapy studies.

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

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	Up to 12 weeks exposure: 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.

Dyslipidemia

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

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

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

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

The proportion of patients who had changes (at least once) in total cholesterol, LDL cholesterol or triglycerides from normal or borderline to high, or changes in HDL cholesterol from normal or borderline to low, was greater in long-term studies (at least 48 weeks) as compared with short-term studies. Table 4 shows categorical changes in fasting lipids values.

Table 4: Changes in Fasting Lipids Values from Adult Olanzapine Monotherapy Studies

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	Up to 12 weeks exposure: 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 mean increase in total cholesterol was 9.4 mg/dL.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine have not been established in patients under the age of 13 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescents, including those with schizophrenia (6 weeks) or bipolar I disorder (manic or mixed episodes) (3 weeks), olanzapine-treated adolescents had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 12.9 mg/dL, 6.5 mg/dL, and 28.4 mg/dL, respectively, compared to increases from baseline in mean fasting total cholesterol and LDL cholesterol of 1.3 mg/dL and 1.0 mg/dL, and a decrease in triglycerides of 1.1 mg/dL for placebo-treated adolescents. For fasting HDL cholesterol, no clinically meaningful differences were observed between olanzapine-treated adolescents and placebo-treated adolescents.

In long-term studies (at least 24 weeks), adolescents had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.5 mg/dL, 5.4 mg/dL, and 20.5 mg/dL, respectively, and a mean decrease in fasting HDL cholesterol of 4.5 mg/dL. Table 5 shows categorical changes in fasting lipids values in adolescents.

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

Laboratory Analyte	Category Change (at least once) from Baseline	Treatment Arm	Up to 6 weeks exposure: 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.

Weight Gain

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

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

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

Table 6 includes data on adult weight gain with olanzapine pooled from 86 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified.

Table 6: Weight Gain with Olanzapine Use in Adults

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

Dose group differences with respect to weight gain have been observed. In a single 8-week randomized, double-blind, fixed-dose study comparing 10 (N=199), 20 (N=200) and 40 (N=200) mg/day of oral olanzapine in adult patients with schizophrenia or schizoaffective disorder, 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.

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

Table 7: Weight Gain with Olanzapine Use in Adolescents from 4 Placebo-Controlled Trials

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

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

Table 8 shows data on adolescent weight gain with olanzapine pooled from 6 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified. Little clinical trial data is available on weight gain in adolescents with olanzapine beyond 6 months of treatment.

Table 8: Weight Gain with Olanzapine Use in Adolescents

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

5.6 Tardive Dyskinesia

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

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

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

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

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

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

5.7 Orthostatic Hypotension

Olanzapine may induce orthostatic hypotension associated with dizziness, tachycardia, bradycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonistic properties *[see Patient Counseling Information (17.8)]*.

From an analysis of the vital sign data in an integrated database of 41 completed clinical studies in adult patients treated with oral olanzapine, orthostatic hypotension was recorded in ≥20% (1277/6030) of patients.

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

Syncope was reported in 0.6% (15/2500) of olanzapine-treated patients in phase 2-3 oral olanzapine studies. The risk for this sequence of hypotension, bradycardia, and sinus pause may be greater in nonpsychiatric patients compared to psychiatric patients who are possibly more adapted to certain effects of psychotropic drugs.

Olanzapine should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications) where the occurrence of syncope, or hypotension and/or bradycardia might put the patient at increased medical risk.

Caution is necessary in patients who receive treatment with other drugs having effects that can induce hypotension, bradycardia, respiratory or central nervous system depression *[see Drug Interactions (7)]*.

5.8 Falls

Olanzapine may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

5.9 Leukopenia, Neutropenia, and Agranulocytosis

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

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

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm³) should discontinue olanzapine and have their WBC followed until recovery.

5.10 Dysphagia

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

5.11 Seizures

During premarketing testing, seizures occurred in 0.9% (22/2500) of olanzapine-treated patients. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. Olanzapine should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Olanzapine is not approved for the treatment of patients with Alzheimer's disease. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

5.12 Potential for Cognitive and Motor Impairment

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

Since olanzapine has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that olanzapine therapy does not affect them adversely *[see Patient Counseling Information (17.9)]*.

5.13 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing olanzapine for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration *[see Patient Counseling Information (17.10)]*.

5.14 Use in Patients with Concomitant Illness

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

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

In 5 placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis (n=1184), the following treatment-emergent adverse reactions were reported in olanzapine-treated patients at an incidence of at least 2% and significantly greater than placebo-treated patients: falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth and visual hallucinations. The rate of discontinuation due to adverse reactions was greater with olanzapine than placebo (13% vs 7%). Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.1), and Patient Counseling Information (17.2)]*.

Olanzapine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with olanzapine, caution should be observed in cardiac patients *[see Warnings and Precautions (5.7)]*.

5.15 Hyperprolactinemia

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

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

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

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

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

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

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

Dose group differences with respect to prolactin elevation have been observed. In a single 8-week randomized, double-blind, fixed-dose study comparing 10 (N=199), 20 (N=200) and 40 (N=200) mg/day of oral olanzapine in adult patients with schizophrenia or schizoaffective disorder, incidence of 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%) indicated significant differences between 10 vs 40 mg/day and 20 vs 40 mg/day.

5.16 Use in Combination with Fluoxetine, Lithium, or Valproate

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

5.17 Laboratory Tests

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

6 ADVERSE REACTIONS

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

6.1 Clinical Trials Experience

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

Clinical Trials in Adults

The information below for olanzapine is derived from a clinical trial database for olanzapine consisting of 10,504 adult patients with approximately 4765 patient-years of exposure to olanzapine. This database includes: (1) 2500 patients who participated in multiple-dose oral olanzapine premarketing trials in schizophrenia and Alzheimer's disease representing approximately 1122 patient-years of exposure as of February 14, 1995; (2) 182 patients who participated in oral olanzapine premarketing bipolar I disorder (manic or mixed episodes) trials representing approximately 66 patient-years of exposure; (3) 191 patients who participated in an oral olanzapine trial of patients having various psychiatric symptoms in association with Alzheimer's disease representing approximately 29 patient-years of exposure; (4) 5788 additional patients from 88 oral olanzapine clinical trials as of December 31, 2001; and (5) 1843 additional patients from 41 olanzapine clinical trials as of October 31, 2011; Also included below is information from the premarketing 6-week clinical study database for olanzapine in combination with lithium or valproate, consisting of 224 patients who participated in bipolar I disorder (manic or mixed episodes) trials with approximately 22 patient-years of exposure.

The conditions and duration of treatment with olanzapine varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse reactions, results of physical examinations, vital signs, weights, laboratory analytes, ECGs, chest x-rays, and results of ophthalmologic examinations.

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

Adverse reactions during exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse reactions without first grouping similar types of reactions into a smaller number of standardized reaction categories. In the tables and tabulations that follow, MedDRA and COSTART Dictionary terminology has been used to classify reported adverse reactions.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. The reported reactions do not include those reaction terms that were so general as to be uninformative. Reactions listed elsewhere in labeling may not be repeated below. It is important to emphasize that, although the reactions occurred during treatment with olanzapine, they were not necessarily caused by it. The entire label should be read to gain a complete understanding of the safety profile of olanzapine.

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

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

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

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

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

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

Medication Guide

Olanzapine Orally Disintegrating Tablets

(oh lan' za peen)

Read the Medication Guide that comes with olanzapine orally disintegrating tablets before you start taking them 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 orally disintegrating tablets.

What is the most important information I should know about olanzapine orally disintegrating tablets?

Olanzapine orally disintegrating tablets may cause serious side effects, including:

1. **Increased risk of death in elderly people who are confused, have memory loss and have lost touch with reality (dementia-related psychosis).**
2. **High blood sugar (hyperglycemia).**
3. **High fat levels in your blood (increased cholesterol and triglycerides), especially in teenagers age 13 to 17 or when used in combination with fluoxetine in children age 10 to 17.**
4. **Weight gain, especially in teenagers age 13 to 17 or when used in combination with fluoxetine in children age 10 to 17.**

These serious side effects are described below.

1. **Increased risk of death in elderly people who are confused, have memory loss and have lost touch with reality (dementia-related psychosis).** Olanzapine orally disintegrating tablets are not approved for treating psychosis in elderly people with dementia.
2. **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:
   - a 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 orally disintegrating tablets and during treatment. In people who do not have diabetes, sometimes high blood sugar goes away when olanzapine orally disintegrating tablets are stopped. People with diabetes and some people who did not have diabetes before taking olanzapine orally disintegrating tablets need to take medicine for high blood sugar even after they stop taking olanzapine orally disintegrating tablets.

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

   Call your doctor if you have any of these symptoms of high blood sugar (hyperglycemia) while taking olanzapine orally disintegrating tablets:
   - 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
3. **High fat levels in your blood (cholesterol and triglycerides).** High fat levels may happen in people treated with olanzapine orally disintegrating tablets, especially in teenagers (13 to 17 years old), or when used in combination with fluoxetine in children (10 to 17 years old). You may not have any symptoms, so your doctor should do blood tests to check your cholesterol and triglyceride levels before you start taking olanzapine orally disintegrating tablets and during treatment.
4. **Weight gain.** Weight gain is very common in people who take olanzapine orally disintegrating tablets. Teenagers (13 to 17 years old) are more likely to gain weight and to gain more weight than adults. Children (10 to 17 years old) are also more likely to gain weight and to gain more weight than adults when olanzapine orally disintegrating tablets are used in combination with fluoxetine. Some people may gain a lot of weight while taking olanzapine orally disintegrating tablets, 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 are olanzapine orally disintegrating tablets?

Olanzapine orally disintegrating tablets are prescription medicine used to treat:

- schizophrenia in people age 13 or older.
- bipolar disorder, including:
  - manic or mixed episodes that happen with bipolar I disorder in people age 13 or older.
  - manic or mixed episodes that happen with bipolar I disorder, when used with the medicine lithium or valproate, in adults.
  - long-term treatment of bipolar I disorder in adults.
- episodes of depression that happen with bipolar I disorder, when used with the medicine fluoxetine (Prozac®) in people age 10 or older.

Olanzapine orally disintegrating tablets have not been approved for use in children under 13 years of age. Olanzapine orally disintegrating tablets in combination with fluoxetine has not been approved for use in children under 10 years of age.

The symptoms of schizophrenia include hearing voices, seeing things that are not there, having beliefs that are not true, and being suspicious or withdrawn.

The symptoms of bipolar I disorder include alternating periods of depression and high or irritable mood, increased activity and restlessness, racing thoughts, talking fast, impulsive behavior, and a decreased need for sleep.

Some of your symptoms may improve with treatment. If you do not think you are getting better, call your doctor.

What should I tell my doctor before taking olanzapine orally disintegrating tablets?

Olanzapine orally disintegrating tablets may not be right for you. Before starting olanzapine orally disintegrating tablets, tell your doctor if you have or had:

- heart problems
- seizures
- diabetes or high blood sugar levels (hyperglycemia)
- high cholesterol or triglyceride levels in your blood
- liver problems
- low or high blood pressure
- strokes or "mini-strokes" also called transient ischemic attacks (TIAs)
- Alzheimer's disease
- narrow-angle glaucoma
- enlarged prostate in men
- bowel obstruction
- phenylketonuria, because olanzapine orally disintegrating tablets contains phenylalanine
- breast cancer
- thoughts of suicide or hurting yourself
- any other medical condition
- are pregnant or plan to become pregnant. It is not known if olanzapine orally disintegrating tablets will harm your unborn baby.
- are breast-feeding or plan to breast-feed. Olanzapine can pass into your breast milk and may harm your baby. You should not breast-feed while taking olanzapine orally disintegrating tablets. Talk to your doctor about the best way to feed your baby if you take olanzapine orally disintegrating tablets.

Tell your doctor if you exercise a lot or are in hot places often.

The symptoms of bipolar I disorder, or schizophrenia may include **thoughts of suicide** or of hurting yourself or others. If you have these thoughts at any time, tell your doctor or go to an emergency room right away.

Tell your doctor about all the medicines that you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Olanzapine orally disintegrating tablets 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 orally disintegrating tablets with your other medicines. Do not start or stop any medicine while taking olanzapine orally disintegrating tablets without talking to your doctor first.

How should I take olanzapine orally disintegrating tablets?

- Take olanzapine orally disintegrating tablets exactly as prescribed. Your doctor may need to change (adjust) the

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Item Code: 50000002513		**Superseded Item Code: 7524000810**
Substrate: 32 GSM Bible paper with folding Dimension 64 x 44 mm		

Site Packaging Development Sign and Date		**Production Sign and Date**		**QA Sign and Date**	

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Neutral Code No.UK/Drugs/58/UA/2007

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

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

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

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

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

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

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

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

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

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

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

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

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

Dose Dependency of Adverse Reactions

A dose group difference has been observed for fatigue, dizziness, weight gain and prolactin elevation. In a single 8-week randomized, double-blind, fixed-dose study comparing 10 (N=199), 20 (N=200) and 40 (N=200) mg/day of oral olanzapine in adult patients with schizophrenia or schizoaffective disorder, incidence of fatigue (10 mg/day: 1.5%; 20 mg/day: 2.1%; 40 mg/day: 6.6%) was observed with significant differences between 10 vs 40 and 20 vs 40 mg/day. The incidence of dizziness (10 mg/day: 2.6%; 20 mg/day: 1.6%; 40 mg/day: 6.6%) was observed with significant differences between 20 vs 40 mg. Dose group differences were also noted for weight gain and prolactin elevation *[see Warnings and Precautions (5.5, 5.15)]*.

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

Table 12: Percentage of Patients from a Schizophrenia Trial with Treatment-Emergent Adverse Reactions for the 3 Dose Range Groups and Placebo

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

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

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

Table 13: Common Treatment-Emergent Adverse Reactions Associated with the Use of Oral Olanzapine in 6-Week Adjunct to Lithium or Valproate Trials — Bipolar I Disorder (Manic or Mixed Episodes)

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

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

Table 14 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred in 2% or more of patients treated with the combination of olanzapine (doses ≥5 mg/day) and lithium or valproate and with incidence greater than lithium or valproate alone who participated in the acute phase of placebo-controlled combination trials.

Table 14: Treatment-Emergent Adverse Reactions: Incidence in Short-Term, Placebo-Controlled Clinical Trials of Oral Olanzapine as Adjunct to Lithium or Valproate

Body System/Adverse Reaction	Percentage of Patients Reporting Event	
	Olanzapine with Lithium or Valproate (N=229)	Placebo with Lithium or Valproate (N=115)
Body as a Whole		
Asthenia	18	13
Back pain	8	4
Accidental injury	4	2
Chest pain	3	2
Cardiovascular System		
Hypertension	2	1
Digestive System		
Dry mouth	32	9
Increased appetite	24	8
Thirst	10	6
Constipation	8	4
Increased salivation	6	2
Metabolic and Nutritional Disorders		
Weight gain	26	7
Peripheral edema	6	4
Edema	2	1
Nervous System		
Somnolence	52	27
Tremor	23	13
Depression	18	17
Dizziness	14	7
Speech disorder	7	1
Amnesia	5	2
Paresthesia	5	2
Apathy	4	3
Confusion	4	1
Euphoria	3	2
Incoordination	2	0
Respiratory System		
Pharyngitis	4	1
Dyspnea	3	1
Skin and Appendages		
Sweating	3	1
Acne	2	0
Dry skin	2	0
Special Senses		
Amblyopia	9	5
Abnormal vision	2	0
Urogenital System		
Dysmenorrheaa	2	0
Vaginitis[a]	2	0

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

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

6.2 Extrapyramidal Symptoms

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

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

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

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

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

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

Table 17: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions Incidence in a Fixed Dosage Range, Placebo-Controlled Clinical Trial of Oral Olanzapine in Schizophrenia — Acute Phase

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

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

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

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

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

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

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

Table 18: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions Incidence in Placebo-Controlled Clinical Trials of Oral Olanzapine in Schizophrenia and Bipolar I Disorder — Adolescents

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

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

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

6.3 Other Adverse Reactions

Other Adverse Reactions Observed During the Clinical Trial Evaluation of Oral Olanzapine

Following is a list of treatment-emergent adverse reactions reported by patients treated with oral olanzapine (at multiple doses ≥1 mg/day) in clinical trials. This listing is not intended to include reactions (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) which occurred at a rate equal to or less than placebo. Reactions are classified by body system using the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients.

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

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

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

Hemic and Lymphatic System — *Infrequent:* thrombocytopenia.

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

Musculoskeletal System — *Rare:* osteoporosis.

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

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

Skin and Appendages — *Infrequent:* alopecia.

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

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

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

[2] Adjusted for gender.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Vital Signs and Laboratory Studies

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

Laboratory Changes

Olanzapine Monotherapy in Adults: An assessment of the premarketing experience for olanzapine revealed an association with asymptomatic increases in ALT, AST, and GGT. Within the original premarketing database of about 2400 adult patients with baseline ALT ≤90 IU/L, the incidence of ALT elevations to >200 IU/L was 2% (50/2381). None of these patients experienced jaundice or other symptoms attributable to liver impairment and most had transient changes that tended to normalize while olanzapine treatment was continued.

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

From an analysis of the laboratory data in an integrated database of 41 completed clinical studies in adult patients treated with oral olanzapine, high GGT levels were recorded in ≥1% (88/5245) of patients.

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

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

From an analysis of the laboratory data in an integrated database of 41 completed clinical studies in adult patients treated with oral olanzapine, elevated uric acid was recorded in ≥3% (171/4641) of patients.

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

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

ECG Changes — In pooled studies of adults as well as pooled studies of adolescents, there were no significant differences between olanzapine and placebo in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc (Fridericia corrected), and PR intervals. Olanzapine use was associated with a mean increase in heart rate compared to placebo (adults: +2.4 beats per minute vs no change with placebo; adolescents: +6.3 beats per minute vs -5.1 beats per minute with placebo). This increase in heart rate may be related to olanzapine's potential for inducing orthostatic changes *[see Warnings and Precautions (5.7)]*.

6.4 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of olanzapine. 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 therapy include the following: allergic reaction (e.g., anaphylactoid reaction, angioedema, pruritus or urticaria), cholestatic or mixed liver injury, diabetic coma, diabetic ketoacidosis, discontinuation reaction (diaphoresis, nausea or vomiting), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), hepatitis, jaundice, neutropenia, pancreatitis, priapism, rash, restless legs syndrome, rhabdomyolysis, and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥240 mg/dL and random triglyceride levels of ≥1000 mg/dL have been reported.

7 DRUG INTERACTIONS

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

7.1 Potential for Other Drugs to Affect Olanzapine

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

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

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

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

Inhibitors of CYP1A2

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

Inhibitors of CYP2D6

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

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

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

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

7.2 Potential for Olanzapine to Affect Other Drugs

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

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

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

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

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

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

8.1 Pregnancy

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

Placental transfer of olanzapine occurs in rat pups.

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

Nonteratogenic Effects - 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.

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

8.2 Labor and Delivery

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

The safety and effectiveness of oral olanzapine in the treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder were established in short-term studies in adolescents (ages 13 to 17 years). Use of olanzapine in adolescents is supported by evidence from adequate and well-controlled studies of olanzapine in which 268 adolescents received olanzapine in a range of 2.5 to 20 mg/day *[see Clinical Studies (14.1, 14.2)]*. Recommended starting dose for adolescents is lower than that for adults *[see Dosage and Administration (2.1, 2.2)]*. Compared to patients from adult clinical trials, adolescents were likely to gain more weight, experience increased sedation, and have greater increases in total cholesterol, triglycerides, LDL cholesterol, prolactin and hepatic aminotransferase levels *[see Warnings and Precautions (5.5, 5.15, 5.17) and Adverse Reactions (6.3)]*. When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential (in adolescents as compared with adults) for weight gain and dyslipidemia. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents *[see Indications and Usage (1.1, 1.2)]*.

Safety and effectiveness of olanzapine in children <13 years of age have not been established *[see Patient Counseling Information (17.14)]*.

Safety and efficacy of olanzapine and fluoxetine in combination in children and adolescents (10 to 17 years of age) have been established for the acute treatment of depressive episodes associated with bipolar I disorder.

Safety and effectiveness of olanzapine and fluoxetine in combination in children < 10 years of age have not been established.

8.5 Geriatric Use

Of the 2500 patients in premarketing clinical studies with oral olanzapine, 11% (263) were 65 years of age or over. In patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared to younger patients. Studies in elderly patients with dementia-related psychosis have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia. Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. In placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis, there was a higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric patient *[see Boxed Warning, Dosage and Administration (2.1), and Warnings and Precautions (5.1)]*.

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

9 DRUG ABUSE AND DEPENDENCE

9.3 Dependence

In studies prospectively designed to assess abuse and dependence potential, olanzapine was shown to have acute depressive CNS effects but little or no potential of abuse or physical dependence in rats administered oral doses up to 15 times the maximum recommended human daily oral dose (20 mg) and rhesus monkeys administered oral doses up to 8 times the maximum recommended human daily oral dose on a mg/m² basis.

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

10 OVERDOSAGE

10.1 Human Experience

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

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

10.2 Management of Overdose

For current information on the management of olanzapine overdose, contact a certified poison control center (1-800-222-1222 or www.poison.org). The possibility of multiple drug involvement should be considered. In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation, which may include intubation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The administration of activated charcoal (1 g) reduced the C_{max} and AUC of oral olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about 6 hours after dosing, charcoal may be a useful treatment for olanzapine overdose.

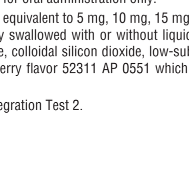
The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to olanzapine. Therefore, appropriate supportive measures should be initiated. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. (Do not use epinephrine, dopamine, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen hypotension in the setting of olanzapine-induced alpha blockade.) Close medical supervision and monitoring should continue until the patient recovers.

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

11 DESCRIPTION

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



Olanzapine, USP is a yellow crystalline solid, which is soluble in n-propanol; sparingly soluble in acetonitrile; slightly soluble in methanol and in dehydrated alcohol; practically insoluble in water.

Olanzapine orally disintegrating tablets, USP are intended for oral administration only.

Each orally disintegrating tablet contains olanzapine, USP equivalent to 5 mg, 10 mg, 15 mg or 20 mg. It begins disintegrating in the mouth within seconds, allowing its contents to be subsequently swallowed with or without liquid. Olanzapine orally disintegrating tablets, USP also contain the following inactive ingredients: aspartame, colloidal silicon dioxide, low-substituted hydroxyl propyl cellulose, magnesium stearate, mannitol, microcrystalline cellulose and strawberry flavor 52311 AP 0551 which contains maltodextrin, triethyl citrate, artificial flavors, benzyl alcohol and propylene glycol.

Olanzapine orally disintegrating tablets meets USP Disintegration Test 2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of olanzapine, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine and serotonin type 2 ($5HT_2$) antagonism. The mechanism of action of olanzapine in the treatment of acute manic or mixed episodes associated with bipolar I disorder is unknown.

12.2 Pharmacodynamics

Olanzapine binds with high affinity to the following receptors: serotonin $5HT_{2A/2C}$, $5HT_6$ (K_i=4, 11, and 5 nM, respectively), dopamine D_{1-4} (K_i=11-31 nM), histamine H_1 (K_i=7 nM), and adrenergic 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).

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

12.3 Pharmacokinetics

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

Olanzapine displays linear kinetics over the clinical dosing range. Its half-life ranges from 21 to 54 hours (5th to 95th percentile; mean of 30 hr), and apparent plasma clearance ranges from 12 to 47 L/hr (5th to 95th percentile; mean of 25 L/hr).

Administration of olanzapine once daily leads to steady-state concentrations in about 1 week that are approximately twice the concentrations after single doses. Plasma concentrations, half-life, and clearance of olanzapine may vary between individuals on the basis of smoking status, gender, and age.

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

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

Direct glucuronidation and cytochrome P450 (CYP) mediated oxidation are the primary metabolic pathways for olanzapine. *In vitro* studies suggest that CYPs 1A2 and 2D6, and the flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6 mediated oxidation appears to be a minor metabolic pathway *in vivo*, because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme.

Specific Populations

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

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

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

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

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

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis — Oral carcinogenicity studies were conducted in mice and rats. Olanzapine was administered to mice in two 78-week studies at doses of 3, 10, 30/20 mg/kg/day (equivalent to 0.8-5 times the maximum recommended human daily oral dose on a mg/m² basis) and 0.25, 2, 8 mg/kg/day (equivalent to 0.06-2 times the maximum recommended human daily oral dose on a mg/m² basis). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, 4 mg/kg/day (males) and 0.25, 1, 4, 8 mg/kg/day (females) (equivalent to 0.13-2 and 0.13-4 times the maximum recommended human daily oral dose on a mg/m² basis, respectively). The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in 1 mouse study in female mice dosed at 8 mg/kg/day (2 times the maximum recommended human daily oral dose on a mg/m² basis). These tumors were not increased in another mouse study in females dosed at 10 or 30/20 mg/kg/day (2-5 times the maximum recommended human daily oral dose on a mg/m² basis); in this study, there was a high incidence of early mortalities in males of the 30/20 mg/kg/day group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice dosed at ≥2 mg/kg/day and in female rats dosed at ≥4 mg/kg/day (0.5 and 2 times the maximum recommended human daily oral dose on a mg/m² basis, respectively). Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the olanzapine carcinogenicity studies; however, measurements during subchronic toxicity studies showed that olanzapine elevated serum prolactin levels up to 4-fold in rats at the same doses used in the carcinogenicity study. An increase in mammary gland neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance for human risk of the finding of prolactin mediated endocrine tumors in rodents is unknown *[see Warnings and Precautions (5.15)]*.

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

Impairment of Fertility — In an oral fertility and reproductive performance study in rats, male mating performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female fertility was decreased at a dose of 3 mg/kg/day (11 and 1.5 times the maximum recommended human daily oral dose on a mg/m² basis, respectively). Discontinuance of olanzapine treatment reversed the effects on male mating performance. In female rats, the precoital period was increased and the mating index reduced at 5 mg/kg/day (2.5 times the maximum recommended human daily oral dose on a mg/m² basis). Diestrous was prolonged and estrous delayed at 1.1 mg/kg/day (0.6 times the maximum recommended human daily oral dose on a mg/m² basis); therefore olanzapine may produce a delay in ovulation.

13.2 Animal Toxicology and/or Pharmacology

In animal studies with olanzapine, the principal hematologic findings were reversible peripheral cytopenias in individual dogs dosed at 10 mg/kg (17 times the maximum recommended human daily oral dose on a mg/m² basis), dose-related decreases in lymphocytes and neutrophils in mice, and lymphopenia in rats. A few dogs treated with 10 mg/kg developed reversible neutropenia and/or reversible hemolytic anemia between 1 and 10 months of treatment. Dose-related decreases in lymphocytes and neutrophils were seen in mice given doses of 10 mg/kg (equal to 2 times the maximum recommended human daily oral dose on a mg/m² basis) in studies of 3 months' duration. Nonspecific lymphopenia, consistent with decreased body weight gain, occurred in rats receiving 22.5 mg/kg (11 times the maximum recommended human daily oral dose on a mg/m² basis) for 3 months or 16 mg/kg (8 times the maximum recommended human daily oral dose on a mg/m² basis) for 6 or 12 months. No evidence of bone marrow cytotoxicity was found in any of the species examined. Bone marrows were normocellular or hypercellular, indicating that the reductions in circulating blood cells were probably due to peripheral (non-marrow) factors.

14 CLINICAL STUDIES

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

14.1 Schizophrenia

Adults

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

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

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

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

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

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

Adolescents

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

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

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

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

14.2 Bipolar I Disorder (Manic or Mixed Episodes)

Adults

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

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

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

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

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

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

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

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

Adolescents

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

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

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Olanzapine orally disintegrating tablets, USP are yellow colored, round, flat face beveled edge, debossed tablets with characteristic flavour. The tablets are available as follows:

	TABLET STRENGTH			
Olanzapine orally disintegrating tablets, USP	5 mg	10 mg	15 mg	20 mg
Debossed	D5; CO	D10; CO	D15; CO	D20; CO
NDC Codes: CR blisters of 10 tablets	59746-306-12	59746-307-12	59746-308-12	59746-309-12
NDC Codes: Carton of 30 tablets (3 x 10 unit-dose)	59746-306-32	59746-307-32	59746-308-32	59746-309-32

16.2 Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. The USP defines controlled room temperature as a temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses.

Protect olanzapine orally disintegrating tablets from light and moisture.

17 PATIENT COUNSELING INFORMATION

See FDA-approved Medication Guide for the oral formulations.

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

17.1 Information on Medication Guide

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

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

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

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

17.3 Neuroleptic Malignant Syndrome (NMS)

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

17.4 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Patients should be advised to report to their health care provider at the earliest onset of any signs and symptoms that may be associated with Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) *[see Warnings and Precautions (5.4)]*.

17.5 Hyperglycemia and Diabetes Mellitus

Patients should be advised of the potential risk of hyperglycemia-related adverse reactions. Patients should be monitored regularly for worsening of glucose control. Patients who have diabetes should follow their doctor's instructions about how often to check their blood sugar while taking olanzapine *[see Warnings and Precautions (5.5)]*.

17.6 Dyslipidemia

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

17.8 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 (5.7) and Drug Interactions (7)]*. Patients should be advised to change positions carefully to help prevent orthostatic hypotension, and to lie down if they feel dizzy or faint, until they feel better. Patients should be advised to call their doctor if they experience any of the following signs and symptoms associated with orthostatic hypotension: dizziness, fast or slow heartbeat, or fainting.

17.9 Potential for Cognitive and Motor Impairment

Because olanzapine has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that olanzapine therapy does not affect them adversely *[see Warnings and Precautions (5.12)]*.

17.10 Body Temperature Regulation

Patients should be advised regarding appropriate care in avoiding overheating and dehydration. Patients should be advised to call their doctor right away if they become severely ill and have some or all of these symptoms of dehydration: sweating too much or not at all, dry mouth, feeling very hot, feeling thirsty, not able to produce urine *[see Warnings and Precautions (5.13)]*.

17.11 Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, Symbyax*. Patients should also be advised to inform their physicians if they are taking, plan to take, or have stopped taking any prescription or over-the-counter drugs, including herbal supplements, since there is a potential for interactions *[see Drug Interactions (7)]*.

17.12 Alcohol

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

17.13 Phenylketonurics

Olanzapine orally disintegrating tablets contain phenylalanine (1.12, 2.24, 3.36, and 4.48 mg per 5, 10, 15, and 20 mg tablet, respectively) *[see Description (11)]*.

17.14 Use in Specific Populations

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

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

Pediatric Use — Olanzapine is indicated for treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder in adolescents 13 to 17 years of age. Compared to patients from adult clinical trials, adolescents were likely to gain more weight, experience increased sedation, and have greater increases in total cholesterol, triglycerides, LDL cholesterol, prolactin, and hepatic aminotransferase levels. Patients should be counseled about the potential long-term risks associated with olanzapine and advised that these risks may lead them to consider other drugs first *[see Indications and Usage (1.1, 1.2)]*. Safety and effectiveness of olanzapine in patients under 13 years of age have not been established. Safety and efficacy of olanzapine and fluoxetine in combination in patients 10 to 17 years of age have been established for the acute treatment of depressive episodes associated with bipolar I disorder. Safety and effectiveness of olanzapine and fluoxetine in combination in patients < 10 years of age have not been established *[see Warnings and Precautions (5.5) and Use in Specific Populations (8.4)]*.

17.15 Need for Comprehensive Treatment Program in Pediatric Patients

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

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Rx Only

Manufactured by:
Jubilant Generics Limited
Roorkee - 247661, India

Marketed by:
Jubilant Cadista Pharmaceuticals Inc.,
Salisbury, MD 21801, USA

Revision: 05/2017

- dose of olanzapine orally disintegrating tablets until it is right for you.
- If you miss a dose of olanzapine orally disintegrating tablets, take the missed dose as soon as you remember. If it is almost time for the next dose, just skip the missed dose and take your next dose at the regular time. Do not take two doses of olanzapine orally disintegrating tablets at the same time.
- **To prevent serious side effects, do not stop taking olanzapine orally disintegrating tablets suddenly. If you need to stop taking olanzapine orally disintegrating tablets, your doctor can tell you how to safely stop taking it.**
- **If you take too much olanzapine orally disintegrating tablets, call your doctor or poison control center at 1-800-222-1222 right away, or get emergency treatment.**
- Olanzapine orally disintegrating tablets can be taken with or without food.
- Olanzapine orally disintegrating tablets are usually taken one time each day.
- Take olanzapine orally disintegrating tablets as follows:
  - Be sure that your hands are dry.
  - Peel back the foil on the blister. Do not push the tablet through the foil.
  - As soon as you open the blister, remove the tablet and put it into your mouth.
  - The tablet will disintegrate quickly in your saliva so that you can easily swallow it with or without drinking liquid.
- Call your doctor if you do not think you are getting better or have any concerns about your condition while taking olanzapine orally disintegrating tablets.

What should I avoid while taking olanzapine orally disintegrating tablets?

- Olanzapine orally disintegrating tablets 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 orally disintegrating tablets affects you.
- Avoid drinking alcohol while taking olanzapine orally disintegrating tablets. Drinking alcohol while you take olanzapine may make you sleepier than if you take olanzapine orally disintegrating tablets alone.

What are the possible side effects of olanzapine orally disintegrating tablets?

Serious side effects may happen when you take olanzapine orally disintegrating tablets, including:

- **See "What is the most important information I should know about olanzapine orally disintegrating tablets?", which describes the increased risk of death in elderly people with dementia-related psychosis and the risks of high blood sugar, high cholesterol and triglyceride levels, and weight gain.**
- **Increased incidence of stroke or "mini-strokes" called transient ischemic attacks (TIAs) in elderly people with dementia-related psychosis** (elderly people who have lost touch with reality due to confusion and memory loss). Olanzapine orally disintegrating tablets are not approved for these patients.
- **Neuroleptic Malignant Syndrome (NMS):** NMS is a rare but very serious condition that can happen in people who take antipsychotic medicines, including olanzapine orally disintegrating tablets. NMS can cause death and must be treated in a hospital. Call your doctor right away if you become severely ill and have any of these symptoms:
  - high fever
  - excessive sweating
  - rigid muscles
  - confusion
  - changes in your breathing, heartbeat, and blood pressure.
- **Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS):** DRESS can occur with olanzapine orally disintegrating tablets. Features of DRESS may include rash, fever, swollen glands and other internal organ involvement such as liver, kidney, lung and heart. DRESS is sometimes fatal; therefore, tell your doctor immediately if you experience any of these signs.
- **Tardive Dyskinesia:** This condition causes body movements that keep happening and that you can not control. These movements usually affect the face and tongue. Tardive dyskinesia may not go away, even if you stop taking olanzapine orally disintegrating tablets. It may also start after you stop taking olanzapine orally disintegrating tablets. Tell your doctor if you get any body movements that you can not control.
- **Decreased blood pressure when you change positions, with symptoms of dizziness, fast or slow heartbeat, or fainting.**
- **Difficulty swallowing, that can cause food or liquid to get into your lungs.**
- **Seizures: Tell your doctor if you have a seizure during treatment with olanzapine orally disintegrating tablets.**
- **Problems with control of body temperature:** You could become very hot, for instance when you exercise a lot or stay in an area that is very hot. It is important for you to drink water to avoid dehydration. Call your doctor right away if you become severely ill and have any of these symptoms of dehydration:
  - sweating too much or not at all
  - dry mouth
  - feeling very hot
  - feeling thirsty
  - not able to produce urine.

Common side effects of olanzapine orally disintegrating tablets include: lack of energy, dry mouth, increased appetite, sleepiness, tremor (shakes), having hard or infrequent stools, dizziness, changes in behavior, or restlessness.

Other common side effects in teenagers (13 to 17 years old) include: headache, stomach-area (abdominal) pain, pain in your arms or legs, or tiredness. Teenagers experienced greater increases in prolactin, liver enzymes, and sleepiness, as compared with adults.

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

These are not all the possible side effects with olanzapine orally disintegrating tablets. 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 orally disintegrating tablets?

- Store olanzapine orally disintegrating tablets at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature].
- Keep olanzapine orally disintegrating tablets away from light.
- Keep olanzapine orally disintegrating tablets dry and away from moisture.

Keep olanzapine orally disintegrating tablets and all medicines out of the reach of children.

General information about olanzapine orally disintegrating tablets

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

This Medication Guide summarizes the most important information about olanzapine orally disintegrating tablets. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about olanzapine orally disintegrating tablets that was written for healthcare professionals. For more information about olanzapine orally disintegrating tablets, call 1-800-313-4623.

What are the ingredients in olanzapine orally disintegrating tablets?

Active ingredient: olanzapine, USP

Inactive ingredients: aspartame, colloidal silicon dioxide, low-substituted hydroxyl propyl cellulose, magnesium stearate, mannitol, microcrystalline cellulose, and strawberry flavor 52311 AP 0551 which contains maltodextrin, triethyl citrate, artificial flavors, benzyl alcohol and propylene glycol.

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

*All trademark names are the property of their respective owners.

Rx Only

Manufactured by:
Jubilant Generics Limited
Roorkee - 247661, India

Marketed by:
Jubilant Cadista Pharmaceuticals Inc.,
Salisbury, MD 21801, USA

Revision: 05/2017

Last modified: 9. May 2017, 2:14 PM
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Reason for Artwork: RLD update; ZYPREXA ZYDIS (dated: 23/02/2017)	JUBILANT GENERICS	Dimension: 880 x 500 mm
Item Code: 50000002513		Superseded Item Code: 7524000810
Substrate: 32 GSM Bible paper with folding Dimension 64 x 44 mm		

Site Packaging Development Sign and Date		Production Sign and Date		QA Sign and Date	