

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LATUDA is not approved for the treatment of patients with dementia-related psychosis [see *Warnings and Precautions (5.1)*].

Suicidal Thoughts and Behaviors

Antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adults in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors [see *Warnings and Precautions (5.2)*].

1 INDICATIONS AND USAGE

LATUDA is indicated for:

- Treatment of adult and adolescent patients (13 to 17 years) with schizophrenia [see *Clinical Studies (14.1)*].
- Monotherapy treatment of adult and pediatric patients (10 to 17 years) with major depressive episode associated with bipolar I disorder (bipolar depression) [see *Clinical Studies (14.2)*].
- Adjunctive treatment with lithium or valproate in adult patients with major depressive episode associated with bipolar I disorder (bipolar depression) [see *Clinical Studies (14.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Schizophrenia

Adults

The recommended starting dose of LATUDA is 40 mg once daily. Initial dose titration is not required. LATUDA has been shown to be effective in a dose range of 40 mg per day to 160 mg per day [see *Clinical Studies (14.1)*]. The maximum recommended dose is 160 mg per day.

Adolescents (13 – 17 years)

The recommended starting dose of LATUDA is 40 mg once daily. Initial dose titration is not required. LATUDA has been shown to be effective in a dose range of 40 mg per day to 80 mg per day [see *Clinical Studies (14.1)*]. The maximum recommended dose is 80 mg per day.

2.2 Depressive Episodes Associated with Bipolar I Disorder

Adults

The recommended starting dose of LATUDA is 20 mg given once daily as monotherapy or as adjunctive therapy with lithium or valproate. Initial dose titration is not required. LATUDA has been shown to be effective in a dose range of 20 mg per day to 60 mg per day as monotherapy or 20 mg per day to 120 mg per day as adjunctive therapy with lithium or valproate [*see Clinical Studies (14.2)*]. The maximum recommended dose as monotherapy is 60 mg per day or as adjunctive therapy with lithium or valproate is 120 mg per day. In the monotherapy study, the higher dose range (80 mg to 120 mg per day) did not provide additional efficacy, on average, compared to the lower dose range (20 to 60 mg per day) [*see Clinical Studies (14.2)*].

Pediatric Patients (10 – 17 years)

The recommended starting dose of LATUDA is 20 mg given once daily as monotherapy. Initial dose titration is not required. The dose may be increased after one week based on clinical response. LATUDA has been shown to be effective in a dose range of 20 mg per day to 80 mg per day as monotherapy. At the end of the clinical study, most of the patients (67%) received 20 mg or 40 mg once daily [*see Clinical Studies (14.2)*]. The maximum recommended dose is 80 mg per day.

The efficacy of LATUDA in the treatment of mania associated with bipolar disorder has not been established.

2.3 Administration Information

LATUDA should be taken with food (at least 350 calories). Administration with food substantially increases the absorption of LATUDA. Administration with food increases the AUC approximately 2-fold and increases the Cmax approximately 3-fold. In the clinical studies, LATUDA was administered with food [*see Clinical Pharmacology (12.3)*].

The effectiveness of LATUDA for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient [*see Dosage and Administration (2.1 and 2.2)*].

2.4 Dose Modifications for Renal Impairment

Dose adjustment is recommended in moderate (creatinine clearance: 30 to <50 mL/min) and severe renal impairment (creatinine clearance <30 mL/min) patients. The recommended starting dose is 20 mg per day. The dose in these patients should not exceed 80 mg per day [*see Use in Specific Populations (8.6)*].

2.5 Dose Modifications for Hepatic Impairment

Dose adjustment is recommended in moderate (Child-Pugh Score = 7 to 9) and severe hepatic impairment (Child-Pugh Score = 10 to 15) patients. The recommended starting dose is 20 mg per day. The dose in moderate hepatic impairment patients should not exceed 80 mg per day and the dose in severe hepatic impairment patients should not exceed 40 mg/day [*see Use in Specific Populations (8.7)*].

2.6 Dose Modifications Due to Drug Interactions of CYP3A4 Inhibitors and CYP3A4 Inducers

Concomitant Use with CYP3A4 Inhibitors

LATUDA should not be used concomitantly with a strong CYP3A4 inhibitor (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, etc.) [see *Contraindications* (4)].

If LATUDA is being prescribed and a moderate CYP3A4 inhibitor (e.g. diltiazem, atazanavir, erythromycin, fluconazole, verapamil etc.) is added to the therapy, the LATUDA dose should be reduced to half of the original dose level. Similarly, if a moderate CYP3A4 inhibitor is being prescribed and LATUDA is added to the therapy, the recommended starting dose of LATUDA is 20 mg per day, and the maximum recommended dose of LATUDA is 80 mg per day [see *Contraindications* (4), *Drug Interactions* (7.1)].

Grapefruit and grapefruit juice should be avoided in patients taking LATUDA, since these may inhibit CYP3A4 and alter LATUDA concentrations [see *Drug Interactions* (7.1)].

Concomitant Use with CYP3A4 Inducers

LATUDA should not be used concomitantly with a strong CYP3A4 inducer (e.g., rifampin, avasimibe, St. John's wort, phenytoin, carbamazepine, etc.) [see *Contraindications* (4); *Drug Interactions* (7.1)]. If LATUDA is used concomitantly with a moderate CYP3A4 inducer, it may be necessary to increase the LATUDA dose after chronic treatment (7 days or more) with the CYP3A4 inducer.

3 DOSAGE FORMS AND STRENGTHS

LATUDA tablets are available in the following shape and color (Table 1) with respective one-sided debossing.

Table 1: LATUDA Tablet Presentations

| Tablet Strength | Tablet Color/Shape | Tablet Markings |
|-----------------|--------------------------|-----------------|
| 20 mg | white to off-white round | L20 |
| 40 mg | white to off-white round | L40 |
| 80 mg | pale green oval | L80 |

4 CONTRAINDICATIONS

- Known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone [see *Adverse Reactions* (6.1)].
- Strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, etc.) [see *Drug Interactions* (7.1)].
- Strong CYP3A4 inducers (e.g., rifampin, avasimibe, St. John's wort, phenytoin, carbamazepine, etc.) [see *Drug Interactions* (7.1)].

5 **WARNINGS AND PRECAUTIONS**

5.1 **Increased Mortality in Elderly Patients with Dementia-Related Psychosis**

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6- to 1.7-times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. LATUDA is not approved for the treatment of patients with dementia-related psychosis [see *Boxed Warning, Warnings and Precautions (5.3)*].

5.2 **Suicidal Thoughts and Behaviors in Pediatric and Young Adult Patients**

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients, and over 4,400 pediatric patients, the incidence of suicidal thoughts and behaviors in pediatric and young adult patients was greater in antidepressant-treated patients than in placebo-treated patients. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in [Table 2](#).

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

Table 2: Risk Differences of the Number of Cases of Suicidal Thoughts or Behaviors in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric and Adult Patients

| Age Range | Drug-Placebo Difference in Number of Patients of Suicidal Thoughts or Behaviors per 1000 Patients Treated |
|-------------------------------|---|
| Increases Compared to Placebo | |
| <18 | 14 additional patients |
| 18-24 | 5 additional patients |
| Decreases Compared to Placebo | |
| 25-64 | 1 fewer patient |
| ≥65 | 6 fewer patients |

It is unknown whether the risk of suicidal thoughts and behaviors in pediatric and young adult patients extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with MDD that antidepressants delay the recurrence of depression.

Monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing LATUDA, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

5.3 Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks), including fatalities, compared to placebo-treated subjects. LATUDA is not approved for the treatment of patients with dementia-related psychosis [see *Boxed Warning, Warnings and Precautions (5.1)*].

5.4 Neuroleptic Malignant Syndrome

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

If NMS is suspected, immediately discontinue LATUDA and provide intensive symptomatic treatment and monitoring.

5.5 Tardive Dyskinesia

Tardive dyskinesia is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can 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.

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, LATUDA 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 who suffer from a chronic illness that (1) 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 LATUDA, drug discontinuation should be considered. However, some patients may require treatment with LATUDA despite the presence of the syndrome.

5.6 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus

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

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Schizophrenia

Adults

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in [Table 3](#).

Table 3: Change in Fasting Glucose in Adult Schizophrenia Studies

| LATUDA | | | | | | |
|--|--------------------------|-------------------------|----------------------------|--------------------------|---------------------------|-------------------------|
| Placebo | 20 mg/day | 40 mg/day | 80 mg/day | 120 mg/day | 160 mg/day | |
| Mean Change from Baseline (mg/dL) | | | | | | |
| n=680 | n=71 | n=478 | n=508 | n=283 | n=113 | |
| Proportion of Patients with Shifts to ≥ 126 mg/dL | | | | | | |
| Serum Glucose | -0.0 | -0.6 | +2.6 | -0.4 | +2.5 | +2.5 |
| Serum Glucose (≥ 126 mg/dL) | 8.3% (52/628) | 11.7% (7/60) | 12.7% (57/449) | 6.8% (32/472) | 10.0% (26/260) | 5.6% (6/108) |

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in glucose of +1.8 mg/dL at week 24 (n=355), +0.8 mg/dL at week 36 (n=299) and +2.3 mg/dL at week 52 (n=307).

Adolescents

In studies of adolescents and adults with schizophrenia, changes in fasting glucose were similar. In the short-term, placebo-controlled study of adolescents, fasting serum glucose mean values were -1.3 mg/dL for placebo (n=95), +0.1 mg/dL for 40 mg/day (n=90), and +1.8 mg/dL for 80 mg/day (n=92).

*Bipolar Depression*Adults*Monotherapy*

Data from the adult short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study are presented in [Table 4](#).

Table 4: Change in Fasting Glucose in the Adult Monotherapy Bipolar Depression Study

| LATUDA | | | |
|--|-----------------|------------------|-----------------|
| Placebo | 20 to 60 mg/day | 80 to 120 mg/day | |
| Mean Change from Baseline (mg/dL) | | | |
| n=148 | n=140 | n=143 | |
| Serum Glucose | +1.8 | -0.8 | +1.8 |
| Proportion of Patients with Shifts to ≥ 126 mg/dL | | | |
| Serum Glucose (≥ 126 mg/dL) | 4.3% (6/141) | 2.2% (3/138) | 6.4% (9/141) |

Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day, or placebo

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy in the short-term study and continued in the longer-term study, had a mean change in glucose of +1.2 mg/dL at week 24 (n=129).

Adjunctive Therapy with Lithium or Valproate

Data from the adult short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies are presented in [Table 5](#).

Table 5: Change in Fasting Glucose in the Adult Adjunctive Therapy Bipolar Depression Studies

| | Placebo | LATUDA 20 to 120 mg/day |
|--|-----------------|----------------------------|
| Mean Change from Baseline (mg/dL) | | |
| | n=302 | n=319 |
| Serum Glucose | | |
| Serum Glucose (\geq 126 mg/dL) | -0.9 | +1.2 |
| Proportion of Patients with Shifts to \geq 126 mg/dL | | |
| | 1.0% (3/290) | 1.3% (4/316) |

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study, had a mean change in glucose of +1.7 mg/dL at week 24 (n=88).

Pediatric Patients (10 to 17 years)

In studies of pediatric patients 10 to 17 years and adults with bipolar depression, changes in fasting glucose were similar. In the 6-week, placebo-controlled study of pediatric patients with bipolar depression, mean change in fasting glucose was +1.6 mg/dL for LATUDA 20 to 80 mg/day (n=145) and -0.5 mg/dL for placebo (n=145).

Pediatric Patients (6 to 17 years)

In a 104-week, open-label study in pediatric patients with schizophrenia, bipolar depression, or autistic disorder, 7 % of patients with a normal baseline fasting glucose experienced a shift to high at endpoint while taking lurasidone.

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Schizophrenia

Adults

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in [Table 6](#).

Table 6: Change in Fasting Lipids in Adult Schizophrenia Studies

| LATUDA | | | | | | |
|---|-------------------|-----------------|-------------------|------------------|-------------------|-----------------|
| Placebo | 20 mg/day | 40 mg/day | 80 mg/day | 120 mg/day | 160 mg/day | |
| Mean Change from Baseline (mg/dL) | | | | | | |
| n=660 | n=71 | n=466 | n=499 | n=268 | n=115 | |
| Total Cholesterol | -5.8 | -12.3 | -5.7 | -6.2 | -3.8 | -6.9 |
| Triglycerides | -13.4 | -29.1 | -5.1 | -13.0 | -3.1 | -10.6 |
| Proportion of Patients with Shifts | | | | | | |
| Total Cholesterol (≥ 240 mg/dL) | 5.3% (30/571) | 13.8% (8/58) | 6.2% (25/402) | 5.3% (23/434) | 3.8% (9/238) | 4.0% (4/101) |
| Triglycerides (≥ 200 mg/dL) | 10.1% (53/526) | 14.3% (7/49) | 10.8% (41/379) | 6.3% (25/400) | 10.5% (22/209) | 7.0% (7/100) |

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in total cholesterol and triglycerides of -3.8 (n=356) and -15.1 (n=357) mg/dL at week 24, -3.1 (n=303) and -4.8 (n=303) mg/dL at week 36 and -2.5 (n=307) and -6.9 (n=307) mg/dL at week 52, respectively.

Adolescents

In the adolescent short-term, placebo-controlled study, fasting serum cholesterol mean values were -9.6 mg/dL for placebo (n=95), -4.4 mg/dL for 40 mg/day (n=89), and +1.6 mg/dL for 80 mg/day (n=92), and fasting serum triglyceride mean values were +0.1 mg/dL for placebo (n=95), -0.6 mg/dL for 40 mg/day (n=89), and +8.5 mg/dL for 80 mg/day (n=92).

Bipolar Depression

Adults

Monotherapy

Data from the adult short-term, flexible-dosed, placebo-controlled, monotherapy bipolar depression study are presented in [Table 7](#).

Table 7: Change in Fasting Lipids in the Adult Monotherapy Bipolar Depression Study

| LATUDA | | | |
|---|-----------------|-------------------|------------------|
| Placebo | 20 to 60 mg/day | 80 to 120 mg/day | |
| Mean Change from Baseline (mg/dL) | | | |
| n=147 | n=140 | n=144 | |
| Total cholesterol | -3.2 | +1.2 | -4.6 |
| Triglycerides | +6.0 | +5.6 | +0.4 |
| Proportion of Patients with Shifts | | | |
| Total cholesterol (\geq 240 mg/dL) | 4.2% (5/118) | 4.4% (5/113) | 4.4% (5/114) |
| Triglycerides (\geq 200 mg/dL) | 4.8% (6/126) | 10.1% (12/119) | 9.8% (12/122) |

Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day, or placebo

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy in the short-term and continued in the longer-term study had a mean change in total cholesterol and triglycerides of -0.5 mg/dL (n=130) and -1.0 mg/dL (n=130) at week 24, respectively.

Adjunctive Therapy with Lithium or Valproate

Data from the adult short-term, flexible-dosed, placebo-controlled, adjunctive therapy bipolar depression studies are presented in [Table 8](#).

Table 8: Change in Fasting Lipids in the Adult Adjunctive Therapy Bipolar Depression Studies

| LATUDA | | |
|---|------------------|-------------------|
| Placebo | 20 to 120 mg/day | |
| Mean Change from Baseline (mg/dL) | | |
| n=303 | n=321 | |
| Total cholesterol | -2.9 | -3.1 |
| Triglycerides | -4.6 | +4.6 |
| Proportion of Patients with Shifts | | |
| Total cholesterol (\geq 240 mg/dL) | 5.7% (15/263) | 5.4% (15/276) |
| Triglycerides (\geq 200 mg/dL) | 8.6% (21/243) | 10.8% (28/260) |

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA, as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study, had a mean change in total cholesterol and triglycerides of -0.9 (n=88) and +5.3 (n=88) mg/dL at week 24, respectively.

Pediatric Patients (10 to 17 years)

In the 6-week, placebo-controlled bipolar depression study with pediatric patients 10 to 17 years, mean change in fasting cholesterol was -6.3 mg/dL for LATUDA 20 to 80 mg/day (n=144) and -1.4 mg/dL for placebo (n=145), and mean change in fasting triglyceride was -7.6 mg/dL for LATUDA 20 to 80 mg/day (n=144) and +5.9 mg/dL for placebo (n=145).

Pediatric Patients (6 to 17 years)

In a 104-week, open-label study of pediatric patients with schizophrenia, bipolar depression, or autistic disorder, shifts in baseline fasting cholesterol from normal to high at endpoint were reported in 12% (total cholesterol), 3% (LDL cholesterol), and shifts in baseline from normal to low were reported in 27% (HDL cholesterol) of patients taking lurasidone. Of patients with normal baseline fasting triglycerides, 12% experienced shifts to high.

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

SchizophreniaAdults

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in [Table 9](#). The mean weight gain was +0.43 kg for LATUDA-treated patients compared to -0.02 kg for placebo-treated patients. Change in weight from baseline for olanzapine was +4.15 kg and for quetiapine extended-release was +2.09 kg in Studies 3 and 5 [see *Clinical Studies (14.1)*], respectively. The proportion of patients with a $\geq 7\%$ increase in body weight (at Endpoint) was 4.8% for LATUDA-treated patients and 3.3% for placebo-treated patients.

Table 9: Mean Change in Weight (kg) from Baseline in Adult Schizophrenia Studies

| LATUDA | | | | | |
|--------------|--------------------|---------------------|----------------------|----------------------|-----------------------|
| | Placebo (n=696) | 20 mg/day (n=71) | 40 mg/day (n=484) | 80 mg/day (n=526) | 120 mg/day (n=291) |
| All Patients | -0.02 | -0.15 | +0.22 | +0.54 | +0.68 |

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in weight of -0.69 kg at week 24 (n=755), -0.59 kg at week 36 (n=443) and -0.73 kg at week 52 (n=377).

Adolescents

Data from the short-term, placebo-controlled adolescent schizophrenia study are presented in [Table 10](#). The mean change in weight gain was +0.5 kg for LATUDA-treated patients compared to +0.2 kg for placebo-treated patients. The proportion of patients with a $\geq 7\%$ increase in body weight (at Endpoint) was 3.3% for LATUDA-treated patients and 4.5% for placebo-treated patients.

Table 10: Mean Change in Weight (kg) from Baseline in the Adolescent Schizophrenia Study

| LATUDA | | |
|--------------|--------------------|----------------------|
| | Placebo (n=111) | 40 mg/day (n=109) |
| All Patients | +0.2 | +0.3 |

*Bipolar Depression*Adults*Monotherapy*

Data from the adult short-term, flexible-dosed, placebo-controlled monotherapy bipolar depression study are presented in [Table 11](#). The mean change in weight gain was +0.29 kg for LATUDA-treated patients compared to -0.04 kg for placebo-treated patients. The proportion of patients with a $\geq 7\%$ increase in body weight (at Endpoint) was 2.4% for LATUDA-treated patients and 0.7% for placebo-treated patients.

Table 11: Mean Change in Weight (kg) from Baseline in the Adult Monotherapy Bipolar Depression Study

| | LATUDA | | |
|--------------|--------------------|----------------------------|-----------------------------|
| | Placebo (n=151) | 20 to 60 mg/day (n=143) | 80 to 120 mg/day (n=147) |
| All Patients | -0.04 | +0.56 | +0.02 |

Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day, or placebo

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy in the short-term and continued in the longer-term study had a mean change in weight of -0.02 kg at week 24 (n=130).

Adjunctive Therapy with Lithium or Valproate

Data from the adult short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies are presented in [Table 12](#). The mean change in weight gain was +0.11 kg for LATUDA-treated patients compared to +0.16 kg for placebo-treated patients. The proportion of patients with a $\geq 7\%$ increase in body weight (at Endpoint) was 3.1% for LATUDA-treated patients and 0.3% for placebo-treated patients.

Table 12: Mean Change in Weight (kg) from Baseline in the Adult Adjunctive Therapy Bipolar Depression Studies

| | LATUDA | |
|--------------|--------------------|-----------------------------|
| | Placebo (n=307) | 20 to 120 mg/day (n=327) |
| All Patients | +0.16 | +0.11 |

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who were treated with LATUDA, as adjunctive therapy with either lithium or valproate in the short-term and continued in the longer-term study, had a mean change in weight of +1.28 kg at week 24 (n=86).

Pediatric Patients (10 to 17 years)

Data from the 6-week, placebo-controlled bipolar depression study in patients 10 to 17 years are presented in [Table 13](#). The mean change in weight gain was +0.7 kg for LATUDA-treated patients compared to +0.5 kg for placebo-treated patients. The proportion of patients with a $\geq 7\%$ increase in body weight (at Endpoint) was 4.0% for LATUDA-treated patients and 5.3% for placebo-treated patients.

Table 13: Mean Change in Weight (kg) from Baseline in the Bipolar Depression Study in Pediatric Patients (10 to 17 years)

| | Placebo (n=170) | LATUDA 20 to 80 mg/day (n=175) |
|--------------|--------------------|--------------------------------------|
| All Patients | +0.5 | +0.7 |

Pediatric Patients (6 to 17 years)

In a long-term, open-label study that enrolled pediatric patients with schizophrenia, bipolar depression, or autistic disorder from three short-term, placebo-controlled trials, 54% (378/701) received lurasidone for 104 weeks. The mean increase in weight from open-label baseline to Week 104 was 5.85 kg. To adjust for normal growth, z-scores were derived (measured in standard deviations [SD]), which normalize for the natural growth of children and adolescents by comparisons to age- and sex-matched population standards. A z-score change <0.5 SD is considered not clinically significant. In this trial, the mean change in z-score from open-label baseline to Week 104 was -0.06 SD for body weight and -0.13 SD for body mass index (BMI), indicating minimal deviation from the normal curve for weight gain.

5.7 Hyperprolactinemia

As with other drugs that antagonize dopamine D₂ receptors, LATUDA elevates prolactin levels.

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin 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 with prolactin-elevating compounds. Long-standing hyperprolactinemia, when associated with hypogonadism, may lead to decreased bone density in both female and male patients [see *Adverse Reactions (6)*].

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 considered 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 a carcinogenicity study conducted with lurasidone in rats and mice [see *Nonclinical Toxicology (13)*]. 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, but the available evidence is too limited to be conclusive.

Schizophrenia**Adults**

In short-term, placebo-controlled schizophrenia studies, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was +0.4 ng/mL and was -1.9 ng/mL in the placebo-treated patients. The median change from baseline to endpoint for males was +0.5 ng/mL and for females was -0.2 ng/mL. Median changes for prolactin by dose are shown in [Table 14](#).

Table 14: Median Change in Prolactin (ng/mL) from Baseline in Adult Schizophrenia Studies

| | LATUDA | | | | | |
|--------------|-----------------|----------------|-----------------|-----------------|-----------------|-----------------|
| | Placebo | 20 mg/day | 40 mg/day | 80 mg/day | 120 mg/day | 160 mg/day |
| All Patients | -1.9 (n=672) | -1.1 (n=70) | -1.4 (n=476) | -0.2 (n=495) | +3.3 (n=284) | +3.3 (n=115) |
| Females | -5.1 (n=200) | -0.7 (n=19) | -4.0 (n=149) | -0.2 (n=150) | +6.7 (n=70) | +7.1 (n=36) |
| Males | -1.3 (n=472) | -1.2 (n=51) | -0.7 (n=327) | -0.2 (n=345) | +3.1 (n=214) | +2.4 (n=79) |

The proportion of patients with prolactin elevations $\geq 5 \times$ upper limit of normal (ULN) was 2.8% for LATUDA-treated patients and = 1.0% for placebo-treated patients. The proportion of female patients with prolactin elevations $\geq 5 \times$ ULN was 5.7% for LATUDA-treated patients and = 2.0% for placebo-treated female patients. The proportion of male patients with prolactin elevations $\geq 5 \times$ ULN was 1.6% and 0.6% for placebo-treated male patients.

In the uncontrolled longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a median change in prolactin of -0.9 ng/mL at week 24 (n=357), -5.3ng/mL at week 36 (n=190) and -2.2 ng/mL at week 52 (n=307).

Adolescents

In the short-term, placebo-controlled adolescent schizophrenia study, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was +1.1 ng/mL and was +0.1 ng/mL for placebo-treated patients. For LATUDA-treated patients, the median change from baseline to endpoint for males was +1.0 ng/mL and for females was +2.6 ng/mL. Median changes for prolactin by dose are shown in [Table 15](#).

Table 15: Median Change in Prolactin (ng/mL) from Baseline in the Adolescent Schizophrenia Study

| | Placebo | LATUDA 40 mg/day | LATUDA 80 mg/day |
|--------------|------------------|---------------------|---------------------|
| All Patients | +0.10 (n=103) | +0.75 (n=102) | +1.20 (n=99) |
| Females | +0.70 (n=39) | +0.60 (n=42) | +4.40 (n=33) |
| Males | 0.00 (n=64) | +0.75 (n=60) | +1.00 (n=66) |

The proportion of patients with prolactin elevations ≥ 5 times ULN was 0.5% for LATUDA-treated patients and 1.0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥ 5 times ULN was 1.3% for LATUDA-treated patients and 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥ 5 times ULN was 0% for LATUDA treated patients and 1.6% for placebo-treated male patients.

Bipolar Depression

Adults

Monotherapy

The median change from baseline to endpoint in prolactin levels, in the adult short-term, flexible-dosed, placebo-controlled monotherapy bipolar depression study, was +1.7 ng/mL and +3.5 ng/mL with LATUDA 20 to 60 mg/day and 80 to 120 mg/day, respectively compared to +0.3 ng/mL with placebo-treated patients. The median change from baseline to endpoint for males was +1.5 ng/mL and for females was +3.1 ng/mL. Median changes for prolactin by dose range are shown in [Table 16](#).

Table 16: Median Change in Prolactin (ng/mL) from Baseline in the Adult Monotherapy Bipolar Depression Study

| | Placebo | LATUDA | |
|--------------|-----------------|-----------------|------------------|
| | | 20 to 60 mg/day | 80 to 120 mg/day |
| All Patients | +0.3 (n=147) | +1.7 (n=140) | +3.5 (n=144) |
| Females | 0.0 (n=82) | +1.8 (n=78) | +5.3 (n=88) |
| Males | +0.4 (n=65) | +1.2 (n=62) | +1.9 (n=56) |

Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day, or placebo

The proportion of patients with prolactin elevations ≥ 5 times upper limit of normal (ULN) was 0.4% for LATUDA-treated patients and 0.0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥ 5 times ULN was 0.6% for LATUDA-treated patients and 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥ 5 times ULN was 0% and 0% for placebo-treated male patients.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who were treated with LATUDA as monotherapy in the short-term and continued in the longer-term study, had a median change in prolactin of -1.15 ng/mL at week 24 (n=130).

Adjunctive Therapy with Lithium or Valproate

The median change from baseline to endpoint in prolactin levels, in the adult short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies was +2.8 ng/mL with LATUDA 20 to 120 mg/day compared to 0.0 ng/mL with placebo-treated patients. The median change from baseline to endpoint for males was +2.4 ng/mL and for females was +3.2 ng/mL. Median changes for prolactin across the dose range are shown in [Table 17](#).

Table 17: Median Change in Prolactin (ng/mL) from Baseline in the Adult Adjunctive Therapy Bipolar Depression Studies

| | Placebo | LATUDA 20 to 120 mg/day |
|--------------|-----------------|----------------------------|
| All Patients | 0.0 (n=301) | +2.8 (n=321) |
| Females | +0.4 (n=156) | +3.2 (n=162) |
| Males | -0.1 (n=145) | +2.4 (n=159) |

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

The proportion of patients with prolactin elevations ≥ 5 times upper limit of normal (ULN) was 0.0% for LATUDA-treated patients and 0.0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥ 5 times ULN was 0% for LATUDA-treated patients and 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥ 5 times ULN was 0% and 0% for placebo-treated male patients.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who were treated with LATUDA, as adjunctive therapy with either lithium or valproate, in the short-term and continued in the longer-term study, had a median change in prolactin of -2.9 ng/mL at week 24 (n=88).

Pediatric Patients (10 to 17 years)

In the 6-week, placebo-controlled bipolar depression study with pediatric patients 10 to 17 years, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was +1.10 ng/mL and was +0.50 ng/mL for placebo-treated patients. For LATUDA-treated patients, the median change from baseline to endpoint for males was +0.85 ng/mL and for females was +2.50 ng/mL. Median changes for prolactin are shown in [Table 18](#).

Table 18: Median Change in Prolactin (ng/mL) from Baseline in the Bipolar Depression Study in Pediatric Patients (10 to 17 years)

| | Placebo | LATUDA 20 to 80 mg/day |
|--------------|------------------|---------------------------|
| All Patients | +0.50 (n=157) | +1.10 (n=165) |
| Females | +0.55 (n=78) | +2.50 (n=83) |
| Males | +0.50 (n=79) | +0.85 (n=82) |

The proportion of patients with prolactin elevations ≥ 5 times the upper limit of normal (ULN) was 0% for LATUDA-treated patients and 0.6% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥ 5 times the ULN was 0% for LATUDA-treated patients and 1.3% for placebo-treated female patients. No male patients in the placebo or LATUDA treatment groups had prolactin elevations ≥ 5 times the ULN.

Pediatric Patients (6 to 17 years)

In a 104-week, open-label study of pediatric patients with schizophrenia, bipolar depression, or autistic disorder, the median changes from baseline to endpoint in serum prolactin levels were -0.20 ng/mL (all patients), -0.30 ng/mL (females), and -0.05 ng/mL (males). The proportions of patients with a markedly high prolactin level (≥ 5 times the upper limit of normal) at any time during open-label treatment were 2% (all patients), 3% (females), and 1% (males).

Adverse events among females in this trial that are potentially prolactin-related include galactorrhea (0.6%). Among male patients in this study, decreased libido was reported in one patient (0.2%) and there were no reports of impotence, gynecomastia, or galactorrhea.

5.8 Leukopenia, Neutropenia and Agranulocytosis

Leukopenia/neutropenia has been reported during treatment with antipsychotic agents. Agranulocytosis (including fatal cases) has been reported with other agents in the class.

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 pre-existing low WBC or a history of drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and LATUDA should be discontinued at the first sign of decline in WBC, in the absence of other causative factors.

Patients with 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 LATUDA and have their WBC followed until recovery.

5.9 Orthostatic Hypotension and Syncope

LATUDA may cause orthostatic hypotension and syncope, perhaps due to its α 1-adrenergic receptor antagonism. Associated adverse reactions can include dizziness, lightheadedness, tachycardia, and bradycardia. Generally, these risks are greatest at the beginning of treatment and during dose escalation.

Patients at increased risk of these adverse reactions or at increased risk of developing complications from hypotension include those with dehydration, hypovolemia, treatment with antihypertensive medication, history of cardiovascular disease (e.g., heart failure, myocardial infarction, ischemia, or conduction abnormalities), history of cerebrovascular disease, as well as patients who are antipsychotic-naïve. In such patients, consider using a lower starting dose and slower titration, and monitor orthostatic vital signs.

Orthostatic hypotension, as assessed by vital sign measurement, was defined by the following vital sign changes: ≥ 20 mm Hg decrease in systolic blood pressure and ≥ 10 bpm increase in pulse from sitting to standing or supine to standing position.

Schizophrenia

Adults

The incidence of orthostatic hypotension and syncope reported as adverse events from short-term, placebo-controlled schizophrenia studies was (LATUDA incidence, placebo incidence): orthostatic hypotension [0.3% (5/1508), 0.1% (1/708)] and syncope [0.1% (2/1508), 0% (0/708)].

In short-term schizophrenia clinical studies, orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 0.8% with LATUDA 40 mg, 2.1% with LATUDA 80 mg, 1.7% with LATUDA 120 mg and 0.8% with LATUDA 160 mg compared to 0.7% with placebo.

Adolescents

The incidence of orthostatic hypotension reported as adverse events from the short-term, placebo-controlled adolescent schizophrenia study was 0.5% (1/214) in LATUDA-treated patients and 0% (0/112) in placebo-treated patients. No syncope event was reported.

Orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 0% with LATUDA 40 mg and 2.9% with LATUDA 80 mg, compared to 1.8% with placebo.

Bipolar Depression

Adults

Monotherapy

In the adult short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, there were no reported adverse events of orthostatic hypotension and syncope.

Orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 0.6% with LATUDA 20 to 60 mg and 0.6% with LATUDA 80 to 120 mg compared to 0% with placebo.

Adjunctive Therapy with Lithium or Valproate

In the adult short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression therapy studies, there were no reported adverse events of orthostatic hypotension and syncope. Orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 1.1% with LATUDA 20 to 120 mg compared to 0.9% with placebo.

Pediatric Patients (10 to 17 years)

In the 6-week, placebo-controlled bipolar depression study in pediatric patients 10 to 17 years, there were no reported adverse events of orthostatic hypotension or syncope.

Orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 1.1% with LATUDA 20 to 80 mg/day, compared to 0.6% with placebo.

5.10 Falls

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

5.11 Seizures

As with other antipsychotic drugs, LATUDA should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

Schizophrenia

In adult short-term, placebo-controlled schizophrenia studies, seizures/convulsions occurred in 0.1% (2/1508) of patients treated with LATUDA compared to 0.1% (1/708) placebo-treated patients.

Bipolar Depression

Monotherapy

In the adult and pediatric 6-week, flexible-dose, placebo-controlled monotherapy bipolar depression studies, no patients experienced seizures/convulsions.

Adjunctive Therapy with Lithium or Valproate

In the adult short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression studies, no patient experienced seizures/convulsions.

5.12 Potential for Cognitive and Motor Impairment

LATUDA, like other antipsychotics, has the potential to impair judgment, thinking or motor skills. Caution patients about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with LATUDA does not affect them adversely.

In clinical studies with LATUDA, somnolence included: hypersomnia, hypersomnolence, sedation and somnolence.

Schizophrenia

Adults

In short-term, placebo-controlled schizophrenia studies, somnolence was reported by 17.0% (256/1508) of patients treated with LATUDA (15.5% LATUDA 20 mg, 15.6% LATUDA 40 mg, 15.2% LATUDA 80 mg, 26.5% LATUDA 120 mg and 8.3% LATUDA 160 mg/day) compared to 7.1% (50/708) of placebo patients.

Adolescents

In the short-term, placebo-controlled adolescent schizophrenia study, somnolence was reported by 14.5% (31/214) of patients treated with LATUDA (15.5% LATUDA 40 mg and 13.5% LATUDA 80 mg/day) compared to 7.1% (8/112) of placebo patients.

Bipolar Depression

Adults

Monotherapy

In the adult short-term, flexible-dosed, placebo-controlled monotherapy bipolar depression study, somnolence was reported by 7.3% (12/164) and 13.8% (23/167) with LATUDA 20 to 60 mg and 80 to 120 mg, respectively compared to 6.5% (11/168) of placebo patients.

Adjunctive Therapy with Lithium or Valproate

In the adult short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies, somnolence was reported by 11.4% (41/360) of patients treated with LATUDA 20-120 mg compared to 5.1% (17/334) of placebo patients.

Pediatric Patients (10 to 17 years)

In the 6-week, placebo-controlled bipolar depression study in pediatric patients 10 to 17 years, somnolence was reported by 11.4% (20/175) of patients treated with LATUDA 20 to 80 mg/day compared to 5.8% (10/172) of placebo treated patients.

5.13 Body Temperature Dysregulation

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

5.14 Activation of Mania/Hypomania

Antidepressant treatment can increase the risk of developing a manic or hypomanic episode, particularly in patients with bipolar disorder. Monitor patients for the emergence of such episodes.

In the adult bipolar depression monotherapy and adjunctive therapy (with lithium or valproate) studies, less than 1% of subjects in the LATUDA and placebo groups developed manic or hypomanic episodes.

5.15 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. LATUDA and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

5.16 Neurological Adverse Reactions in Patients with Parkinson's Disease or Dementia with Lewy Bodies

Patients with Parkinson's Disease or Dementia with Lewy Bodies are reported to have an increased sensitivity to antipsychotic medication. Manifestations of this increased sensitivity include confusion,

obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome.

5.17 Cardiovascular disorders/QT prolongation

Caution should be exercised when lurasidone is prescribed in patients with known cardiovascular disease or family history of QT prolongation, hypokalaemia, and in concomitant use with other medicinal products thought to prolong the QT interval.

5.18 Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicinal products. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with lurasidone and preventive measures undertaken.

5.19 Serotonin syndrome

Concomitant administration of Latuda and other serotonergic agents, such as buprenorphine/opioids, MAO inhibitors, selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants may result in serotonin syndrome, a potentially life-threatening condition. If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Symptoms of serotonin syndrome may include mental status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms. If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis [*see Boxed Warning and Warnings and Precautions (5.1)*]
- Suicidal Thoughts and Behaviors [*see Boxed Warning and Warnings and Precautions (5.2)*]
- Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-related Psychosis [*see Warnings and Precautions (5.3)*]
- Neuroleptic Malignant Syndrome [*see Warnings and Precautions (5.4)*]
- Tardive Dyskinesia [*see Warnings and Precautions (5.5)*]
- Metabolic Changes [*see Warnings and Precautions (5.6)*]
- Hyperprolactinemia [*see Warnings and Precautions (5.7)*]
- Leukopenia, Neutropenia, and Agranulocytosis [*see Warnings and Precautions (5.8)*]
- Orthostatic Hypotension and Syncope [*see Warnings and Precautions (5.9)*]
- Falls [*see Warnings and Precautions (5.10)*]
- Seizures [*see Warnings and Precautions (5.11)*]
- Potential for Cognitive and Motor Impairment [*see Warnings and Precautions (5.12)*]
- Body Temperature Dysregulation [*see Warnings and Precautions (5.13)*]

- Activation of Mania/Hypomania [*see Warnings and Precautions (5.14)*]
- Dysphagia [*see Warnings and Precautions (5.15)*]
- Neurological Adverse Reactions in Patients with Parkinson's Disease or Dementia with Lewy Bodies [*see Warnings and Precautions (5.16)*]
- Cardiovascular disorders/QT prolongation [*see Warnings and Precautions (5.17)*]
- Venous thromboembolism [*see Warnings and Precautions (5.18)*]
- Serotonin syndrome [*see Warnings and Precautions (5.19)*]

6.1 Clinical Trials Experience

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

Adults

The information below is derived from an integrated clinical study database for LATUDA consisting of 3799 adult patients exposed to one or more doses of LATUDA for the treatment of schizophrenia, and bipolar depression in placebo-controlled studies. This experience corresponds with a total experience of 1250.9 patient-years. A total of 1106 LATUDA-treated patients had at least 24 weeks and 371 LATUDA-treated patients had at least 52 weeks of exposure.

Adverse events during exposure to study treatment were obtained by general inquiry and voluntarily reported adverse experiences, as well as results from physical examinations, vital signs, ECGs, weights and laboratory investigations. Adverse experiences were recorded by clinical investigators using their own terminology. In order to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

Schizophrenia

The following findings are based on the short-term, placebo-controlled premarketing adult studies for schizophrenia in which LATUDA was administered at daily doses ranging from 20 to 160 mg (n=1508).

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence $\geq 5\%$ and at least twice the rate of placebo) in patients treated with LATUDA were somnolence, akathisia, extrapyramidal symptoms, and nausea.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 9.5% (143/1508) LATUDA-treated patients and 9.3% (66/708) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients: Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in patients with schizophrenia) are shown in [Table 19](#).

Table 19: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in Adult Short-term Schizophrenia Studies

| Body System or Organ Class | Percentage of Patients Reporting Reaction | | | | | | |
|--|---|-------------------------------|--------------------------------|--------------------------------|---------------------------------|---------------------------------|----------------------------------|
| | LATUDA | | | | | | |
| | Placebo (N=708) (%) | 20 mg/day (N=71) (%) | 40 mg/day (N=487) (%) | 80 mg/day (N=538) (%) | 120 mg/day (N=291) (%) | 160 mg/day (N=121) (%) | All LATUDA (N=1508) (%) |
| Gastrointestinal Disorders | | | | | | | |
| Nausea | 5 | 11 | 10 | 9 | 13 | 7 | 10 |
| Vomiting | 6 | 7 | 6 | 9 | 9 | 7 | 8 |
| Dyspepsia | 5 | 11 | 6 | 5 | 8 | 6 | 6 |
| Salivary Hypersecretion | <1 | 1 | 1 | 2 | 4 | 2 | 2 |
| Musculoskeletal and Connective Tissue Disorders | | | | | | | |
| Back Pain | 2 | 0 | 4 | 3 | 4 | 0 | 3 |
| Nervous System Disorders | | | | | | | |
| Somnolence* | 7 | 15 | 16 | 15 | 26 | 8 | 17 |
| Akathisia | 3 | 6 | 11 | 12 | 22 | 7 | 13 |
| Extrapyramidal Disorder** | 6 | 6 | 11 | 12 | 22 | 13 | 14 |
| Dizziness | 2 | 6 | 4 | 4 | 5 | 6 | 4 |
| Psychiatric Disorders | | | | | | | |
| Insomnia | 8 | 8 | 10 | 11 | 9 | 7 | 10 |
| Agitation | 4 | 10 | 7 | 3 | 6 | 5 | 5 |
| Anxiety | 4 | 3 | 6 | 4 | 7 | 3 | 5 |
| Restlessness | 1 | 1 | 3 | 1 | 3 | 2 | 2 |

Note: Figures rounded to the nearest integer

* Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence

** Extrapyramidal symptoms include adverse event terms: bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, hypokinesia, muscle rigidity, oculogyric crisis, oromandibular dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and trismus

Dose-Related Adverse Reactions in the Schizophrenia Studies

Akathisia and extrapyramidal symptoms were dose-related. The frequency of akathisia increased with dose up to 120 mg/day (5.6% for LATUDA 20 mg, 10.7% for LATUDA 40 mg, 12.3% for LATUDA 80 mg, and 22.0% for LATUDA 120 mg). Akathisia was reported by 7.4% (9/121) of patients receiving 160 mg/day. Akathisia occurred in 3.0% of subjects receiving placebo. The frequency of extrapyramidal symptoms increased with dose up to 120 mg/day (5.6% for LATUDA 20 mg, 11.5% for LATUDA 40 mg, 11.9% for LATUDA 80 mg, and 22.0% for LATUDA 120 mg).

Bipolar Depression (Monotherapy)

The following findings are based on the adult short-term, placebo-controlled premarketing study for bipolar depression in which LATUDA was administered at daily doses ranging from 20 to 120 mg (n=331).

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence $\geq 5\%$, in either dose group, and at least twice the rate of placebo) in patients treated with LATUDA were akathisia, extrapyramidal symptoms, somnolence, nausea, vomiting, diarrhea, and anxiety.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 6.0% (20/331) LATUDA-treated patients and 5.4% (9/168) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients: Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in patients with bipolar depression) are shown in [Table 20](#).

Table 20: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in the Adult Short-term Monotherapy Bipolar Depression Study

| Body System or Organ Class Dictionary-derived Term | Percentage of Patients Reporting Reaction | | | |
|--|---|--------------------------------------|---------------------------------------|---------------------------------|
| | Placebo (N=168) (%) | LATUDA 20-60 mg/day (N=164) | LATUDA 80-120 mg/day (N=167) | All LATUDA (N=331) (%) |
| Gastrointestinal Disorders | | | | |
| Nausea | 8 | 10 | 17 | 14 |
| Dry Mouth | 4 | 6 | 4 | 5 |
| Vomiting | 2 | 2 | 6 | 4 |
| Diarrhea | 2 | 5 | 3 | 4 |
| Infections and Infestations | | | | |
| Nasopharyngitis | 1 | 4 | 4 | 4 |
| Influenza | 1 | <1 | 2 | 2 |
| Urinary Tract Infection | <1 | 2 | 1 | 2 |
| Musculoskeletal and Connective Tissue Disorders | | | | |
| Back Pain | <1 | 3 | <1 | 2 |
| Nervous System Disorders | | | | |
| Extrapyramidal Symptoms* | 2 | 5 | 9 | 7 |
| Akathisia | 2 | 8 | 11 | 9 |
| Somnolence** | 7 | 7 | 14 | 11 |
| Psychiatric Disorders | | | | |
| Anxiety | 1 | 4 | 5 | 4 |

Note: Figures rounded to the nearest integer

*Extrapyramidal symptoms include adverse event terms: bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, oculogyric crisis, oromandibular dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and trismus

** Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence

Dose-Related Adverse Reactions in the Monotherapy Study:

In the adult short-term, placebo-controlled study (involving lower and higher LATUDA dose ranges) [see *Clinical Studies (14.2)*] the adverse reactions that occurred with a greater than 5% incidence in the patients treated with LATUDA in any dose group and greater than placebo in both groups were nausea (10.4%, 17.4%), somnolence (7.3%, 13.8%), akathisia (7.9%, 10.8%), and extrapyramidal symptoms (4.9%, 9.0%) for LATUDA 20 to 60 mg/day and LATUDA 80 to 120 mg/day, respectively.

Bipolar Depression

Adjunctive Therapy with Lithium or Valproate

The following findings are based on two adult short-term, placebo-controlled premarketing studies for bipolar depression in which LATUDA was administered at daily doses ranging from 20 to 120 mg as adjunctive therapy with lithium or valproate (n=360).

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence $\geq 5\%$ and at least twice the rate of placebo) in subjects treated with LATUDA were akathisia and somnolence.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 5.8% (21/360) LATUDA-treated patients and 4.8% (16/334) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients: Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in patients with bipolar depression) are shown in [Table 21](#).

Table 21: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in the Adult Short-term Adjunctive Therapy Bipolar Depression Studies

| Body System or Organ Class Dictionary-derived Term | Percentage of Patients Reporting Reaction | |
|---|---|--|
| | Placebo (N=334) (%) | LATUDA 20 to 120 mg/day (N=360) (%) |
| Gastrointestinal Disorders | | |
| Nausea | 10 | 14 |
| Vomiting | 1 | 4 |
| General Disorders | | |
| Fatigue | 1 | 3 |
| Infections and Infestations | | |
| Nasopharyngitis | 2 | 4 |
| Investigations | | |
| Weight Increased | <1 | 3 |
| Metabolism and Nutrition Disorders | | |
| Increased Appetite | 1 | 3 |
| Nervous System Disorders | | |
| Extrapyramidal Symptoms* | 9 | 14 |
| Somnolence** | 5 | 11 |
| Akathisia | 5 | 11 |
| Psychiatric Disorders | | |
| Restlessness | <1 | 4 |

Note: Figures rounded to the nearest integer

*Extrapyramidal symptoms include adverse event terms: bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, oculogyric crisis, oromandibular dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and trismus

** Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence

Adolescents

Schizophrenia

The following findings are based on the short-term, placebo-controlled adolescent study for schizophrenia in which LATUDA was administered at daily doses ranging from 40 (N=110) to 80 mg (N=104).

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence $\geq 5\%$ and at least twice the rate of placebo) in adolescent patients (13 to 17 years) treated with LATUDA were somnolence, nausea, akathisia, extrapyramidal symptoms (non-akathisia, 40mg only), vomiting, and rhinorrhea/rhinitis (80mg only).

Adverse Reactions Associated with Discontinuation of Treatment: The incidence of discontinuation due to adverse reactions between LATUDA- and placebo-treated adolescent patients (13 to 17 years) was 4% and 8%, respectively.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients: Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6-weeks in adolescent patients with schizophrenia) are shown in [Table 22](#).

Table 22: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in the Adolescent Short-term Schizophrenia Study

| Body System or Organ Class Dictionary-derived Term | Percentage of Patients Reporting Reaction | | | |
|---|---|--------------------------------|--------------------------------|-----------------------|
| | Placebo (N=112) | LATUDA 40 mg/day (N=110) | LATUDA 80 mg/day (N=104) | All LATUDA (N=214) |
| | | | | |
| Gastrointestinal Disorders | | | | |
| Nausea | 3 | 13 | 14 | 14 |
| Vomiting | 2 | 8 | 6 | 8 |
| Diarrhea | 1 | 3 | 5 | 4 |
| Dry Mouth | 0 | 2 | 3 | 2 |
| Infections and Infestations | | | | |
| Viral Infection** | 6 | 11 | 10 | 10 |
| Rhinitis *** | 2 | <1 | 8 | 4 |
| Oropharyngeal pain | 0 | <1 | 3 | 2 |
| Tachycardia | 0 | 0 | 3 | 1 |
| Nervous System Disorders | | | | |
| Somnolence* | 7 | 15 | 13 | 15 |
| Akathisia | 2 | 9 | 9 | 9 |
| Dizziness | 1 | 5 | 5 | 5 |

Note: Figures rounded to the nearest integer

* Somnolence includes adverse event terms: hypersomnia, sedation, and somnolence

** Viral Infection includes adverse event terms: nasopharyngitis, influenza, viral infection, upper respiratory tract infection

*** Rhinitis includes adverse event terms: rhinitis, allergic rhinitis, rhinorrhea, and nasal congestion

Pediatric Patients (10 to 17 years)

Bipolar Depression

The following findings are based on the 6-week, placebo-controlled study for bipolar depression in pediatric patients 10 to 17 years in which LATUDA was administered at daily doses ranging from 20 to 80 mg (N=175).

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence $\geq 5\%$, and at least twice the rate of placebo) in pediatric patients (10 to 17 years) treated with LATUDA were nausea, weight increase, and insomnia.

Adverse Reactions Associated with Discontinuation of Treatment: The incidence of discontinuation due to adverse reactions between LATUDA- and placebo-treated pediatric patients 10 to 17 years was 2% and 2%, respectively.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients: Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in pediatric patients with bipolar depression) are shown in [Table 23](#).

Table 23: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in the 6-Week Bipolar Depression Study in Pediatric Patients (10 to 17 years)

| Body System or Organ Class Dictionary-derived Term | Percentage of Patients Reporting Reaction | |
|---|---|--------------------------------------|
| | Placebo (N=172) | LATUDA 20 to 80 mg/day (N=175) |
| Gastrointestinal Disorders | | |
| Nausea | 6 | 16 |
| Vomiting | 4 | 6 |
| Abdominal Pain Upper | 2 | 3 |
| Diarrhea | 2 | 3 |
| Abdominal Pain | 1 | 3 |
| General Disorders And Administration Site Conditions | | |
| Fatigue | 2 | 3 |
| Investigations | | |
| Weight Increased | 2 | 7 |
| Metabolism and Nutrition Disorders | | |
| Decreased Appetite | 2 | 4 |
| Nervous System Disorders | | |
| Somnolence* | 6 | 11 |
| Extrapyramidal symptoms** | 5 | 6 |
| Dizziness | 5 | 6 |
| Psychiatric Disorders | | |
| Insomnia | 2 | 5 |
| Abnormal Dreams | 2 | 2 |
| Respiratory, Thoracic and Mediastinal Disorders | | |
| Oropharyngeal Pain | 2 | 2 |

Note: Figures rounded to the nearest integer

*Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence

**EPS includes adverse event terms: akathisia, cogwheel rigidity, dyskinesia, dystonia, hyperkinesia, joint stiffness, muscle rigidity, muscle spasms, musculoskeletal stiffness, oculogyric crisis, parkinsonism, tardive dyskinesia, and tremor

Extrapyramidal Symptoms*Schizophrenia*Adults

In the short-term, placebo-controlled schizophrenia studies, for LATUDA-treated patients, the incidence of reported events related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness, was 13.5% and 5.8% for placebo-treated patients. The incidence of akathisia for LATUDA-treated patients was 12.9% and 3.0% for placebo-treated patients. Incidence of EPS by dose is provided in [Table 24](#).

Table 24: Incidence of EPS Compared to Placebo in Adult Schizophrenia Studies

| Adverse Event Term | LATUDA | | | | | |
|---|--------------------|---------------------|----------------------|----------------------|-----------------------|-----------------------|
| | Placebo (N=708) | 20 mg/day (N=71) | 40 mg/day (N=487) | 80 mg/day (N=538) | 120 mg/day (N=291) | 160 mg/day (N=121) |
| | (%) | (%) | (%) | (%) | (%) | (%) |
| All EPS events | 9 | 10 | 21 | 23 | 39 | 20 |
| All EPS events, excluding Akathisia/Restlessness | 6 | 6 | 11 | 12 | 22 | 13 |
| Akathisia | 3 | 6 | 11 | 12 | 22 | 7 |
| Dystonia* | <1 | 0 | 4 | 5 | 7 | 2 |
| Parkinsonism** | 5 | 6 | 9 | 8 | 17 | 11 |
| Restlessness | 1 | 1 | 3 | 1 | 3 | 2 |

Note: Figures rounded to the nearest integer

* Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus

** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

Adolescents

In the short-term, placebo-controlled, study of schizophrenia in adolescents, the incidence of EPS, excluding events related to akathisia, for LATUDA-treated patients was higher in the 40 mg (10%) and the 80 mg (7.7%) treatment groups vs. placebo (3.6%); and the incidence of akathisia-related events for LATUDA-treated patients was 8.9% vs. 1.8% for placebo-treated patients. Incidence of EPS by dose is provided in [Table 25](#).

Table 25: Incidence of EPS Compared to Placebo in the Adolescent Schizophrenia Study

| LATUDA | | | |
|---|---------------------------|-----------------------------|-----------------------------|
| Adverse Event Term | Placebo (N=112) (%) | 40 mg/day (N=110) (%) | 80 mg/day (N=104) (%) |
| All EPS events | 5 (%) | 14 (%) | 14 (%) |
| All EPS events, excluding Akathisia/Restlessness | 4 (%) | 7 (%) | 7 (%) |
| Akathisia | 2 (%) | 9 (%) | 9 (%) |
| Parkinsonism** | <1 (%) | 4 (%) | 0 (%) |
| Dyskinesia | <1 (%) | <1 (%) | 1 (%) |
| Dystonia* | 0 (%) | <1 (%) | 1 (%) |

Note: Figures rounded to the nearest integer

* Dystonia includes adverse event terms: dystonia, trismus, oculogyric crisis, oromandibular dystonia, tongue spasm, and torticollis

** Parkinsonism includes adverse event terms: bradykinesia, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, parkinsonism, and psychomotor retardation

Bipolar Depression

Adults

Monotherapy

In the adult short-term, placebo-controlled monotherapy bipolar depression study, for LATUDA-treated patients, the incidence of reported events related to EPS, excluding akathisia and restlessness was 6.9% and 2.4% for placebo-treated patients. The incidence of akathisia for LATUDA-treated patients was 9.4% and 2.4% for placebo-treated patients. Incidence of EPS by dose groups is provided in [Table 26](#).

Table 26: Incidence of EPS Compared to Placebo in the Adult Monotherapy Bipolar Depression Study

| Adverse Event Term | LATUDA | | |
|---|---------------------------|-----------------------------------|------------------------------------|
| | Placebo (N=168) (%) | 20 to 60 mg/day (N=164) (%) | 80 to 120 mg/day (N=167) (%) |
| | | | |
| All EPS events | 5 | 12 | 20 |
| All EPS events, excluding Akathisia/Restlessness | 2 | 5 | 9 |
| Akathisia | 2 | 8 | 11 |
| Dystonia* | 0 | 0 | 2 |
| Parkinsonism** | 2 | 5 | 8 |
| Restlessness | <1 | 0 | 3 |

Note: Figures rounded to the nearest integer

* Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus

** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

Adjunctive Therapy with Lithium or Valproate

In the adult short-term, placebo-controlled adjunctive therapy bipolar depression studies, for LATUDA-treated patients, the incidence of EPS, excluding akathisia and restlessness, was 13.9% and 8.7% for placebo. The incidence of akathisia for LATUDA-treated patients was 10.8% and 4.8% for placebo-treated patients. Incidence of EPS is provided in [Table 27](#).

Table 27: Incidence of EPS Compared to Placebo in the Adult Adjunctive Therapy Bipolar Depression Studies

| Adverse Event Term | Placebo (N=334) (%) | LATUDA 20 to 120 mg/day (N=360) (%) |
|---|---------------------------|--|
| All EPS events | 13 | 24 |
| All EPS events, excluding Akathisia/Restlessness | 9 | 14 |
| Akathisia | 5 | 11 |
| Dystonia* | <1 | 1 |
| Parkinsonism** | 8 | 13 |
| Restlessness | <1 | 4 |

Note: Figures rounded to the nearest integer

* Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus

** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

In the short-term, placebo-controlled schizophrenia and bipolar depression studies, data was objectively collected on the Simpson Angus Rating Scale (SAS) for extrapyramidal symptoms (EPS), the Barnes Akathisia Scale (BAS) for akathisia and the Abnormal Involuntary Movement Scale (AIMS) for dyskinesias.

Pediatric Patients (10 to 17 years)

In the 6-week, placebo-controlled study of bipolar depression in pediatric patients 10 to 17 years, the incidence of EPS, excluding events related to akathisia, for LATUDA-treated patients was similar in the LATUDA 20 to 80 mg/day (3.4%) treatment group vs. placebo (3.5%); and the incidence of akathisia-related events for LATUDA-treated patients was 2.9% vs. 3.5% for placebo-treated patients. Incidence of EPS by dose is provided in [Table 28](#).

Table 28: Incidence of EPS Compared to Placebo in the Bipolar Depression Study in Pediatric Patients (10 to 17 years)

| Adverse Event Term | Placebo (N=172) (%) | LATUDA 20 to 80 mg/day (N=175) (%) |
|--|---------------------------|---|
| All EPS events* | 5 | 6 |
| All EPS events, excluding Akathisia/Restlessness | 4 | 3 |
| Akathisia | 4 | 3 |
| Parkinsonism** | <1 | <1 |
| Dystonia*** | 1 | <1 |
| Salivary hypersecretion | <1 | <1 |
| Psychomotor hyperactivity | 0 | <1 |
| Tardive Dyskinesia | <1 | 0 |

Note: Figures rounded to the nearest integer

* EPS include adverse event terms: akathisia, cogwheel rigidity, dyskinesia, dystonia, hyperkinesia, joint stiffness, muscle rigidity, muscle spasms, musculoskeletal stiffness, oculogyric crisis, parkinsonism, tardive dyskinesia, and tremor

** Parkinsonism includes adverse event terms: bradykinesia, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, parkinsonism, and psychomotor retardation

***Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus

Schizophrenia

Adults

The mean change from baseline for LATUDA-treated patients for the SAS, BAS and AIMS was comparable to placebo-treated patients, with the exception of the Barnes Akathisia Scale global score (LATUDA, 0.1; placebo, 0.0). The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients and placebo for the BAS (LATUDA, 14.4%; placebo, 7.1%), the SAS (LATUDA, 5.0%; placebo, 2.3%) and the AIMS (LATUDA, 7.4%; placebo, 5.8%).

Adolescents

The mean change from baseline for LATUDA- treated patients with adolescent schizophrenia for the SAS, BAS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients and placebo for the BAS (LATUDA, 7.0%; placebo, 1.8%), the SAS (LATUDA, 8.3%; placebo, 2.7%) and the AIMS (LATUDA, 2.8%; placebo, 0.9%).

Adults

Monotherapy

The mean change from baseline for LATUDA-treated adult patients for the SAS, BAS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients and placebo for the BAS (LATUDA, 8.4%; placebo, 5.6%), the SAS (LATUDA, 3.7%; placebo, 1.9%) and the AIMS (LATUDA, 3.4%; placebo, 1.2%).

Adjunctive Therapy with Lithium or Valproate

The mean change from baseline for LATUDA-treated adult patients for the SAS, BAS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients and placebo for the BAS (LATUDA, 8.7%; placebo, 2.1%), the SAS (LATUDA, 2.8%; placebo, 2.1%) and the AIMS (LATUDA, 2.8%; placebo, 0.6%).

Pediatric Patients (10 to 17 years)

The mean change from baseline for LATUDA- treated pediatric patients 10 to 17 years with bipolar depression for the SAS, BAS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients and placebo for the BAS (LATUDA, 4.6%; placebo, 2.4%), the SAS (LATUDA, 0.6%; placebo, 0%) and was the same for the AIMS (LATUDA, 0%; placebo, 0%).

Dystonia

Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first-generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Schizophrenia

Adults

In the short-term, placebo-controlled schizophrenia clinical studies, dystonia occurred in 4.2% of LATUDA-treated subjects (0.0% LATUDA 20 mg, 3.5% LATUDA 40 mg, 4.5% LATUDA 80 mg, 6.5% LATUDA 120 mg and 2.5% LATUDA 160 mg) compared to 0.8% of subjects receiving placebo. Seven subjects (0.5%, 7/1508) discontinued clinical trials due to dystonic events – four were receiving LATUDA 80 mg/day and three were receiving LATUDA 120 mg/day.

Adolescents

In the short-term, placebo-controlled, adolescent schizophrenia study, dystonia occurred in 1% of LATUDA-treated patients (1% LATUDA 40 mg and 1% LATUDA 80 mg) compared to 0% of patients receiving placebo. No patients discontinued the clinical study due to dystonic events.

Bipolar Depression

Adults

Monotherapy

In the adult short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, dystonia occurred in 0.9% of LATUDA-treated subjects (0.0% and 1.8% for LATUDA 20 to 60 mg/day and LATUDA 80 to 120 mg/day, respectively) compared to 0.0% of subjects receiving placebo. No subject discontinued the clinical study due to dystonic events.

Adjunctive Therapy with Lithium or Valproate

In the adult short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression studies, dystonia occurred in 1.1% of LATUDA-treated subjects (20 to 120 mg) compared to 0.6% of subjects receiving placebo. No subject discontinued the clinical study due to dystonic events.

Pediatric Patients (10 to 17 years)

In the 6-week, placebo-controlled bipolar depression study in pediatric patients 10 to 17 years, dystonia occurred in 0.6% of LATUDA-treated patients compared to 1.2% of patients receiving placebo. No patients discontinued the clinical study due to dystonic events.

Other Adverse Reactions Observed During the Premarketing Evaluation of LATUDA

Following is a list of adverse reactions reported by adult patients treated with LATUDA at multiple doses of ≥ 20 mg once daily within the premarketing database of 2905 patients with schizophrenia. The reactions listed are those that could be of clinical importance, as well as reactions that are plausibly drug-related on pharmacologic or other grounds. Reactions listed in [Table 19](#) or those that appear elsewhere in the LATUDA label are not included.

Reactions are further categorized by organ class and listed in order of decreasing frequency according to the following definitions: those occurring in at least 1/100 patients (frequent) (only those not already listed in the tabulated results from placebo-controlled studies appear in this listing); those occurring in 1/100 to 1/1000 patients (infrequent); and those occurring in fewer than 1/1000 patients (rare).

Blood and Lymphatic System Disorders: Infrequent: anemia

Cardiac Disorders: Frequent: tachycardia; Infrequent: AV block 1st degree, angina pectoris, bradycardia

Ear and Labyrinth Disorders: Infrequent: vertigo

Eye Disorders: Frequent: blurred vision

Gastrointestinal Disorders: Frequent: abdominal pain, diarrhea; Infrequent: gastritis

General Disorders and Administrative Site Conditions: Rare: sudden death

Investigations: Frequent: CPK increased

Metabolism and Nutritional System Disorders: Frequent: decreased appetite

Musculoskeletal and Connective Tissue Disorders: Rare: rhabdomyolysis

Nervous System Disorders: Infrequent: cerebrovascular accident, dysarthria

Psychiatric Disorders: Infrequent: abnormal dreams, panic attack, sleep disorder

Renal and Urinary Disorders: Infrequent: dysuria; Rare: renal failure

Reproductive System and Breast Disorders: Infrequent: amenorrhea, dysmenorrhea; Rare: breast enlargement, breast pain, galactorrhea, erectile dysfunction, priapism

Skin and Subcutaneous Tissue Disorders: Frequent: rash, pruritus; Rare: angioedema

Vascular Disorders: Frequent: hypertension

Clinical Laboratory Changes

Schizophrenia

Adults

Serum Creatinine: In short-term, placebo-controlled trials, the mean change from Baseline in serum creatinine was +0.05 mg/dL for LATUDA-treated patients compared to +0.02 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 3.0% (43/1453) of LATUDA-treated patients and 1.6% (11/681) on placebo. The threshold for high creatinine value varied from > 0.79 to > 1.3 mg/dL based on the centralized laboratory definition for each study ([Table 29](#)).

Table 29: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in Adult Schizophrenia Studies

| Laboratory Parameter | Placebo (N=708) | LATUDA 20 mg/day (N=71) | LATUDA 40 mg/day (N=487) | LATUDA 80 mg/day (N=538) | LATUDA 120 mg/day (N=291) | LATUDA 160 mg/day (N=121) |
|----------------------------------|-----------------|-------------------------|--------------------------|--------------------------|---------------------------|---------------------------|
| Serum Creatinine Elevated | 2% | 1% | 2% | 2% | 5% | 7% |

Adolescents

Serum Creatinine: In the short-term, placebo-controlled, adolescent schizophrenia study, the mean change from Baseline in serum creatinine was -0.009 mg/dL for LATUDA-treated patients compared to +0.017 mg/dL for placebo-treated patients. A creatinine shift from normal to high (based on the centralized laboratory definition) occurred in 7.2% (14/194) of LATUDA-treated patients and 2.9% (3/103) on placebo ([Table 30](#)).

Table 30: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in the Adolescent Schizophrenia Study

| Laboratory Parameter | Placebo (N=103) | LATUDA 40 mg/day (N=97) | LATUDA 80 mg/day (N=97) |
|----------------------------------|--------------------|-------------------------------|-------------------------------|
| Serum Creatinine Elevated | 2.9% | 7.2% | 7.2% |

*Bipolar Depression*Adults*Monotherapy*

Serum Creatinine: In the adult short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, the mean change from Baseline in serum creatinine was +0.01 mg/dL for LATUDA-treated patients compared to -0.02 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 2.8% (9/322) of LATUDA-treated patients and 0.6% (1/162) on placebo ([Table 31](#)).

Table 31: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in the Adult Monotherapy Bipolar Depression Study

| Laboratory Parameter | Placebo (N=168) | LATUDA 20 to 60 mg/day (N=164) | LATUDA 80 to 120 mg/day (N=167) |
|----------------------------------|--------------------|--------------------------------------|---------------------------------------|
| Serum Creatinine Elevated | <1% | 2% | 4% |

Adjunctive Therapy with Lithium or Valproate

Serum Creatinine: In adult short-term, placebo-controlled premarketing adjunctive studies for bipolar depression, the mean change from Baseline in serum creatinine was +0.04 mg/dL for LATUDA-treated patients compared to -0.01 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 4.3% (15/360) of LATUDA-treated patients and 1.6% (5/334) on placebo ([Table 32](#)).

Table 32: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in the Adult Adjunctive Therapy Bipolar Depression Studies

| Laboratory Parameter | Placebo (N=334) | LATUDA 20 to 120 mg/day (N=360) |
|----------------------------------|--------------------|---------------------------------------|
| Serum Creatinine Elevated | 2% | 4% |

Pediatric Patients (10 to 17 years)

Serum Creatinine: In the 6-week, placebo-controlled bipolar depression study in pediatric patients 10 to 17 years, the mean change from Baseline in serum creatinine was +0.021 mg/dL for LATUDA-treated patients compared to +0.009 mg/dL for placebo-treated patients. A creatinine shift from normal to high (based on the centralized laboratory definition) occurred in 6.7% (11/163) of LATUDA-treated patients and 4.5% (7/155) on placebo (Table 33).

Table 33: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in the Bipolar Depression Study in Pediatric Patients (10 to 17 years)

| Laboratory Parameter | Placebo (N=155) | LATUDA 20 to 80 mg/day (N=163) |
|----------------------------------|--------------------|--------------------------------------|
| Serum Creatinine Elevated | 4.5% | 6.7% |

Pediatric Patients (6 to 17 years)

In a 104-week, open-label study in pediatric patients with schizophrenia, bipolar depression, or autistic disorder, the mean change from baseline to Week 104 in serum creatinine was +0.07 mg/dL. In patients with a normal serum creatinine at baseline, 6% experienced a shift to high at endpoint.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of LATUDA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity Reactions: Urticaria, throat swelling, tongue swelling, dyspnea, and rash.

Metabolism and Nutrition Disorders: Hyponatremia

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with LATUDA

Table 34: Clinically Important Drug Interactions with LATUDA

| Strong CYP3A4 Inhibitors | |
|-----------------------------------|--|
| Clinical Impact: | Concomitant use of LATUDA with strong CYP3A4 inhibitors increased the exposure of lurasidone compared to the use of LATUDA alone [see <i>Clinical Pharmacology (12.3)</i>]. |
| Intervention: | LATUDA should not be used concomitantly with strong CYP3A4 inhibitors [see <i>Contraindications (4)</i>]. |
| Examples: | Ketoconazole, clarithromycin, ritonavir, voriconazole, mibepradil |
| Moderate CYP3A4 Inhibitors | |
| Clinical Impact: | Concomitant use of LATUDA with moderate CYP3A4 inhibitors increased the exposure of lurasidone compared to the use of LATUDA alone [see <i>Clinical Pharmacology (12.3)</i>]. |
| Intervention: | LATUDA dose should be reduced to half of the original level when used concomitantly with moderate inhibitors of CYP3A4 [see <i>Dosage and Administration (2.6)</i>]. |
| Examples: | Diltiazem, atazanavir, erythromycin, fluconazole, verapamil |
| Strong CYP3A4 Inducers | |
| Clinical Impact: | Concomitant use of LATUDA with strong CYP3A4 inducers decreased the exposure of lurasidone compared to the use of LATUDA alone [see <i>Clinical Pharmacology (12.3)</i>]. |
| Intervention: | LATUDA should not be used concomitantly with strong CYP3A4 inducers [see <i>Contraindications (4)</i>]. |
| Examples: | Rifampin, avasimibe, St. John's wort, phenytoin, carbamazepine |
| Moderate CYP3A4 Inducers | |
| Clinical Impact: | Concomitant use of LATUDA with moderate CYP3A4 inducers decreased the exposure of lurasidone compared to the use of LATUDA alone [see <i>Clinical Pharmacology (12.3)</i>]. |
| Intervention: | LATUDA dose should be increased when used concomitantly with moderate inducers of CYP3A4 [see <i>Dosage and Administration (2.6)</i>]. |
| Examples: | Bosentan, efavirenz, etravirine, modafinil, nafcillin |

7.2 Drugs Having No Clinically Important Interactions with LATUDA

Based on pharmacokinetic studies, no dosage adjustment of LATUDA is required when administered concomitantly with lithium, valproate, or substrates of P-gp or CYP3A4 [see *Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to LATUDA during pregnancy.

Risk Summary

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery [*see Clinical Considerations*]. There are no studies of LATUDA use in pregnant women. The limited available data are not sufficient to inform a drug-associated risk of birth defects or miscarriage. In animal reproduction studies, no teratogenic effects were seen in pregnant rats and rabbits given lurasidone during the period of organogenesis at doses approximately 1.5- and 6-times, the maximum recommended human dose (MRHD) of 160 mg/day, respectively based on mg/m² body surface area [*see Data*].

The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs during the third trimester of pregnancy. These symptoms have varied in severity. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately.

Data

Animal Data

Pregnant rats were treated with oral lurasidone at doses of 3, 10, and 25 mg/kg/day during the period of organogenesis. These doses are 0.2, 0.6, and 1.5 times the MRHD of 160 mg/day based on mg/m² body surface area. No teratogenic or embryo-fetal effects were observed up to 1.5 times the MRHD of 160 mg/day, based on mg/m².

Pregnant rabbits were treated with oral lurasidone at doses of 2, 10, and 50 mg/kg/day during the period of organogenesis. These doses are 0.2, 1.2 and 6 times the MRHD of 160 mg/day based on mg/m². No teratogenic or embryo-fetal effects were observed up to 6 times the MRHD of 160 mg/day based on mg/m².

Pregnant rats were treated with oral lurasidone at doses of 0.4, 2, and 10 mg/kg/day during the periods of organogenesis and lactation. These doses are 0.02, 0.1 and 0.6 times the MRHD of 160 mg/day based on mg/m². No pre- and postnatal developmental effects were observed up to 0.6 times the MRHD of 160 mg/day, based on mg/m².

8.2 Lactation

Risk Summary

Lactation studies have not been conducted to assess the presence of lurasidone in human milk, the effects on the breastfed infant, or the effects on milk production. Lurasidone is present in rat milk. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for LATUDA and any potential adverse effects on the breastfed infant from LATUDA or from the underlying maternal condition.

8.4 Pediatric Use

Schizophrenia

The safety and effectiveness of LATUDA 40-mg/day and 80-mg/day for the treatment of schizophrenia in adolescents (13 to 17 years) was established in a 6-week, placebo-controlled clinical study in 326 adolescent patients [see *Dosage and Administration (2.1)*, *Adverse Reactions (6.1)*, and *Clinical Studies (14.1)*].

The safety and effectiveness of LATUDA has not been established in pediatric patients less than 13 years of age with schizophrenia.

Bipolar Depression

The safety and effectiveness of LATUDA 20 to 80 mg/day for the treatment of bipolar depression in pediatric patients (10 to 17 years) was established in a 6-week, placebo-controlled clinical study in 347 pediatric patients [see *Dosage and Administration (2.2)*, *Adverse Reactions (6.1)*, and *Clinical Studies (14.2)*].

The safety and effectiveness of LATUDA has not been established in pediatric patients less than 10 years of age with bipolar depression.

Irritability Associated with Autistic Disorder

The effectiveness of LATUDA in pediatric patients for the treatment of irritability associated with autistic disorder has not been established.

Efficacy was not demonstrated in a 6-week study evaluating LATUDA 20 mg/day and 60 mg/day for the treatment of pediatric patients 6 to 17 years of age with irritability associated with autistic disorder diagnosed by Diagnostic and Statistical Manual of Mental Disorders, 4th Ed., Text Revision [DSM-IV-TR] criteria. The primary objective of the study as measured by improvement from Baseline in the irritability subscale of the Aberrant Behavior Checklist (ABC) at Endpoint (Week 6) was not met. A total of 149 patients were randomized to LATUDA or placebo. Vomiting occurred at a higher rate than reported in other LATUDA studies (4/49 or 8% for 20mg, 14/51 or 27% for 60mg, and 2/49 or 4% for placebo), particularly in children ages 6 to 12 (13 out of 18 patients on LATUDA with vomiting).

In a long-term, open-label study that enrolled pediatric patients (age 6 to 17 years) with schizophrenia, bipolar depression, or autistic disorder from three short-term, placebo-controlled trials, 54% (378/701) received lurasidone for 104 weeks. There was one adverse event in this trial that was considered possibly drug-related and has not been reported in adults receiving lurasidone: a 10 year old male experienced a prolonged, painful erection, consistent with priapism, that led to treatment discontinuation.

In this trial, the mean increase in height from open-label baseline to Week 104 was 4.94 cm. To adjust for normal growth, z-scores were derived (measured in standard deviations [SD]), which normalize for the natural growth of children and adolescents by comparisons to age- and sex-matched population standards. A z-score change <0.5 SD is considered not clinically significant. In this trial, the mean change in height

z-score from open-label baseline to Week 104 was +0.05 SD, indicating minimal deviation from the normal growth curve.

Juvenile animal studies

Adverse effects were seen on growth, physical and neurobehavioral development at doses as low as 0.2 times the MRHD based on mg/m². Lurasidone was orally administered to rats from postnatal days 21 through 91 (this period corresponds to childhood, adolescence, and young adulthood in humans) at doses of 3, 30, and 150 (males) or 300 (females) mg/kg/day which are 0.2 to 10 times (males) and 20 times (females) the maximum recommended adult human dose (MRHD) of 160 mg/day based on mg/m². The adverse effects included dose-dependent decreases in femoral length, bone mineral content, body and brain weights at 2 times the MRHD in both sexes, and motor hyperactivity at 0.2 and 2 times the MRHD in both sexes based on mg/m². In females, there was a delay in attainment of sexual maturity at 2 times the MRHD, associated with decreased serum estradiol. Mortality occurred in both sexes during early post-weaning period and some of the male weanlings died after only 4 treatments at doses as low as 2 times the MRHD based on mg/m². Histopathological findings included increased colloid in the thyroids and inflammation of the prostate in males at 10 times MRHD based on mg/m² and mammary gland hyperplasia, increased vaginal mucification, and increased ovarian atretic follicles at doses as low as 0.2 times the MRHD based on mg/m². Some of these findings were attributed to transiently elevated serum prolactin which was seen in both sexes at all doses. However, there were no changes at any dose level in reproductive parameters (fertility, conception indices, spermatogenesis, estrous cycle, gestation length, parturition, number of pups born). The no effect dose for neurobehavioral changes in males is 0.2 times the MRHD based on mg/m² and could not be determined in females. The no effect dose for growth and physical development in both sexes is 0.2 times the MRHD based on mg/m².

8.5 Geriatric Use

Clinical studies with LATUDA did not include sufficient numbers of patients aged 65 and older to determine whether or not they respond differently from younger patients. In elderly patients with psychosis (65 to 85), LATUDA concentrations (20 mg/day) were similar to those in young subjects. It is unknown whether dose adjustment is necessary on the basis of age alone.

Elderly patients with dementia-related psychosis treated with LATUDA are at an increased risk of death compared to placebo. LATUDA is not approved for the treatment of patients with dementia-related psychosis [see *Boxed Warning, Warnings and Precautions (5.1, 5.3)*].

8.6 Renal Impairment

Reduce the maximum recommended dosage in patients with moderate or severe renal impairment (CLcr<50 mL/minute). Patients with impaired renal function (CLcr<50 mL/minute) had higher exposure to lurasidone than patients with normal renal function [see *Clinical Pharmacology (12.3)*]. Greater exposure may increase the risk of LATUDA-associated adverse reactions [see *Dosage and Administration (2.4)*].

8.7 Hepatic Impairment

Reduce the maximum recommended dosage in patients with moderate to severe hepatic impairment (Child-Pugh score ≥ 7). Patients with moderate to severe hepatic impairment (Child-Pugh score ≥ 7) generally had higher exposure to lurasidone than patients with normal hepatic function [see *Clinical Pharmacology (12.3)*]. Greater exposure may increase the risk of LATUDA-associated adverse reactions [see *Dosage and Administration (2.5)*].

8.8 Other Specific Populations

No dosage adjustment for LATUDA is required on the basis of a patient's sex, race, or smoking status [*see Clinical Pharmacology (12.3)*].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

LATUDA is not a controlled substance.

9.2 Abuse

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

10 OVERDOSAGE

10.1 Human Experience

In premarketing clinical studies, accidental or intentional overdosage of LATUDA was identified in one patient who ingested an estimated 560 mg of LATUDA. This patient recovered without sequelae. This patient resumed LATUDA treatment for an additional two months.

10.2 Management of Overdosage

No specific antidotes for LATUDA are known. In managing overdose, provide supportive care, including close medical supervision and monitoring, and consider the possibility of multiple drug involvement. If an overdose occurs, consult a Certified Poison Control Center.

Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with an acute overdose of LATUDA. Similarly, the alpha-blocking properties of bretylium might be additive to those of LATUDA, resulting in problematic hypotension.

Hypotension and circulatory collapse should be treated with appropriate measures. Epinephrine and dopamine should not be used, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen hypotension in the setting of LATUDA-induced alpha blockade. In case of severe extrapyramidal symptoms, anticholinergic medication should be administered.

Gastric lavage (after intubation if patient is unconscious) and administration of activated charcoal together with a laxative should be considered.

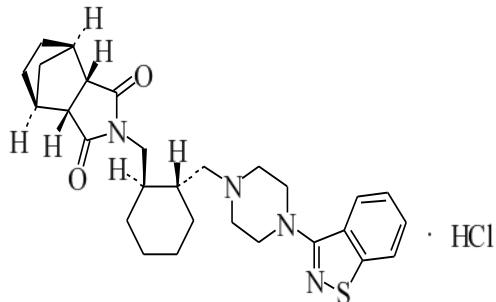
The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

11 DESCRIPTION

LATUDA is an atypical antipsychotic belonging to the chemical class of benzisothiazol derivatives.

Its chemical name is (3a*R*,4*S*,7*R*,7a*S*)-2-[(1*R*,2*R*)-2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-ylmethyl]cyclohexylmethyl]hexahydro-4,7-methano-2*H*-isoindole-1,3-dione hydrochloride. Its molecular formula is C₂₈H₃₆N₄O₂S·HCl and its molecular weight is 529.14.

The chemical structure is:



Lurasidone hydrochloride is a white to off-white powder. It is very slightly soluble in water, practically insoluble or insoluble in 0.1 N HCl, slightly soluble in ethanol, sparingly soluble in methanol, practically insoluble or insoluble in toluene and very slightly soluble in acetone.

LATUDA tablets are intended for oral administration only. Each tablet contains 20 mg, 40 mg, or 80 mg of lurasidone hydrochloride.

Inactive ingredients are mannitol, pregelatinized starch, croscarmellose sodium, hypromellose, magnesium stearate, Opadry® and carnauba wax. Additionally, the 80 mg tablet contains yellow ferric oxide and FD&C Blue No. 2 Aluminum Lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of lurasidone in the treatment of schizophrenia and bipolar depression is unclear. However, its efficacy in schizophrenia and bipolar depression could be mediated through a combination of central dopamine D₂ and serotonin Type 2 (5HT_{2A}) receptor antagonism.

12.2 Pharmacodynamics

Lurasidone is an antagonist with high affinity binding at the dopamine D₂ receptors (Ki of 1 nM) and the serotonin 5-HT_{2A} (Ki of 0.5 nM) and 5-HT₇ (Ki of 0.5 nM) receptors. It also binds with moderate affinity to the human α_{2C} adrenergic receptors (Ki of 11 nM), is a partial agonist at serotonin 5-HT_{1A} (Ki of 6.4 nM) receptors, and is an antagonist at the α_{2A} adrenergic receptors (Ki of 41 nM). Lurasidone exhibits little or no affinity for histamine H₁ and muscarinic M₁ receptors (IC₅₀ > 1,000 nM).

ECG Changes

The effects of LATUDA on the QTc interval were evaluated in a randomized, double-blind, multiple-dose, parallel-dedicated thorough QT study in 43 patients with schizophrenia or schizoaffective disorder, who were treated with LATUDA doses of 120 mg daily, 600 mg daily and completed the study. The maximum mean (upper 1-sided, 95% CI) increase in baseline-adjusted QTc intervals based on individual correction method (QTcI) was 7.5 (11.7) ms and 4.6 (9.5) ms, for the 120 mg and 600 mg dose groups respectively, observed at 2 to 4 hours after dosing. In this study, there was no apparent dose (exposure)-response relationship.

In short-term, placebo-controlled studies in schizophrenia and bipolar depression, no post-baseline QT prolongations exceeding 500 msec were reported in patients treated with LATUDA or placebo.

12.3 Pharmacokinetics

Adults

The activity of LATUDA is primarily due to the parent drug. The pharmacokinetics of LATUDA is dose-proportional within a total daily dose range of 20 mg to 160 mg. Steady-state concentrations of LATUDA are reached within 7 days of starting LATUDA.

Following administration of 40 mg of LATUDA, the mean (%CV) elimination half-life was 18 (7) hours.

Absorption and Distribution: LATUDA is absorbed and reaches peak serum concentrations in approximately 1-3 hours. It is estimated that 9-19% of an administered dose is absorbed. Following administration of 40 mg of LATUDA, the mean (%CV) apparent volume of distribution was 6173 (17.2) L. LATUDA is highly bound (~99%) to serum proteins.

In a food effect study, LATUDA mean C_{max} and AUC were about 3-times and 2-times, respectively, when administered with food compared to the levels observed under fasting conditions. LATUDA exposure was not affected as meal size was increased from 350 to 1000 calories and was independent of meal fat content [see *Dosage and Administration* (2.3)].

In clinical studies, establishing the safety and efficacy of LATUDA, patients were instructed to take their daily dose with food [see *Dosage and Administration* (2.3)].

Metabolism and Elimination: LATUDA is metabolized mainly via CYP3A4. The major biotransformation pathways are oxidative N-dealkylation, hydroxylation of norbornane ring, and S-oxidation. LATUDA is metabolized into two active metabolites (ID-14283 and ID-14326) and two major non-active metabolites (ID-20219 and ID-20220). Based on *in vitro* studies, LATUDA is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP4A11, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 enzymes. Because LATUDA is not a substrate for CYP1A2, smoking is not expected to have an effect on the pharmacokinetics of LATUDA.

Transporter proteins: *In vitro* studies suggest LATUDA is not a substrate of OATP1B1 or OATP1B3, however, is probably a substrate of P-gp and BCRP. *In vitro* studies indicate that LATUDA is not expected to inhibit transporters OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2-K and BSEP

at clinically relevant concentrations. LATUDA is not a clinically significant inhibitor of P-gp. However, it may inhibit BCRP.

Total excretion of radioactivity in urine and feces combined was approximately 89%, with about 80% recovered in feces and 9% recovered in urine, after a single dose of [¹⁴C]-labeled LATUDA.

Following administration of 40 mg of LATUDA, the mean (%CV) apparent clearance was 3902 (18.0) mL/min.

Drug Interaction Studies

Effects of other drugs on the exposure of lurasidone are summarized in [Figure 1](#). A population PK analyses concluded that coadministration of lithium 300-2400 mg/day or valproate 300-2000 mg/day with lurasidone for up to 6 weeks has minimal effect on lurasidone exposure.

And the effects of LATUDA on the exposures of other drugs are summarized in [Figure 2](#). A population PK analyses concluded that coadministration of lurasidone has minimal effect on lithium and valproate exposure when it is coadministered with lithium 300-2400 mg/day or valproate 300-2000 mg/day.

Figure 1: Impact of Other Drugs on LATUDA Pharmacokinetics

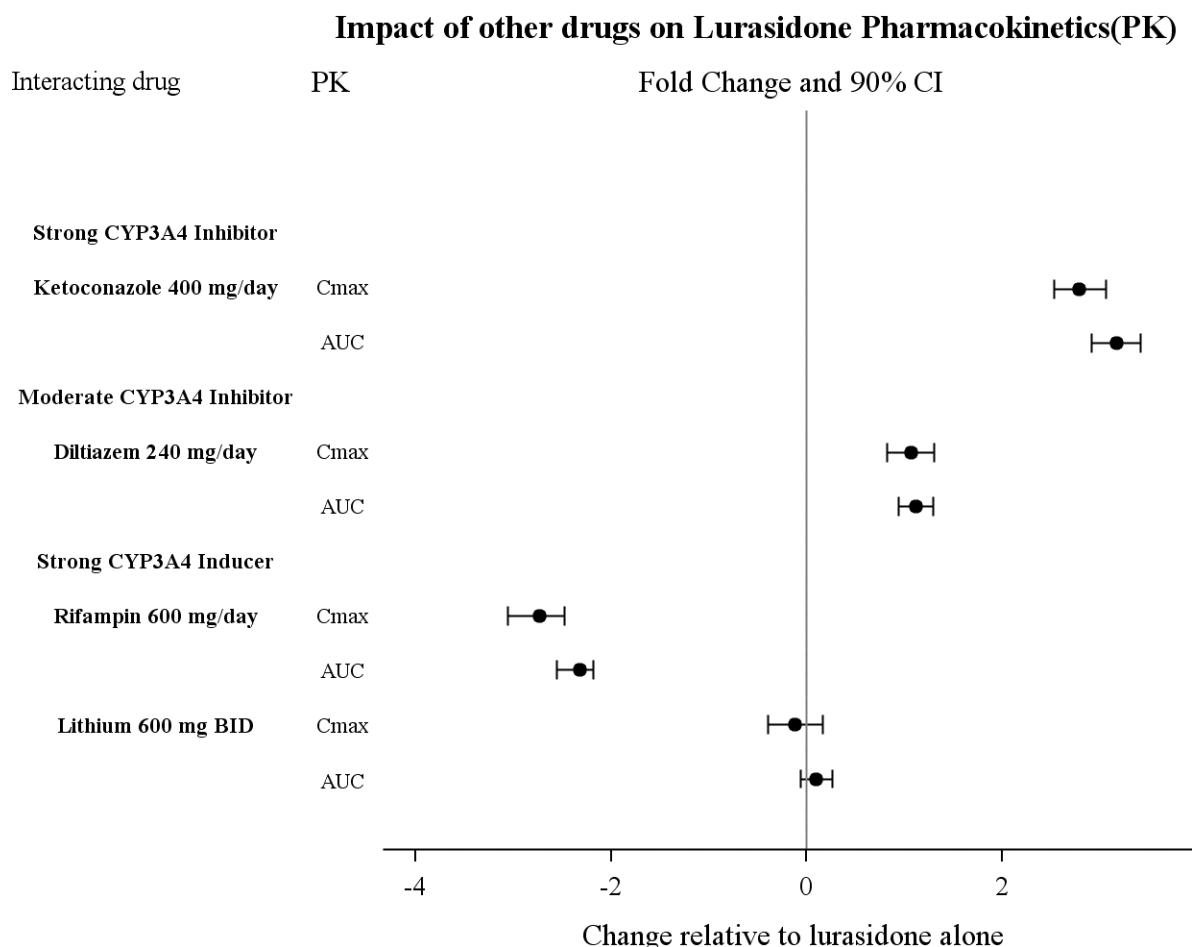
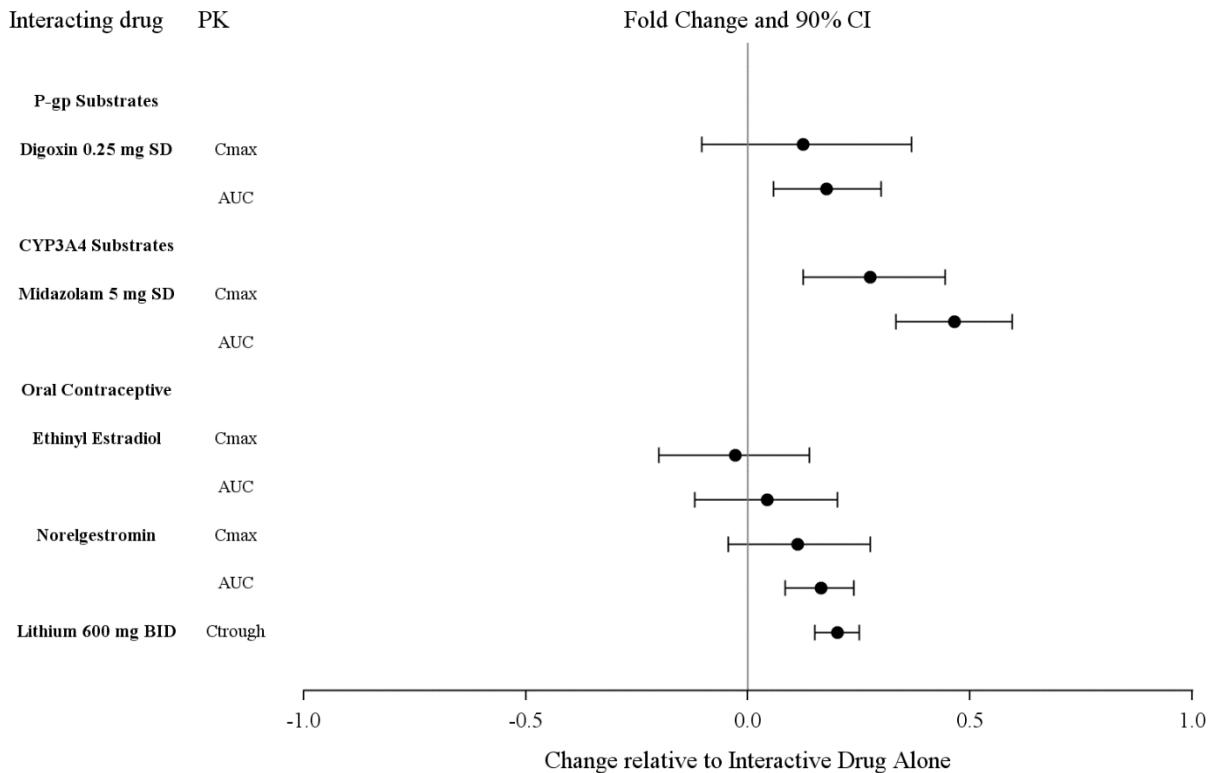
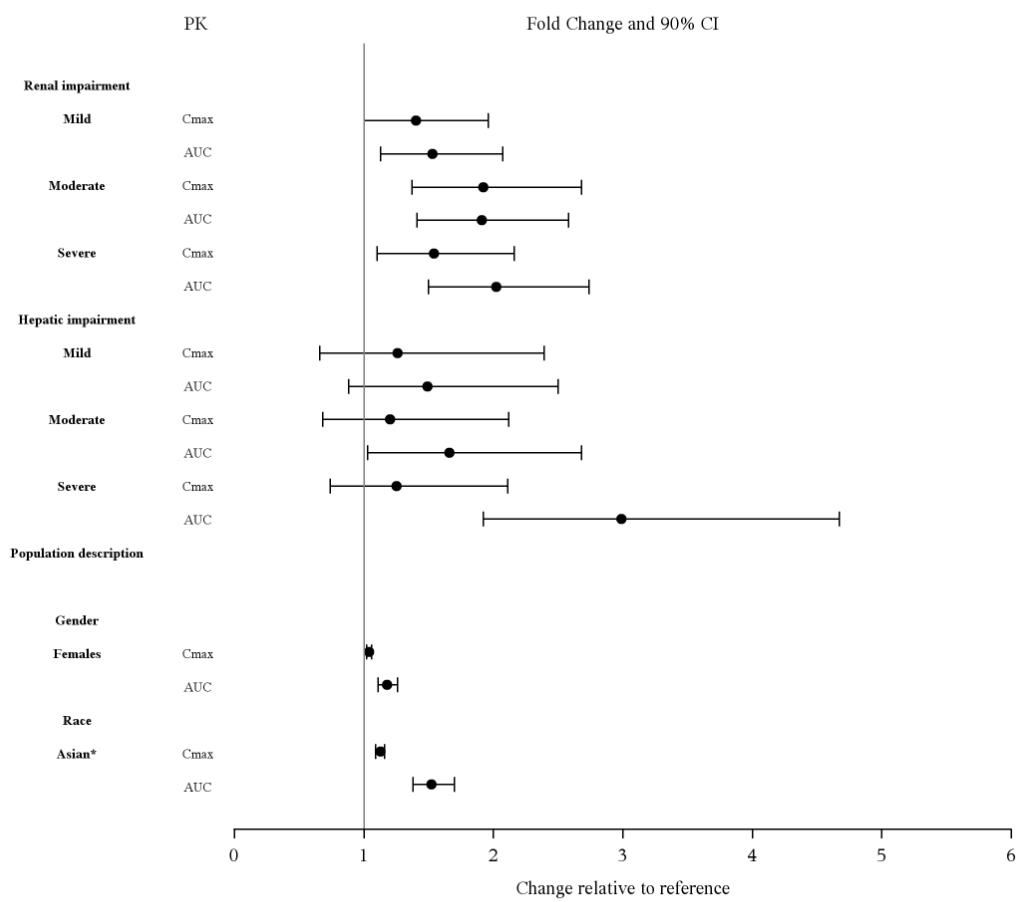


Figure 2:Impact of LATUDA on Other DrugsStudies in Specific Populations

The effect of intrinsic patient factors on the pharmacokinetics of LATUDA is presented in [Figure 3](#).

Pediatric Patients

LATUDA exposure (i.e., steady-state Cmax and AUC) in children and adolescent patients (10 to 17 years of age) was generally similar to that in adults across the dose range from 40 to 160 mg, without adjusting for body weight.

Figure 3: Impact of Other Patient Factors on LATUDA Pharmacokinetics

* Compare to Caucasian

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Lurasidone increased incidences of malignant mammary gland tumors and pituitary gland adenomas in female mice orally dosed with 30, 100, 300, or 650 mg/kg/day. The lowest dose produced plasma levels (AUC) approximately equal to those in humans receiving the MRHD of 160 mg/day. No increases in tumors were seen in male mice up to the highest dose tested, which produced plasma levels (AUC) 14 times those in humans receiving the MRHD.

Lurasidone increased the incidence of mammary gland carcinomas in female rats orally dosed at 12 and 36 mg/kg/day: the lowest dose; 3 mg/kg/day is the no-effect dose which produced plasma levels (AUC) 0.4 times those in humans receiving the MRHD. No increases in tumors were seen in male rats up to the highest dose tested, which produced plasma levels (AUC) 6 times those in humans receiving the MRHD.

Proliferative and/or neoplastic changes in the mammary and pituitary glands of rodents have been observed following chronic administration of antipsychotic drugs and are considered to be prolactin-mediated [see *Warnings and Precautions (5.7)*].

Mutagenesis: Lurasidone did not cause mutation or chromosomal aberration when tested *in vitro* and *in vivo* test battery. Lurasidone was negative in the Ames gene mutation test, the Chinese Hamster Lung

(CHL) cells, and in the *in vivo* mouse bone marrow micronucleus test up to 2000 mg/kg which is 61 times the MRHD of 160 mg/day based on mg/m² body surface area.

Impairment of Fertility: Estrus cycle irregularities were seen in rats orally administered lurasidone at 1.5, 15 and 150 mg/kg/day for 15 consecutive days prior to mating, during the mating period, and through gestation day 7. No effect was seen at the lowest dose of 0.1 mg/kg which is approximately 0.006 times the MRHD of 160 mg/day based on mg/m². Fertility was reduced only at the highest dose, which was reversible after a 14 day drug-free period. The no-effect dose for reduced fertility was approximately equal to the MRHD based on mg/m².

Lurasidone had no effect on fertility in male rats treated orally for 64 consecutive days prior to mating and during the mating period at doses up to 9 times the MRHD based on mg/m².

14 CLINICAL STUDIES

14.1 Schizophrenia

Adults

The efficacy of LATUDA for the treatment of schizophrenia was established in five short-term (6-week), placebo-controlled studies in adult patients (mean age of 38.4 years, range 18-72) who met DSM-IV criteria for schizophrenia. An active-control arm (olanzapine or quetiapine extended-release) was included in two studies to assess assay sensitivity.

Several instruments were used for assessing psychiatric signs and symptoms in these studies:

1. Positive and Negative Syndrome Scale (PANSS), is a multi-item inventory of general psychopathology used to evaluate the effects of drug treatment in schizophrenia. PANSS total scores may range from 30 to 210.
2. Brief Psychiatric Rating Scale derived (BPRSd), derived from the PANSS, is a multi-item inventory primarily focusing on positive symptoms of schizophrenia, whereas the PANSS includes a wider range of positive, negative and other symptoms of schizophrenia. The BPRSd consists of 18 items rated on a scale of 1 (not present) to 7 (severe). BPRSd scores may range from 18 to 126.
3. The Clinical Global Impression severity scale (CGI-S) is a clinician-rated scale that measures the subject's current illness state on a 1- to 7-point scale.

The endpoint associated with each instrument is change from baseline in the total score to the end of week 6. These changes are then compared to placebo changes for the drug and control groups.

The results of the studies follow:

1. Study 1: In a 6-week, placebo-controlled trial (N=145) involving two fixed doses of LATUDA (40 or 120 mg/day), both doses of LATUDA at Endpoint were superior to placebo on the BPRSd total score, and the CGI-S.
2. Study 2: In a 6-week, placebo-controlled trial (N=180) involving a fixed dose of LATUDA (80 mg/day), LATUDA at Endpoint was superior to placebo on the BPRSd total score, and the CGI-S.
3. Study 3: In a 6-week, placebo- and active-controlled trial (N=473) involving two fixed doses of LATUDA (40 or 120 mg/day) and an active control (olanzapine), both LATUDA doses and the active control at Endpoint were superior to placebo on the PANSS total score, and the CGI-S.
4. Study 4: In a 6-week, placebo-controlled trial (N=489) involving three fixed doses of LATUDA (40, 80 or 120 mg/day), only the 80 mg/day dose of LATUDA at Endpoint was superior to placebo on the PANSS total score, and the CGI-S.
5. Study 5: In a 6-week, placebo- and active-controlled trial (N=482) involving two fixed doses of LATUDA (80 or 160 mg/day) and an active control (quetiapine extended-release), both LATUDA doses and the active control at Endpoint were superior to placebo on the PANSS total score, and the CGI-S.

Thus, the efficacy of LATUDA at doses of 40, 80, 120 and 160 mg/day has been established ([Table 35](#)).

Table 35: Primary Efficacy Results for Studies in Adult Patients with Schizophrenia (BPRSd or PANSS Scores)

| Study | Treatment Group | Primary Efficacy Measure: BPRSd | | |
|---------------------------------|--|---------------------------------|-----------------------------------|---|
| | | Mean Baseline Score (SD) | LS Mean Change from Baseline (SE) | Placebo-subtracted Difference ^a (95% CI) |
| 1 | LATUDA (40 mg/day)* | 54.2 (8.8) | -9.4 (1.6) | -5.6 (-9.8, -1.4) |
| | LATUDA (120 mg/day)* | 52.7 (7.6) | -11.0 (1.6) | -6.7 (-11.0, -2.5) |
| | Placebo | 54.7 (8.1) | -3.8 (1.6) | -- |
| 2 | LATUDA (80 mg/day)* | 55.1 (6.0) | -8.9 (1.3) | -4.7 (-8.3, -1.1) |
| | Placebo | 56.1 (6.8) | -4.2 (1.4) | -- |
| Primary Efficacy Measure: PANSS | | | | |
| 3 | LATUDA (40 mg/day)* | 96.6 (10.7) | -25.7 (2.0) | -9.7 (-15.3, -4.1) |
| | LATUDA (120 mg/day)* | 97.9 (11.3) | -23.6 (2.1) | -7.5 (-13.4, -1.7) |
| | Olanzapine (15 mg/day)* ^b | 96.3 (12.2) | -28.7 (1.9) | -12.6 (-18.2, -7.9) |
| | Placebo | 95.8 (10.8) | -16.0 (2.1) | -- |
| 4 | LATUDA (40 mg/day) | 96.5 (11.5) | -19.2 (1.7) | -2.1 (-7.0, 2.8) |
| | LATUDA (80 mg/day)* | 96.0 (10.8) | -23.4 (1.8) | -6.4 (-11.3, -1.5) |
| | LATUDA (120 mg/day) | 96.0 (9.7) | -20.5 (1.8) | -3.5 (-8.4, 1.4) |
| | Placebo | 96.8 (11.1) | -17.0 (1.8) | -- |
| 5 | LATUDA (80 mg/day)* | 97.7 (9.7) | -22.2 (1.8) | -11.9 (-16.9, -6.9) |
| | LATUDA (160 mg/day)* | 97.5 (11.8) | -26.5 (1.8) | -16.2 (-21.2, -11.2) |
| | Quetiapine Extended-release (600 mg/day)* ^b | 97.7 (10.2) | -27.8 (1.8) | -17.5 (-22.5, -12.4) |
| | Placebo | 96.6 (10.2) | -10.3 (1.8) | -- |

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval, unadjusted for multiple comparisons.

^a Difference (drug minus placebo) in least-squares mean change from baseline.

^b Included for assay sensitivity.

* Doses statistically significantly superior to placebo.

Examination of population subgroups based on age (there were few patients over 65), gender and race did not reveal any clear evidence of differential responsiveness.

Adolescents (13-17 years)

The efficacy of LATUDA, was established in a 6-week, multicenter, randomized, double-blind, placebo-controlled study of adolescents (13 to 17 years) who met DSM-IV-TR criteria for schizophrenia (N=326). Patients were randomized to one of two fixed-doses of LATUDA (40 or 80 mg/day) or placebo.

The primary rating instrument used to assess psychiatric signs and symptoms was the PANSS. The key secondary instrument was the CGI-S.

For both dose groups, LATUDA was superior to placebo in reduction of PANSS and CGI-S scores at Week 6. On average, the 80 mg/day dose did not provide additional benefit compared to the 40 mg/day dose.

The primary efficacy results are provided in [Table 36](#).

Table 36: Primary Efficacy Results (PANSS Total Score) for the Adolescent Schizophrenia Study

| Treatment Group | Primary Efficacy Measure: PANSS | | |
|---------------------|---------------------------------|-----------------------------------|---|
| | Mean Baseline Score (SD) | LS Mean Change from Baseline (SE) | Placebo-subtracted Difference ^a (95% CI) |
| LATUDA (40 mg/day)* | 94.5 (10.97) | -18.6 (1.59) | -8.0 (-12.4, -3.7) |
| LATUDA (80 mg/day)* | 94.0 (11.12) | -18.3 (1.60) | -7.7 (-12.1, -3.4) |
| Placebo | 92.8 (11.08) | -10.5 (1.59) | -- |

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval, unadjusted for multiple comparisons.

^a Difference (drug minus placebo) in least-squares mean change from baseline.

* Doses statistically significantly superior to placebo.

14.2 Depressive Episodes Associated with Bipolar I Disorder

Adults

Monotherapy

The efficacy of LATUDA, as monotherapy, was established in a 6-week, multicenter, randomized, double-blind, placebo-controlled study of adult patients (mean age of 41.5 years, range 18 to 74) who met DSM-IV-TR criteria for major depressive episodes associated with bipolar I disorder, with or without rapid cycling, and without psychotic features (N=485). Patients were randomized to one of two flexible-dose ranges of LATUDA (20 to 60 mg/day, or 80 to 120 mg/day) or placebo.

The primary rating instrument used to assess depressive symptoms in this study was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale with total scores ranging from 0 (no depressive features) to 60 (maximum score). The primary endpoint was the change from baseline in MADRS score at Week 6. The key secondary instrument was the Clinical Global Impression-Bipolar-Severity of Illness scale (CGI-BP-S), a clinician-rated scale that measures the subject's current illness state on a 7-point scale, where a higher score is associated with greater illness severity.

For both dose groups, LATUDA was superior to placebo in reduction of MADRS and CGI-BP-S scores at Week 6. The primary efficacy results are provided in [Table 37](#). The high dose range (80 to 120 mg per day) did not provide additional efficacy on average, compared to the low dose range (20 to 60 mg per day).

Adjunctive Therapy with Lithium or Valproate

The efficacy of LATUDA, as an adjunctive therapy with lithium or valproate, was established in a 6-week, multicenter, randomized, double-blind, placebo-controlled study of adult patients (mean age of 41.7 years, range 18 to 72) who met DSM-IV-TR criteria for major depressive episodes associated with bipolar I disorder, with or without rapid cycling, and without psychotic features (N=340). Patients who remained symptomatic after treatment with lithium or valproate were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo.

The primary rating instrument used to assess depressive symptoms in this study was the MADRS. The primary endpoint was the change from baseline in MADRS score at Week 6. The key secondary instrument was the CGI-BP-S scale.

LATUDA was superior to placebo in reduction of MADRS and CGI-BP-S scores at Week 6, as an adjunctive therapy with lithium or valproate ([Table 37](#)).

Table 37: Primary Efficacy Results for Adult Studies in Depressive Episodes Associated with Bipolar I Disorder (MADRS Scores)

| Study | Treatment Group | Primary Efficacy Measure: MADRS | | |
|--------------------------|--|---------------------------------|-----------------------------------|---|
| | | Mean Baseline Score (SD) | LS Mean Change from Baseline (SE) | Placebo-subtracted Difference ^a (95% CI) |
| Monotherapy study | LATUDA (20-60 mg/day)* | 30.3 (5.0) | -15.4 (0.8) | -4.6 (-6.9, -2.3) |
| | LATUDA (80-120 mg/day)* | 30.6 (4.9) | -15.4 (0.8) | -4.6 (-6.9, -2.3) |
| | Placebo | 30.5 (5.0) | -10.7 (0.8) | -- |
| Adjunctive Therapy study | LATUDA (20-120 mg/day)* + lithium or valproate | 30.6 (5.3) | -17.1 (0.9) | -3.6 (-6.0, -1.1) |
| | Placebo + lithium or valproate | 30.8 (4.8) | -13.5 (0.9) | -- |

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval, unadjusted for multiple comparisons.

^a Difference (drug minus placebo) in least-squares mean change from baseline. * Treatment group statistically significantly superior to placebo.

Pediatric Patients (10 to 17 years)

The efficacy of LATUDA was established in a 6-week, multicenter, randomized, double-blind, placebo-controlled study of pediatric patients (10 to 17 years) who met DSM-5 criteria for a major depressive episode associated with bipolar I disorder, with or without rapid cycling, and without psychotic features (N=343). Patients were randomized to flexibly dosed LATUDA 20 to 80 mg/day or placebo. At the end of the clinical study, most patients (67%) received 20 mg/day or 40 mg/day.

The primary rating scale used to assess depressive symptoms in this study was the Children's Depression Rating Scale, Revised (CDRS-R) total score. The CDRS-R is a 17-item clinician-rated scale with total scores ranging from 17 to 113. The primary endpoint was the change from baseline in CDRS-R score at Week 6. The key secondary endpoint was the change from baseline in CGI-BP-S depression score.

LATUDA was superior to placebo in reduction of CDRS-R total score and CGI-BP-S depression score at Week 6. The primary efficacy results are provided in [Table 38](#).

Table 38: Primary Efficacy Results for the Study in Depressive Episodes Associated with Bipolar I Disorder (CDRS-R Total Score) in Pediatric Patients (10 to 17 years)

| Treatment Group | Primary Efficacy Measure: CDRS-R | | |
|---------------------------|----------------------------------|-----------------------------------|---|
| | Mean Baseline Score (SD) | LS Mean Change from Baseline (SE) | Placebo-subtracted Difference ^a (95% CI) |
| LATUDA (20 to 80 mg/day)* | 59.2 (8.24) | -21.0 (1.06) | -5.7 (-8.4,-3.0) |
| Placebo | 58.6 (8.26) | -15.3 (1.08) | -- |

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval, unadjusted for multiple comparisons.

^a Difference (drug minus placebo) in least-squares mean change from baseline.

* Treatment group statistically significantly superior to placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

LATUDA tablets are white to off-white, round (20 mg or 40 mg), or pale green, oval (80 mg) and identified with strength-specific one-sided debossing, “L20” (20 mg), “L40” (40 mg), or “L80” (80 mg). Tablets are supplied in the following strengths and package configurations (Table 39).

Table 39: Package Configuration for LATUDA Tablets

| Tablet Strength | Package Configuration |
|-----------------|--|
| 20 mg | Box of 3 blisters @ 10 film coated tablets |
| 40 mg | Box of 3 blisters @ 10 film coated tablets |
| 80 mg | Box of 3 blisters @ 10 film coated tablets |

Storage

Store LATUDA tablets below 30°C.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the approved patient labeling (Bahasa: Informasi Produk untuk Pasien).

Suicidal Thoughts and Behavior

Advise patients and caregivers to look for the emergence of suicidality, especially early during treatment and when the dosage is adjusted up or down and instruct them to report such symptoms to the healthcare provider [see *Boxed Warning, Warnings and Precautions (5.2)*].

Neuroleptic Malignant Syndrome

Counsel patients about a potentially fatal adverse reaction referred to as Neuroleptic Malignant Syndrome (NMS). Advise patients, family members, or caregivers to contact healthcare provider or to report to the emergency room if they experience signs and symptoms of NMS [see *Warnings and Precautions (5.4)*].

Tardive Dyskinesia

Counsel patients on the signs and symptoms of tardive dyskinesia and to contact their healthcare provider if these abnormal movements occur [see *Warnings and Precautions (5.5)*].

Metabolic Changes

Educate patients about the risk of metabolic changes, how to recognize symptoms of hyperglycemia and diabetes mellitus, and the need for specific monitoring, including blood glucose, lipids, and weight [see *Warnings and Precautions (5.6)*].

Hyperprolactinemia

Counsel patients on signs and symptoms of hyperprolactinemia that may be associated with chronic use of LATUDA. Advise them to seek medical attention if they experience any of the following: amenorrhea or galactorrhea in females, erectile dysfunction or gynecomastia in males [see *Warnings and Precautions (5.7)*].

Leukopenia/Neutropenia

Advise patients with a pre-existing low WBC or a history of drug-induced leukopenia/neutropenia that they should have their CBC monitored while taking LATUDA [see *Warnings and Precautions (5.8)*].

Orthostatic Hypotension

Educate patients about the risk of orthostatic hypotension, particularly at the time of initiating treatment, re-initiating treatment, or increasing the dose [see *Warnings and Precautions (5.9)*].

Interference with Cognitive and Motor Performance

Caution patients about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that LATUDA therapy does not affect them adversely [see *Warnings and Precautions (5.12)*].

Heat Exposure and Dehydration

Educate patients regarding appropriate care in avoiding overheating and dehydration [see *Warnings and Precautions (5.13)*].

Activation of Mania or Hypomania

Advise patients and their caregivers to observe for signs of activation of mania/hypomania [see *Warnings and Precautions (5.14)*].

Concomitant Medication

Advise patients to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, because there is a potential for drug interactions [see *Drug Interactions (7)*].

Pregnancy

Advise patients that LATUDA may cause extrapyramidal and/or withdrawal symptoms in a neonate. Advise patients to notify their healthcare provider with a known or suspected pregnancy [see *Use in Specific Populations (8.1)*]. Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to LATUDA during pregnancy [see *Use in Specific Populations (8.1)*].

HARUS DENGAN RESEP DOKTER

Reg. No.: DKIxxxxxxxxxx; LATUDA 20 mg; Box of 3 blisters @ 10 film coated tablets

Reg. No.: DKIxxxxxxxxxx; LATUDA 40 mg; Box of 3 blisters @ 10 film coated tablets

Reg. No.: DKIxxxxxxxxxx; LATUDA 80 mg; Box of 3 blisters @ 10 film coated tablets

Manufactured by: Bushu Pharmaceuticals Ltd., 1 Takeno, Kawagoe, Saitama, Japan

Repacked by: OLIC (Thailand) Limited, Ayutthaya, Thailand

Registered by: PT Pyridam Farma Tbk. Kabupaten Cianjur, Indonesia

INFORMASI PRODUK UNTUK PASIEN**LATUDA****(lurasidone hydrochloride)****tablet****Apa informasi terpenting yang harus saya ketahui tentang LATUDA?****LATUDA dapat menyebabkan efek samping yang serius, termasuk:**

- **Peningkatan risiko kematian pada orang lanjut usia dengan psikosis terkait demensia.** Obat-obatan seperti LATUDA dapat meningkatkan risiko kematian pada lansia yang kehilangan kontak dengan kenyataan (psikosis) karena kebingungan dan kehilangan ingatan (demensia). LATUDA tidak disetujui untuk pengobatan orang dengan psikosis terkait demensia.
- **Meningkatnya risiko pikiran atau tindakan bunuh diri pada anak-anak dan dewasa muda.** Obat antidepresan dapat meningkatkan pikiran atau tindakan bunuh diri pada beberapa anak dan dewasa muda dalam beberapa bulan pertama pengobatan dan ketika dosis diubah.
 - **Depresi dan penyakit mental serius lainnya adalah penyebab terpenting dari pikiran dan tindakan bunuh diri. Beberapa orang mungkin memiliki risiko sangat tinggi untuk memiliki pikiran atau tindakan bunuh diri.** Ini termasuk orang-orang yang memiliki (atau memiliki riwayat keluarga dengan) depresi, penyakit bipolar (juga disebut penyakit manik-depresif), atau riwayat pikiran atau tindakan bunuh diri.

Bagaimana saya dapat mengawasi dan mencoba mencegah pikiran dan tindakan bunuh diri dalam diri saya atau anggota keluarga?

- Perhatikan dengan seksama setiap perubahan, terutama perubahan tiba-tiba dalam suasana hati, perilaku, pikiran, atau perasaan. Ini sangat penting ketika terapi dengan obat antidepresan dimulai atau ketika dosisnya diubah.
- Hubungi penyedia layanan kesehatan segera untuk melaporkan perubahan baru atau tiba-tiba dalam suasana hati, perilaku, pikiran, atau perasaan.
- Jaga semua kunjungan tindak lanjut dengan penyedia layanan kesehatan sesuai jadwal. Hubungi penyedia layanan kesehatan di antara kunjungan jika diperlukan, terutama jika Anda memiliki kekhawatiran tentang gejala.

Hubungi penyedia layanan kesehatan segera jika Anda atau anggota keluarga Anda memiliki salah satu dari gejala berikut, terutama jika mereka baru, lebih buruk, atau membuat Anda khawatir:

- pikiran tentang bunuh diri atau sekarat
- depresi baru atau yang memburuk
- merasa sangat gelisah atau resah
- kesulitan tidur (insomnia)
- bertindak agresif, marah, atau kasar
- peningkatan ekstrim dalam aktivitas dan berbicara (mania)
- mencoba bunuh diri
- gangguan kecemasan baru atau yang memburuk
- serangan panik
- lekas marah baru atau yang memburuk
- bertindak berdasarkan impuls yang berbahaya
- perubahan tidak biasa lainnya dalam perilaku atau suasana hati

Apakah LATUDA itu?

LATUDA tablet adalah obat dengan zat aktif Lurasidone hidroklorida, tersedia dalam kekuatan 20 mg, 40 mg dan 80 mg. Tablet 20 mg dan 40 mg berbentuk bulat dan berwarna putih hingga putih pucat dengan emboss kekuatan di satu sisi "L20" dan "L40". Tablet 80 mg berbentuk oval berwarna hijau pucat dengan emboss kekuatan di satu sisi "L80".

LATUDA adalah obat dengan resep dokter yang digunakan:

- Untuk mengobati dewasa dan remaja (usia 13-17 tahun) dengan skizofrenia.
- Untuk pengobatan tunggal pada dewasa dan anak (usia 10-17 tahun) dengan episode depresi mayor yang terjadi dengan Gangguan Bipolar I (depresi bipolar).
- Untuk pengobatan tambahan dengan obat lithium atau valproate pada dewasa dengan episode depresi mayor yang terjadi dengan Gangguan Bipolar I (depresi bipolar).

Tidak diketahui apakah LATUDA aman dan efektif pada anak-anak:

- berusia kurang dari 13 tahun dengan skizofrenia.
- berusia kurang dari 10 tahun dengan depresi bipolar.
- untuk pengobatan iritabilitas yang berhubungan dengan gangguan autistik.

Jangan menggunakan LATUDA jika:

- alergi terhadap lurasidone hidroklorida atau salah satu bahan dalam LATUDA. Lihat bagian akhir Informasi Produk untuk Pasien ini untuk daftar lengkap bahan dalam LATUDA.
- menggunakan obat tertentu lainnya yang disebut penghambat atau penginduksi CYP3A4 termasuk ketokonazol, klaritromisin, ritonavir, vorikonazol, mibefradil, rifampisin, avasimibe, *St. John's wort*, fenitoin, atau karbamazepin. Tanyakan kepada penyedia layanan kesehatan Anda jika Anda tidak yakin apakah Anda menggunakan obat-obatan ini.

Sebelum menggunakan LATUDA, beri tahu penyedia layanan kesehatan Anda tentang semua kondisi medis Anda, termasuk jika Anda:

- memiliki atau pernah mengalami masalah jantung atau stroke
- memiliki atau pernah mengalami tekanan darah rendah atau tinggi
- mengalami atau pernah menderita diabetes atau gula darah tinggi, atau memiliki riwayat keluarga diabetes atau gula darah tinggi
- mempunyai atau pernah memiliki kadar kolesterol total atau trigliserida yang tinggi
- mempunyai atau pernah memiliki kadar prolaktin yang tinggi
- mempunyai atau pernah memiliki jumlah sel darah putih rendah
- mempunyai atau pernah mengalami kejang
- mempunyai atau pernah mengalami masalah ginjal atau hati
- sedang hamil atau berencana untuk hamil. Tidak diketahui apakah LATUDA dapat membahayakan bayi Anda yang belum lahir. Bicaralah dengan penyedia layanan kesehatan Anda tentang risiko bayi Anda yang belum lahir jika Anda menggunakan LATUDA selama kehamilan.
 - Beritahu penyedia layanan kesehatan Anda jika Anda hamil atau merasa hamil selama pengobatan dengan LATUDA.

- sedang menyusui atau berencana untuk menyusui. Tidak diketahui apakah LATUDA masuk ke dalam ASI Anda. Bicaralah dengan penyedia layanan kesehatan Anda tentang cara terbaik dalam memberikan asupan ASI untuk bayi Anda selama perawatan dengan LATUDA.

Beri tahu penyedia layanan kesehatan Anda tentang semua obat yang Anda minum, termasuk obat resep dan obat bebas/obat bebas terbatas, vitamin, dan suplemen herbal.

LATUDA dan obat lain dapat mempengaruhi kinerja satu sama lain dan menyebabkan kemungkinan efek samping yang serius. LATUDA dapat mempengaruhi cara kerja obat lain, dan obat lain dapat mempengaruhi cara kerja LATUDA.

Penyedia layanan kesehatan Anda dapat memberi tahu Anda apakah aman menggunakan LATUDA dengan obat-obatan Anda yang lain. Jangan memulai atau menghentikan obat lain selama pengobatan dengan LATUDA tanpa berbicara dengan penyedia layanan kesehatan Anda terlebih dahulu.

Ketahui obat-obatan yang Anda minum. Simpan daftar obat-obatan Anda untuk ditunjukkan kepada penyedia layanan kesehatan dan apoteker Anda ketika Anda mendapatkan obat baru.

Bagaimana saya harus menggunakan LATUDA?

- Minum LATUDA persis seperti yang dikatakan oleh penyedia layanan kesehatan Anda. Jangan mengubah dosis atau berhenti minum LATUDA tanpa terlebih dahulu berbicara dengan penyedia layanan kesehatan Anda.
- Minum LATUDA melalui mulut, dengan makanan (setidaknya 350 kalori).
- Latuda harus ditelan utuh dan tidak dibelah, dikunyah atau dihancurkan.
- Jika Anda melewatkam satu dosis Latuda, minumlah segera setelah Anda ingat. Jika Anda mendekati dosis berikutnya, lewati dosis yang terlewati. Ambil saja dosis berikutnya pada waktu reguler Anda. Jangan minum 2 dosis pada waktu yang sama kecuali penyedia layanan kesehatan Anda memberi tahu Anda. Jika Anda tidak yakin tentang dosis Anda, hubungi penyedia layanan kesehatan Anda.
- Jika Anda minum terlalu banyak LATUDA, hubungi penyedia layanan kesehatan atau pusat kendali racun Anda atau segera pergi ke ruang gawat darurat rumah sakit terdekat.

Apa yang harus saya hindari saat menggunakan LATUDA?

- Jangan mengemudi, mengoperasikan alat berat, atau melakukan aktivitas berbahaya lainnya sampai Anda tahu bagaimana LATUDA memengaruhi Anda. LATUDA dapat membuat Anda mengantuk.
- Hindari makan jeruk bali atau minum jus jeruk bali selama pengobatan dengan LATUDA. Jus jeruk bali dan jeruk bali dapat memengaruhi jumlah konsentrasi LATUDA dalam darah Anda.
- Tubuh Anda tidak boleh pada suhu yang terlalu panas atau mengalami dehidrasi selama pengobatan dengan LATUDA.
 - Jangan terlalu banyak berolahraga.
 - Dalam cuaca panas, tetaplah di dalam tempat yang sejuk jika memungkinkan.
 - Hindari sinar matahari.
 - Jangan memakai terlalu banyak pakaian atau pakaian tebal
 - Minum banyak air.

Apa kemungkinan efek samping dari LATUDA?

LATUDA dapat menyebabkan efek samping yang serius, termasuk:

- Lihat "Apa informasi terpenting yang harus saya ketahui tentang LATUDA?"

- **Stroke (masalah cerebrovaskular) pada lansia dengan psikosis terkait demensia yang dapat menyebabkan kematian.**
- **Neuroleptic malignant syndrome (NMS) suatu kondisi serius yang dapat menyebabkan kematian.** Hubungi penyedia layanan kesehatan Anda atau segera pergi ke ruang gawat darurat rumah sakit terdekat jika Anda memiliki beberapa atau semua tanda dan gejala NMS berikut:
 - demam tinggi
 - kebingungan
 - perubahan pernapasan, detak jantung, dan tekanan darah Anda
 - kekakuan otot
 - peningkatan dalam berkeringat
- **Gerakan tubuh yang tidak terkontrol (tardive dyskinesia).** LATUDA dapat menyebabkan gerakan yang tidak dapat Anda kendalikan di wajah, lidah, atau bagian tubuh lainnya. *Tardive dyskinesia* mungkin tidak kunjung sembuh, bahkan jika Anda berhenti minum LATUDA. *Tardive dyskinesia* juga dapat muncul setelah Anda berhenti menggunakan LATUDA.
- **Masalah dengan metabolisme Anda seperti:**
 - **gula darah tinggi (hiperglikemia) dan diabetes.** Peningkatan gula darah bisa terjadi pada beberapa orang yang menggunakan LATUDA. Gula darah yang sangat tinggi dapat menyebabkan koma atau kematian. Jika Anda menderita diabetes atau memiliki faktor risiko diabetes (seperti kelebihan berat badan atau riwayat keluarga diabetes), penyedia layanan kesehatan Anda harus memeriksa gula darah Anda sebelum Anda mulai dan selama pengobatan dengan LATUDA.

Hubungi penyedia layanan kesehatan Anda jika Anda memiliki gejala gula darah tinggi ini selama pengobatan dengan LATUDA:

- merasa sangat haus
- merasa sangat lapar
- merasa mual
- perlu buang air kecil lebih sering dari biasanya
- merasa lemah atau lelah
- merasa bingung, atau napas Anda berbau seperti buah
- **peningkatan kadar lemak (kolesterol dan trigliserida) dalam darah Anda.**
- **penambahan berat badan.** Anda dan penyedia layanan kesehatan Anda harus memeriksa berat badan Anda secara teratur selama pengobatan dengan LATUDA.
- **Peningkatan kadar prolaktin dalam darah Anda (hiperprolaktinemia).** Penyedia layanan kesehatan Anda mungkin melakukan tes darah untuk memeriksa kadar prolaktin Anda selama pengobatan dengan LATUDA. Beri tahu penyedia layanan kesehatan Anda jika Anda memiliki salah satu dari tanda dan gejala hiperprolaktinemia berikut:

Wanita:

- tidak adanya siklus menstruasi Anda
- sekresi ASI saat Anda tidak menyusui

Pria:

- masalah mendapatkan atau mempertahankan ereksi (disfungsi ereksi)
- pembesaran payudara (ginekomastia)

Jumlah sel darah putih rendah. Penyedia layanan kesehatan Anda mungkin melakukan tes darah selama beberapa bulan pertama pengobatan dengan LATUDA.

Penurunan tekanan darah (hipotensi ortostatik). Anda mungkin merasa pusing atau pingsan saat bangun terlalu cepat dari posisi duduk atau berbaring.

Jatuh. LATUDA dapat membuat Anda mengantuk atau pusing, dapat menyebabkan penurunan tekanan darah Anda saat berganti posisi (hipotensi ortostatik), dan dapat memperlambat kemampuan berpikir dan respon motorik Anda yang dapat menyebabkan jatuh dan dapat menyebabkan patah tulang atau cedera lainnya.

Kejang

- **Masalah pengaturan suhu tubuh Anda sehingga Anda merasa terlalu hangat.** Lihat "Apa yang harus saya hindari saat menggunakan LATUDA?"
- **Mania atau hipomania (episode manik) pada orang dengan riwayat gangguan bipolar.** Gejala mungkin termasuk:
 - peningkatan energi
 - pikiran yang berkecamuk
 - ide yang luar biasa tidak lazim
 - berbicara lebih banyak atau lebih cepat dari biasanya
 - masalah tidur yang parah
 - perilaku gegabah
 - kebahagiaan berlebihan atau mudah tersinggung

Kesulitan menelan

Efek samping LATUDA yang paling umum meliputi:

- **Orang dewasa dengan skizofrenia:**
 - mudah tertidur atau mengantuk
 - kegelisahan dan perasaan seperti Anda perlu bergerak (akathisia)
 - kesulitan bergerak, gerakan yang lambat, kekakuan pada otot, atau tremor
 - mual
- **Anak-anak usia 13 sampai 17 tahun dengan skizofrenia:**
 - Mudah tertidur atau mengantuk
 - mual
 - kegelisahan dan perasaan seperti Anda perlu bergerak (akathisia)
 - kesulitan bergerak, gerakan yang lambat, kekakuan otot, atau tremor
 - hidung berair
 - muntah
- **Orang dewasa dengan depresi bipolar:**
 - kegelisahan dan perasaan seperti Anda perlu bergerak (akathisia)
 - kesulitan bergerak, gerakan yang lambat, kekakuan otot, atau tremor
 - mudah tertidur atau mengantuk
- **Anak-anak usia 10 sampai 17 tahun dengan skizofrenia:**
 - mual
 - penambahan berat badan
 - masalah tidur (insomnia)

Efek samping diatas belum merupakan semua kemungkinan efek samping yang dapat terjadi dari LATUDA.

Hubungi dokter Anda untuk nasihat medis tentang efek samping.

Bagaimana cara menyimpan LATUDA?

- Simpan tablet LATUDA di bawah 30°C.
- Jauhkan LATUDA dan semua obat dari jangkauan anak-anak.

Informasi umum tentang penggunaan LATUDA yang aman dan efektif.

Obat kadang-kadang diresepkan untuk tujuan selain yang tercantum dalam Panduan Pengobatan. Jangan gunakan LATUDA untuk kondisi yang tidak diresepkan. Jangan berikan LATUDA kepada orang lain, meskipun mereka memiliki gejala yang sama dengan Anda. Itu bisa membahayakan mereka. Anda dapat bertanya kepada apoteker atau penyedia layanan kesehatan Anda untuk informasi tentang LATUDA yang ditulis untuk profesional kesehatan.

Apa saja bahan dalam LATUDA?

Zat aktif: lurasidone hydrochloride

Zat tambahan atau tidak aktif: mannitol, pregelatinized starch, croscarmellose sodium, hypromellose, magnesium stearate, Opadry® dan carnauba wax. Selain itu, tablet 80 mg mengandung yellow ferric oxide and FD&C Blue No. 2 Aluminum Lake.

HARUS DENGAN RESEP DOKTER

Reg. No.: DKIxxxxxxxxxx; LATUDA 20 mg; Box of 3 blisters @ 10 film coated tablets

Reg. No.: DKIxxxxxxxxxx; LATUDA 40 mg; Box of 3 blisters @ 10 film coated tablets

Reg. No.: DKIxxxxxxxxxx; LATUDA 80 mg; Box of 3 blisters @ 10 film coated tablets

Manufactured by: Bushu Pharmaceuticals Ltd., 1 Takeno, Kawagoe, Saitama, Japan

Repacked by: OLIC (Thailand) Limited, Ayutthaya, Thailand

Registered by: PT Pyridam Farma Tbk. Kabupaten Cianjur, Indonesia