

### 1.2 Bipolar I Disorder (Manic or Mixed Episodes)

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

When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential (in adolescents as compared with adults) for weight gain and hyperlipidemia. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents [see *Warnings and Precautions (5.5, 5.6)*].

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

### 1.3 Special Considerations in Treating Pediatric Schizophrenia and Bipolar I Disorder

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

#### 1.4 ZYPREXA IntraMuscular: Agitation Associated with Schizophrenia and Bipolar I Mania

ZYPREXA IntraMuscular is indicated for the treatment of acute agitation associated with schizophrenia and bipolar I mania. Efficacy was demonstrated in 3 short-term (24 hours of IM treatment) placebo-controlled trials in agitated adult inpatients with: schizophrenia or bipolar I disorder (manic or mixed episodes) [see *Clinical Studies (14.3)*].

“Psychomotor agitation” is defined in DSM-IV as “excessive motor activity associated with a feeling of inner tension.” Patients experiencing agitation often manifest behaviors that interfere with their diagnosis and care, e.g., threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior, leading clinicians to the use of intramuscular antipsychotic medications to achieve immediate control of the agitation.

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

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

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

#### 1.6 ZYPREXA and Fluoxetine in Combination: Treatment Resistant Depression

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

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

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Schizophrenia

#### Adults

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

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

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

**Maintenance Treatment** — The effectiveness of oral olanzapine, 10 mg/day to 20 mg/day, in maintaining treatment response in schizophrenic patients who had been stable on ZYPREXA for approximately 8 weeks and were then followed for relapse has been

demonstrated in a placebo-controlled trial [see *Clinical Studies (14.1)*]. The physician who elects to use ZYPREXA for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

### Adolescents

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

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

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

### 2.2 Bipolar I Disorder (Manic or Mixed Episodes)

#### Adults

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

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

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

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

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

#### Adolescents

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

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

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

### 2.3 Administration of ZYPREXA ZYDIS (olanzapine orally disintegrating tablets)

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

### 2.4 ZYPREXA IntraMuscular: Agitation Associated with Schizophrenia and Bipolar I Mania

**Dose Selection for Agitated Adult Patients with Schizophrenia and Bipolar I Mania** — The efficacy of intramuscular olanzapine for injection in controlling agitation in these disorders was demonstrated in a dose range of 2.5 mg to 10 mg. The recommended dose in these patients is 10 mg. A lower dose of 5 or 7.5 mg may be considered when clinical factors warrant [see *Clinical Studies (14.3)*]. If agitation warranting additional intramuscular doses persists following the initial dose, subsequent doses up to 10 mg may be given. However, the efficacy of repeated doses of intramuscular olanzapine for injection in agitated patients has not been systematically evaluated in controlled clinical trials. Also, the safety of total daily doses greater than 30 mg, or 10 mg injections given more frequently than 2 hours after the initial dose, and 4 hours after the second dose have not been evaluated in clinical trials. Maximal dosing of intramuscular olanzapine (e.g., 3 doses of 10 mg administered 2-4 hours apart) may be associated with a substantial occurrence of significant orthostatic hypotension [see *Warnings and Precautions (5.8)*]. Thus, it is recommended that patients requiring subsequent intramuscular injections be assessed for orthostatic hypotension prior to the administration of any subsequent doses of intramuscular olanzapine for injection. The administration of an additional dose to a patient with a clinically significant postural change in systolic blood pressure is not recommended.

If ongoing olanzapine therapy is clinically indicated, oral olanzapine may be initiated in a range of 5-20 mg/day as soon as clinically appropriate [see *Dosage and Administration* (2.1, 2.2)].

**Intramuscular Dosing in Special Populations** — A dose of 5 mg/injection should be considered for geriatric patients or when other clinical factors warrant. A lower dose of 2.5 mg/injection should be considered for patients who otherwise might be debilitated, be predisposed to hypotensive reactions, or be more pharmacodynamically sensitive to olanzapine [see *Warnings and Precautions* (5.14), *Drug Interactions* (7), and *Clinical Pharmacology* (12.3)].

**Administration of ZYPREXA IntraMuscular** — ZYPREXA IntraMuscular is intended for intramuscular use only. Do not administer intravenously or subcutaneously. Inject slowly, deep into the muscle mass.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

**Directions for Preparation of ZYPREXA IntraMuscular with Sterile Water for Injection** — Dissolve the contents of the vial using 2.1 mL of Sterile Water for Injection to provide a solution containing approximately 5 mg/mL of olanzapine. The resulting solution should appear clear and yellow. ZYPREXA IntraMuscular reconstituted with Sterile Water for Injection should be used immediately (within 1 hour) after reconstitution. *Discard any unused portion.*

The following table provides injection volumes for delivering various doses of intramuscular olanzapine for injection reconstituted with Sterile Water for Injection.

| Dose, mg Olanzapine | Volume of Injection, mL         |
|---------------------|---------------------------------|
| 10                  | Withdraw total contents of vial |
| 7.5                 | 1.5                             |
| 5                   | 1                               |
| 2.5                 | 0.5                             |

**Physical Incompatibility Information** — ZYPREXA IntraMuscular should be reconstituted only with Sterile Water for Injection. ZYPREXA IntraMuscular should not be combined in a syringe with diazepam injection because precipitation occurs when these products are mixed. Lorazepam injection should not be used to reconstitute ZYPREXA IntraMuscular as this combination results in a delayed reconstitution time. ZYPREXA IntraMuscular should not be combined in a syringe with haloperidol injection because the resulting low pH has been shown to degrade olanzapine over time.

#### 2.5 ZYPREXA and Fluoxetine in Combination: Depressive Episodes Associated with Bipolar I Disorder

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

Oral olanzapine should be administered in combination with fluoxetine once daily in the evening, without regard to meals, generally beginning with 5 mg of oral olanzapine and 20 mg of fluoxetine. Dosage adjustments, if indicated, can be made according to efficacy and tolerability within dose ranges of oral olanzapine 5 to 12.5 mg and fluoxetine 20 to 50 mg. Antidepressant efficacy was demonstrated with ZYPREXA and fluoxetine in combination in adult patients with a dose range of olanzapine 6 to 12 mg and fluoxetine 25 to 50 mg.

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

**Table 1: Approximate Dose Correspondence Between Symbyax<sup>a</sup> and the Combination of ZYPREXA and Fluoxetine**

| For<br>Symbyax<br>(mg/day)        | Use in Combination  |                        |
|-----------------------------------|---------------------|------------------------|
|                                   | ZYPREXA<br>(mg/day) | Fluoxetine<br>(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                  |

<sup>a</sup> Symbyax (olanzapine/fluoxetine HCl) is a fixed-dose combination of ZYPREXA and fluoxetine.

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

Safety of co-administration of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated in clinical studies. ZYPREXA monotherapy is not indicated for the treatment of depressive episodes associated with bipolar I disorder.

#### 2.6 ZYPREXA and Fluoxetine in Combination: Treatment Resistant Depression

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

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

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

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

Safety of co-administration of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated in clinical studies. ZYPREXA monotherapy is not indicated for treatment of treatment resistant depression (major depressive disorder in patients who do not respond to 2 antidepressants of adequate dose and duration in the current episode).

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

The starting dose of oral olanzapine 2.5-5 mg with fluoxetine 20 mg should be used for patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of olanzapine or fluoxetine in combination (female gender, geriatric age, nonsmoking status), or those patients who may be pharmacodynamically sensitive to olanzapine. Dosing modification may be necessary in patients who exhibit a combination of factors that may slow metabolism. When indicated, dose escalation should be performed with caution in these patients. ZYPREXA and fluoxetine in combination have not been systematically studied in patients over 65 years of age or in patients <18 years of age [see *Warnings and Precautions (5.14), Drug Interactions (7), and Clinical Pharmacology (12.3)*].

## 3 DOSAGE FORMS AND STRENGTHS

The ZYPREXA 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are white, round, and imprinted in blue ink with LILLY and tablet number. The 15 mg tablets are elliptical, blue, and debossed with LILLY and tablet number. The 20 mg tablets are elliptical, pink, and debossed with LILLY and tablet number. Tablets are not scored. The tablets are available as follows:

|                | TABLET STRENGTH |               |               |               |               |               |
|----------------|-----------------|---------------|---------------|---------------|---------------|---------------|
|                | 2.5 mg          | 5 mg          | 7.5 mg        | 10 mg         | 15 mg         | 20 mg         |
| Tablet No.     | 4112            | 4115          | 4116          | 4117          | 4415          | 4420          |
| Identification | LILLY<br>4112   | LILLY<br>4115 | LILLY<br>4116 | LILLY<br>4117 | LILLY<br>4415 | LILLY<br>4420 |

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) are yellow, round, and debossed with the tablet strength. Tablets are not scored. The tablets are available as follows:

| ZYPREXA ZYDIS Tablets | TABLET STRENGTH |       |       |       |
|-----------------------|-----------------|-------|-------|-------|
|                       | 5 mg            | 10 mg | 15 mg | 20 mg |
| Tablet No.            | 4453            | 4454  | 4455  | 4456  |
| Debossed              | 5               | 10    | 15    | 20    |

ZYPREXA IntraMuscular is available in 10 mg vial (1s).

## 4 CONTRAINDICATIONS

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

## 5 WARNINGS AND PRECAUTIONS

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

### 5.1 Elderly Patients with Dementia-Related Psychosis

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

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

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

#### 5.2 Suicide

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

#### 5.3 Neuroleptic Malignant Syndrome (NMS)

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

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

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

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

#### 5.4 Hyperglycemia

Physicians should consider the risks and benefits when prescribing olanzapine to patients with an established diagnosis of diabetes mellitus, or having borderline increased blood glucose level (fasting 100-126 mg/dL, nonfasting 140-200 mg/dL). Patients taking olanzapine should be monitored regularly for worsening of glucose control. Patients starting treatment with olanzapine should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug [see *Patient Counseling Information (17.4)*].

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

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

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

**Olanzapine Monotherapy in Adults** — In an analysis of 5 placebo-controlled adult olanzapine monotherapy studies with a median treatment duration of approximately 3 weeks, olanzapine was associated with a greater mean change in fasting glucose levels compared to placebo (2.76 mg/dL versus 0.17 mg/dL). The difference in mean changes between olanzapine and placebo was greater in patients with evidence of glucose dysregulation at baseline (patients diagnosed with diabetes mellitus or related adverse reactions, patients treated with anti-diabetic agents, patients with a baseline random glucose level  $\geq 200$  mg/dL, and/or a baseline fasting glucose

level  $\geq 126$  mg/dL). Olanzapine-treated patients had a greater mean HbA1c increase from baseline of 0.04% (median exposure 21 days), compared to a mean HbA1c decrease of 0.06% in placebo-treated subjects (median exposure 17 days).

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

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

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

<sup>a</sup> Not Applicable.

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

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

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

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

<sup>a</sup> Not Applicable.

## 5.5 Hyperlipidemia

Undesirable alterations in lipids have been observed with olanzapine use. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using olanzapine, is recommended [see *Patient Counseling Information (17.5)*].

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

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

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

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

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

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

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

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

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

| Laboratory Analyte        | Category Change (at least once) from Baseline                             | Treatment Arm | Up to 6 weeks exposure |          | At least 24 weeks exposure |                 |
|---------------------------|---------------------------------------------------------------------------|---------------|------------------------|----------|----------------------------|-----------------|
|                           |                                                                           |               | N                      | Patients | N                          | Patients        |
| Fasting Triglycerides     | Increase by $\geq 50$ mg/dL                                               | Olanzapine    | 138                    | 37.0%    | 122                        | 45.9%           |
|                           |                                                                           | Placebo       | 66                     | 15.2%    | NA <sup>a</sup>            | NA <sup>a</sup> |
|                           | Normal to High (<90 mg/dL to >130 mg/dL)                                  | Olanzapine    | 67                     | 26.9%    | 66                         | 36.4%           |
|                           |                                                                           | Placebo       | 28                     | 10.7%    | NA <sup>a</sup>            | NA <sup>a</sup> |
|                           | Borderline to High ( $\geq 90$ mg/dL and $\leq 130$ mg/dL to >130 mg/dL)  | Olanzapine    | 37                     | 59.5%    | 31                         | 64.5%           |
|                           |                                                                           | Placebo       | 17                     | 35.3%    | NA <sup>a</sup>            | NA <sup>a</sup> |
| Fasting Total Cholesterol | Increase by $\geq 40$ mg/dL                                               | Olanzapine    | 138                    | 14.5%    | 122                        | 14.8%           |
|                           |                                                                           | Placebo       | 66                     | 4.5%     | NA <sup>a</sup>            | NA <sup>a</sup> |
|                           | Normal to High (<170 mg/dL to $\geq 200$ mg/dL)                           | Olanzapine    | 87                     | 6.9%     | 78                         | 7.7%            |
|                           |                                                                           | Placebo       | 43                     | 2.3%     | NA <sup>a</sup>            | NA <sup>a</sup> |
|                           | Borderline to High ( $\geq 170$ mg/dL and <200 mg/dL to $\geq 200$ mg/dL) | Olanzapine    | 36                     | 38.9%    | 33                         | 57.6%           |
|                           |                                                                           | Placebo       | 13                     | 7.7%     | NA <sup>a</sup>            | NA <sup>a</sup> |

|                         |                                                                                |            |     |       |                 |                 |
|-------------------------|--------------------------------------------------------------------------------|------------|-----|-------|-----------------|-----------------|
| Fasting LDL Cholesterol | Increase by $\geq 30$ mg/dL                                                    | Olanzapine | 137 | 17.5% | 121             | 22.3%           |
|                         |                                                                                | Placebo    | 63  | 11.1% | NA <sup>a</sup> | NA <sup>a</sup> |
|                         | Normal to High<br>( $<110$ mg/dL to $\geq 130$ mg/dL)                          | Olanzapine | 98  | 5.1%  | 92              | 10.9%           |
|                         |                                                                                | Placebo    | 44  | 4.5%  | NA <sup>a</sup> | NA <sup>a</sup> |
|                         | Borderline to High<br>( $\geq 110$ mg/dL and $<130$ mg/dL to $\geq 130$ mg/dL) | Olanzapine | 29  | 48.3% | 21              | 47.6%           |
|                         |                                                                                | Placebo    | 9   | 0%    | NA <sup>a</sup> | NA <sup>a</sup> |

<sup>a</sup> Not Applicable.

## 5.6 Weight Gain

Potential consequences of weight gain should be considered prior to starting olanzapine. Patients receiving olanzapine should receive regular monitoring of weight [see *Patient Counseling Information* (17.6)].

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

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

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

**Table 6: Weight Gain with Olanzapine Use in Adults**

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

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

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

|                                                                        | Olanzapine-treated patients                 | Placebo-treated patients                   |
|------------------------------------------------------------------------|---------------------------------------------|--------------------------------------------|
| Mean change in body weight from baseline (median exposure = 3 weeks)   | 4.6 kg (10.1 lb)                            | 0.3 kg (0.7 lb)                            |
| Percentage of patients who gained at least 7% of baseline body weight  | 40.6%<br>(median exposure to 7% = 4 weeks)  | 9.8%<br>(median exposure to 7% = 8 weeks)  |
| Percentage of patients who gained at least 15% of baseline body weight | 7.1%<br>(median exposure to 15% = 19 weeks) | 2.7%<br>(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<br>kg (lb) | 6 Weeks<br>(N=243)<br>(%) | 6 Months<br>(N=191)<br>(%) |
|--------------------------|---------------------------|----------------------------|
| ≤0                       | 2.9                       | 2.1                        |
| 0 to ≤5 (0-11 lb)        | 47.3                      | 24.6                       |
| >5 to ≤10 (11-22 lb)     | 42.4                      | 26.7                       |
| >10 to ≤15 (22-33 lb)    | 5.8                       | 22.0                       |
| >15 to ≤20 (33-44 lb)    | 0.8                       | 12.6                       |
| >20 to ≤25 (44-55 lb)    | 0.8                       | 9.4                        |
| >25 to ≤30 (55-66 lb)    | 0                         | 2.1                        |
| >30 to ≤35 (66-77 lb)    | 0                         | 0                          |
| >35 to ≤40 (77-88 lb)    | 0                         | 0                          |
| >40 (>88 lb)             | 0                         | 0.5                        |

### 5.7 Tardive Dyskinesia

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

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

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

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

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

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

### 5.8 Orthostatic Hypotension

Olanzapine may induce orthostatic hypotension associated with dizziness, tachycardia, bradycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its  $\alpha_1$ -adrenergic antagonistic properties [see *Patient Counseling Information* (17.7)].

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

Hypotension, bradycardia with or without hypotension, tachycardia, and syncope were also reported during the clinical trials with intramuscular olanzapine for injection. In an open-label clinical pharmacology study in nonagitated patients with schizophrenia in which the safety and tolerability of intramuscular olanzapine were evaluated under a maximal dosing regimen (three 10 mg doses administered 4 hours apart), approximately one-third of these patients experienced a significant orthostatic decrease in systolic blood pressure (i.e., decrease  $\geq 30$  mmHg) [see *Dosage and Administration* (2.4)]. Syncope was reported in 0.6% (15/2500) of olanzapine-treated patients in phase 2-3 oral olanzapine studies and in 0.3% (2/722) of olanzapine-treated patients with agitation in the intramuscular olanzapine for injection studies. Three normal volunteers in phase 1 studies with intramuscular olanzapine experienced hypotension, bradycardia, and sinus pauses of up to 6 seconds that spontaneously resolved (in 2 cases the reactions occurred on intramuscular olanzapine, and in 1 case, on oral olanzapine). The risk for this sequence of hypotension, bradycardia, and sinus pause may be greater in nonpsychiatric patients compared to psychiatric patients who are possibly more adapted to certain effects of psychotropic drugs. For intramuscular olanzapine for injection therapy, patients should remain recumbent if drowsy or dizzy after injection until examination has indicated that they are not experiencing postural hypotension, bradycardia, and/or hypoventilation.

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

Caution is necessary in patients who receive treatment with other drugs having effects that can induce hypotension, bradycardia, respiratory or central nervous system depression [see *Drug Interactions (7)*]. Concomitant administration of intramuscular olanzapine and parenteral benzodiazepine has not been studied and is therefore not recommended. If use of intramuscular olanzapine in combination with parenteral benzodiazepines is considered, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended.

### 5.9 Leukopenia, Neutropenia, and Agranulocytosis

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

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

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

### 5.10 Dysphagia

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

### 5.11 Seizures

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

### 5.12 Potential for Cognitive and Motor Impairment

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

Since olanzapine has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that olanzapine therapy does not affect them adversely [see *Patient Counseling Information (17.8)*].

### 5.13 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing olanzapine for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration [see *Patient Counseling Information (17.9)*].

### 5.14 Use in Patients with Concomitant Illness

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

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

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

Olanzapine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with olanzapine, caution should be observed in cardiac patients [see *Warnings and Precautions (5.8)*].

### 5.15 Hyperprolactinemia

As with other drugs that antagonize dopamine D<sub>2</sub> receptors, olanzapine elevates prolactin levels, and a modest 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 clinical studies, elevated plasma prolactin concentrations were observed in 34% of adults treated with olanzapine compared to 13.1% of placebo-treated patients. In a pooled analysis from clinical studies including 8136 adults treated with olanzapine, potentially associated clinical manifestations such as galactorrhea (14/8136; 0.2%), gynecomastia (8/4896; 0.2% of males), and breast enlargement (2/3240; 0.06% of females) were reported.

In placebo-controlled olanzapine monotherapy studies in adolescent patients with schizophrenia or bipolar I disorder (manic or mixed episodes), elevated prolactin concentrations compared to baseline occurred in 47.4% of olanzapine-treated patients compared to 6.8% of placebo-treated patients. In long-term clinical trials of olanzapine in adolescents, gynecomastia occurred in 2.4% of males (7/286) and galactorrhea occurred in 1.8% of females (3/168) [see *Use in Specific Populations (8.4)*].

#### 5.16 Use in Combination with Fluoxetine, Lithium, or Valproate

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

#### 5.17 Laboratory Tests

Fasting blood glucose testing and lipid profile at the beginning of, and periodically during, treatment is recommended [see *Warnings and Precautions (5.4, 5.5) and Patient Counseling Information (17.4, 17.5)*].

## 6 ADVERSE REACTIONS

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

### 6.1 Clinical Trials Experience

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

#### Clinical Trials in Adults

The information below for olanzapine is derived from a clinical trial database for olanzapine consisting of 8661 adult patients with approximately 4165 patient-years of exposure to oral olanzapine and 722 patients with exposure to intramuscular olanzapine for injection. This database includes: (1) 2500 patients who participated in multiple-dose oral olanzapine premarketing trials in schizophrenia and Alzheimer's disease representing approximately 1122 patient-years of exposure as of February 14, 1995; (2) 182 patients who participated in oral olanzapine premarketing bipolar I disorder (manic or mixed episodes) trials representing approximately 66 patient-years of exposure; (3) 191 patients who participated in an oral olanzapine trial of patients having various psychiatric symptoms in association with Alzheimer's disease representing approximately 29 patient-years of exposure; (4) 5788 patients from 88 additional oral olanzapine clinical trials as of December 31, 2001; and (5) 722 patients who participated in intramuscular olanzapine for injection premarketing trials in agitated patients with schizophrenia, bipolar I disorder (manic or mixed episodes), or dementia. In addition, information from the premarketing 6-week clinical study database for olanzapine in combination with lithium or valproate, consisting of 224 patients who participated in bipolar I disorder (manic or mixed episodes) trials with approximately 22 patient-years of exposure, is included below.

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

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

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

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

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

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

The following findings are based on premarketing trials of (1) oral olanzapine for schizophrenia, bipolar I disorder (manic or mixed episodes), a subsequent trial of patients having various psychiatric symptoms in association with Alzheimer's disease, and premarketing combination trials, and (2) intramuscular olanzapine for injection in agitated patients with schizophrenia or bipolar I mania.

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

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

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

**Agitation** — Overall, there was no difference in the incidence of discontinuation due to adverse reactions (0.4% for intramuscular olanzapine for injection vs 0% for placebo).

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

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

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

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

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

| Adverse Reaction                  | Percentage of Patients Reporting Event |                    |
|-----------------------------------|----------------------------------------|--------------------|
|                                   | Olanzapine<br>(N=248)                  | Placebo<br>(N=118) |
| Postural hypotension              | 5                                      | 2                  |
| Constipation                      | 9                                      | 3                  |
| Weight gain                       | 6                                      | 1                  |
| Dizziness                         | 11                                     | 4                  |
| Personality disorder <sup>a</sup> | 8                                      | 4                  |
| Akathisia                         | 5                                      | 1                  |

<sup>a</sup> 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<br>(N=125)                  | Placebo<br>(N=129) |
| Asthenia           | 15                                     | 6                  |
| Dry mouth          | 22                                     | 7                  |
| Constipation       | 11                                     | 5                  |
| Dyspepsia          | 11                                     | 5                  |
| Increased appetite | 6                                      | 3                  |

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|            |    |    |
|------------|----|----|
| Somnolence | 35 | 13 |
| Dizziness  | 18 | 6  |
| Tremor     | 6  | 3  |

**Olanzapine Intramuscular** — There was 1 adverse reaction (somnolence) observed at an incidence of 5% or greater among intramuscular olanzapine for injection-treated patients and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) during the placebo-controlled premarketing studies. The incidence of somnolence during the 24 hour IM treatment period in clinical trials in agitated patients with schizophrenia or bipolar I mania was 6% for intramuscular olanzapine for injection and 3% for placebo.

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

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

**Table 11: Treatment-Emergent Adverse Reactions:  
Incidence in Short-Term, Placebo-Controlled Clinical Trials with Oral Olanzapine  
Percentage of Patients Reporting Event**

| Body System/Adverse Reaction               | Olanzapine<br>(N=532) | Placebo<br>(N=294) |
|--------------------------------------------|-----------------------|--------------------|
| <b>Body as a Whole</b>                     |                       |                    |
| Accidental injury                          | 12                    | 8                  |
| Asthenia                                   | 10                    | 9                  |
| Fever                                      | 6                     | 2                  |
| Back pain                                  | 5                     | 2                  |
| Chest pain                                 | 3                     | 1                  |
| <b>Cardiovascular System</b>               |                       |                    |
| Postural hypotension                       | 3                     | 1                  |
| Tachycardia                                | 3                     | 1                  |
| Hypertension                               | 2                     | 1                  |
| <b>Digestive System</b>                    |                       |                    |
| Dry mouth                                  | 9                     | 5                  |
| Constipation                               | 9                     | 4                  |
| Dyspepsia                                  | 7                     | 5                  |
| Vomiting                                   | 4                     | 3                  |
| Increased appetite                         | 3                     | 2                  |
| <b>Hemic and Lymphatic System</b>          |                       |                    |
| Ecchymosis                                 | 5                     | 3                  |
| <b>Metabolic and Nutritional Disorders</b> |                       |                    |
| Weight gain                                | 5                     | 3                  |
| Peripheral edema                           | 3                     | 1                  |
| <b>Musculoskeletal System</b>              |                       |                    |
| Extremity pain (other than joint)          | 5                     | 3                  |
| Joint pain                                 | 5                     | 3                  |
| <b>Nervous System</b>                      |                       |                    |
| 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                  |
| <b>Respiratory System</b>                  |                       |                    |
| Rhinitis                                   | 7                     | 6                  |
| Cough increased                            | 6                     | 3                  |
| Pharyngitis                                | 4                     | 3                  |
| <b>Special Senses</b>                      |                       |                    |
| Amblyopia                                  | 3                     | 2                  |
| <b>Urogenital System</b>                   |                       |                    |

|                         |   |   |
|-------------------------|---|---|
| Urinary incontinence    | 2 | 1 |
| Urinary tract infection | 2 | 1 |

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

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

**Table 12: Common Treatment-Emergent Adverse Reactions Associated with the Use of Oral Olanzapine in 6-Week Adjunct to Lithium or Valproate Trials — Bipolar I Disorder (Manic or Mixed Episodes)**  
Percentage of Patients Reporting Event

| Adverse Reaction     | Olanzapine with<br>lithium or valproate<br>(N=229) | Placebo with<br>lithium or valproate<br>(N=115) |
|----------------------|----------------------------------------------------|-------------------------------------------------|
| Dry mouth            | 32                                                 | 9                                               |
| Weight gain          | 26                                                 | 7                                               |
| Increased appetite   | 24                                                 | 8                                               |
| Dizziness            | 14                                                 | 7                                               |
| Back pain            | 8                                                  | 4                                               |
| Constipation         | 8                                                  | 4                                               |
| Speech disorder      | 7                                                  | 1                                               |
| Increased salivation | 6                                                  | 2                                               |
| Amnesia              | 5                                                  | 2                                               |
| Paresthesia          | 5                                                  | 2                                               |

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

Table 13 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred in 2% or more of patients treated with the combination of olanzapine (doses  $\geq 5$  mg/day) and lithium or valproate and with incidence greater than lithium or valproate alone who participated in the acute phase of placebo-controlled combination trials.

**Table 13: Treatment-Emergent Adverse Reactions: Incidence in Short-Term, Placebo-Controlled Clinical Trials of Oral Olanzapine as Adjunct to Lithium or Valproate**  
Percentage of Patients Reporting Event

| Body System/Adverse Reaction               | Olanzapine with<br>lithium or valproate<br>(N=229) | Placebo with<br>lithium or valproate<br>(N=115) |
|--------------------------------------------|----------------------------------------------------|-------------------------------------------------|
| <b>Body as a Whole</b>                     |                                                    |                                                 |
| Asthenia                                   | 18                                                 | 13                                              |
| Back pain                                  | 8                                                  | 4                                               |
| Accidental injury                          | 4                                                  | 2                                               |
| Chest pain                                 | 3                                                  | 2                                               |
| <b>Cardiovascular System</b>               |                                                    |                                                 |
| Hypertension                               | 2                                                  | 1                                               |
| <b>Digestive System</b>                    |                                                    |                                                 |
| Dry mouth                                  | 32                                                 | 9                                               |
| Increased appetite                         | 24                                                 | 8                                               |
| Thirst                                     | 10                                                 | 6                                               |
| Constipation                               | 8                                                  | 4                                               |
| Increased salivation                       | 6                                                  | 2                                               |
| <b>Metabolic and Nutritional Disorders</b> |                                                    |                                                 |
| Weight gain                                | 26                                                 | 7                                               |
| Peripheral edema                           | 6                                                  | 4                                               |
| Edema                                      | 2                                                  | 1                                               |
| <b>Nervous System</b>                      |                                                    |                                                 |
| Somnolence                                 | 52                                                 | 27                                              |
| Tremor                                     | 23                                                 | 13                                              |
| Depression                                 | 18                                                 | 17                                              |
| Dizziness                                  | 14                                                 | 7                                               |
| Speech disorder                            | 7                                                  | 1                                               |
| Amnesia                                    | 5                                                  | 2                                               |
| Paresthesia                                | 5                                                  | 2                                               |

|                            |   |   |
|----------------------------|---|---|
| 18                         |   |   |
| Apathy                     | 4 | 3 |
| Confusion                  | 4 | 1 |
| Euphoria                   | 3 | 2 |
| Incoordination             | 2 | 0 |
| <b>Respiratory System</b>  |   |   |
| Pharyngitis                | 4 | 1 |
| Dyspnea                    | 3 | 1 |
| <b>Skin and Appendages</b> |   |   |
| Sweating                   | 3 | 1 |
| Acne                       | 2 | 0 |
| Dry skin                   | 2 | 0 |
| <b>Special Senses</b>      |   |   |
| Amblyopia                  | 9 | 5 |
| Abnormal vision            | 2 | 0 |
| <b>Urogenital System</b>   |   |   |
| Dysmenorrhea <sup>a</sup>  | 2 | 0 |
| Vaginitis <sup>a</sup>     | 2 | 0 |

<sup>a</sup> Denominator used was for females only (olanzapine, N=128; placebo, N=51).

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

*Adverse Reactions Occurring at an Incidence of 1% or More among Intramuscular Olanzapine for Injection-Treated Patients in Short-Term, Placebo-Controlled Trials*

Table 14 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred in 1% or more of patients treated with intramuscular olanzapine for injection (dose range of 2.5-10 mg/injection) and with incidence greater than placebo who participated in the short-term, placebo-controlled trials in agitated patients with schizophrenia or bipolar I mania.

**Table 14: Treatment-Emergent Adverse Reactions: Incidence in Short-Term (24 Hour), Placebo-Controlled Clinical Trials with Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia or Bipolar I Mania**  
Percentage of Patients Reporting Event

| Body System/Adverse Reaction | Olanzapine<br>(N=415) | Placebo<br>(N=150) |
|------------------------------|-----------------------|--------------------|
| <b>Body as a Whole</b>       |                       |                    |
| Asthenia                     | 2                     | 1                  |
| <b>Cardiovascular System</b> |                       |                    |
| Hypotension                  | 2                     | 0                  |
| Postural hypotension         | 1                     | 0                  |
| <b>Nervous System</b>        |                       |                    |
| Somnolence                   | 6                     | 3                  |
| Dizziness                    | 4                     | 2                  |
| Tremor                       | 1                     | 0                  |

**Additional Findings Observed in Clinical Trials**

Dose Dependency of Adverse Reactions in Short-Term, Placebo-Controlled Trials

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

**Table 15: Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidence in a Fixed Dosage Range, Placebo-Controlled Clinical Trial of Oral Olanzapine in Schizophrenia — Acute Phase**

|                           | Percentage of Patients Reporting Event |                              |                               |                               |
|---------------------------|----------------------------------------|------------------------------|-------------------------------|-------------------------------|
|                           | Placebo                                | Olanzapine<br>5 ± 2.5 mg/day | Olanzapine<br>10 ± 2.5 mg/day | Olanzapine<br>15 ± 2.5 mg/day |
| Parkinsonism <sup>a</sup> | 15                                     | 14                           | 12                            | 14                            |
| Akathisia <sup>b</sup>    | 23                                     | 16                           | 19                            | 27                            |

<sup>a</sup> Percentage of patients with a Simpson-Angus Scale total score >3.

<sup>b</sup> Percentage of patients with a Barnes Akathisia Scale global score ≥2.

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

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

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

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

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

<sup>c</sup> Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.

<sup>d</sup> Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.

<sup>e</sup> Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

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

**Table 17: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions Incidence in Placebo-Controlled Clinical Trials of Oral Olanzapine in Schizophrenia and Bipolar I Disorder — Adolescents**

| Categories <sup>a</sup>  | Percentage of Patients Reporting Event |                       |
|--------------------------|----------------------------------------|-----------------------|
|                          | Placebo<br>(N=89)                      | Olanzapine<br>(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                    |

<sup>a</sup> Categories are based on Standard MedDRA Queries (SMQ) for extrapyramidal symptoms as defined in MedDRA version 12.0.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during controlled clinical trials comparing fixed doses of intramuscular olanzapine for injection with placebo in agitation. Patients in each dose group could receive up to 3 injections during the trials [see *Clinical Studies (14.3)*]. Patient assessments were conducted during the 24 hours following the initial dose of intramuscular olanzapine for injection.

**Table 18: Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidence in a Fixed Dose, Placebo-Controlled Clinical Trial of Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia**

|                           | Percentage of Patients Reporting Event |                            |                          |                            |                           |
|---------------------------|----------------------------------------|----------------------------|--------------------------|----------------------------|---------------------------|
|                           | Placebo                                | Olanzapine<br>IM<br>2.5 mg | Olanzapine<br>IM<br>5 mg | Olanzapine<br>IM<br>7.5 mg | Olanzapine<br>IM<br>10 mg |
| Parkinsonism <sup>a</sup> | 0                                      | 0                          | 0                        | 0                          | 3                         |
| Akathisia <sup>b</sup>    | 0                                      | 0                          | 5                        | 0                          | 0                         |

<sup>a</sup> Percentage of patients with a Simpson-Angus Scale total score >3.

<sup>b</sup> Percentage of patients with a Barnes Akathisia Scale global score ≥2.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse reactions in the same controlled clinical trial comparing fixed doses of intramuscular olanzapine for injection with placebo in agitated patients with schizophrenia.

**Table 19: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions Incidence in a Fixed Dose, Placebo-Controlled Clinical Trial of Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia**

|                                  | Percentage of Patients Reporting Event |                                      |                                    |                                      |                                     |
|----------------------------------|----------------------------------------|--------------------------------------|------------------------------------|--------------------------------------|-------------------------------------|
|                                  | Placebo<br>(N=45)                      | Olanzapine<br>IM<br>2.5 mg<br>(N=48) | Olanzapine<br>IM<br>5 mg<br>(N=45) | Olanzapine<br>IM<br>7.5 mg<br>(N=46) | Olanzapine<br>IM<br>10 mg<br>(N=46) |
| Dystonic events <sup>a</sup>     | 0                                      | 0                                    | 0                                  | 0                                    | 0                                   |
| Parkinsonism events <sup>b</sup> | 0                                      | 4                                    | 2                                  | 0                                    | 0                                   |
| Akathisia events <sup>c</sup>    | 0                                      | 2                                    | 0                                  | 0                                    | 0                                   |
| Dyskinetic events <sup>d</sup>   | 0                                      | 0                                    | 0                                  | 0                                    | 0                                   |
| Residual events <sup>e</sup>     | 0                                      | 0                                    | 0                                  | 0                                    | 0                                   |
| Any extrapyramidal events        | 0                                      | 4                                    | 2                                  | 0                                    | 0                                   |

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

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

<sup>c</sup> Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.

<sup>d</sup> Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.

<sup>e</sup> Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

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

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

**Table 20: Percentage of Patients from a Schizophrenia Trial with Treatment-Emergent Adverse Reactions for the 3 Dose Range Groups and Placebo**

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

#### Differences among Fixed-Dose Groups Observed in Other Olanzapine Clinical Trials

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

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

Following is a list of treatment-emergent adverse reactions reported by patients treated with oral olanzapine (at multiple doses  $\geq 1$  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<sup>1</sup>; *Rare*: chills and fever, hangover effect, sudden death<sup>1</sup>.

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

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

**Hemic and Lymphatic System** — *Infrequent*: leukopenia, thrombocytopenia.

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

**Musculoskeletal System** — *Rare*: osteoporosis.

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

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

**Skin and Appendages** — *Infrequent*: alopecia.

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

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

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

<sup>2</sup> Adjusted for gender.

### Other Adverse Reactions Observed During the Clinical Trial Evaluation of Intramuscular Olanzapine for Injection

Following is a list of treatment-emergent adverse reactions reported by patients treated with intramuscular olanzapine for injection (at 1 or more doses  $\geq 2.5$  mg/injection) in clinical trials. This listing is not intended to include reactions (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) for which occurred at a rate equal to or less than placebo. Reactions are classified by body system using the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients.

**Body as a Whole** — *Frequent*: injection site pain.

**Cardiovascular System** — *Infrequent*: syncope.

**Digestive System** — *Infrequent*: nausea.

**Metabolic and Nutritional Disorders** — *Infrequent*: creatine phosphokinase increased.

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

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

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

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

| Adverse Reactions           | Percentage of Patients Reporting Event   |                   |                                    |                   |
|-----------------------------|------------------------------------------|-------------------|------------------------------------|-------------------|
|                             | 6 Week Trial<br>% Schizophrenia Patients |                   | 3 Week Trial<br>% Bipolar Patients |                   |
|                             | Olanzapine<br>(N=72)                     | Placebo<br>(N=35) | Olanzapine<br>(N=107)              | Placebo<br>(N=54) |
| Sedation <sup>a</sup>       | 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 <sup>b</sup> | 6                                        | 3                 | 6                                  | 7                 |
| Pain in extremity           | 6                                        | 3                 | 5                                  | 0                 |
| Fatigue                     | 3                                        | 3                 | 14                                 | 6                 |
| Dry mouth                   | 4                                        | 0                 | 7                                  | 0                 |

<sup>a</sup> Patients with the following MedDRA terms were counted in this category: hypersomnia, lethargy, sedation, somnolence.

<sup>b</sup> 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  $\geq 2.5$  mg) reported with an incidence of 2% or more and greater than placebo are listed in Table 22.

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

| Adverse Reaction                         | Percentage of Patients Reporting Event |                   |
|------------------------------------------|----------------------------------------|-------------------|
|                                          | Olanzapine<br>(N=179)                  | Placebo<br>(N=89) |
| Sedation <sup>a</sup>                    | 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 <sup>b</sup>     | 8                                      | 1                 |
| Dyspepsia                                | 3                                      | 1                 |
| Epistaxis                                | 3                                      | 0                 |
| Respiratory tract infection <sup>c</sup> | 3                                      | 2                 |
| Sinusitis                                | 3                                      | 0                 |
| Arthralgia                               | 2                                      | 0                 |
| Musculoskeletal stiffness                | 2                                      | 0                 |

<sup>a</sup> Patients with the following MedDRA terms were counted in this category: hypersomnia, lethargy, sedation, somnolence.

<sup>b</sup> The terms alanine aminotransferase (ALT), aspartate aminotransferase (AST), and hepatic enzyme were combined under liver enzymes.

<sup>c</sup> Patients with the following MedDRA terms were counted in this category: lower respiratory tract infection, respiratory tract infection, respiratory tract infection viral, upper respiratory tract infection, viral upper respiratory tract infection.

## 6.2 Vital Signs and Laboratory Studies

**Vital Sign Changes** — Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials.

Intramuscular olanzapine for injection was associated with bradycardia, hypotension, and tachycardia in clinical trials [see *Warnings and Precautions (5)*].

**Laboratory Changes** — An assessment of the premarketing experience for olanzapine revealed an association with asymptomatic increases in ALT, AST, and GGT. In placebo-controlled olanzapine monotherapy studies in adults, clinically significant ALT elevations ( $\geq 3$  times the upper limit of the normal range) were observed in 2% (6/243) of patients exposed to olanzapine compared to none (0/115) of the placebo patients. None of these patients experienced jaundice. In 2 of these patients, liver enzymes decreased toward normal despite continued treatment and, in 2 others, enzymes decreased upon discontinuation of olanzapine. In the remaining 2 patients, 1, seropositive for hepatitis C, had persistent enzyme elevations for 4 months after discontinuation, and the other had insufficient follow-up to determine if enzymes normalized.

Within the larger premarketing database of about 2400 adult patients with baseline ALT  $\leq 90$  IU/L, the incidence of ALT elevation to  $>200$  IU/L was 2% (50/2381). Again, none of these patients experienced jaundice or other symptoms attributable to liver impairment and most had transient changes that tended to normalize while olanzapine treatment was continued.

Among 2500 adult patients in oral olanzapine clinical trials, about 1% (23/2500) discontinued treatment due to transaminase increases.

In placebo-controlled olanzapine monotherapy studies in adolescents, clinically significant ALT elevations (change from  $<3$  times the upper limit of normal at baseline to  $\geq 3$  times the upper limit of the normal range) were observed in 12% (21/174) of patients exposed to olanzapine compared to 2% (2/87) of the placebo-treated patients. Discontinuation due to transaminase increases occurred in 3.4% (6/179) of patients exposed to olanzapine.

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

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

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

Given the concern about neutropenia associated with other psychotropic compounds and the finding of leukopenia associated with the administration of olanzapine in several animal models [see *Nonclinical Toxicology (13.2)*], careful attention was given to examination of hematologic parameters in premarketing studies with olanzapine. There was no indication of a risk of clinically significant neutropenia associated with olanzapine treatment in the premarketing database for this drug.

**Olanzapine Monotherapy in Adolescents:** In placebo-controlled clinical trials of adolescent patients with schizophrenia or bipolar I disorder (manic or mixed episodes), greater frequencies for the following treatment-emergent findings, at anytime, were observed in laboratory analytes compared to placebo: elevated ALT ( $\geq 3$  X ULN in patients with ALT at baseline  $< 3$  X ULN), (12.1% vs 2.3%); elevated AST (27.6% vs 3.8%); low total bilirubin (22.1% vs 6.7%); elevated GGT (10.1% vs 1.2%); and elevated prolactin (47.4% vs 6.8%).

**ECG Changes** — In pooled studies of adults as well as pooled studies of adolescents, there were no significant differences between olanzapine and placebo in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc (Fridericia corrected), and PR intervals. Olanzapine use was associated with a mean increase in heart rate compared to placebo (adults: +2.4 beats per minute vs no change with placebo; adolescents: +6.3 beats per minute vs -5.1 beats per minute with placebo). This increase in heart rate may be related to olanzapine's potential for inducing orthostatic changes [see *Warnings and Precautions (5.8)*].

### 6.3 Postmarketing Experience

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

Adverse reactions reported since market introduction that were temporally (but not necessarily causally) related to ZYPREXA therapy include the following: allergic reaction (e.g., anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, diabetic ketoacidosis, discontinuation reaction (diaphoresis, nausea or vomiting), jaundice, neutropenia, pancreatitis, priapism, rash, rhabdomyolysis, and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of  $\geq 240$  mg/dL and random triglyceride levels of  $\geq 1000$  mg/dL have been reported.

## 7 DRUG INTERACTIONS

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

### 7.1 Potential for Other Drugs to Affect Olanzapine

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

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

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

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

#### **Inhibitors of CYP1A2**

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

#### **Inhibitors of CYP2D6**

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

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

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

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

### 7.2 Potential for Olanzapine to Affect Other Drugs

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

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

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

**Lorazepam (IM)** — Administration of intramuscular lorazepam (2 mg) 1 hour after intramuscular olanzapine for injection (5 mg) did not significantly affect the pharmacokinetics of olanzapine, unconjugated lorazepam, or total lorazepam. However, this co-administration of intramuscular lorazepam and intramuscular olanzapine for injection added to the somnolence observed with either drug alone [see *Warnings and Precautions (5.8)*].

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

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

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

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

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

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

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

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

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

## 8 USE IN SPECIFIC POPULATIONS

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

### 8.1 Pregnancy

**Teratogenic Effects, Pregnancy Category C** — In oral reproduction studies in rats at doses up to 18 mg/kg/day and in rabbits at doses up to 30 mg/kg/day (9 and 30 times the maximum recommended human daily oral dose on a mg/m<sup>2</sup> 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/m<sup>2</sup> basis). Gestation was prolonged at 10 mg/kg/day (5 times the maximum recommended human daily oral dose on a mg/m<sup>2</sup> 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/m<sup>2</sup> basis). Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Placental transfer of olanzapine occurs in rat pups.

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

### 8.2 Labor and Delivery

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

### 8.3 Nursing Mothers

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

### 8.4 Pediatric Use

The safety and effectiveness of oral ZYPREXA in the treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder were established in short-term studies in adolescents (ages 13 to 17 years). Use of ZYPREXA in adolescents is supported by evidence from adequate and well-controlled studies of ZYPREXA in which 268 adolescents received ZYPREXA in a range of 2.5 to 20 mg/day [see *Clinical Studies (14.1, 14.2)*]. Recommended starting dose for adolescents is lower than that for adults [see *Dosage and Administration (2.1, 2.2)*]. Compared to patients from adult clinical trials, adolescents were likely to gain more weight, experience increased sedation, and have greater increases in total cholesterol, triglycerides, LDL cholesterol, prolactin and hepatic transaminase levels [see *Warnings and Precautions (5.5, 5.6, 5.15, 5.17)* and *Adverse Reactions (6.2)*]. When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential (in adolescents as compared with adults) for weight gain and hyperlipidemia. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents [see *Indications and Usage (1.1, 1.2)*].

Safety and effectiveness of olanzapine in children <13 years of age have not been established [see *Patient Counseling Information* (17.13)].

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

### 8.5 Geriatric Use

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

Clinical studies of ZYPREXA and fluoxetine in combination did not include sufficient numbers of patients  $\geq 65$  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/m<sup>2</sup> basis.

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

## 10 OVERDOSAGE

### 10.1 Human Experience

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

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

### 10.2 Management of Overdose

The possibility of multiple drug involvement should be considered. In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation, which may include intubation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The administration of activated charcoal (1 g) reduced the C<sub>max</sub> and AUC of oral olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about 6 hours after dosing, charcoal may be a useful treatment for olanzapine overdose.

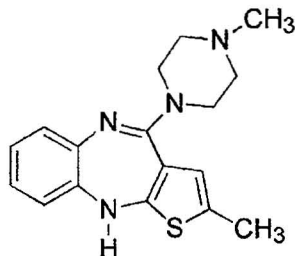
The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

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

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

## 11 DESCRIPTION

ZYPREXA (olanzapine) is an atypical antipsychotic that belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10H-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.

ZYPREXA tablets are intended for oral administration only.

Each tablet contains olanzapine equivalent to 2.5 mg (8  $\mu$ mol), 5 mg (16  $\mu$ mol), 7.5 mg (24  $\mu$ mol), 10 mg (32  $\mu$ mol), 15 mg (48  $\mu$ mol), or 20 mg (64  $\mu$ mol). Inactive ingredients are carnauba wax, crospovidone, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients. The color coating contains Titanium Dioxide (all strengths), FD&C Blue No. 2 Aluminum Lake (15 mg), or Synthetic Red Iron Oxide (20 mg). The 2.5, 5, 7.5, and 10 mg tablets are imprinted with edible ink which contains FD&C Blue No. 2 Aluminum Lake.

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is intended for oral administration only.

Each orally disintegrating tablet contains olanzapine equivalent to 5 mg (16  $\mu$ mol), 10 mg (32  $\mu$ mol), 15 mg (48  $\mu$ mol) or 20 mg (64  $\mu$ mol). It begins disintegrating in the mouth within seconds, allowing its contents to be subsequently swallowed with or without liquid. ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) also contains the following inactive ingredients: gelatin, mannitol, aspartame, sodium methyl paraben, and sodium propyl paraben.

ZYPREXA IntraMuscular (olanzapine for injection) is intended for intramuscular use only.

Each vial provides for the administration of 10 mg (32  $\mu$ mol) olanzapine with inactive ingredients 50 mg lactose monohydrate and 3.5 mg tartaric acid. Hydrochloric acid and/or sodium hydroxide may have been added during manufacturing to adjust pH.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The mechanism of action of olanzapine, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine and serotonin type 2 (5HT<sub>2</sub>) 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<sub>2A/2C</sub>, 5HT<sub>6</sub> ( $K_i$ =4, 11, and 5 nM, respectively), dopamine D<sub>1-4</sub> ( $K_i$ =11-31 nM), histamine H<sub>1</sub> ( $K_i$ =7 nM), and adrenergic  $\alpha_1$  receptors ( $K_i$ =19 nM). Olanzapine is an antagonist with moderate affinity binding for serotonin 5HT<sub>3</sub> ( $K_i$ =57 nM) and muscarinic M<sub>1-5</sub> ( $K_i$ =73, 96, 132, 32, and 48 nM, respectively). Olanzapine binds weakly to GABA<sub>A</sub>, BZD, and  $\beta$ -adrenergic receptors ( $K_i$ >10  $\mu$ M).

Antagonism at receptors other than dopamine and 5HT<sub>2</sub> may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic M<sub>1-5</sub> receptors may explain its anticholinergic-like effects. Olanzapine's antagonism of histamine H<sub>1</sub> receptors may explain the somnolence observed with this drug. Olanzapine's antagonism of adrenergic  $\alpha_1$  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 ZYPREXA tablets and ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) dosage forms of olanzapine are bioequivalent.

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

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

Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100 ng/mL, binding primarily to albumin and  $\alpha_1$ -acid glycoprotein.

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

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

**Intramuscular Administration** — ZYPREXA IntraMuscular results in rapid absorption with peak plasma concentrations occurring within 15 to 45 minutes. Based upon a pharmacokinetic study in healthy volunteers, a 5 mg dose of intramuscular olanzapine for injection produces, on average, a maximum plasma concentration approximately 5 times higher than the maximum plasma concentration produced by a 5 mg dose of oral olanzapine. Area under the curve achieved after an intramuscular dose is similar to that achieved after oral administration of the same dose. The half-life observed after intramuscular administration is similar to that observed after oral dosing. The pharmacokinetics are linear over the clinical dosing range. Metabolic profiles after intramuscular administration are qualitatively similar to metabolic profiles after oral administration.

#### *Specific Populations*

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

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

**Geriatric** — In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1.5 times greater in elderly ( $\geq 65$  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  $\text{mg}/\text{m}^2$  basis) and 0.25, 2, 8 mg/kg/day (equivalent to 0.06-2 times the maximum recommended human daily oral dose on a  $\text{mg}/\text{m}^2$  basis). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, 4 mg/kg/day (males) and 0.25, 1, 4, 8 mg/kg/day (females) (equivalent to 0.13-2 and 0.13-4 times the maximum recommended human daily oral dose on a  $\text{mg}/\text{m}^2$  basis, respectively). The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in 1 mouse study in female mice dosed at 8 mg/kg/day (2 times the maximum recommended human daily oral dose on a  $\text{mg}/\text{m}^2$  basis). These tumors were not increased in another mouse study in females dosed at 10 or 30/20 mg/kg/day (2-5 times the maximum recommended human daily oral dose on a  $\text{mg}/\text{m}^2$  basis); in this study, there was a high incidence of early mortalities in males of the 30/20 mg/kg/day group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice dosed at  $\geq 2$  mg/kg/day and in female rats dosed at  $\geq 4$  mg/kg/day (0.5 and 2 times the maximum recommended human daily oral dose on a  $\text{mg}/\text{m}^2$  basis, respectively). Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the olanzapine carcinogenicity studies; however, measurements during subchronic toxicity studies showed that olanzapine elevated serum prolactin levels up to 4-fold in rats at the same doses used in the carcinogenicity study. An increase in mammary gland neoplasms has

been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance for human risk of the finding of prolactin mediated endocrine tumors in rodents is unknown [see *Warnings and Precautions* (5.15)].

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

**Impairment of Fertility** — In an oral fertility and reproductive performance study in rats, male mating performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female fertility was decreased at a dose of 3 mg/kg/day (1 and 1.5 times the maximum recommended human daily oral dose on a mg/m<sup>2</sup> 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/m<sup>2</sup> basis). Diestrus was prolonged and estrus delayed at 1.1 mg/kg/day (0.6 times the maximum recommended human daily oral dose on a mg/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> basis) for 3 months or 16 mg/kg (8 times the maximum recommended human daily oral dose on a mg/m<sup>2</sup> basis) for 6 or 12 months. No evidence of bone marrow cytotoxicity was found in any of the species examined. Bone marrows were normocellular or hypercellular, indicating that the reductions in circulating blood cells were probably due to peripheral (non-marrow) factors.

## 14 CLINICAL STUDIES

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

### 14.1 Schizophrenia

#### Adults

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

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

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

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

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

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

### Adolescents

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

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

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

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

### 14.2 Bipolar I Disorder (Manic or Mixed Episodes)

#### Adults

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

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

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

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

(3) In another trial, 361 patients meeting DSM-IV criteria for a manic or mixed episode of bipolar I disorder who had responded during an initial open-label treatment phase for about 2 weeks, on average, to olanzapine 5 to 20 mg/day were randomized to either continuation of olanzapine at their same dose (n=225) or to placebo (n=136), for observation of relapse. Approximately 50% of the patients had discontinued from the olanzapine group by day 59 and 50% of the placebo group had discontinued by day 23 of double-blind treatment. Response during the open-label phase was defined by having a decrease of the Y-MRS total score to  $\leq 12$  and HAM-D 21 to  $\leq 8$ . Relapse during the double-blind phase was defined as an increase of the Y-MRS or HAM-D 21 total score to  $\geq 15$ , 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  $\geq 16$ ) were randomized to receive either olanzapine or placebo, in combination with their original therapy. Olanzapine (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50  $\mu$ g/mL to 125  $\mu$ g/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

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

#### Adolescents

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

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

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

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

### 14.3 Agitation Associated with Schizophrenia and Bipolar I Mania

The efficacy of intramuscular olanzapine for injection for the treatment of agitation was established in 3 short-term (24 hours of IM treatment) placebo-controlled trials in agitated adult inpatients from 2 diagnostic groups: schizophrenia and bipolar I disorder (manic or mixed episodes). Each of the trials included a single active comparator treatment arm of either haloperidol injection (schizophrenia studies) or lorazepam injection (bipolar I mania study). Patients enrolled in the trials needed to be: (1) judged by the clinical investigators as clinically agitated and clinically appropriate candidates for treatment with intramuscular medication, and (2) exhibiting a level of agitation that met or exceeded a threshold score of  $\geq 14$  on the 5 items comprising the Positive and Negative Syndrome Scale (PANSS) Excited Component (i.e., poor impulse control, tension, hostility, uncooperativeness and excitement items) with at least 1 individual item score  $\geq 4$  using a 1-7 scoring system (1=absent, 4=moderate, 7=extreme). In the studies, the mean baseline PANSS Excited Component score was 18.4, with scores ranging from 13 to 32 (out of a maximum score of 35), thus suggesting predominantly moderate levels of agitation with some patients experiencing mild or severe levels of agitation. The primary efficacy measure used for assessing agitation signs and symptoms in these trials was the change from baseline in the PANSS Excited Component at 2 hours post-injection. Patients could receive up to 3 injections during the 24 hour IM treatment periods; however, patients could not receive the second injection until after the initial 2 hour period when the primary efficacy measure was assessed. The results of the trials follow:

(1) In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for schizophrenia (n=270), 4 fixed intramuscular olanzapine for injection doses of 2.5 mg, 5 mg, 7.5 mg and 10 mg were evaluated. All doses were statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection. However, the effect was larger and more consistent for the 3 highest doses. There were no significant pairwise differences for the 7.5 and 10 mg doses over the 5 mg dose.

(2) In a second placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for schizophrenia (n=311), 1 fixed intramuscular olanzapine for injection dose of 10 mg was evaluated. Olanzapine for injection was statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection.

(3) In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for bipolar I disorder (and currently displaying an acute manic or mixed episode with or without psychotic features) (n=201), 1 fixed intramuscular olanzapine for injection dose of 10 mg was evaluated. Olanzapine for injection was statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection.

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

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

The ZYPREXA 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are white, round, and imprinted in blue ink with LILLY and tablet number. The 15 mg tablets are elliptical, blue, and debossed with LILLY and tablet number. The 20 mg tablets are elliptical, pink, and debossed with LILLY and tablet number. The tablets are available as follows:

|                                | TABLET STRENGTH      |                      |                      |                      |                      |                      |
|--------------------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
|                                | 2.5 mg               | 5 mg                 | 7.5 mg               | 10 mg                | 15 mg                | 20 mg                |
| Tablet No.                     | 4112                 | 4115                 | 4116                 | 4117                 | 4415                 | 4420                 |
| Identification                 | LILLY<br>4112        | LILLY<br>4115        | LILLY<br>4116        | LILLY<br>4117        | LILLY<br>4415        | LILLY<br>4420        |
| NDC Codes:                     |                      |                      |                      |                      |                      |                      |
| Bottles 30                     | NDC 0002-<br>4112-30 | NDC 0002-<br>4115-30 | NDC 0002-<br>4116-30 | NDC 0002-<br>4117-30 | NDC 0002-<br>4415-30 | NDC 0002-<br>4420-30 |
| Blisters – ID <sup>a</sup> 100 | NDC 0002-<br>4112-33 | NDC 0002-<br>4115-33 | NDC 0002-<br>4116-33 | NDC 0002-<br>4117-33 | NDC 0002-<br>4415-33 | NDC 0002-<br>4420-33 |
| Bottles 1000                   | NDC 0002-<br>4112-04 | NDC 0002-<br>4115-04 | NDC 0002-<br>4116-04 | NDC 0002-<br>4117-04 | NDC 0002-<br>4415-04 | NDC 0002-<br>4420-04 |

<sup>a</sup> Identi-Dose<sup>®</sup> (unit dose medication, Lilly).

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) are yellow, round, and debossed with the tablet strength. The tablets are available as follows:

| ZYPREXA ZYDIS Tablets <sup>a</sup> | TABLET STRENGTH  |                  |                  |                  |
|------------------------------------|------------------|------------------|------------------|------------------|
|                                    | 5 mg             | 10 mg            | 15 mg            | 20 mg            |
| Tablet No.                         | 4453             | 4454             | 4455             | 4456             |
| Debossed                           | 5                | 10               | 15               | 20               |
| NDC Codes:                         |                  |                  |                  |                  |
| Dose Pack 30 (Child Resistant)     | NDC 0002-4453-85 | NDC 0002-4454-85 | NDC 0002-4455-85 | NDC 0002-4456-85 |

ZYPREXA is a registered trademark of Eli Lilly and Company.

ZYDIS is a registered trademark of Catalent Pharma Solutions.

<sup>a</sup> ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is manufactured for Eli Lilly and Company by Catalent Pharma Solutions, United Kingdom, SN5 8RU.

ZYPREXA IntraMuscular is available in:

NDC 0002-7597-01 (No. VL7597) – 10 mg vial (1s)

## 16.2 Storage and Handling

Store ZYPREXA tablets, ZYPREXA ZYDIS, and ZYPREXA IntraMuscular vials (before reconstitution) at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP]. Reconstituted ZYPREXA IntraMuscular may be stored at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP] for up to 1 hour if necessary. *Discard any unused portion of reconstituted ZYPREXA IntraMuscular.* The USP defines controlled room temperature as a temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses.

Protect ZYPREXA tablets and ZYPREXA ZYDIS from light and moisture. Protect ZYPREXA IntraMuscular from light, do not freeze.

## 17 PATIENT COUNSELING INFORMATION

See FDA-approved Medication Guide for the oral formulations.

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

### 17.1 Information on Medication Guide

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

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

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

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

### 17.3 Neuroleptic Malignant Syndrome (NMS)

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

### 17.4 Hyperglycemia

Patients should be advised of the potential risk of hyperglycemia-related adverse reactions. Patients should be monitored regularly for worsening of glucose control. Patients who have diabetes should follow their doctor's instructions about how often to check their blood sugar while taking ZYPREXA [see Warnings and Precautions (5.4)].

**17.5 Hyperlipidemia**

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

**17.6 Weight Gain**

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

**17.7 Orthostatic Hypotension**

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration and in association with the use of concomitant drugs that may potentiate the orthostatic effect of ZYPREXA, e.g., diazepam or alcohol [see *Warnings and Precautions* (5.8) and *Drug Interactions* (7)]. Patients should be advised to change positions carefully to help prevent orthostatic hypotension, and to lie down if they feel dizzy or faint, until they feel better. Patients should be advised to call their doctor if they experience any of the following signs and symptoms associated with orthostatic hypotension: dizziness, fast or slow heart beat, or fainting.

**17.8 Potential for Cognitive and Motor Impairment**

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

**17.9 Body Temperature Regulation**

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

**17.10 Concomitant Medication**

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

**17.11 Alcohol**

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

**17.12 Phenylketonurics**

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) contains phenylalanine (0.34, 0.45, 0.67, or 0.90 mg per 5, 10, 15, or 20 mg tablet, respectively) [see *Description* (11)].

**17.13 Use in Specific Populations**

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

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

**Pediatric Use** — ZYPREXA is indicated for treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder in adolescents 13 to 17 years of age. Compared to patients from adult clinical trials, adolescents were likely to gain more weight, experience increased sedation, and have greater increases in total cholesterol, triglycerides, LDL cholesterol, prolactin, and hepatic transaminase levels. Patients should be counseled about the potential long-term risks associated with ZYPREXA and advised that these risks may lead them to consider other drugs first [see *Indications and Usage* (1.1, 1.2)]. Safety and effectiveness of ZYPREXA in patients under 13 years of age have not been established. Safety and effectiveness of ZYPREXA and fluoxetine in combination in patients <18 years of age have not been established [see *Warnings and Precautions* (5.5, 5.6) and *Use in Specific Populations* (8.4)].

**17.14 Need for Comprehensive Treatment Program in Pediatric Patients**

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

Literature revised Month dd, 2009

Eli Lilly and Company, Indianapolis, IN 46285, USA

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## Medication Guide

ZYPREXA<sup>®</sup> (zy-PREX-a)

(olanzapine)

Tablet

ZYPREXA<sup>®</sup> ZYDIS<sup>®</sup> (zy-PREX-a ZY-dis)

(olanzapine)

Tablet, Orally Disintegrating

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

### What is the most important information I should know about ZYPREXA?

**Serious side effects may happen when you take ZYPREXA, including:**

**Increased risk of death in elderly patients with dementia-related psychosis:** Medicines like ZYPREXA can raise the risk of death in elderly people who have lost touch with reality (psychosis) due to confusion and memory loss (dementia). ZYPREXA is not approved for treating psychosis in the elderly with dementia.

**High blood sugar (hyperglycemia):** High blood sugar can happen if you have diabetes already or even if you have never had diabetes. In rare cases, this could lead to ketoacidosis (build up of acid in the blood due to ketones), coma, or death. Your doctor should do lab tests to check your blood sugar before you start taking ZYPREXA and during treatment. In people who do not have diabetes, sometimes high blood sugar goes away when ZYPREXA is stopped. People with diabetes and some people who did not have diabetes before taking ZYPREXA need to take medicine for high blood sugar even after they stop taking ZYPREXA.

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

**Call your doctor** if you have any of these symptoms of high blood sugar (hyperglycemia) while taking ZYPREXA:

- 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.

**High cholesterol and triglyceride levels in the blood (fat in the blood)** may happen in people treated with ZYPREXA, especially in teenagers (13-17 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 ZYPREXA and during treatment.

**Increase in weight (weight gain):** Weight gain is very common in people who take ZYPREXA. Teenagers (13-17 years old) are more likely to gain weight and to gain more weight than adults. Some people may gain a lot of weight while taking ZYPREXA, 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.

**Increased risk in teenagers (13-17 years old):** Possible serious risks of weight gain and increases in cholesterol and triglycerides are more common in teenagers than in adults. You and your doctor should decide if other available treatments should be used first. Before your teenager takes ZYPREXA, talk with your doctor about the possible long-term risks of teenagers taking ZYPREXA.

### **What is ZYPREXA?**

**ZYPREXA is a 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<sup>®</sup>), in adults.
- episodes of depression that do not get better after 2 other medicines, also called treatment resistant depression, when used with the medicine fluoxetine (Prozac), in adults.

ZYPREXA has not been approved for use in children under 13 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.

The symptoms of treatment resistant depression include decreased mood, decreased interest, increased guilty feelings, decreased energy, decreased concentration, changes in appetite, and suicidal thoughts or behavior.

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 ZYPREXA?**

ZYPREXA may not be right for you. Before starting ZYPREXA, 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 ZYPREXA ZYDIS 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 ZYPREXA will harm your unborn baby.
- are breast-feeding or plan to breast-feed. ZYPREXA can pass into your breast milk and may harm your baby. You should not breast-feed while taking ZYPREXA. Talk to your doctor about the best way to feed your baby if you take ZYPREXA.

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

The symptoms of bipolar I disorder, treatment resistant depression, 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. ZYPREXA 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 ZYPREXA with your other medicines. Do not start or stop any medicine while taking ZYPREXA without talking to your doctor first.

#### How should I take ZYPREXA?

- Take ZYPREXA exactly as prescribed. Your doctor may need to change (adjust) the dose of ZYPREXA until it is right for you.
- If you miss a dose of ZYPREXA, 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 ZYPREXA at the same time.
- **To prevent serious side effects, do not stop taking ZYPREXA suddenly. If you need to stop taking ZYPREXA, your doctor can tell you how to safely stop taking it.**
- **If you take too much ZYPREXA, call your doctor or poison control center at 1-800-222-1212 right away, or get emergency treatment.**
- ZYPREXA can be taken with or without food.
- ZYPREXA is usually taken one time each day.
- Take ZYPREXA ZYDIS as follows:
  - Be sure that your hands are dry.
  - Open the sachet and 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 ZYPREXA.

#### What should I avoid while taking ZYPREXA?

- ZYPREXA 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 ZYPREXA affects you.
- Avoid drinking alcohol while taking ZYPREXA. Drinking alcohol while you take ZYPREXA may make you sleepier than if you take ZYPREXA alone.

#### What are the possible side effects of ZYPREXA?

**Serious side effects may happen when you take ZYPREXA, including:**

- See “What is the most important information I should know about ZYPREXA?”, 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). ZYPREXA is 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 ZYPREXA. 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.
- **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 ZYPREXA. It may also start after you stop taking ZYPREXA. 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 ZYPREXA.**
- **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 ZYPREXA 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 (13-17 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 ZYPREXA. 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 ZYPREXA?**

- Store ZYPREXA at room temperature, between 68°F to 77°F (20°C to 25°C).

- Keep ZYPREXA away from light.
- Keep ZYPREXA dry and away from moisture.

**Keep ZYPREXA and all medicines out of the reach of children.**

### **General information about ZYPREXA**

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

This Medication Guide summarizes the most important information about ZYPREXA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about ZYPREXA that was written for healthcare professionals. For more information about ZYPREXA call 1-800-Lilly-Rx (1-800-545-5979) or visit [www.zyprexa.com](http://www.zyprexa.com).

### **What are the ingredients in ZYPREXA?**

**Active ingredient:** olanzapine

**Inactive ingredients:**

**Tablets** — carnauba wax, crospovidone, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients. The color coating contains: Titanium Dioxide, FD&C Blue No. 2 Aluminum Lake, or Synthetic Red Iron Oxide.

**ZYDIS** — gelatin, mannitol, aspartame, sodium methyl paraben, and sodium propyl paraben.

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

Medication Guide revised Month dd, 2009

**Eli Lilly and Company**  
**Indianapolis, IN 46285, USA**

[www.zyprexa.com](http://www.zyprexa.com)

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**NDA 20-592, ZYPREXA (olanzapine) Tablet for Oral Use  
NDA 21-086, ZYPREXA ZYDIS (olanzapine) Tablet, Orally Disintegrating  
for Oral Use**

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

**I. Goals(s)**

The goal of the REMS is to inform patients of the serious risks associated with the use of Zyprexa (olanzapine) Tablet for Oral Use and Tablet, Orally Disintegrating for Oral Use, including the risks of hyperglycemia, hyperlipidemia, and weight gain.

**II. REMS Elements**

**A. Medication Guide**

The Medication Guide will be dispensed with each Zyprexa prescription in accordance with 21 CFR 208.24.

**B. Communication Plan**

This REMS for Zyprexa does not include a Communication Plan.

**C. Elements to Assure Safe Use**

This REMS for Zyprexa does not include elements to assure safe use.

**D. Implementation System**

Because this REMS for Zyprexa does not include elements to assure safe use, an implementation system is not required.

**E. Timetable for Submission of Assessments**

The Timetable for Assessments is as follows:

- The first assessment is due 18 months from the original approval date of the REMS (September 19, 2010).  
The second assessment is due 3 years from the original approval date of the REMS (March 19, 2012).
- The third assessment is due 7 years from the original approval date of the REMS (March 19, 2016).

To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Eli Lilly and Company will submit each assessment so it will be received by the FDA on or before the due dates listed above.

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**020592 / S-035, 039, 040, 041, 049,053, 055**

**021086 / S-21, 031, 032, 034**

**021253 / S-037, 039, 043**

**OFFICER/EMPLOYEE LIST**

**Officer/Employee List**  
**Application: 20-592 S040/S041: Zyprexa**  
**Pediatric Schizophrenia/BiPolar**

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Cara Alfaro  
Doris Bates  
Mary Dempsey  
Ida-Lina Diak  
Jessica Diaz  
Jodi Duckhorn  
Fanhui Kong  
Thomas Laughren  
Mitchell Mathis  
Marilyn Pitts  
Sarah Simon  
Ellis Unger  
James Vidra  
Peiling Yang

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

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**021086 / S-21, 031, 032, 034**

**021253 / S-037, 039, 043**

**MEDICAL REVIEW(S)**

**Review and Evaluation of Clinical Data  
NDA 020592, NDA 021086, NDA 021253**

**Sponsor:** Eli Lilly and Company  
**Drug:** Zyprexa® (olanzapine)  
**Material Submitted:** NDA 020592/053, NDA 021253/039  
NDA 021086/032  
**Correspondence Date:** 10/23/2009  
**Date Received:** 10/26/2009

**I. Background**

This submission dated October 23, 2009, NDA 20592/053 (eCTD Sequence No. 0042), provides for a Prior Approval Labeling Supplement for Zyprexa oral tablets and intramuscular injection. The sponsor proposed changes include revisions to laboratory and clinical findings regarding liver enzyme elevations and neutropenia in **Section 6.2 Vital Signs and Laboratory Studies**. It also provides new language regarding cardiac death in the Highlights Section of the USPI. The safety team in the DPP will review the cardiac death issue separately. Therefore, this review will only focus on the revisions in Section 6.2 Vital Signs and Laboratory Studies.

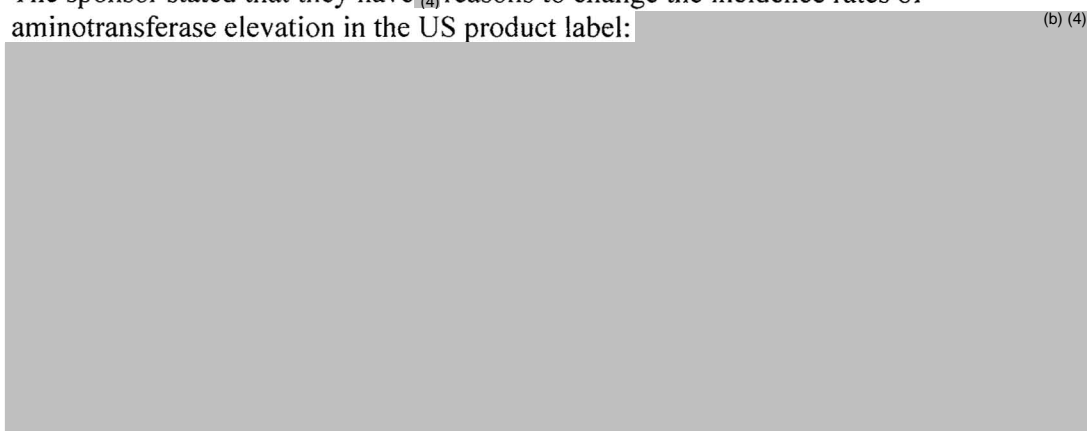
**II. Summary of Proposed Changes in Section 6.2 Vital Signs and Laboratory Studies**

**Aminotransferase**

Changing the Incidence Rates of Aminotransferase Elevations

The sponsor stated that they have (b) (4) reasons to change the incidence rates of aminotransferase elevation in the US product label:

(b) (4)



(b) (4)



(b) (4)

#### Adding New Additional Analysis Results of Aminotransferase to the Labeling

The sponsor is proposing to add to the labeling the new analysis results which include the incidence rates of patients with ALT elevations  $\geq 5x$  ULN, (b) (4), and the incidence rates of meeting criteria for Hy's rule. They also reviewed and added the data on AEs and ALT values for patients with ALT elevations at least 3x ULN.

(b) (4)

The sponsor reviewed the recently published FDA's Guidance for Industry: Drug-Induced Liver Injury which listed the specific criteria for discontinuation of treatment due to liver injury. (b) (4)

(b) (4). They concluded that they did not find any subjects who met the discontinuation criteria listed in the FDA guidance. (b) (4)

#### **Neutropenia**

(b) (4)

neutropenia, and agranulocytosis was added to the US product label on 31 August 2009 (Section 5.9 titled Leukopenia, Neutropenia, and Agranulocytosis). The warning/precaution supersedes information included in (b) (4).

#### **III. Review of Proposed Labeling Revisions**

The changes proposed by the sponsor in section 6.2 of Zyprexa labeling are identified as follows: deletions are identified by strikethrough, additions are identified by underlining.

Section 6.2:

(b) (4) :

(b) (4)

The sponsor moved the original premarketing data from the 3<sup>rd</sup> paragraph to the first paragraph, and added the new criteria they used in the analyses of ALT elevation: (change from <3 times the upper limit of normal [ULN] at baseline to  $\geq 3$  times ULN). They corrected the incidence rates according to the new analysis results using the new criteria and a larger data set which included additional trials. The new incidence rates are supported by the following table.

**Table 1.5. Incidence of ALT Abnormalities Using 3X Upper Limit of the Central Lab Reference Range Adult Placebo-Controlled Olanzapine Integrated Database Double-Blind Acute and Extension Phases**

| Therapy | N    | n  | %    |
|---------|------|----|------|
| Olz     | 1426 | 77 | 5.4% |
| Placebo | 1187 | 10 | 0.8% |

N = The number of patients with no abnormal baseline values and at least one post-baseline value.  
n = The number of patients with no abnormal baseline values and at least one abnormal post-baseline value.  
An abnormal value is defined as a value  $\geq 3$  times the upper limit of the central lab reference range.  
Fixed dose olanzapine arms < 5 mg were excluded from this analysis.  
Studies included in the analysis: HBBD, HBBI, HGAD, HGAP, HGBH, HGEH, HOGA, HGGF, HGGW, HGGY, HGKK, HGKL, HGKQ

They added the analysis result of incidence rate of ALT  $\geq 5x$  ULN, which is shown in the table below:

The sponsor added the following statement:

“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”.

I have reviewed all the ALT Lab values for patients with ALT abnormalities  $\geq 3x$ ,  $5x$ , or  $10x$  ULN in the adult placebo-controlled olanzapine integrated database. There were a total of 87 patients who had at least one elevated post-baseline ALT value in this database. Seventy-seven were from the olanzapine monotherapy group and 10 were from the placebo group. Most patients had ALT normalized or decreasing at the last follow up except 5 patients who did not have further follow up. All of these 5 patients discontinued from the treatment. The table below listed the information for these 5 patients.

| Patient ID    | Indication    | Olanzapine dosage | Reason for discontinuation                             | Date last study drug taken | Last Lab Sample date | Last ALT result      |
|---------------|---------------|-------------------|--------------------------------------------------------|----------------------------|----------------------|----------------------|
| HGGW-022-2060 | Bipolar Mania | No data           | Lack of efficacy, MD and patient's perception          | 1998-06-07                 | 1998-06-09           | 409 H ( $\geq 10X$ ) |
| HGKQ-2-203    | Bipolar Mania | 15mg              | Adverse Event - Blood creatine phosphokinase increased | 2005-02-03                 | 2005-02-03           | 347 H ( $\geq 5X$ )  |
| HGKQ-84-8403  | Bipolar Mania | 10mg              | Adverse Event - Hepatitis toxic                        | 2005-10-01                 | 2005-09-27           | 229 H ( $\geq 5X$ )  |
| HGBH-334-3347 | Schizophrenia | 5mg               | Patient moved                                          | 1997-03-04                 | 1997-03-05           | 517 H ( $\geq 10X$ ) |
| HGBH-355-3551 | Schizophrenia | 5mg               | Personal conflict                                      | 1995-07-17                 | 1995-07-18           | 186 H ( $\geq 3X$ )  |

Based on my review, the statement “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” is accurate.

The sponsor also added the following statement in the same paragraph:

“No (b) (4) patient (b) (4) with elevated ALT values experienced jaundice, liver failure, or met the criteria for Hy's Rule.”

The sponsor listed AEs for adult patients with ALT abnormality  $\geq 3x$  ULN in the submission. Among all of the patients, four had SAEs which were believed to be related to aminotransferase elevations but not jaundice.

Patient (ID: HGAD-011-1526) had increased GGT and SGPT.

Patient (ID: HGAD-015-1704) had increased SGPT.

Patient (ID: HGAD-020-1951) had increased SGPT.

Patient (ID: HGBH-325-3250) had increased ALT.

The sponsor did not include the actual GGT and SGPT lab results in the submission. However, all of these patients' ALT values either returned to normal or were decreasing at the last follow up. Therefore, I believe the statement that "No (b) (4) patient with elevated ALT values experienced jaundice, liver failure, or met the criteria for Hy's Rule" is also accurate.

The sponsor deleted the following sentences. This is acceptable.



The sponsor also deleted the following statement regarding the discontinuation treatment due to transaminase increases.

~~"Among 2500 adult patients in oral olanzapine clinical trials, about 1% (23/2500) discontinued treatment due to transaminase increases"~~

The sponsor has examined the cases of discontinuation due to transaminase increases. There were a total of 23 adult cases from the premarketing database and 8 cases from the adolescent database that discontinued from the treatment due to transaminase increases. The following table listed the highest transaminase values of all the discontinuation cases.

**Table 1.12. Cases of Discontinuations due to Elevated Aminotransferases  
Adult and Adolescent Patients Exposed to Olanzapine**

| Patient               | Reason for Discontinuation | Highest Aminotransferases |                        |         | Additional Labs/Information/Outcome                                                                                                  |
|-----------------------|----------------------------|---------------------------|------------------------|---------|--------------------------------------------------------------------------------------------------------------------------------------|
|                       |                            | ALT                       | AST                    | GGT     |                                                                                                                                      |
| <b>Adult Patients</b> |                            |                           |                        |         |                                                                                                                                      |
| HGAD 011-1526         | ALT increased              | 237 U/L                   | 102 U/L                | NR      | DC from study. Approximately 4 months after DC, LFTs remained elevated, but not increasing.                                          |
| HGAD 014-1651         | ALT increased              | 187 U/L                   | 82 U/L                 | NR      | DC from study. Hx of elevated LFTs 2 months prior to entering study, also, Hx of heroin use. Hepatitis C was diagnosed at follow-up. |
| HGAD 015-1701         | ALT increased              | 239 U/L<br>(BL 12 U/L)    | 94 U/L                 | NR      | DC from study. Four days after DC, ALT remained elevated, AST was approaching normal limits.                                         |
| HGAD 015-1704         | ALT increased              | 394 U/L                   | 172 U/L                | NR      | DC from study. Values returned to within normal limits 18 days after DC.                                                             |
| HGAD 019-1870         | ALT increased              | 685 U/L<br>(BL 48 U/L)    | 225 U/L<br>(BL 29 U/L) | NR      | DC from study. Follow-up continued until values returned to normal. ALT in 20 days; AST in 13 days.                                  |
| HGAD 019-1878         | ALT increased              | 181 U/L                   | NR                     | NR      | DC from study. Follow-up 15 days after DC, ALT within normal limits.                                                                 |
| E003 151-1511         | ALT increased              | 109 IU/L                  | NR                     | NR      | DC from study. No follow-up reported.                                                                                                |
| E003 152-1527         | ALT increased              | 102 IU/L                  | NR                     | NR      | DC from study. Follow-up: 8 days after DC - ALT 51 IU/L; 29 days after DC - ALT 33 IU/L.                                             |
| E003 404-4070         | ALT increased              | 86 IU/L                   | NR                     | NR      | DC from study. Follow-up 13 days after DC - ALT 30 IU/L.                                                                             |
| E003 602-6053         | ALT increased              | 171 U/L                   | NR                     | NR      | DC from study. Follow-up 4 days after DC - ALT 38 IU/L.                                                                              |
| E003 724-7270         | ALT increased              | 165 U/L                   | NR                     | NR      | DC from study. Follow-up 21 days after DC - ALT 84 U/L.                                                                              |
| E003 802-8053         | ALT increased              | 315 IU/L                  | 113 IU/L               | NR      | DC from study. Elevated LFTs spontaneously returned to normal.                                                                       |
| E003 902-9023         | ALT increased              | 228 U/L<br>(BL 9 U/L)     | NR                     | NR      | DC from study. Follow-up 2 weeks after DC - ALT 29 U/L.                                                                              |
| E003 941-9413         | ALT increased              | 170 IU/L                  | 98 IU/L                | 75 IU/L | DC from study. No follow-up reported.                                                                                                |

(continued)

**Table 1.12. Cases of Discontinuations due to Elevated Aminotransferases  
Adult and Adolescent Patients Exposed to Olanzapine (continued)**

| Patient                          | Reason for Discontinuation | Highest Aminotransferases |                        |                        | Additional Labs/Information/Outcome                                                                                                                  |
|----------------------------------|----------------------------|---------------------------|------------------------|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                  |                            | ALT                       | AST                    | GGT                    |                                                                                                                                                      |
| <b>Adult Patients, continued</b> |                            |                           |                        |                        |                                                                                                                                                      |
| HGAJ 325-2955                    | ALT increased              | 376 U/L<br>(BL 35 U/L)    | 150 U/L                | NR                     | DC from study. Positive Hepatitis A antibody after DC.                                                                                               |
| E003 151-1508                    | GGT increased              | 300 U/L                   | 142 U/L                | 118 U/L                | DC from study. No follow-up reported.                                                                                                                |
| E003 401-4002                    | GGT increased              | 48 IU/L                   | 20 IU/L                | 50 IU/L                | Also Tbil: 2.907 micromoles/L (WNL). DC from study. Received alternative neuroleptic. Increased liver enzymes did not return to normal.              |
| E003 702-7026                    | GGT increased              | 206 IU/L<br>(BL 95 U/L)   | 145 IU/L               | 293 IU/L               | Also: Alk phos: 327 (IU/L). Elevated liver enzymes at Visit 1. DC from study after several increases in LFTs. Patient refused further blood tests.   |
| HGAJ 062-1080                    | GGT increased              | NR                        | 109 U/L                | 287 U/L<br>(BL 71 U/L) | DC from study. Probable chronic viral hepatitis. no clinical symptoms from the elevated hepatic enzymes.                                             |
| HGAJ 021-1247                    | LFT abnormal               | 304 U/L<br>(BL 14 U/L)    | 553 U/L<br>(BL 21 U/L) | 610 U/L<br>(BL 21 U/L) | Also: Alk Phos: 163 U/L. DC from study. Increase in alcohol intake for 3 months prior to DC from study.                                              |
| HGAJ 029-0173                    | LFT abnormal               | 396 U/L (BL 38 U/L)       | 148 U/L                | NR                     | DC from study. Hepatitis C antibody tests performed after DC from study were found to be reactive although the patient continued to be asymptomatic. |
| HGAJ 816-6514                    | LFT abnormal               | 107 U/L                   | NR                     | 328 U/L                | Also: Alk Phos: 184 U/L. Significant hx of liver disease (jaundice) of unknown origin. DC from study.                                                |
| HGAP 005-1210                    | LFT abnormal               | 412 U/L                   | 150 U/L                | NR                     | ALT and AST elevated prior to entering study. DC from study. Follow-up 2 months after DC. ALT: 122 U/L. Follow-up 46 days after DC. AST: 58 U/L.     |

(continued)

**Table 1.12. Cases of Discontinuations due to Elevated Aminotransferases Adult and Adolescent Patients Exposed to Olanzapine (concluded)**

| Patient                    | Reason for Discontinuation | Highest Aminotransferases |                        |                        | Additional Labs/Information/Outcome                                                                                      |
|----------------------------|----------------------------|---------------------------|------------------------|------------------------|--------------------------------------------------------------------------------------------------------------------------|
|                            |                            | ALT                       | AST                    | GGT                    |                                                                                                                          |
| <b>Adolescent Patients</b> |                            |                           |                        |                        |                                                                                                                          |
| HGIN 007-0703              | ALT increased              | 231 U/L<br>(BL 17 U/L)    | 142 U/L                | 34 U/L                 | DC from study. Follow up 22 days weeks after DC - ALT: 18 U/L. Follow-up 6 days after DC, AST: 33 U/L                    |
| HGIN 010-1001              | LFT abnormal               | 597 U/L<br>(BL 22 U/L)    | 410 U/L<br>(BL 26 U/L) | 129 U/L<br>(BL 23 U/L) | DC from study. Follow up 20 days after DC, different lab ALT: 82 U/L (21-27 U/L, AST: 43 U/L (17-59 U/L).                |
| HGIN 021-2103              | Transaminases increased    | 396 U/L<br>(BL 16 U/L)    | 136 U/L<br>(BL 20 U/L) | 63 U/L                 | DC from study. Follow up 14 days after DC ALT: 43 U/L, AST: 25 U/L.                                                      |
| HGIN 910-9110              | AST increased              | 321 U/L                   | 190 U/L<br>(BL 66 U/L) | NR                     | DC from study. Follow up 21 days after DC. AST and ALT: normal.                                                          |
| HGIN 920-9202              | ALT increased              | 393 U/L<br>(BL 13 U/L)    | 179 U/L<br>(BL 13 U/L) | 82 U/L<br>(BL 22 U/L)  | DC from study. Follow up 22 days after DC, ALT: 20 U/L.                                                                  |
| HGIU 012-1203              | Hepatic enzyme increased   | 325 U/L                   | 148 U/L                | 53 U/L                 | DC from study. Follow up 7 days after DC, liver enzymes were within normal limits.                                       |
| HGIU 020-2007              | LFT abnormal               | 530 U/L                   | 204 U/L                | NR                     | DC from study in open-label phase. Follow up 6 days after DC, AST: normal, ALT: decreasing but still above normal limit. |
| HGIU 720-7217              | Hepatic enzyme increased   | 125 U/L                   | 103 U/L                | NR                     | DC from study in open-label phase. Follow up 56 days after DC, liver enzymes were within normal limits.                  |

Abbreviations: Alk Phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DC = discontinued; GGT = gamma glutamyl transferase; Hx = history of; LDH = lactate dehydrogenase; LFT = liver function transaminase; NR = not reported; WNL = with no limits.

The sponsor further reviewed the recently published FDA's Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation (07/2009), which listed the following specific criteria for discontinuation of treatment due to transaminase increases:

- ALT or AST >8x ULN
- ALT or AST >5x ULN for more than 2 weeks
- ALT or AST >3x ULN and (TBL >2x ULN or INR >1.5)
- ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

As you can see from the yellow highlight in the table above, four adult cases and 3 adolescent cases had ALT >8x ULN and therefore these cases have met the criteria for discontinuation of treatment due to transaminase increases. However, since the readings in the table were the highest ALT values during the studies, it is not clear if these were the readings when patients were discontinued. One patient, HGAJ 029-0173, was tested hepatitis C antibody positive after discontinuation.

Since at least the majority of cases did not meet the criteria specified in the FDA guidance regarding drug-induced liver injury, I consider it is acceptable for the sponsor to delete the language regarding the drug discontinuation due to aminotransferase increase.

**Section 6.2: Aminotransferase - Olanzapine Monotherapy in Adolescents:**

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

In placebo-controlled olanzapine monotherapy studies in adolescents, clinically significant ALT elevations (change from  $< 3$  times ULN at baseline to  $\geq 3$  times ULN) were observed in 12% (22/192) of patients exposed to olanzapine compared to 2% (2/109) of patients exposed to placebo. Reg Resp Table 1.9. ALT elevations  $\geq 5$  times ULN were observed in 4% (8/192) of olanzapine-treated patients, compared to 1% (1/109) of placebo-treated patients. Reg Resp Table 1.10. 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. Reg Resp Attachment 3. No adolescent patient with elevated ALT values experienced jaundice, liver failure, or met the criteria for Hy's Rule. Reg Resp Table 1.11. Reg Resp Attachment 4.

In the first paragraph, the sponsor rounded up the incidence rates for elevated ALT, AST, low total bilirubin, GGT and prolactin. This is acceptable.

In the 2<sup>nd</sup> paragraph, the sponsor specified the incidence rates of ALT elevations  $\geq 3x$  ULN and  $\geq 5x$  ULN. This is supported by the following tables.

**Table 1.9. Incidence of ALT Abnormalities Using 3X Upper Limit of the Central Lab Reference Range Adolescent Placebo-Controlled Olanzapine Integrated Database Double-Blind Acute and Extension Phases**

| Therapy | N   | n  | %     |
|---------|-----|----|-------|
| Olz     | 192 | 22 | 11.5% |
| Placebo | 109 | 2  | 1.8%  |

N = The number of patients with no abnormal baseline values and at least one post-baseline value.  
n = The number of patients with no abnormal baseline values and at least one abnormal post-baseline value.  
An abnormal value is defined as a value  $\geq 3$  times the upper limit of the central lab reference range.  
Fixed dose olanzapine arms  $< 5$  mg were excluded from this analysis.  
Studies included in the analysis: HGGF, HGIN, HGIU, HGKL

**Table 1.10. Incidence of ALT Abnormalities Using 5X Upper Limit of the Central Lab Reference Range Adolescent Placebo-Controlled Olanzapine Integrated Database Double-Blind Acute and Extension Phases**

| Therapy | N   | n | %    |
|---------|-----|---|------|
| Olz     | 192 | 8 | 4.2% |
| Placebo | 109 | 1 | 0.9% |

N = The number of patients with no abnormal baseline values and at least one post-baseline value.  
n = The number of patients with no abnormal baseline values and at least one abnormal post-baseline value.  
An abnormal value is defined as a value  $\geq 5$  times the upper limit of the central lab reference range.  
Fixed dose olanzapine arms  $< 5$  mg were excluded from this analysis.  
Studies included in the analysis: HGGF, HGIN, HGIU, HGKL

I have reviewed all ALT Lab values for patients with ALT abnormalities  $\geq 3, 5, \text{ or } 10x$  ULN in adolescent placebo-controlled olanzapine integrated database in the submission. All ALT values were normalized or decreasing at the last follow up. I also have reviewed all the AEs for adolescent patients with ALT abnormality  $\geq 3x$  ULN. There were no SAEs related to aminotransferase elevations or jaundice. Therefore, the statement in the 2<sup>nd</sup> paragraph is accurate. These changes are acceptable.

## Section 6.2: Neutropenia

(b) (4)

(b) (4)

. This is acceptable.

### III. Conclusions and Recommendations

The sponsor proposed changes are acceptable. I recommend that these labeling supplements to be approved.

Jenn Sellers, M.D., Ph.D., FAAP  
May 6, 2010

cc: NDA  
Laughren, T/Mathis, M/David, P/Kiedrow, K/Zhang, J

| Application Type/Number | Submission Type/Number | Submitter Name   | Product Name                              |
|-------------------------|------------------------|------------------|-------------------------------------------|
| NDA-20592               | SUPPL-53               | ELI LILLY AND CO | ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/  |
| NDA-21253               | SUPPL-39               | ELI LILLY AND CO | ZYPREXA IM (OLANZAPINE) 10MG VIALS INJ    |
| NDA-21086               | SUPPL-32               | ELI LILLY AND CO | ZYPREXA ZYDIS(OLANZAPINE)5/10/15/20/ MGTS |

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/s/

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JENN W SELLERS  
05/06/2010

JING ZHANG  
05/06/2010

## Review and Evaluation of Clinical Data

### NDA 20-592, 21-086, 21-253

Sponsor: Eli Lilly and Company  
Drug: Zyprexa (olanzapine) oral tablets, TS, injection.  
Material Submitted: N 20592/-035, -040;  
Related NDAs: N 21086/-<sup>(b) (4)</sup>; 21253/-<sup>(b) (4)</sup>;  
Correspondence Date: 1 Sep 2009, 6 Oct 2009

#### I. Background

This submission provides for Prior Approval labeling supplement for Zyprexa to include updated language regarding hyperprolactinemia. This review encompasses two submissions, eCTD 0035 submitted 1 Sep 2009 and eCTD 0040 submitted 6 Oct 2009.

The submission 0035 includes results from an updated analyses of prolactin data collected during placebo controlled trials in adults and adolescents with schizophrenia and other psychiatric disorders treated with olanzapine monotherapy. This was done in Q1-Q2 2009 by Eli Lilly. This was done as the number of exposures in this database has more than doubled since the approval of olanzapine in 1996.

This submission also includes results from an analysis of the clinical manifestations potentially associated with hyperprolactinemia using comprehensive groupings (breast-, menstrual-, and sexual- function related).

In submission 0040, the sponsor requested to delete the term <sup>(b) (4)</sup> in paragraph 1 of the section on hyperprolactinemia of Zyprexa labeling.

#### II. Clinical Data and Analyses

Data from two adult databases were used to present hyperprolactinemia related AEs in the proposed Zyprexa labeling: the Adult Olanzapine Monotherapy Placebo-Controlled Database and the Olanzapine Adult Overall Database.

The placebo-controlled database was used to analyze the incidence and frequencies of hyperprolactinemia and the Olanzapine Adult Overall Database was used to analyze categorized hyperprolactin associated AEs.

For adolescents, data from 4 studies in the olanzapine Adolescent Overall Database was used to analyze both the incidence and frequencies of hyperprolactinemia and also categorized hyperprolactin associated AE's.

Analyses included

- incidence of treatment-emergent high prolactin values anytime during the study (provided for adults only, as incidence for adolescents remains unchanged in the USPI)
- incidence of treatment-emergent adverse events by category
- frequencies of treatment-emergent adverse events by category.

Because laboratories with disparate reference ranges were used to assay prolactin in studies evaluated, prolactin data were normalized for pooling and analysis. Normalization involved the use of a conversion factor that is both lab-specific and analyte-specific for the purpose of analyzing data across studies. The number of patients with normal baseline and at least one treatment-emergent high prolactin value at any time during the placebo-controlled period was summarized by treatment.

The sponsor looked at the incidence and frequencies of possible prolactin-related, treatment emergent adverse events by categories (Table 1). The terms included were chosen from a list of prolactin-related MedDRA preferred terms (version 12).

**Table 1: MedRA Preferred Term Categories for Potential Clinical Manifestations Associated with Prolactin Elevations.**

| <b>Sexual Function-Related Preferred Terms</b> | <b>Menstrual-Related Preferred Terms</b> | <b>Breast-Related Preferred Terms</b> |
|------------------------------------------------|------------------------------------------|---------------------------------------|
| Anorgasmia                                     | Amenorrhoea                              | Breast discharge                      |
| Ejaculation delayed                            | Hypomenorrhoea                           | Breast enlargement                    |
| Erectile dysfunction                           | Menstruation delayed                     | Breast swelling                       |
| Libido decreased                               | Oligomenorrhoea                          | Galactorrhoea                         |
| Loss of libido                                 |                                          | Gynaecomastia                         |
| Orgasm abnormal                                |                                          | Lactation disorder                    |
| Sexual dysfunction                             |                                          |                                       |

The number of possible prolactin-related, treatment emergent adverse events were summarized from a list of prolactin-related MedRA Preferred Terms. Hyperprolactinemia may also be associated with infertility, oligospermia, osteopenia, and osteoporosis. However, these conditions may take months to years to appear, and since the median exposure was 97 days in the olanzapine adult database and 88 days in the adolescent database, these terms were excluded.

#### Adult Olanzapine Placebo-Controlled Database

The current adult olanzapine monotherapy placebo-controlled database consists of 14 studies including 2118 olanzapine treated and 1467 placebo-treated patients, with exposure up to 52 weeks. For the current proposed changes to the USPI, analyses were performed on the data from only 9 studies (Table 2) included in the adult olanzapine placebo-controlled database, as the others did not contain prolactin measurements. This

subset of the larger database included data from 1471 olanzapine-treated and 918 placebo-treated patients. For both databases, the mean ages were 38 and 37 years.

Table 2: Subset of 9 trials from the Olanzapine Adult Placebo-Controlled Database

| Study       | Formulation | Indication                      | OLZ Dose(s) or Dose Range              | Placebo-Controlled Duration (weeks) |
|-------------|-------------|---------------------------------|----------------------------------------|-------------------------------------|
| F1D-MC-HGAD | Oral        | Schizophrenia                   | 2.5 to 17.5                            | 6                                   |
| F1D-MC-HGAP | Oral        | Schizophrenia                   | 1, 10                                  | 6                                   |
| F1D-MC-HGGA | Oral        | Psychotic depression            | 5 to 20                                | 8                                   |
| F1D-MC-HGJZ | Depot       | Schizophrenia                   | 210 mg/2 wk<br>300 mg/2 wk 405 mg/4 wk | 8                                   |
| F1D-MC-HGKK | Oral        | Borderline personality disorder | 2.5, 5-10                              | 12                                  |
| F1D-MC-HGKL | Oral        | Borderline personality disorder | 2.5 to 20                              | 12                                  |
| F1D-MC-HGKQ | Oral        | Bipolar mania                   | 5 to 20                                | 3                                   |
| H8Y-BD-HBBD | Oral        | Schizophrenia                   | 15                                     | 4                                   |
| H8Y-MC-HBBI | Oral        | Schizophrenia                   | 15                                     | 4                                   |

Using the subset of 9 adult trials, Table 3 summarizes the incidence of patients with treatment-emergent high prolactin values at any time. Differences were shown between different treatment groups, with 30.3% of olanzapine treated patients and 10.5% of placebo-treated patients having high prolactin values.

Table 3: Treatment Emergent High prolactin Values Anytime in Adult Olanzapine Placebo-Controlled Database

| Treatment  | N   | n   | (%) <sup>a</sup> | P-value <sup>b</sup> |
|------------|-----|-----|------------------|----------------------|
| olanzapine | 943 | 286 | 30.3%            | <.001                |
| Placebo    | 582 | 61  | 10.5%            |                      |

N= number of subjects with a normal baseline and at least one post baseline result.  
n= number of subjects with an abnormal post-baseline result at anytime.

#### Olanzapine Adult Overall Database

To examine the incidence of treatment emergent adverse events that may possibly be related to increases in prolactin levels by category, the olanzapine adult overall database was used. This integrated database has 84 studies that were conducted in adults with a diagnosis of schizophrenia or bipolar disorder, and studies that administered doses approved in the label (5 mg to 20 mg/day). (Table 4)

Table 4: Studies included in the Olanzapine Adult Overall Database  
studies

-----

|             |             |             |             |             |             |             |             |             |             |
|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| <b>E003</b> | <b>HGAD</b> | <b>HGAJ</b> | <b>HGAP</b> | <b>HGBB</b> | <b>HGBF</b> | <b>HGBG</b> | <b>HGBH</b> | <b>HGBI</b> | <b>HGBJ</b> |
| <b>HGBK</b> | <b>HGBL</b> | <b>HGBM</b> | <b>HGBO</b> | <b>HGBQ</b> | <b>HGBR</b> | <b>HGBS</b> | <b>HGBU</b> | <b>HGBX</b> | <b>HGCA</b> |
| <b>HGCF</b> | <b>HGCG</b> | <b>HGCH</b> | <b>HGCJ</b> | <b>HGCK</b> | <b>HGCL</b> | <b>HGCM</b> | <b>HGCO</b> | <b>HGCP</b> | <b>HGCQ</b> |
| <b>HGCU</b> | <b>HGCV</b> | <b>HGCK</b> | <b>HGCY</b> | <b>HGCZ</b> | <b>HGDB</b> | <b>HGDD</b> | <b>HGDG</b> | <b>HGDH</b> | <b>HGDI</b> |
| <b>HGDM</b> | <b>HGDQ</b> | <b>HGDT</b> | <b>HGDU</b> | <b>HGDV</b> | <b>HGDY</b> | <b>HGDZ</b> | <b>HGEB</b> | <b>HGEC</b> | <b>HGEF</b> |
| <b>HGEH</b> | <b>HGEJ</b> | <b>HGEP</b> | <b>HGEQ</b> | <b>HGER</b> | <b>HGES</b> | <b>HGET</b> | <b>HGEZ</b> | <b>HGFH</b> | <b>HGFH</b> |
| <b>HGFT</b> | <b>HGFW</b> | <b>HGGD</b> | <b>HGGF</b> | <b>HGGI</b> | <b>HGGN</b> | <b>HGGW</b> | <b>HGGY</b> | <b>HGHD</b> | <b>HGHG</b> |
| <b>HGHH</b> | <b>HGHJ</b> | <b>HGHL</b> | <b>HGHO</b> | <b>HGHQ</b> | <b>HGHR</b> | <b>HGIA</b> | <b>HGIJ</b> | <b>HGIY</b> | <b>HGJB</b> |
| <b>HGJT</b> | <b>HGJU</b> | <b>LOBU</b> | <b>P022</b> |             |             |             |             |             |             |

-----

This 84- study database includes data from 8136 olanzapine-treated subjects, with a median exposure of 97 days. Table 5 summarizes possible prolactin-related TEAE's by category and gender.

Table 5: Frequencies of possible prolactin-related treatment emergent adverse events by category and gender.

| <b>Category</b>                | <b>Males<br/>(N=4896)<br/>n (%)</b> | <b>Females<br/>(N=3240)<br/>n (%)</b> | <b>Total<br/>(N=8136)<br/>n (%)</b> | <b>CIOMS Frequency<br/>(Based on Total)</b> |
|--------------------------------|-------------------------------------|---------------------------------------|-------------------------------------|---------------------------------------------|
| <b>Breast-related</b>          | 9 (0.2%)                            | 23 (0.7%)                             | 32 (0.4%)                           | <b>Uncommon</b>                             |
| <b>Menstrual-related</b>       |                                     | 49 (2%)                               | 49 (2%)*                            | <b>Common</b>                               |
| <b>Sexual function-related</b> | 117 (2%)                            | 33 (1%)                               | 150 (2%)                            | <b>Common</b>                               |

Olanzapine Adolescent Overall Database

For analyses of prolactin related AE's in adolescents, there were 4 studies that are included in the Olanzapine Adolescent Overall Database. This integrated database contains data for 454 patients aged 13 through 18 years (Table 6).

Table 6: Studies in the Olanzapine Adolescent Overall Database

| <b>Study</b>       | <b>Formulation</b> | <b>Indication</b>                                                                 | <b>OLZ Dose(s) or<br/>Dose Range</b> | <b>Duration (weeks)</b>        |
|--------------------|--------------------|-----------------------------------------------------------------------------------|--------------------------------------|--------------------------------|
| <b>F1D-MC-HGIN</b> | <b>Oral</b>        | <b>Schizophrenia</b>                                                              | <b>2.5 to 20<br/>mg/day</b>          | <b>6 weeks DB, 26 weeks OL</b> |
| <b>F1D-MC-HGIU</b> | <b>Oral</b>        | <b>Bipolar mania</b>                                                              | <b>2.5 to 20<br/>mg/day</b>          | <b>3 weeks DB, 26 weeks OL</b> |
| <b>F1D-MC-HGMF</b> | <b>Oral</b>        | <b>Schizophrenia or<br/>bipolar disorder</b>                                      | <b>2.5 to 20<br/>mg/day</b>          | <b>4.5 weeks OL</b>            |
| <b>F1D-SB-LOAY</b> | <b>Oral</b>        | <b>Schizophrenia,<br/>schizoaffective, and<br/>schizophreniform<br/>disorders</b> | <b>5 to 20 mg/day</b>                | <b>6 weeks DB; 24 weeks OL</b> |

Analyses of data from the 4 adolescent studies showed that there is no change in the incidence of treatment-emergent high prolactin values for adolescents treated with olanzapine compared to that in the currently approved Zyprexa labeling.

Table 7 summarizes possible prolactin-related TEAEs by category and gender.

Table 7: Prolactin-Related TEAE's by Category and Gender in Adolescents.

| Category                | Males<br>(N=236)<br>n (%) | Females<br>(N=168)<br>n (%) | Total<br>(N=454)<br>n (%) | CIOMS<br>Frequency<br>(Based on Totals) |
|-------------------------|---------------------------|-----------------------------|---------------------------|-----------------------------------------|
| Breast-related          | 7 (2%)                    | 3 (2%)                      | 10 (2%)                   | Common                                  |
| Menstrual-related       |                           | 2 (1%)                      | 2 (1%)*                   | Common                                  |
| Sexual function-related | 3 (1%)                    |                             | 3 (0.7%)                  | Uncommon                                |

### III. Proposed Labeling Revisions

The changes proposed by the sponsor in section 5.15 of Zyprexa labeling are identified as follows: deletions are identified by ~~strike through~~ and additions by use of underline. The additions proposed by the reviewer are identified by additions



#### **IV. Conclusions and Recommendations**

The sponsor has included updated results from analyses of prolactin data. These analyses were conducted in 2009. They also propose including prolactin-related treatment adverse effects summarized by categories of sexual function-, menstrual- and breast-related terms. These additions are more clinically relevant compared to the previous label which only had manifestations related to the breast. It recognizes that prolactin increases affect organ systems other than the breast.

However, the terms of menstrual-related, sexual function related and breast related events are non-specific. I recommend a foot note at the end of the hyperprolactinemia section to give more explanation for what is included in these categories. For example, breast-related events include breast discharge, enlargement and swelling, galactorrhoea, gynaecomastia and lactation disorders.

The elimination of the term ‘(b) (4)’ in section 5.15 paragraph 1 also is appropriate.

The sponsor notes in their regulatory response document that they propose to change section 5.14. However, they actually propose to change 5.15, which is the section on hyperprolactinemia.

I recommend that this labeling revision be approved with the minor changes proposed by us.

-----  
Maju Mathews, MD, MRCPsych, Dip Psych.  
Medical Officer Reviewer  
FDA CDER ODE1 DPP HFD 130  
12/16/2009

Cc: Laughren, T/Mathis, M/David, P/Kiedrow, K/Zhang, J

| Application Type/Number | Submission Type/Number | Submitter Name   | Product Name                              |
|-------------------------|------------------------|------------------|-------------------------------------------|
| NDA-20592               | SUPPL-52               | ELI LILLY AND CO | ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/  |
| NDA-21086               | SUPPL-31               | ELI LILLY AND CO | ZYPREXA ZYDIS(OLANZAPINE)5/10/15/20/ MGTS |
| NDA-21253               | SUPPL-37               | ELI LILLY AND CO | ZYPREXA IM (OLANZAPINE) 10MG VIALS INJ    |

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MAJU MATHEWS  
12/17/2009

JING ZHANG  
12/17/2009

**Review and Evaluation of Clinical Data**  
**NDA #20-592, 21-086, 18-936**

**NDA#:** 20-592/S039, 21-086/S021, & 18-936/S077  
**Sponsor:** Eli Lilly and Company  
**Drug:** Zyprexa tablet, Zydys, & Prozac  
**Material Submitted:** Resubmission of Response to Approvable Letter  
**Date Submitted:** 4 February 2008  
**Proposed Indication:** Treatment Resistant Depression  
**Intended Population:** Adults  
**Related Supplements:** N21-520/S012  
**Medical Reviewer:** Jing Zhang, MD. PhD.

On 28 September 2006, Lilly submitted a supplemental New Drug Application (sNDA) for the use of fluoxetine in combination with olanzapine for the treatment of treatment-resistant depression (TRD). FDA issued a Refuse to File for these applications on 27 November 2006. Lilly responded with a briefing document, dated 4 January 2007. After review of this document and further evaluation from the FDA, these applications were considered re-filed on 5 January 2007. Revised labeling, in accordance with that described in the 4 January 2007 briefing document, was submitted to FDA on 21 March 2007.

The FDA sent an Approvable Letter dated 21 September 2007 regarding these sNDAs. This letter indicated that FDA had completed their review of these applications and that they are approvable. Before these applications may be approved, the following deficiency must be addressed:

"Clinical studies for the TRD indication were submitted to the Symbyax (olanzapine/fluoxetine) application, NDA 21-520/s012. The addition of TRD language to each of the individual components is dependent on this application. Therefore, we cannot approve these applications until we take an approval action on NDA 21-520/s012 (Symbyax for treatment resistant depression)."

Lilly re-submitted these applications on 4 February 2008 in response to the Approvable Letter dated on 27 September 2007. After extensive reviewing risks of hyperglycemia, hyperlipidemia, and weight gain associated with Zyprexa and olanzapine/fluoxetine combination (OFC) by a safety team in FDA, numerous changes on Zyprexa and Symbyax labelings had been recommended. Currently the FDA is in the processing to approve sNDA 21,520/S-012, Symbyax for treatment resistant depression in adults. The deficiency listed above has been addressed. It is recommended that these applications be approved.

Jing Zhang, MD. PhD.  
July 23, 2008

cc: NDA 21-520  
HFD-130 (Div. File)  
HFD-130/JZhang  
    /GZornberg  
    /MMathis  
    /TLaughren  
    /RGrewal  
    /KKiedrow  
    /Dbates

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/s/  
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Jing Zhang  
7/23/2008 09:30:45 PM  
MEDICAL OFFICER

Gwen Zornberg  
7/24/2008 06:59:14 AM  
MEDICAL OFFICER

I concur with Dr. Zhang's recommendation of an Approval  
action for these supplements submitted by Lilly.

## CLINICAL REVIEW

|                        |                                                                  |
|------------------------|------------------------------------------------------------------|
| Application Type       | NDA<br>(Complete Response to Approvable Action)                  |
| Submission Number      | 020592                                                           |
| Submission Code        | SE5 040/041                                                      |
| Letter Date            | 2/5/2008                                                         |
| Stamp Date             | 2/5/2008                                                         |
| PDUFA Goal Date        | 8/5/2008                                                         |
| Reviewer Name          | Cara Alfaro, Pharm.D.                                            |
| Review Completion Date | 7/14/2008                                                        |
| Established Name       | Olanzapine                                                       |
| Trade Name             | Zyprexa                                                          |
| Therapeutic Class      | Antipsychotic                                                    |
| Applicant              | Eli Lilly & Co                                                   |
| Priority Designation   | S                                                                |
| Formulation            | Oral tablets                                                     |
| Dosing Regimen         | 2.5 – 5 mg starting, maximum<br>dose 20 mg/day                   |
| Indications            | Treatment of Bipolar I Disorder<br>(040) and Schizophrenia (041) |
| Intended Population    | Adolescents                                                      |

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## 1 EXECUTIVE SUMMARY

### 1.1 Recommendation on Regulatory Action

This is a review of the complete response to the approvable action taken on 4/30/07 for NDAs 20-592 SE5-040 “treatment of acute mixed and manic episodes associated with bipolar disorder in adolescents” and SE5-041 “treatment of schizophrenia in adolescents”. It is recommended that the Division take an approvable action on these supplements and that olanzapine be considered as second line treatment for bipolar disorder and schizophrenia in the adolescent population.

The Sponsor responded to all additional requests for information pertaining to pivotal trials HGIU (bipolar disorder) and HGIN (schizophrenia) outlined in the 4/30/2007 approvable letter (other requests for additional safety data in adults and adolescents were also submitted and reviewed by another clinical reviewer). A review of these data did not reveal new safety risks or significant changes to already known safety risks that warranted significant changes to proposed product labeling beyond the changes suggested in the approvable letter. However, it is recommended that gynecomastia and galactorrhea be included as adverse events in product labeling as they appear to occur more frequently in the adolescent population compared to adults. The Sponsor also adequately addressed the disparity in the efficacy signal primarily driven by the differential placebo response between the United States and Russian sites in study HGIN (schizophrenia).

The recommendation for an approvable action (rather than an approval action) is based on the need for the development of a medication guide discussing significant adverse events in adolescents (b) (4)

Though these adverse events are well known for olanzapine, they occur much more frequently in the adolescent population. Weight gain, hyperglycemia, and hyperlipidemia are significant risk factors for cardiovascular morbidity, especially in disease states such as schizophrenia or bipolar disorder in which it is likely that patients will be taking these medications chronically.

Given these safety concerns, it is recommended that olanzapine be considered as second line therapy for the treatment of bipolar disorder and schizophrenia in the adolescent population. Recently two other antipsychotics, risperidone and aripiprazole, received approval for treatment of bipolar disorder and schizophrenia in adolescents. In comparison to olanzapine, these antipsychotics are not associated with the same magnitude of risk with regard to weight gain, hyperglycemia and hyperlipidemia.

## **1.2 Recommendation on Postmarketing Actions**

### **1.2.1 Risk Management Activity**

The Sponsor submitted a “risk management plan” document, however, it was not a typical risk management plan. The Sponsor has proposed education, labeling changes and some further clinical trials to address the safety risks of olanzapine in both adults and adolescents.

### **1.2.2 Required Phase 4 Commitments**

The Sponsor is planning to conduct a 52-week open-label safety study (Study F1D-MC-HGMX) in adolescent subjects with bipolar disorder or schizophrenia (see Section 7 of review - Studies to be Conducted In Adolescents ). This study is being considered as a Phase 4 commitment. As of this time, the protocol for this study has not been submitted.

No additional Phase 4 commitments are recommended.

## 2 INTRODUCTION AND BACKGROUND

On 10/30/06, Eli Lilly and Company submitted NDA 20-592 SE5-040 and SE5-041 to support the indications “treatment of acute mixed and manic episodes associated with bipolar disorder in adolescents” and “treatment of schizophrenia in adolescents” respectively. An approvable action was taken 4/30/2007 and the Sponsor was asked to submit additional safety analyses as well as further exploration of the disparity in efficacy results between the US and Russian sites (largely driven by a very low placebo response in the Russian sites) in the pivotal adolescent schizophrenia trial (HGIN). The Sponsor was also asked to submit updated information on risks of weight gain, hyperglycemia and hyperlipidemia that would be reflected not only in Zyprexa labeling, but also in Symbyax labeling.

The Sponsor submitted a response on 8/30/2007, this response was considered incomplete (letter date 9/13/2007) since the submission did not include all requested data regarding the risks of weight gain, hyperglycemia and hyperlipidemia. The Sponsor submitted a response on 2/5/2008 and it was considered a complete response. For the purposes of this review, this reviewer is addressing the portions of the complete response pertaining to SE5-040 and SE5-041, specifically the questions posed to the Sponsor for issues relating to the pivotal trials for the bipolar and schizophrenia adolescent trials. Another clinical reviewer (Evelyn Mentari, M.D.) will be reviewing the requested safety information relating to risks of weight gain, hyperglycemia and hyperlipidemia for both adult and adolescent populations.

### 2.1 Brief Overview of Pivotal Trials HGIU and HGIN

Study HGIU was the pivotal trial for establishing efficacy and safety for the indication “treatment of acute mixed or manic episodes associated with bipolar I disorder in adolescents”. This was a multicenter, double-blind, placebo-controlled study in adolescent patients (13 to 17 years of age) with bipolar I disorder. The study consisted of a 3-week acute phase followed by an optional 26 week open-label extension. Patients were randomized (2:1) to flexible dose olanzapine, 2.5 to 20 mg/day (n = 107), or placebo (n = 54).

Study HGIN was the pivotal trial for establishing efficacy and safety for the indication “treatment of schizophrenia in adolescent patients”. This was a multicenter, double-blind, placebo-controlled study in adolescent patients (13 to 17 years of age) with schizophrenia. The study consisted of a 6-week acute phase followed by an optional 26 week open-label extension. Patients were randomized (2:1) to flexible dose olanzapine, 2.5 to 20 mg/day (n = 72), or placebo (n = 35).

## 2.2 Summary Table of Clinical Trials in Original Submission

This summary table is included in this review as some of the Sponsor's responses included additional data from some of the supportive trials.

| Study | Description                                                                                                                                            | Length                              | Age Range (years) | Number of Patients                            |
|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|-------------------|-----------------------------------------------|
| HGIN  | MC, DB, PC study in adolescent patients with schizophrenia.<br>Flexible dose olanzapine (2.5 – 20 mg)<br>U.S. and Russia sites                         | 6 weeks DB<br>26 weeks OL extension | 13 to 17          | 107<br>(n = 72 olanzapine, n = 35 placebo)    |
| HGIU  | MC, DB, PC study in adolescent patients with mixed/manic episode of bipolar I disorder.<br>Flexible dose olanzapine (2.5 – 20 mg)<br>U.S., Puerto Rico | 3 weeks DB<br>26 weeks OL extension | 13 – 17           | 161<br>(n = 107 olanzapine, n = 54 placebo)   |
| LOAY  | OL study in patients with schizophrenia, schizoaffective, and schizophreniform disorders<br>Flexible dose olanzapine (5 – 20 mg)<br>German sites       | 24 weeks                            | 12 – 21           | 96<br>(n = 89, 13-17 years)                   |
| HGMF  | OL study in adolescent patients with schizophrenia or bipolar I disorder<br>Flexible dose olanzapine (2.5 – 20 mg)<br>U.S., Puerto Rico, Russia        | 4.5 weeks                           | 13 – 17           | 107<br>(n = 37 schizophrenia, n = 70 bipolar) |
| HGCS  | OL study in adolescent patients with schizophrenia<br>Dosing: 2.5 to 20 mg/day<br>Single site                                                          | 8 weeks                             | 10 – 18           | 8                                             |
| HGCR  | DB study in adolescent patients with schizophrenia, haloperidol as active comparator<br>Dosing: 2.5 qod – 20 mg/day<br>Single site                     | 8 weeks                             | 12 – 16           | 2                                             |
| HGGC  | OL study in children and adolescents with bipolar disorder<br>Dosing: 2.5 to 20 mg/day<br>Single site (U.S.)                                           | 8 weeks                             | 5 – 14            | 23                                            |

### 3. REQUESTS FOR INFORMATION

This section includes the requests for information that were outlined in the 4/30/2007 approvable letter, the Sponsor’s response and reviewer’s comments.

Table 3.1, below, is from the original NDA submission and defines the different databases used to address various safety signals. Some of the requests for information asked for reanalysis in the Overall Olanzapine Exposure Database.

Table 3.1. Sponsor’s Table – Databases for Summary of Clinical Safety

**Table 2.7.4.1. Databases for Summary of Clinical Safety**

| Database                              | Indication    | Studies Used                  | Number of Patients         |
|---------------------------------------|---------------|-------------------------------|----------------------------|
| Acute Placebo-Controlled Databases    | Schizophrenia | HGIN                          | N=107<br>(Olz=72, Pla=35)  |
|                                       | Bipolar       | HGIU                          | N=161<br>(Olz=107, Pla=54) |
|                                       | Combined      | HGIN, HGIU                    | N=268<br>(Olz=179, Pla=89) |
| Overall Olanzapine Exposure Databases | Schizophrenia | HGIN, LOAY, HGMF <sup>a</sup> | N=227                      |
|                                       | Bipolar       | HGIU, HGMF <sup>a</sup>       | N=227                      |
|                                       | Combined      | HGIN, HGIU, LOAY, HGMF        | N=454                      |

<sup>a</sup> Because Study HGMF enrolled patients with schizophrenia or bipolar disorder, some patients from Study HGMF were included in the Overall Olanzapine Exposure Bipolar Database and some patients from Study HGMF were included in the Overall Olanzapine Exposure Schizophrenia Database.

#### 3.1 Prolactin

##### *Division Request #1*

For the acute phases of HGIU and HGIN, many patients have elevated prolactin at baseline, therefore the change from baseline to endpoint analyses can be difficult to interpret. Please provide additional analyses for the change from baseline to endpoint on the subset of patients with baseline prolactin within the normal range. Please also provide a separate analysis for gender and age.

##### *Data Submitted in the Original Submission*

Prolactin reference ranges for adolescents (13 – 17 years) in study HGIN and HGIU<sup>1</sup>: males = 2.8 – 11 ng/ml; females = 3.2 – 20 ng/ml

In the original analysis of the HGIN + HGIU acute studies, the following change from baseline to endpoint in prolactin concentrations were provided (Table 3.1.1). However, this analysis included subjects with abnormal (usually elevated due to prior therapies) prolactin concentrations making a change from baseline difficult to interpret.

<sup>1</sup> Covance did not have pediatric reference ranges for prolactin. The Sponsor obtained these reference ranges from the Tietz Textbook of Clinical Chemistry (Burtis CA and Ashwood ER 1999).

Clinical Review  
 Cara Alfaro, Pharm.D.  
 NDA 020592 SE5 040/041 – Complete Response to AE Action  
 Zyprexa (olanzapine) tablets

Table 3.1.1. Prolactin: Change from Baseline To Endpoint, All Subjects (HGIN + HGIU)

|                   |            | N   | Baseline |       | Change to Endpoint |       | LS Mean Change | LS Mean Difference | P-value |
|-------------------|------------|-----|----------|-------|--------------------|-------|----------------|--------------------|---------|
|                   |            |     | Mean     | Std   | Mean               | Std   |                |                    |         |
| Prolactin (mcg/L) | Olanzapine | 163 | 14.06    | 9.92  | <b>11.44</b>       | 14.52 | 10.51          |                    |         |
|                   | Placebo    | 80  | 14.95    | 11.86 | <b>-0.16</b>       | 10.69 | -1.15          | 11.66              | < 0.001 |

The Sponsor also included a prolactin analysis by gender since it is well established that females have a more pronounced elevation in prolactin concentration with antipsychotic therapy.

Table 3.1.2. Prolactin Analysis by Gender

| Laboratory Evaluations | Gender | Therapy | Baseline |       |       | Change to Endpoint |       |               | LSMean Change | LSMean Difference | *P-value | **P-value |
|------------------------|--------|---------|----------|-------|-------|--------------------|-------|---------------|---------------|-------------------|----------|-----------|
|                        |        |         | N        | Mean  | Std   | Mean               | Std   | LSMean Change |               |                   |          |           |
| PROLACTIN              | Female | olz     | 63       | 15.87 | 10.06 | 15.63              | 16.86 | 14.26         | 14.25         | <.001             | .236     |           |
|                        |        | Placebo | 37       | 15.25 | 7.59  | 1.35               | 9.20  | 0.00          |               |                   |          |           |
|                        | Male   | olz     | 100      | 12.92 | 9.71  | 8.80               | 12.20 | 8.70          | 10.12         | <.001             |          |           |
|                        |        | Placebo | 43       | 14.70 | 14.67 | -1.46              | 11.78 | -1.42         |               |                   |          |           |

In the original analysis, the Sponsor did not provide a prolactin analysis by age.

*Sponsor's Response*

Seventy percent of olanzapine-treated subjects (114/163) and 71% of placebo-treated subjects (57/80) had normal baseline prolactin concentrations. Table 3.1.3 provides the reanalysis by the Sponsor including only those subjects with normal baseline prolactin levels.

Table 3.1.3. Prolactin: Change from Baseline To Endpoint, Subjects with Normal Baseline Prolactin (HGIN + HGIU)

|                   |            | N   | Baseline |      | Change to Endpoint |       | LS Mean Change | LS Mean Difference | P-value |
|-------------------|------------|-----|----------|------|--------------------|-------|----------------|--------------------|---------|
|                   |            |     | Mean     | Std  | Mean               | Std   |                |                    |         |
| Prolactin (mcg/L) | Olanzapine | 114 | 11.72    | 6.63 | <b>12.98</b>       | 11.93 | 12.24          |                    |         |
|                   | Placebo    | 57  | 12.07    | 6.34 | <b>2.32</b>        | 7.30  | 1.48           | 10.76              | < 0.001 |

From Sponsor table APP.1.1 in Regulatory Response document

Table 3.1.4. Prolactin Analysis by Gender and Age, Subjects with Normal Baseline Prolactin (HGIN + HGIU)

| Laboratory Evaluations | Subgroup | Group   | Therapy | N    | Baseline |       | Change to Endpoint |       | LSMean Change | LSMean Difference | *P-value | **P-value |
|------------------------|----------|---------|---------|------|----------|-------|--------------------|-------|---------------|-------------------|----------|-----------|
|                        |          |         |         |      | Mean     | Std   | Mean               | Std   |               |                   |          |           |
| PROLACTIN              | Gender   | Female  | Olz     | 47   | 14.65    | 8.68  | 15.14              | 15.25 | 12.66         | 11.96             | <.001    | .574      |
|                        |          |         | Placebo | 29   | 15.14    | 7.21  | 3.19               | 8.98  | 0.70          |                   |          |           |
|                        | Male     | Olz     | 67      | 9.67 | 3.53     | 11.47 | 8.72               | 11.57 | 10.01         | <.001             |          |           |
|                        |          | Placebo | 28      | 8.90 | 2.99     | 1.41  | 5.01               | 1.56  |               |                   |          |           |
|                        | Age      | <15     | Olz     | 46   | 12.02    | 6.37  | 14.70              | 13.60 | 11.15         | 14.86             | <.001    | .080      |
|                        |          |         | Placebo | 18   | 10.97    | 2.98  | -0.22              | 3.72  | -3.71         |                   |          |           |
| >=15                   | Olz      | 68      | 11.52   | 6.84 | 11.82    | 10.61 | 11.76              | 8.53  | <.001         |                   |          |           |
|                        | Placebo  | 39      | 12.58   | 7.38 | 3.49     | 8.24  | 3.23               |       |               |                   |          |           |

*Reviewer Comments*

In the reanalysis including only those subjects with normal baseline prolactin (Table 3.1.3), the change from baseline to endpoint in olanzapine-treated subjects is slightly greater (12.98 mcg/L) compared to the original analysis (11.44 mcg/L). However, change from baseline to endpoint in placebo-treated subjects was also greater (2.32 mcg/L) compared to the original analysis (-0.16 mcg/L) such that the LS mean difference is lower in this analysis (10.76) compared to the original analysis (11.66). Both analyses found these differences between treatment groups to be statistically significant ( $p < 0.001$ ).

For the gender analysis, the results from this reanalysis including only those subjects with normal baseline prolactin concentrations was similar to the original analysis; however, the change from baseline to endpoint in olanzapine-treated males was higher in this analysis (11.47 mcg/L) compared to the original analysis (8.80 mcg/L). The LS mean differences in this analysis were less than the original analysis primarily due to an increase in change from baseline to endpoint in placebo-treated subjects. The overall results are essentially the same – no differential gender effects were noted; olanzapine increases prolactin concentrations to the same degree in both male and female adolescents.

The Sponsor had not provided an age subgroup analysis in the original submission. This analysis (including only those subjects with normal baseline prolactin concentrations) found a statistically significant ( $p = 0.08$ ) increase in prolactin concentrations in olanzapine-treated subjects < 15 years old compared to subjects  $\geq 15$  years old. Mean change from baseline to endpoint for olanzapine-treated subjects < 15 years old was 14.7 mcg/L compared to 11.82 mcg/L in subjects  $\geq 15$  years old. It does appear, however, that the statistical differences may have been driven by differences in the placebo-treated subjects: change in prolactin for subjects < 15 years old was -0.22 mcg/L compared to 3.49 mcg/L for subjects  $\geq 15$  years old.

*Division Request #2*

Table APP.2.7.4.24 in summary-clin-safe-app provides prolactin data over time for the overall combined database. Please provide a similar table for only those patients who completed 19-32

weeks in the study (n = 83 bipolar, n = 93 schizophrenia) – e.g. provide baseline, 1-6 week, 7-18 week and 19-32 week data for only those patients completing 19-32 weeks.

*Data Submitted in the Original Submission*

In the original submission, the Sponsor had included prolactin concentrations for all subjects in the Overall Olanzapine Exposure Combined Database (see Table 3.1.5). However, it was difficult to evaluate patterns over time in subjects completing the trials since these data also included subjects who dropped out over the course of these trials. Therefore, the Sponsor was asked to provide these data only for subjects completing these trials in order to evaluate a potential pattern in prolactin concentration for subjects with exposures up to 6-8 months.

Table 3.1.5 Sponsor’s Table. Mean Prolactin Concentrations at Various Timepoints: Overall Olanzapine Exposure Combined Database

**Table APP.2.7.4.7.4.24. Mean Prolactin Values at Various Time Points  
 Overall Olanzapine Exposure Combined Database**

| Database      | Olz Exposure | Summary |       |       |        |        |
|---------------|--------------|---------|-------|-------|--------|--------|
|               |              | N       | Mean  | Std   | Median | Max    |
| Bipolar       | Baseline     | 217     | 15.35 | 12.58 | 11.28  | 110.30 |
|               | 1-6 weeks    | 174     | 26.60 | 16.18 | 23.10  | 129.66 |
|               | 7-18 weeks   | 122     | 19.24 | 11.89 | 16.71  | 59.49  |
|               | 19-32 weeks  | 83      | 18.03 | 10.42 | 14.36  | 49.53  |
| Schizophrenia | Baseline     | 214     | 18.84 | 19.97 | 11.87  | 131.57 |
|               | 1-6 weeks    | 190     | 31.82 | 20.75 | 26.48  | 110.84 |
|               | 7-18 weeks   | 88      | 22.75 | 16.24 | 18.62  | 112.00 |
|               | 19-32 weeks  | 93      | 19.01 | 15.60 | 14.81  | 109.97 |
| Overall       | Baseline     | 431     | 17.08 | 16.74 | 11.60  | 131.57 |
|               | 1-6 weeks    | 364     | 29.33 | 18.86 | 25.00  | 129.66 |
|               | 7-18 weeks   | 210     | 20.71 | 13.95 | 17.13  | 112.00 |
|               | 19-32 weeks  | 176     | 18.55 | 13.38 | 14.70  | 109.97 |

*Sponsor's Response*

Table 3.1.6. Sponsor's Table. Mean Prolactin Concentrations at Various Timepoints: Overall Combined Database for Subjects Completing 19-32 weeks of Olanzapine Exposure

| Database      | Olz Exposure | Summary |       |       |        |        |
|---------------|--------------|---------|-------|-------|--------|--------|
|               |              | N       | Mean  | Std   | Median | Max    |
| Bipolar       | Baseline     | 83      | 12.91 | 8.04  | 10.36  | 37.41  |
|               | 1-6 weeks    | 49      | 27.21 | 11.65 | 25.86  | 60.72  |
|               | 7-18 weeks   | 83      | 18.88 | 10.78 | 17.11  | 59.49  |
|               | 19-32 weeks  | 83      | 18.03 | 10.42 | 14.36  | 49.53  |
| Schizophrenia | Baseline     | 93      | 18.03 | 17.37 | 11.98  | 100.00 |
|               | 1-6 weeks    | 74      | 31.22 | 21.54 | 24.34  | 104.00 |
|               | 7-18 weeks   | 55      | 20.03 | 11.60 | 16.83  | 54.11  |
|               | 19-32 weeks  | 93      | 19.01 | 15.60 | 14.81  | 109.97 |
| Overall       | Baseline     | 176     | 15.62 | 13.98 | 11.17  | 100.00 |
|               | 1-6 weeks    | 123     | 29.62 | 18.30 | 24.68  | 104.00 |
|               | 7-18 weeks   | 138     | 19.34 | 11.09 | 16.87  | 59.49  |
|               | 19-32 weeks  | 176     | 18.55 | 13.38 | 14.70  | 109.97 |

*Reviewer Comments*

For this reanalysis (as in the original analysis), sample sizes vary by timepoint likely due to differences in the various protocols. Similar to the original analysis, the increase in mean prolactin values appears to occur early (1-6 weeks) and decreases at subsequent timepoints; though still elevated compared to baseline concentrations. This analysis was requested so that data could be evaluated over time in the same group of subjects – however, obviously, if subjects dropped out of the study due to prolactin elevations (or other reasons but also had elevated prolactin concentrations), this analysis would not include those subjects and may underestimate the effect. However, the prior analysis did include all subjects and results between the analyses were very similar.

*Proposed Language in Product Labeling re: Prolactin*

The Sponsor was asked to include the frequency of hyperprolactinemia in adolescents in this section and also included this data for the adult populations.

Section 5 – WARNINGS AND PRECAUTIONS; 5.16 Hyperprolactinemia

“In clinical studies, plasma prolactin concentrations were elevated in 34% of adults treated with olanzapine. These elevations were mild and transient (end-point mean not above upper limits of normal and not statistically significantly different from placebo). Associated clinical manifestations (e.g. gynecomastia, galactorrhea, and breast enlargement) were rare. In most patients, levels returned to normal ranges without cessation of treatment.

In placebo-controlled olanzapine monotherapy studies in adolescent patients with schizophrenia or bipolar disorder (manic or mixed episodes), elevated prolactin concentrations occurred in 47.4% of olanzapine-treated patients compared to 6.8% of patients in the placebo group.”

This frequency data is also reflected in Section 6 ADVERSE REACTIONS, 6.2 Vital Signs and Laboratory Studies.

The frequency data do not indicate the magnitude of the elevations in prolactin, the adult data included in currently approved labeling also do not indicate the magnitude of prolactin elevation (only the frequency of occurrence). Unlike adverse events of weight gain or ALT increases, there is not a well recognized potentially clinically significant change in which to further categorize these increases. Therefore, it is reasonable to include only the frequencies of prolactin increases and then to note elsewhere in labeling adverse events that may be related to hyperprolactinemia.

Since the Sponsor has now included data about the frequency of potentially prolactin-related adverse events for adults, this data should also be included for adolescents – however, these effects are not rare in the latter population (refer to Sections 3.2 [Additional Narrative Summaries] and 4 [Safety Update] of review).

I would propose to add the following data which is from the original submission (Table 2.7.4.31 in summary-clin-safety document):

In clinical trials of olanzapine in adolescents, gynecomastia occurred in 2.4% of males (7/286) and galactorrhea occurred in 1.8% of females (3/168).

These adverse events (gynecomastia and galactorrhea) should also be noted in the section of labeling: 6 ADVERSE REACTIONS, 6.1 Clinical Trials Experience, Other Adverse Events Observed During the Clinical Trial Evaluation of Oral Olanzapine. These events would be considered frequent (based on the 1/100 definition).

### 3.2 Additional Narrative Summaries

#### *Division Request #3*

Please provide narrative summaries for the following: 8 cases of gynecomastia, 2 cases with high prolactin concentrations (HGIN 005-503, HGIN 900-9009) and the case with a CPK of 7289 U/L.

The Sponsor supplied the requested narratives. This reviewer compiled a table (Table 3.2.1) summarizing some of the relevant information for the cases of gynecomastia (7 cases, one subject experienced the adverse event twice).

Prolactin reference ranges for adolescents (13 – 17 years) in study HGIN and HGIU: males = 2.8 – 11 ng/ml; females = 3.2 – 20 ng/ml

Prolactin reference ranges for adolescents in study LOAY:

Males  $\geq 12$  but  $\leq 13$  years = 2.8 – 24 ng/ml;  $\geq 14$  but  $\leq 16$  years = 2.8 – 16.1 ng/ml;  $> 16$  but  $\leq 19$  years = 2.1 – 17.7 ng/ml

Females  $\geq 12$  but  $\leq 13$  years = 2.5 – 16.9 ng/ml;  $\geq 14$  but  $\leq 16$  years = 4.2 – 29 ng/ml;  $> 16$  but  $\leq 19$  years = 2.8 – 29.2 ng/ml

Table 3.2.1. Summary Table for Gynecomastia Cases

| Patient ID     | Demographics | Baseline Prolactin (mcg/L) | Prolactin During Study (mcg/L)<br>*indicates prolactin at time of AE report | Clinical Description          | Resolved?                                                                                            |
|----------------|--------------|----------------------------|-----------------------------------------------------------------------------|-------------------------------|------------------------------------------------------------------------------------------------------|
| HGIN-910-9103* | 15 YOM       | 6.12                       | 21.3 (~5 weeks)*<br>19.1 (3 months)<br>12.2 (7 months)                      | Left side gynecomastia (mild) | Ongoing at study completion                                                                          |
| LOAY-400-4008  | 17 YOM       | 10.50                      | 23.0 (~2 weeks)*<br>16.8 (1 month)<br>16.8 (2 months)<br>7.4 (6 months)     | Gynecomastia (mild)           | Ongoing at study completion                                                                          |
| LOAY-400-4009  | 14 YOM       | 3.90                       | 30 (2 weeks)<br>28 (3 weeks)<br>32 (5 weeks)<br>NA*<br>41 (2 months)        | Gynecomastia (moderate)       | Noted at baseline visit. Severity changed to severe at 2 months. Ongoing at time of discontinuation. |
| LOAY-406-4063  | 17 YOM       | 5.50                       | 25 (2 weeks)<br>36 (1 month)<br>34 (5 weeks)<br>30 (6 weeks)*               | Gynecomastia (mild)           | NA                                                                                                   |
| LOAY-407-4074  | 17 YOM       | 9.50                       | 23 (2 weeks)<br>24 (1 month)<br>20 (5 weeks)<br>12.80 (6 months)*           | Gynecomastia (mild)           | AE noted at last study visit                                                                         |
| LOAY-407-4077  | 16 YOM       | 17.7                       | 31 (2 weeks)<br>37 (1 month)<br>37 (6 weeks)<br>14.7 (7 months)*            | Gynecomastia (mild)           | AE noted at last study visit                                                                         |
| LOAY-407-4201  | 16 YOM       | 17.3                       | 27 (2 weeks)<br>24 (1 month)*<br>20 (6 weeks)*<br>28 (2 months)             | Gynecomastia (mild)           | Ongoing at study discontinuation.                                                                    |

\* Sponsor indicates that 2 cases of gynecomastia occurred in this patient – the narrative indicates that the subject had these symptoms “periodically” since ~2 years prior to study participation. It is noteworthy that this subject had a prolactin concentration of 95.35 mcg/ml at Visit 1 (presumably screening visit).

*Reviewer Comments*

Seven subjects participating in the clinical trials for bipolar disorder and schizophrenia had an adverse event “gynecomastia”. Interestingly, six of these subjects participated in the 24-week open label LOAY study conducted exclusively in Germany (these cases occurred at 3 different sites and 3 different investigators). These cases were associated with some elevations in prolactin concentration and most were considered by the investigators to be of mild severity. Though the narratives did not include vital sign data, this reviewer wanted to evaluate the weight gain in these subjects since fat deposition in the breast area, “pseudogynecomastia”, might be mistaken as gynecomastia. Not surprisingly, these subjects gained a significant amount of weight over the course of these studies – from 9.1 to 24.6 kg over ~24 weeks (Table 3.2.2).

Table 3.2.2. Weight Changes in Subjects with the Adverse Event Gynecomastia

|               | Baseline |      | End of Study |      | Change from Baseline to Endpoint |     |
|---------------|----------|------|--------------|------|----------------------------------|-----|
|               | Weight   | BMI  | Weight       | BMI  | Weight                           | BMI |
| HGIN-910-9103 | 58 kg    | 20.1 | 82 kg        | 28.4 | 24 kg                            | 8.3 |
| LOAY-400-4008 | 83.5 kg  | 24.7 | 108.1 kg     | 31.9 | 24.6 kg                          | 7.2 |
| LOAY-400-4009 | 66.6 kg  | 23.6 | 78.8 kg      | 27.9 | 12.2 kg                          | 4.3 |
| LOAY-406-4063 | 62.7 kg  | 20   | 71.8 kg      | 22.9 | 9.1 kg                           | 2.9 |
| LOAY-407-4074 | 65.9 kg  | 20.3 | 82.6 kg      | 25.5 | 16.7 kg                          | 5.2 |
| LOAY-407-4077 | 63.3 kg  | 19.8 | 82 kg        | 25.6 | 18.7 kg                          | 5.8 |
| LOAY-407-4201 | 65.5 kg  | 22.7 | 81.7 kg      | 28.3 | 16.2 kg                          | 5.6 |

According to Harrison’s medical textbook, gynecomastia is not uncommon in teenage boys with 65% of 14 year-old boys having gynecomastia that usually goes away on its own in 2 or 3 years (hormonally-related). However, the temporal association with olanzapine therapy may implicate the antipsychotic in this adverse event. These cases are not, however, associated with remarkably elevated prolactin concentrations (upper range of normal in males in this age range = 16 to 18 ng/ml for reference ranged used in LOAY) such that it is not clear that these were in fact cases of gynecomastia and may be cases of pseudogynecomastia secondary to significant weight gain. However, since the investigators used the term “gynecomastia” as an adverse event term for these cases, this reviewer will assume this to be correct (since it does not appear to have been queried by the Sponsor) and will recommend some labeling changes to reflect this information (see Section 3.1 [Prolactin] of review). It is not clear to this reviewer why the majority of these cases were from one clinical trial (LOAY).

Elevated Prolactin Cases

HGIN-005-0503 14 YOF. Baseline prolactin 17.2 mcg/L, increased to 90.68 mcg/L at ~6 weeks (no other labs available between these two values). Subsequent prolactin concentrations were 40.2 mcg/L at ~4.5 months and 45.5 mcg/L at ~7.5 months. The subject was receiving olanzapine 20 mg/day when the 90.68 and 45.5 mcg/L concentrations were obtained. No adverse events reported that were associated with elevated prolactin.

HGIN-900-9009 17 YOF. Baseline prolactin 17.5, elevation to 109.97 mcg/L noted at study completion (~8 months); prolactin concentration prior to this was 17.0 mcg/L at ~4 months. Subject was receiving olanzapine 10 mg/day when elevated concentration obtained. No adverse events associated with elevated prolactin were noted.

CPK Elevation Case

HGIN-004-0401 14 YOM. No baseline CPK available. Elevated CPK of 7289 U/L (reference range = 0 – 363 U/L noted one week after randomization – this was the highest CPK value obtained. CPKs were monitored weekly/monthly thereafter and ranged from 445 – 1766 U/L with no clear trend; last CPK noted as 781 U/L at ~8 months. CK-MB concentrations were obtained at some timepoints and most were elevated (5.2 – 10 ng/ml; reference range 0 – 4.9 ng/ml). Urine myoglobin obtained once (at ~2 months when CPK = 531 U/L) and was < 0.006.

Of note, the subject was receiving haloperidol decanoate prior to the study and, if narrative is correct, received his last dose approximately 9 days prior to randomization. No comments regarding extent of exercise or other potential contributing causes.

*Reviewer Comments*

This reviewer has recommended some labeling language to reflect the gynecomastia cases (see section 3.1 [Prolactin] of review).

The elevated prolactin cases appear to be related to olanzapine therapy and both occurred in female subjects who tend to have a more robust prolactin response to antipsychotics. These were the most significant elevations noted during the original review and appear to represent outliers. Per the Sponsor, there were no adverse events associated with the elevated prolactin, though it is not clear how this was determined (spontaneous reports vs. specific queries for prolactin-related adverse events).

The elevated CPK case was impressive and the highest value (7289 U/L) was noted one week after randomization – it is possible that this could have been secondary to a haloperidol decanoate injection which appears to have been received 9 days prior to randomization (protocol violation). The CPK was consistently elevated over the course of the 8 month trial, though concentrations were quite variable.

No further labeling changes based on these additional cases (elevated prolactin and CPK) is recommended.

**3.3 Hepatic Analytes**

*Division Request #4*

The summary-clin-safe-app document includes comparisons of adult and adolescent data for metabolic parameters and prolactin but not for hepatic laboratory analytes. Please provide these comparisons for hepatic laboratory analytes. Although it is stated in the submission that the hepatic laboratory analyte comparisons were not provided due to differences in reference ranges for adults and adolescents, these comparisons were provided for the prolactin data despite differences in reference ranges for these populations.

*Sponsor's Response*

The Sponsor provided the following data for mean change from baseline to endpoint in hepatic analytes using normalized units for comparing the adolescent and adult populations. Statistically significant, though small, changes were noted for alkaline phosphatase (adolescents > adults) and total bilirubin (decreases noted in both populations).

Table 3.3.1. Sponsor's Table. Mean Change from Baseline to Endpoint in Hepatic Analytes (Normalized Units). Comparison of Adult Versus Adolescent Patients (Overall Exposure Database)

| Laboratory Evaluations | Unit   | Population | N    | Baseline |       | Change to Endpoint |        | LSMean Change | LSMean Difference | *P-value |
|------------------------|--------|------------|------|----------|-------|--------------------|--------|---------------|-------------------|----------|
|                        |        |            |      | Mean     | Std   | Mean               | Std    |               |                   |          |
| AST/SGOT               | %URL   | Adolescent | 446  | 59.35    | 51.72 | 9.00               | 54.59  | 7.29          | -0.81             | .767     |
|                        |        | Adult      | 7074 | 63.19    | 36.97 | 7.99               | 59.21  | 8.10          |                   |          |
| ALT/SGPT               | %URL   | Adolescent | 446  | 57.30    | 74.23 | 21.39              | 82.65  | 18.09         | 3.49              | .520     |
|                        |        | Adult      | 7084 | 66.00    | 57.78 | 14.39              | 115.43 | 14.60         |                   |          |
| ALKALINE PHOSPHATASE   | %URL   | Adolescent | 446  | 65.27    | 30.13 | 4.38               | 18.19  | 4.33          | 1.96              | .019     |
|                        |        | Adult      | 7132 | 65.59    | 20.42 | 2.37               | 17.36  | 2.37          |                   |          |
| GGT (GGGT/SGGT/YGGT)   | %URL   | Adolescent | 446  | 43.60    | 31.34 | 8.19               | 32.44  | 5.88          | 1.33              | .582     |
|                        |        | Adult      | 7051 | 54.40    | 52.99 | 4.40               | 51.93  | 4.54          |                   |          |
| BILIRUBIN, TOTAL       | umol/L | Adolescent | 446  | 8.56     | 5.96  | -1.12              | 4.60   | -1.19         | -0.94             | <.001    |
|                        |        | Adult      | 7182 | 8.71     | 5.22  | -0.26              | 6.05   | -0.25         |                   |          |

The Sponsor also provided an analysis for treatment-emergent abnormally high hepatic analyte values (> 1X ULN) at anytime for adolescent and adult populations – the Sponsor did not include these data for ALT ≥ 3x ULN. In general, a greater percentage of adolescent subjects had increases in AST, ALT and alkaline phosphatase compared to adult subjects.

Table 3.3.2. Sponsor's Table. Treatment-Emergent Abnormally High Hepatic Analyte Values (> 1X ULN) at Anytime, Adult versus Adolescents (Overall Exposure Database)

| Laboratory Analyte   | Direction | Population | N    | n    | (%)   | *P-Value |
|----------------------|-----------|------------|------|------|-------|----------|
| AST/SGOT             | High      | Adolescent | 418  | 127  | 30.4% | <.001    |
|                      |           | Adult      | 6338 | 1459 | 23.0% |          |
| ALT/SGPT             | High      | Adolescent | 396  | 169  | 42.7% | <.001    |
|                      |           | Adult      | 5891 | 1791 | 30.4% |          |
| ALKALINE PHOSPHATASE | High      | Adolescent | 387  | 52   | 13.4% | <.001    |
|                      |           | Adult      | 6655 | 469  | 7.0%  |          |
| GGT (GGGT/SGGT/YGGT) | High      | Adolescent | 432  | 34   | 7.9%  | .136     |
|                      |           | Adult      | 6292 | 642  | 10.2% |          |
| BILIRUBIN, TOTAL     | High      | Adolescent | 423  | 9    | 2.1%  | .054     |
|                      |           | Adult      | 7080 | 75   | 1.1%  |          |

*Reviewer Comments*

The mean change from baseline to endpoint in hepatic analytes for adult versus adolescents (including the open-label trials) did not indicate significant differences between these populations. In contrast, the percentage of subjects experiencing an abnormally high hepatic analyte concentration was generally higher for adolescents compared to adults; especially for AST, ALT and alkaline phosphatase.

*Proposed Language in Product Labeling re: Hepatic Analytes*

The proposed labeling includes data from the placebo-controlled trials and indicates the increased incidence of elevations in ALT ( $\geq 3x$  ULN) in adolescents compared to adults. This reviewer has no additional recommendations for further labeling based on these additional analyses.

**In Section 5 Warnings and Precautions (5.12 Transaminase Elevations)**

“In placebo-controlled olanzapine monotherapy studies in adolescents, clinically significant ALT elevations (change from  $< 3$  times the upper limit of normal at baseline to  $> 3$  times the upper limit of the normal range) were observed in 12% (21/174) of patients exposed to olanzapine compared to 2% (2/87) of the placebo-treated patients. Discontinuation due to transaminase increases occurred in 3.4% (6/179) of patients exposed to olanzapine”.

**In Section 6.2 Vital Signs and Laboratory Studies**

“In placebo-controlled clinical trials of adolescent patients with schizophrenia or bipolar 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  $< 3 X$  ULN) (12.1% vs. 2.3%); elevated AST (27.6% vs 3.8%); low total bilirubin (22.1% vs 6.7%); elevated GGT (10.1% vs 1.2%)...”

**3.4 Fatalities**

*Division Request #5*

Please review the MedWatch reports for fatalities and submit updates where possible for incomplete data. It was noted that these MedWatch reports had “DRAFT” at the top of the page and the date of the report was 7/27/06. Have all of these reports been previously filed with the Agency?

*Sponsor's Response*

The Sponsor indicated that because these MedWatch forms were generated for the purposes of a submission dossier, they all showed the date that they were generated (7/27/06) and were marked “draft”. The Sponsor also stated that all of the MedWatch forms for fatalities had been previously filed to NDA 20-592 (submission dates 12/16/97 to 5/19/06).

*Reviewer Comments*

No further information is requested.

*Division Request #6*

For MedWatch fatality case US\_010158510, the narrative states “this is one of five deaths (Cases: US\_01058498, US\_010158510, US\_010158520, US\_010158524, US\_010158537) reported by the same reporter. All deaths occurred in (b) (4). The reported stated he has also notified the FDA...”. The only MedWatch report included in this submission