500 mm

300 mm | 200 mm

50 mm | 50 mm

120 mm

830 mm

Olanzapine Orally Disintegrating Tablets, USP
1054280

Olanzapine Orally Disintegrating Tablets, USP
1054280

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, for oral use

Initial U.S. Approval: 1996

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

See full prescribing information for complete boxed warning.

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Olanzapine orally disintegrating tablets are not approved for the treatment of patients with dementia-related psychosis. (5.1, 8.5, 17)**

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

INDICATIONS AND USAGE

Olanzapine is an atypical antipsychotic indicated:

As oral formulation for the:

- Treatment of schizophrenia. **(1.1)**
  - Adults: Efficacy was established in three clinical trials in patients with schizophrenia: two 6-week trials and one maintenance trial. **(14.1)**
  - Adolescents (ages 13 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 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.
- Treatment of treatment resistant depression. **(1.6)**
  - Efficacy was established with Symbyax (olanzapine and fluoxetine in combination) in adults; refer to the product label for Symbyax.

DOSAGE AND ADMINISTRATION

Schizophrenia in adults (**2.1**)	Oral: Start at 5 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
Treatment Resistant Depression in adults **(2.6)**	Oral in combination with fluoxetine: Start at 5 mg of oral olanzapine and 20 mg of fluoxetine once daily

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

Olanzapine and Fluoxetine in Combination:

- Dosage adjustments, if indicated, should be made with the individual components according to efficacy and tolerability. **(2.5, 2.6)**
- Olanzapine monotherapy is not indicated for the treatment of depressive episodes associated with bipolar I disorder or treatment resistant depression. **(2.5, 2.6)**
- Safety of co-administration of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated in adults. **(2.5, 2.6)**
- 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, USP (not scored): 5, 10, 15, 20 mg **(3)**

CONTRAINDICATIONS

- None with olanzapine monotherapy. **(4)**
- When using olanzapine 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)**
- *Anticholinergic (antimuscarinic) Effects:* Use with caution with other anticholinergic drugs and in patients with urinary retention, prostatic hypertrophy, constipation, paralytic ileus or related conditions. **(5.14)**
- *Hyperprolactinemia:* May elevate prolactin levels. **(5.15)**
- *Use in Combination with Fluoxetine, Lithium or Valproate:* Also refer to the package inserts for Symbyax, lithium, or valproate. **(5.16)**
- *Laboratory Tests:* Monitor fasting blood glucose and lipid profiles at the beginning of, and periodically during, treatment. **(5.17)**

ADVERSE REACTIONS

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

Oral Olanzapine Monotherapy:

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

Combination of 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 Strides Pharma Inc at 1-877-244-9825 and www.strides.com 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:* May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. **(8.1)**
- *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 Medication Guide

Revised: 03/2026

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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), Use in Specific Populations (8.5), and Patient Counseling Information (17)].

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

Oral olanzapine is indicated for the treatment of schizophrenia. Efficacy was established in three clinical trials in adult patients with schizophrenia: two 6-week trials and one maintenance trial. In adolescent patients with schizophrenia (ages 13 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 — Oral olanzapine is indicated for the acute treatment of manic or mixed episodes associated with bipolar I disorder and maintenance treatment of bipolar I disorder. Efficacy was established in three clinical trials in adult patients with manic or mixed episodes of bipolar I disorder: two 3- to 4-week trials and one monotherapy maintenance trial. In adolescent patients with manic or mixed episodes associated with bipolar I disorder (ages 13 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 — Oral olanzapine is indicated for the treatment of manic or mixed episodes associated with bipolar I disorder as an adjunct to lithium or valproate. Efficacy was established in two 6-week clinical trials in adults. The effectiveness of adjunctive therapy for longer-term use has not been systematically evaluated in controlled trials [see **Clinical Studies (14.2)**].

1.3 Special Considerations in Treating Pediatric Schizophrenia and Bipolar I Disorder

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

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

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

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

1.6 Olanzapine and Fluoxetine in Combination: Treatment Resistant Depression

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

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

2 DOSAGE AND ADMINISTRATION

2.1 Schizophrenia

Adults

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

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

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

Maintenance Treatment — The effectiveness of oral olanzapine, 10 mg/day to 20 mg/day, in maintaining treatment response in schizophrenic patients who had been stable on olanzapine for approximately 8 weeks and were then followed for relapse has been demonstrated in a placebo-controlled trial [see **Clinical Studies (14.1)**]. The healthcare provider who elects to use olanzapine 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 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 to 4 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials [see **Clinical Studies (14.2)**].

Maintenance Monotherapy — The benefit of maintaining bipolar I patients on monotherapy with oral olanzapine 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 healthcare provider who elects to use olanzapine 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 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 and Fluoxetine in Combination: Depressive Episodes Associated with Bipolar I Disorder

When using olanzapine 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 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 and fluoxetine in combination was determined in clinical trials supporting approval of Symbyax (fixed dose combination of olanzapine and fluoxetine). Symbyax is dosed between 3 mg/25 mg (olanzapine/fluoxetine) per day and 12 mg/50 mg (olanzapine/fluoxetine) per day. The following table demonstrates the appropriate individual component doses of olanzapine 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® and the Combination of Olanzapine and Fluoxetine

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

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

While there is no body of evidence to answer the question of how long a patient treated with olanzapine 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 healthcare provider should periodically reexamine the need for continued pharmacotherapy.

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

2.6 Olanzapine and Fluoxetine in Combination: Treatment Resistant Depression

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

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

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

While there is no body of evidence to answer the question of how long a patient treated with olanzapine and fluoxetine in combination should remain on it, it is generally accepted that treatment resistant depression (major depressive disorder in adult patients who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode) is a chronic illness requiring chronic treatment. The healthcare provider should periodically reexamine the need for continued pharmacotherapy.

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

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

2.7 Olanzapine 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 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, round, and debossed with "P" and the Par tablet number as described below. Tablets are not scored. The tablets are available as follows:

Olanzapine orally disintegrating tablets, USP 5 mg are yellow, round, flat faced, beveled edge tablets debossed "P" on one side of the tablet and "320" on the other.

Olanzapine orally disintegrating tablets, USP 10 mg are yellow, round, flat faced, beveled edge tablets debossed "P" on one side of the tablet and "321" on the other.

Olanzapine orally disintegrating tablets, USP 15 mg are yellow, round, flat faced, beveled edge tablets debossed "P" on one side of the tablet and "322" on the other.

Olanzapine orally disintegrating tablets, USP 20 mg are yellow, round, flat faced, beveled edge tablets debossed "P" on one side of the tablet and "323" on the other.

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, Use in Specific Populations (8.5), and Patient Counseling Information (17)].

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)**].

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**)].

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**)].

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

Healthcare providers 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**)].

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 increased 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 base

500 mm

830 mm

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		
Dysmenorrhea[a]	2	0
Vaginitis[a]	2	0

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

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

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

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

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

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

Other Adverse Reactions
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, hyperproteinemia.
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 to 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 to 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**)].

6.2 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, salivary hypersecretion, stuttering[1], venous thromboembolic events (including pulmonary embolism and deep venous thrombosis), fecal incontinence, somnambulism, and syndrome of inappropriate antidiuretic hormone secretion (SIADH). Random cholesterol levels of ≥240 mg/dL and random triglyceride levels of ≥1000 mg/dL have been reported.
[1] Stuttering was only studied in oral and long acting injection (LAI) formulations.

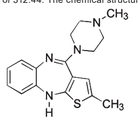
7 DRUG INTERACTIONS
The risks of using olanzapine in combination with other drugs have not been extensively evaluated in systematic studies.
7.1 Potential Effect of Other Drugs to Affect Olanzapine
Diazepam — The co-administration of diazepam with olanzapine potentiated the orthostatic hypotension observed 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 coadministration 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 in olanzapine dose response. 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.
Anticholinergic Drugs — Concomitant treatment with olanzapine and other drugs with anticholinergic activity can increase the risk for severe gastrointestinal adverse reactions related to hypomotility. Olanzapine should be used with caution in patients receiving medications having anticholinergic (antimuscarinic) effects [see **Warnings and Precautions** (**5.14**)].
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
Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics, including olanzapine, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.
Risk Summary
Neonates exposed to antipsychotic drugs, including olanzapine, during the third trimester are at risk for extrapyramidal and/or withdrawal symptoms following delivery (see *Clinical Considerations*). Overall available data from published epidemiologic studies of pregnant women exposed to olanzapine have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes (see *Data*). There are risks to the mother associated with untreated schizophrenia or bipolar I disorder and with exposure to antipsychotics, including olanzapine, during pregnancy (see *Clinical Considerations*).
Olanzapine was not teratogenic when administered orally to pregnant rats and rabbits at doses that are 9- and 30-times the daily oral maximum recommended human dose (MRHD), based on mg/m^2 body surface area; some fetal toxicities were observed at these doses (see *Data*).
The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.
Clinical Considerations
Disease-associated maternal and embryo/fetal risk
There is a risk to the mother from untreated schizophrenia or bipolar I disorder, including increased risk of relapse, hospitalization, and suicide. Schizophrenia and bipolar I disorder are associated with increased adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of the illness or other comorbid factors.
Fetal/Neonatal adverse reactions
Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs, including olanzapine, during the third trimester of pregnancy. These symptoms have varied in severity. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization.
Data
Human Data
Placental passage has been reported in published study reports; however, the placental passage ratio was highly variable ranging between 7% to 167% at birth following exposure during pregnancy. The clinical relevance of this finding is unknown.
Published data from observational studies, birth registries, and case reports that have evaluated the use of atypical antipsychotics during pregnancy do not establish an increased risk of major birth defects. A retrospective cohort study from a Medicaid database of 9258 women exposed to antipsychotics during pregnancy did not indicate an overall increased risk for major birth defects.
Animal Data
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 daily oral MRHD based on mg/m^2 body surface area, 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 daily oral MRHD based on mg/m^2 body surface area), and gestation was prolonged at 10 mg/kg/day (5 times the daily oral MRHD based on mg/m^2 body surface area). 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 daily oral MRHD based on mg/m^2 body surface area).
8.2 Lactation
Risk Summary
Olanzapine is present in human milk. There are reports of excess sedation, irritability, poor feeding and extrapyramidal symptoms (tremors and abnormal muscle movements) in infants exposed to olanzapine through breast milk (see *Clinical Considerations*). There is no information on the effects of olanzapine on milk production.
The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for olanzapine and any potential adverse effects on the breastfed child from olanzapine or from the mother's underlying condition.
Clinical Considerations
Infants exposed to olanzapine should be monitored for excess sedation, irritability, poor feeding, and extrapyramidal symptoms (tremors and abnormal muscle movements).
8.3 Females and Males of Reproductive Potential
Infertility
Females
Based on the pharmacologic action of olanzapine (D_2 receptor antagonism), treatment with olanzapine may result in an increase in serum prolactin levels, which may lead to a reversible reduction in fertility in females of reproductive potential [see **Warnings and Precautions** (**5.15**)].
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** (**6.1**)]. When considering 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**)].
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. In 5 placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis (n=1184), the following 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**)]. 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 daily oral MRHD (20 mg) and rhesus monkeys administered oral doses up to 8 times the daily oral MRHD based on mg/m^2 body surface area.
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 analyses or ECG. Vital signs were usually within normal limits following overdoses.
In postmarketing reports of overdose with olanzapine alone, symptoms have been reported in the majority of cases. In symptomatic patients, symptoms with ≥10% incidence included agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma. Among less commonly reported symptoms were the following potentially medically serious reactions: aspiration, cardiopulmonary arrest, cardiac arrhythmias (such as supraventricular tachycardia and 1 patient experiencing sinus pause with spontaneous resumption of normal rhythm), delirium, possible neuroleptic malignant syndrome, respiratory depression/arrest, convulsion, hypertension, and hypotension. Eli Lilly and Company has received reports of fatality in association with overdose of olanzapine alone. In 1 case of death, the amount of acutely ingested olanzapine was reported to be possibly as low as 450 mg of oral olanzapine; however, in another case, a patient was reported to survive an acute olanzapine ingestion of approximately 2 g of oral olanzapine.
10.2 Management of Overdose
There is no specific antidote to an overdose of olanzapine. The possibility of multiple drug involvement should be considered. Establish and maintain an airway and ensure adequate oxygenation and ventilation. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.
Contact a Certified Poison Control Center for the most up to date information on the management of overdosage (1-800-222-1222).
For specific information about overdosage with lithium or valproate, refer to the Overdosage section of the prescribing information for those products. For specific information about overdosage with olanzapine and fluoxetine in combination, refer to the Overdosage section of the Symbyax prescribing information.

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



Olanzapine is a yellow crystalline solid, which is practically insoluble in water.
Olanzapine orally disintegrating tablets, USP are intended for oral administration only.
Each orally disintegrating tablet contains olanzapine equivalent to 5 mg (16 μmol), 10 mg (32 μmol), 15 mg (48 μmol) or 20 mg (64 μmol). It begins disintegrating in the mouth within seconds, allowing its contents to be subsequently swallowed with or without liquid. Olan