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

LATUDA (lurasidone hydrochloride) tablets, for oral use
Initial U.S. Approval: 2010

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; AND SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LATUDA is not approved for the treatment of patients with dementia-related psychosis (5.1).
- Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients. Closely monitor for clinical worsening and emergence of suicidal thoughts and behaviors (5.2).

RECENT MAJOR CHANGES
Boxed Warning 3/2018
Indications and Usage (1) 3/2018
Dosage and Administration (2.2) 3/2018
Warnings and Precautions (5.1, 5.2, 5.4, 5.5, 5.6, 5.7, 5.9, 5.11, 5.12, 5.14) 3/2018

INDICATIONS AND USAGE
LATUDA is an atypical antipsychotic indicated for the treatment of:
- Schizophrenia in adults and adolescents (13 to 17 years) (1.4, 1.1)
- Depressive episode associated with Bipolar I Disorder (bipolar depression) in adults and pediatric patients (10 to 17 years) as monotherapy (1.4, 2.2)
- Depressive episode associated with Bipolar I Disorder (bipolar depression) in adults as adjunctive therapy with lithium or valproate (1.4, 2.2)

DOSEAGE AND ADMINISTRATION
LATUDA should be taken with food (at least 350 calories). Administration with food substantially increases the absorption of LATUDA (2.3, 12.3).

<table>
<thead>
<tr>
<th>Indication</th>
<th>Starting Dose</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia – adults (2.1)</td>
<td>40 mg per day</td>
<td>40 mg to 160 mg per day</td>
</tr>
<tr>
<td>Schizophrenia – adolescents (13 to 17 years) (2.1)</td>
<td>40 mg per day</td>
<td>40 mg to 80 mg per day</td>
</tr>
<tr>
<td>Bipolar Depression - adults (2.2)</td>
<td>20 mg per day</td>
<td>20 mg to 120 mg per day</td>
</tr>
<tr>
<td>Bipolar Depression – pediatric patients (10 to 17 years) (2.2)</td>
<td>20 mg per day</td>
<td>20 mg to 80 mg per day</td>
</tr>
</tbody>
</table>

- Moderate and Severe Renal Impairment: Recommended starting dose is 20 mg per day, and the maximum recommended dose is 80 mg per day (2.4, 8.6).
- Moderate and Severe Hepatic Impairment: Recommended starting dose is 20 mg per day. The maximum recommended dose is 80 mg per day in moderate hepatic impairment and 40 mg per day in severe hepatic impairment (2.5, 8.7).
- Concomitant Use of a Moderate CYP3A4 Inhibitor (e.g., diltiazem): LATUDA dose should be reduced to half of the original dose level. Recommended starting dose is 20 mg per day. Maximum recommended dose is 80 mg per day (2.6, 7.1).

ADVERSE REACTIONS
Commonly observed adverse reactions (incidence ≥ 5% and at least twice the rate for placebo) were (6.1):
- Adult patients with schizophrenia: somnolence, akathisia, extrapyramidal symptoms, and nausea
- Adolescent patients (13-17 years) with schizophrenia: somnolence, nausea, akathisia, EPS (non-akathisia), rhinitis (80 mg only), and vomiting
- Adult patients with bipolar depression: akathisia, extrapyramidal symptoms, and somnolence
- Pediatric patients (10-17 years) with bipolar depression: nausea, weight increase, and insomnia.

To report SUSPECTED ADVERSE REACTIONS, contact Sunovion Pharmaceuticals Inc. at 1-877-737-7226 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS
- Pregnancy: May cause extrapyramidal or withdrawal symptoms in neonates with third trimester exposure (8.1).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 3/2018

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING:
INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; AND SUICIDAL THOUGHTS AND BEHAVIORS

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*Sections or subsections omitted from the Full Prescribing Information are not listed.
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, erlotinib, 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

<table>
<thead>
<tr>
<th>Tablet Strength</th>
<th>Tablet Color/Shape</th>
<th>Tablet Markings</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg</td>
<td>white to off-white round</td>
<td>L20</td>
</tr>
<tr>
<td>40 mg</td>
<td>white to off-white round</td>
<td>L40</td>
</tr>
<tr>
<td>60 mg</td>
<td>white to off-white oblong</td>
<td>L60</td>
</tr>
<tr>
<td>80 mg</td>
<td>pale green oval</td>
<td>L80</td>
</tr>
<tr>
<td>120 mg</td>
<td>white to off-white oval</td>
<td>L120</td>
</tr>
</tbody>
</table>

4. CONTRAINDICATIONS

• Known hypersensitivity to luradone HCl or any components in the formulation. Angioedema has been observed with luradone [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

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Drug-Placebo Difference in Number of Patients of Suicidal Thoughts or Behaviors per 1000 Patients Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>Increases Compared to Placebo 14 additional patients</td>
</tr>
<tr>
<td>18-24</td>
<td>Decreases Compared to Placebo 5 additional patients</td>
</tr>
<tr>
<td>25-64</td>
<td>1 fewer patient</td>
</tr>
<tr>
<td>≥65</td>
<td>6 fewer patients</td>
</tr>
</tbody>
</table>

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 regiment, or 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) in 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 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 increase cardiovascular/cerebrovascular risk.

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 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.

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine (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)].

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).

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 3: Change in Fasting Glucose in Adult Schizophrenia Studies |
|-------------------------|----------------------|----------------------|----------------------|----------------------|
|                        | Placebo                     | LATUDA 20 mg/day | LATUDA 40 mg/day | LATUDA 80 mg/day |
| Mean Change from Baseline (mg/dL) |                       |                     |                     |                     |
| n=680                   | n=71                        | n=478               | n=508               | n=283               | n=113               |
| Serum Glucose           | -0.0                       | -0.6                | +2.6                | -0.4                | +2.5                | +2.5                |
| Proportion of Patients with Shifts to ≥ 126 mg/dL |
| Serum Glucose (≥ 126 mg/dL) | (52/626)                   | (7/60)              | (57/449)            | (32/472)            | (20/260)            | (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 |
|-------------------------|----------------------|----------------------|----------------------|----------------------|
|                        | Placebo                     | LATUDA 20 to 60 mg/day | LATUDA 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) | (6/141)                   | (3/138)             | (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).

Adjuvant 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           | -0.9                       | +1.2                |
| Proportion of Patients with Shifts to ≥ 126 mg/dL |
| Serum Glucose (≥ 126 mg/dL) | (3/290)                   | (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).
Demise 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).

Dystidemia

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

Schizophrenia

Adolescents

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 6: Change in Fasting Lipids in Adult Schizophrenia Studies.

| Table 6: Change in Fasting Lipids in Adult Schizophrenia Studies |
|---------------------|---------------------|---------------------|---------------------|---------------------|
|                     | Placebo             | LATUDA 20 mg/day    | LATUDA 40 mg/day    | LATUDA 80 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 |

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 -8.6 (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

Monotherapy

Data from the adult short-term, flexible-dosed, placebo-controlled, monotherapy bipolar depression study are presented in Table 7: Change in Fasting Lipids in the Adult Monotherapy Bipolar Depression Study.

| Table 7: Change in Fasting Lipids in the Adult Monotherapy Bipolar Depression Study |
|---------------------|---------------------|---------------------|---------------------|
|                     | Placebo             | LATUDA 20 to 60 mg/day | LATUDA 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  (≥ 240 mg/dL) | 4.2% (5/118) | 4.4% (5/113) | 4.4% (5/114) |
| Triglycerides (≥ 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

| Mean Change from Baseline (mg/dL) |
|---------------------|---------------------|---------------------|
| Total cholesterol  | LATUDA 20 to 120 mg/day |
| Placebo             | n=303               | n=321               |
| Triglycerides     | -2.9               | -3.1               |
| Proportion of Patients with Shifts |
| Total cholesterol  (≥ 240 mg/dL) | 5.7% (15/263) | 5.4% (15/276) |
| Triglycerides (≥ 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 triglycerides was -7.6 mg/dL for LATUDA 20 to 80 mg/day (n=144) and +5.9 mg/dL for placebo (n=145).

Weight Gain

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

Schizophrenia

Adolescents

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 +14.5 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 ≥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

| Weight Gain |
|---------------------|---------------------|---------------------|
| Placebo             | LATUDA 20 to 120 mg/day |
| All Patients        | n=696               | n=71                |
| Triglycerides (≥ 240 mg/dL) | +0.15 (n=111) | +0.22 (n=109) |
| Triglycerides (≥ 200 mg/dL) | +0.68 (n=110) | +0.60 (n=108) |

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 ≥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

| Weight Gain |
|---------------------|---------------------|---------------------|
| Placebo             | LATUDA 20 to 120 mg/day |
| All Patients        | n=111               | n=109               |
| Triglycerides (≥ 240 mg/dL) | +0.2 (n=111) | +0.3 (n=109) |
| Triglycerides (≥ 200 mg/dL) | +0.7 (n=104) | +0.7 (n=104) |

Bipolar Depression

Adults

Monotherapy

Data from the adult short-term, flexible-dosed, placebo-controlled, monotherapy bipolar depression study are presented in Table 8.

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.
In short-term, placebo-controlled schizophrenia studies, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was -0.9 ng/mL at week 24 (n=130). 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), -5.3 ng/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.

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 gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported 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.
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. In the adult short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression studies, there were no reported adverse events of orthostatic hypotension or 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.

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

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

In the adult short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression studies, there were no reported adverse events of orthostatic hypotension or syncope. 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.

Adjuvant Therapy with Lithium or Valproate

In the adult short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression 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 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.

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.

Adjuvant 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, hypomnia, 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% (23/176) 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.

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 Warnings and Precautions (5.3)]
- 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)]

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 12509 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 premarkinget 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 ≥5% and at least twice the rate of placebo) in patients treated with LATUDA were somnolence, akathisia, extrapyramidal symptoms, and nausea.

Bipolar Depression (Monotherapy)

The following findings are based on the adult short-term, placebo-controlled premarkinget adult studies 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 ≥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.

<table>
<thead>
<tr>
<th>Class</th>
<th>Body System or Organ Class</th>
<th>Placebo (N=708)</th>
<th>LATUDA (N=1508)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20 mg/day</td>
<td>40 mg/day</td>
<td>80 mg/day</td>
</tr>
<tr>
<td></td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>5</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>5</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Salivary</td>
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<td><strong>Psychiatric Disorders</strong></td>
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<td></td>
</tr>
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<td>Insomnia</td>
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<td>10</td>
</tr>
<tr>
<td>Agitation</td>
<td>4</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Anxiety</td>
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<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Restlessness</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

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, ocular dystonia, tics, akathisia, disorders of gait and posture, and tardive dyskinesia

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.

Bipolar Depression (Monotherapy)

The following findings are based on the adult short-term, placebo-controlled premarkinget 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 ≥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

<table>
<thead>
<tr>
<th>Body System or Organ Class</th>
<th>Placebo (N=168) (%)</th>
<th>LATUDA 20-60 mg/day (N=164) (%)</th>
<th>LATUDA 80-120 mg/day (N=167) (%)</th>
<th>All LATUDA (N=331) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>10</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>4</td>
<td>6</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Influenza</td>
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</tr>
<tr>
<td>Urinary Tract Infection</td>
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<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
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<td></td>
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<td>&lt;1</td>
<td>2</td>
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<td>Nervous System Disorders</td>
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<td></td>
</tr>
<tr>
<td>Extrapyramidal Symptoms*</td>
<td>2</td>
<td>5</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Akathisia</td>
<td>2</td>
<td>8</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Somnolence**</td>
<td>7</td>
<td>7</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
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</tr>
<tr>
<td>Anxiety</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

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, hyper somnolence, sedation, and somnolence

Dose-Related Adverse Reactions in the Monotherapy Bipolar Depression 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 ≥5% and at least twice the rate of placebo) in subjects treated with LATUDA were somnolence, nausea, akathisia, extrapyramidal symptoms (non-akathisia, 40 mg only), vomiting, and rhinorrhea/rhinitis (80 mg only).

Adverse Reactions Associated with Discontinuation of Treatment: The incidence of discontinuation due to adverse reactions between LATUDA- and placebo-treated adolescents (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 adolescents with schizophrenia) are shown in Table 22.

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

<table>
<thead>
<tr>
<th>Body System or Organ Class</th>
<th>Placebo (N=334) (%)</th>
<th>LATUDA 20 to 120 mg/day (N=360) (%)</th>
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</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
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</tr>
<tr>
<td>Nausea</td>
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<td>14</td>
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<tr>
<td>Vomiting</td>
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<td>General Disorders</td>
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<td>Fatigue</td>
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<td>Infections and Infestations</td>
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<td>Investigations</td>
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<td>Metabolism and Nutrition Disorders</td>
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<td>Increased Appetite</td>
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<td>3</td>
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<tr>
<td>Nervous System Disorders</td>
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</tr>
<tr>
<td>Extrapyramidal Symptoms*</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Somnolence**</td>
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<td>Akathisia</td>
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</tr>
<tr>
<td>Restlessness</td>
<td>&lt;1</td>
<td>4</td>
</tr>
</tbody>
</table>

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=118) to 80 mg (N=104).

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

<table>
<thead>
<tr>
<th>Body System or Organ Class</th>
<th>Placebo (N=112) (%)</th>
<th>LATUDA 40 mg/day (N=110) (%)</th>
<th>LATUDA 80 mg/day (N=104) (%)</th>
<th>All LATUDA (N=214) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
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<tr>
<td>Nausea</td>
<td>3</td>
<td>13</td>
<td>14</td>
<td>14</td>
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<tr>
<td>Vomiting</td>
<td>2</td>
<td>8</td>
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<td>8</td>
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<tr>
<td>Diarrhea</td>
<td>1</td>
<td>3</td>
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<td>4</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>2</td>
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<tr>
<td>Infections and Infestations</td>
<td></td>
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</tr>
<tr>
<td>Viral Infection**</td>
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<td>11</td>
<td>10</td>
<td>10</td>
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<td>Rhinitis*</td>
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<td>&lt;1</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>0</td>
<td>&lt;1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence*</td>
<td>7</td>
<td>15</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Akathisia</td>
<td>2</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

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 ≥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>
<thead>
<tr>
<th>Body System or Organ Class</th>
<th>Percentage of Patients Reporting Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=172)</td>
</tr>
</tbody>
</table>

Gastrointestinal Disorders
- Nausea: 6%
- Vomiting: 4%
- Abdominal Pain Upper: 2%
- Diarrhea: 2%
- Abdominal Pain: 1%

General Disorders And Administration Site Conditions
- Fatigue: 2%
- Fatigue: 3%

Investigations
- Weight Increased: 2%
- Weight Increased: 7%

Metabolism and Nutrition Disorders
- Decreased Appetite: 2%
- Decreased Appetite: 4%

Nervous System Disorders
- Somnolence*: 6%
- Extrapyramidal symptoms**: 5%
- Dizziness: 5%

Psychiatric Disorders
- Insomnia: 2%
- Abnormal Dreams: 2%

Respiratory, Thoracic and Mediastinal Disorders
- Oropharyngeal Pain: 2%
- Oropharyngeal Pain: 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>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>Placebo (N=708) (%)</th>
<th>20 mg/day (N=71) (%)</th>
<th>40 mg/day (N=487) (%)</th>
<th>80 mg/day (N=538) (%)</th>
<th>120 mg/day (N=291) (%)</th>
<th>160 mg/day (N=121) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All EPS events</td>
<td>9</td>
<td>10</td>
<td>21</td>
<td>23</td>
<td>39</td>
<td>20</td>
</tr>
<tr>
<td>All EPS events, excluding Akathisia/Restlessness</td>
<td>6</td>
<td>6</td>
<td>11</td>
<td>12</td>
<td>22</td>
<td>13</td>
</tr>
<tr>
<td>Akathisia</td>
<td>3</td>
<td>6</td>
<td>11</td>
<td>12</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td>Dystonia*</td>
<td>&lt;1</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Parkinsonism**</td>
<td>5</td>
<td>6</td>
<td>9</td>
<td>8</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Restlessness</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>Placebo (N=112) (%)</th>
<th>40 mg/day (N=110) (%)</th>
<th>80 mg/day (N=104) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All EPS events</td>
<td>5</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>All EPS events, excluding Akathisia/Restlessness</td>
<td>4</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Akathisia</td>
<td>2</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Parkinsonism**</td>
<td>&lt;1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>1</td>
</tr>
<tr>
<td>Dystonia*</td>
<td>0</td>
<td>&lt;1</td>
<td>1</td>
</tr>
</tbody>
</table>

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

Adolescents

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

<table>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>Placebo (N=334) (%)</th>
<th>LATUDA 20 to 120 mg/day (N=360) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All EPS events</td>
<td>13</td>
<td>24</td>
</tr>
<tr>
<td>All EPS events, excluding Akathisia/Restlessness</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Akathisia</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Dystonia</td>
<td>&lt;1</td>
<td>1</td>
</tr>
<tr>
<td>Parkinsonism**</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Restlessness</td>
<td>&lt;1</td>
<td>4</td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer
* Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticolis, and trismus
** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

Table 28: Incidence of EPS Compared to Placebo in the Adult Monotherapy Bipolar Depression Study

<table>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>Placebo (N=168) (%)</th>
<th>LATUDA 20 to 60 mg/day (N=164) (%)</th>
<th>LATUDA 80 to 120 mg/day (N=167) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All EPS events</td>
<td>5</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>All EPS events, excluding Akathisia/Restlessness</td>
<td>2</td>
<td>5</td>
<td>9</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>Placebo (N=172) (%)</th>
<th>LATUDA 20 to 80 mg/day (N=175) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All EPS events*</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>All EPS events, excluding Akathisia/Restlessness</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Akathisia</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Parkinsonism**</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Dystonia***</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Salivary hypersalivation</td>
<td>0</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Psychomotor hyperactivity</td>
<td>0</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Tardive Dyskinesia</td>
<td>&lt;1</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer
* EPS includes adverse event terms: akathisia, cogwheel rigidity, dystonia, hypokinesia, joint stiffness, muscle rigidity, tardive dyskinesia, oculogyric crisis, tongue spasm, torticolis, and salivation
** Parkinsonism includes adverse event terms: bradykinesia, drooling, dystonia, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor
*** Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticolis, and trismus

Schizophrenia

**Adulthood**
The mean change from baseline for LATUDA-treated patients was 10.8% and 4.8% for placebo-treated patients. Incidence of EPS is provided in Table 27.

**Adolescents**
The mean change from baseline for LATUDA-treated patients was 12.9% 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.

**Pediatric Patients (10 to 17 years)**
The mean change from baseline for LATUDA-treated pediatric patients was 10.8% and 4.8% 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.

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 in children 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, 6.2% LATUDA 120 mg, and 2.5% LATUDA 160 mg) compared to 0.6% 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.
Clinical Laboratory Changes

Adolescents

Serum Creatinine: In the short-term, placebo-controlled, adolescent schizophrenia study, the mean change from Baseline in serum creatinine was −0.027 mg/dL for LATUDA-treated patients compared to +0.007 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 2.6% (14/539) of LATUDA-treated patients and 0.6% (3/517) on placebo (Table 30).

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

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Placebo (N=163)</th>
<th>LATUDA 40 mg/day (N=97)</th>
<th>LATUDA 80 mg/day (N=97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine Elevated</td>
<td>2.9%</td>
<td>7.2%</td>
<td>7.2%</td>
</tr>
</tbody>
</table>

Bipolar Depression

Adolescents

Serum Creatinine: In the adult short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, the mean change from Baseline in serum creatinine was +0.011 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 2.5% (14/539) of LATUDA-treated patients and 0.6% (3/517) 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 Studies

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Placebo (N=168)</th>
<th>LATUDA 20 to 60 mg/day (N=164)</th>
<th>LATUDA 80 to 120 mg/day (N=167)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine Elevated</td>
<td>&lt;1%</td>
<td>2%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Adjuvant Therapy with Lithium or Valproate

Serum Creatinine: In the adult short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, the mean change from Baseline in serum creatinine was +0.011 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 2.5% (14/539) of LATUDA-treated patients and 0.6% (3/517) 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

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Placebo (N=334)</th>
<th>LATUDA 20 to 120 mg/day (N=360)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine Elevated</td>
<td>2%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Pediatric Patients (10 to 17 years)

Serum Creatinine: In adult short-term, placebo-controlled premarketing adjunctive studies for bipolar depression, 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 1.4% (5/357) 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)

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Placebo (N=155)</th>
<th>LATUDA 20 to 80 mg/day (N=163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine Elevated</td>
<td>4.5%</td>
<td>6.7%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Strong CYP3A4 Inhibitors</th>
<th>Clinical Impact:</th>
<th>Concomitant use of LATUDA with strong CYP3A4 inhibitors increased the exposure of lurasidone compared to the use of LATUDA alone [see Clinical Pharmacology (12.3)].</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>LATUDA should not be used concomitantly with strong CYP3A4 inhibitors [see Contraindications (4)].</td>
<td></td>
</tr>
<tr>
<td>Examples:</td>
<td>Ketocnazole, clarithromycin, ritonavir, voriconazole, mifepristone.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate CYP3A4 Inhibitors</th>
<th>Clinical Impact:</th>
<th>Concomitant use of LATUDA with moderate CYP3A4 inhibitors increased the exposure of lurasidone compared to the use of LATUDA alone [see Clinical Pharmacology (12.3)].</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>LATUDA dose should be reduced to half of the original level when used concomitantly with moderate inhibitors of CYP3A4 [see Dosage and Administration (2.6)].</td>
<td></td>
</tr>
<tr>
<td>Examples:</td>
<td>Diltiazem, atazanavir, erythromycin, fluconazole, verapamil.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strong CYP3A4 Inducers</th>
<th>Clinical Impact:</th>
<th>Concomitant use of LATUDA with strong CYP3A4 inducers decreased the exposure of lurasidone compared to the use of LATUDA alone [see Clinical Pharmacology (12.3)].</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>LATUDA should not be used concomitantly with strong CYP3A4 inducers [see Contraindications (4)].</td>
<td></td>
</tr>
<tr>
<td>Examples:</td>
<td>Rifampin, avasimibe, St. John’s wort, phenytoin, carbamazepine.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate CYP3A4 Inducers</th>
<th>Clinical Impact:</th>
<th>Concomitant use of LATUDA with moderate CYP3A4 inducers decreased the exposure of lurasidone compared to the use of LATUDA alone [see Clinical Pharmacology (12.3)].</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>LATUDA dose should be increased when used concomitantly with moderate inducers of CYP3A4 [see Dosage and Administration (2.6)].</td>
<td></td>
</tr>
<tr>
<td>Examples:</td>
<td>Bosantan, efavirenz, etravirine, modafinil, naltrexone.</td>
<td></td>
</tr>
</tbody>
</table>

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. For more information, contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

Risk Summary

Neonates exposed to antipsychotic drugs 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, hyperactivity, 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 period 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 when the decision to use LATUDA is made for the patient 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 Disorder

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 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 autism diagnosed by Diagnostic and Statistical Manual of Mental Disorders, 4th Ed., Text Revision (DSM-IV-TR) criteria. The primary outcome 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 (14% vs. 8% for 20 mg, 14/51 or 27% for 60 mg, and 2/49 or 4% for placebo, particularly in children ages 6 to 12 (13 out of 18 patients on LATUDA with vomiting).

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 weight 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 mucusification, 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)].
Inactive ingredients are mannitol, pregelatinized starch, croscarmellose sodium, 40 mg, 60 mg, 80 mg, or 120 mg of lurasidone hydrochloride. LATUDA tablets are intended for oral administration only. Each tablet contains 20 mg, methanol, practically insoluble or insoluble in toluene and very slightly soluble in acetone. It is practically insoluble or insoluble in 0.1 N HCl, slightly soluble in ethanol, sparingly soluble in water.

S

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, 60 mg, 80 mg, or 120 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.
**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).

---

**Figure 1: Impact of Other Drugs on LATUDA Pharmacokinetics**

<table>
<thead>
<tr>
<th>Interacting drug</th>
<th>PK</th>
<th>Fold Change and 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP3A4 Inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoconazole 400 mg/day</td>
<td>Cmax</td>
<td>AUC</td>
</tr>
<tr>
<td>Moderate CYP3A4 Inhibitor</td>
<td>Cmax</td>
<td>AUC</td>
</tr>
<tr>
<td>Diltiazem 240 mg/day</td>
<td>Cmax</td>
<td>AUC</td>
</tr>
<tr>
<td>Strong CYP3A4 Inducer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin 600 mg/day</td>
<td>Cmax</td>
<td>AUC</td>
</tr>
<tr>
<td>Lithium 600 mg BID</td>
<td>Cmax</td>
<td>AUC</td>
</tr>
</tbody>
</table>

**Figure 2: Impact of LATUDA on Other Drugs**

<table>
<thead>
<tr>
<th>Interacting drug</th>
<th>PK</th>
<th>Fold Change and 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-gp Substrates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digestase 6.25 mg SD</td>
<td>Cmax</td>
<td>AUC</td>
</tr>
<tr>
<td>CYP3A4 Substrates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolam 5 mg SD</td>
<td>Cmax</td>
<td>AUC</td>
</tr>
<tr>
<td>Oral Contraceptive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethinyl Estradiol</td>
<td>Cmax</td>
<td>AUC</td>
</tr>
<tr>
<td>Norelgestromin</td>
<td>Cmax</td>
<td>AUC</td>
</tr>
<tr>
<td>Lithium 600 mg BID</td>
<td>Chrough</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 3: Impact of Other Patient Factors on LATUDA Pharmacokinetics**

<table>
<thead>
<tr>
<th>Population description</th>
<th>PK</th>
<th>Fold Change and 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal impairment</td>
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<td></td>
</tr>
<tr>
<td>Mild</td>
<td>Cmax</td>
<td>AUC</td>
</tr>
<tr>
<td>Moderate</td>
<td>Cmax</td>
<td>AUC</td>
</tr>
<tr>
<td>Severe</td>
<td>Cmax</td>
<td>AUC</td>
</tr>
<tr>
<td>Hepatic impairment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>Cmax</td>
<td>AUC</td>
</tr>
<tr>
<td>Moderate</td>
<td>Cmax</td>
<td>AUC</td>
</tr>
<tr>
<td>Severe</td>
<td>Cmax</td>
<td>AUC</td>
</tr>
<tr>
<td>Population description</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender Females</td>
<td>Cmax</td>
<td>AUC</td>
</tr>
<tr>
<td>Race Asian*</td>
<td>Cmax</td>
<td>AUC</td>
</tr>
</tbody>
</table>

*Compare to Caucasian
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).

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

| Study | Treatment Group | Primary Efficacy Measure: BPRSd | | Placebo-Subtracted Difference* (95% CI) | | Mean Baseline Score (SD) | LS Mean Change from Baseline (SE) | LS Mean Change from Baseline (SE) | Placebo-Subtracted Difference* (95% CI) |
|---|---|---|---|---|---|---|---|---|
| 1 | LATUDA (40 mg/day)* | 54.2 (8.8) | -9.4 (1.6) | -5.8 (-9.8, -1.4) | --- |
| 2 | 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

| Study | Treatment Group | Primary Efficacy Measure: PANSS | | Placebo-Subtracted Difference* (95% CI) | | Mean Baseline Score (SD) | LS Mean Change from Baseline (SE) | LS Mean Change from Baseline (SE) | Placebo-Subtracted Difference* (95% CI) |
|---|---|---|---|---|---|---|---|---|
| 3 | LATUDA (40 mg/day)* | 96.6 (10.7) | -25.7 (2.0) | -7.7 (-15.3, -4.1) | --- |
| 4 | LATUDA (120 mg/day)* | 97.9 (11.3) | -23.6 (2.1) | -7.5 (-13.4, -1.4) | --- |
| | Olanzapine (15 mg/day)*a | 96.3 (12.2) | -28.7 (1.9) | -12.6 (-18.2, -7.9) | --- |
| | Placebo | 95.8 (10.8) | -16.0 (2.1) | --- | --- |
| 5 | LATUDA (80 mg/day)* | 96.5 (11.5) | -19.2 (1.7) | -2.1 (-7.0, 2.8) | --- |
| | LATUDA (160 mg/day)* | 96.0 (10.8) | -23.4 (1.8) | -6.4 (-11.3, -1.5) | --- |
| | Placebo | 96.8 (11.1) | -17.0 (1.8) | --- | --- |
| 6 | LATUDA (600 mg/day)* | 97.7 (9.7) | -22.2 (1.8) | -11.9 (-16.9, -6.9) | --- |
| | Quetiapine Extended-release (600 mg/day)*b | 97.5 (11.8) | -26.5 (1.8) | -16.2 (-21.2, -11.2) | --- |
| | Placebo | 96.6 (10.2) | -10.3 (1.8) | --- | --- |

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

| Study | Treatment Group | Primary Efficacy Measure: PANSS | | Placebo-Subtracted Difference* (95% CI) | | Mean Baseline Score (SD) | LS Mean Change from Baseline (SE) | LS Mean Change from Baseline (SE) | Placebo-Subtracted Difference* (95% CI) |
|---|---|---|---|---|---|---|---|---|
| 1 | MONOTHERAPY | 30.3 (5.0) | -15.4 (0.8) | -6.4 (-6.9, -2.3) | --- |
| | ADJUNCTIVE | 30.6 (4.9) | -15.4 (0.8) | -6.4 (-6.9, -2.3) | --- |
| | Placebo | 30.5 (5.0) | -10.7 (0.8) | --- | --- |

### 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 | | Placebo-Subtracted Difference* (95% CI) | | Mean Baseline Score (SD) | LS Mean Change from Baseline (SE) | LS Mean Change from Baseline (SE) | Placebo-Subtracted Difference* (95% CI) |
|---|---|---|---|---|---|---|---|---|
| 1 | MONOTHERAPY | 59.2 (8.24) | -21.0 (1.06) | -5.7 (-8.4, -3.0) | --- |
| | Placebo | 58.6 (8.26) | -15.3 (1.08) | --- | --- |

### 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)

| Study | Treatment Group | Primary Efficacy Measure: CDRS-R | | Placebo-Subtracted Difference* (95% CI) | | Mean Baseline Score (SD) | LS Mean Change from Baseline (SE) | LS Mean Change from Baseline (SE) | Placebo-Subtracted Difference* (95% CI) |
|---|---|---|---|---|---|---|---|---|
| 1 | MONOTHERAPY | 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.

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

* Treatment group statistically significantly superior to placebo.

**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.

**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.
LATUDA tablets are white to off-white, round (20 mg or 40 mg), white to off-white, oblong (60 mg), pale green, oval (80 mg) or white to off-white, oval (120 mg) and identified with strength-specific one-sided debossing, “L20” (20 mg), “L40” (40 mg), “L80” (80 mg) or “L120” (120 mg). Tablets are supplied in the following strengths and package configurations (Table 39).

Table 39: Package Configuration for LATUDA Tablets

<table>
<thead>
<tr>
<th>Tablet Strength</th>
<th>Package Configuration</th>
<th>NDC Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg</td>
<td>Bottles of 30</td>
<td>63402-302-30</td>
</tr>
<tr>
<td></td>
<td>Bottles of 90</td>
<td>63402-302-90</td>
</tr>
<tr>
<td></td>
<td>Bottles of 300</td>
<td>63402-302-50</td>
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<td></td>
<td>Box of 100 (Hospital Unit Dose) 10 blister cards, 10 tablets each</td>
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<tr>
<td>40 mg</td>
<td>Bottles of 30</td>
<td>63402-304-30</td>
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<tr>
<td></td>
<td>Bottles of 90</td>
<td>63402-304-90</td>
</tr>
<tr>
<td></td>
<td>Bottles of 500</td>
<td>63402-304-50</td>
</tr>
<tr>
<td></td>
<td>Box of 100 (Hospital Unit Dose) 10 blister cards, 10 tablets each</td>
<td>63402-304-10 Carton 63402-304-01 Blister</td>
</tr>
<tr>
<td>60 mg</td>
<td>Bottles of 30</td>
<td>63402-306-30</td>
</tr>
<tr>
<td></td>
<td>Bottles of 90</td>
<td>63402-306-90</td>
</tr>
<tr>
<td></td>
<td>Bottles of 500</td>
<td>63402-306-50</td>
</tr>
<tr>
<td></td>
<td>Box of 100 (Hospital Unit Dose) 10 blister cards, 10 tablets each</td>
<td>63402-306-10 Carton 63402-306-01 Blister</td>
</tr>
<tr>
<td>80 mg</td>
<td>Bottles of 30</td>
<td>63402-308-30</td>
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<tr>
<td></td>
<td>Bottles of 90</td>
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<tr>
<td></td>
<td>Bottles of 500</td>
<td>63402-308-50</td>
</tr>
<tr>
<td></td>
<td>Box of 100 (Hospital Unit Dose) 10 blister cards, 10 tablets each</td>
<td>63402-308-10 Carton 63402-308-01 Blister</td>
</tr>
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<td>120 mg</td>
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<td></td>
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<td>63402-312-90</td>
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<tr>
<td></td>
<td>Bottles of 500</td>
<td>63402-312-50</td>
</tr>
<tr>
<td></td>
<td>Box of 100 (Hospital Unit Dose) 10 blister cards, 10 tablets each</td>
<td>63402-312-10 Carton 63402-312-01 Blister</td>
</tr>
</tbody>
</table>

Storage
Store LATUDA tablets at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advertise the patient to read the FDA-approved patient labeling (Medication Guide).

Suicidal Thoughts and Behavior
Advertise 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 (5.4)].

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 their healthcare provider or to report to the emergency room if they experience signs and symptoms of NMS [see Warnings and Precautions (5.5)].

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)].

What is the most important information I should know about LATUDA?
LATUDA may cause serious side effects, including:

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

- Increased risk of suicidal thoughts or actions in children and young adults. Antidepressant medicines may increase suicidal thoughts or actions in some children and young adults within the first few months of treatment and when the dose is changed.

- Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions. These include people who have (or have a family history of) depression, bipolar illness (also called manic-depressive illness), or a history of suicidal thoughts or actions.
How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?

- Pay close attention to any changes, especially sudden changes in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
- Call a healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
- Keep all follow-up visits with the healthcare provider as scheduled. Call a healthcare provider between visits as needed, especially if you have concerns about symptoms.

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

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

What is LATUDA?
LATUDA is a prescription medicine used:
- To treat people 13 years of age or older with schizophrenia.
- Alone to treat people 10 years of age and older with depressive episodes that happen with Bipolar I Disorder (bipolar depression).
- With the medicine lithium or valproate to treat adults with depressive episodes that happen with Bipolar I Disorder (bipolar depression).

It is not known if LATUDA is safe and effective in children:
- less than 13 years of age with schizophrenia.
- less than 10 years of age with bipolar depression.
- for the treatment of irritability associated with autistic disorder.

Do not take LATUDA if you are:

- allergic to lurasidone hydrochloride or any of the ingredients in LATUDA. See the end of this Medication Guide for a complete list of ingredients in LATUDA.
- taking certain other medicines called CYP3A4 inhibitors or inducers including ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, rifampin, avasimibe, St. John’s wort, phenytoin, or carbamazepine. Ask your healthcare provider if you are not sure if you are taking any of these medicines.

Before taking LATUDA, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had heart problems or stroke
- have or have had low or high blood pressure
- have or have had diabetes or high blood sugar, or have a family history of diabetes or high blood sugar.
- have or have had high levels of total cholesterol or triglycerides
- have or have had high prolactin levels
- have or have had low white blood cell count
- have or have had seizures
- have or have had kidney or liver problems
- are pregnant or plan to become pregnant. It is not known if LATUDA will harm your unborn baby. Talk to your healthcare provider about the risk to your unborn baby if you take LATUDA during pregnancy.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

LATUDA and other medicines may affect each other causing possible serious side effects. LATUDA may affect the way other medicines work, and other medicines may affect how LATUDA works.

Your healthcare provider can tell you if it is safe to take LATUDA with your other medicines. Do not start or stop any other medicines during treatment with LATUDA without talking to your healthcare provider first.

Know the medicines you take. Keep a list of your medicines to show your healthcare provider and pharmacist when you get a new medicine.

How should I take LATUDA?

- Take LATUDA exactly as your healthcare provider tells you to take it. Do not change the dose or stop taking LATUDA without first talking to your healthcare provider.
- Take LATUDA by mouth, with food (at least 350 calories).
- If you take too much LATUDA, call your healthcare provider or poison control center or go to the nearest hospital emergency room right away.

What should I avoid while taking LATUDA?

- Do not drive, operate heavy machinery, or do other dangerous activities until you know how LATUDA affects you. LATUDA may make you drowsy.
- Avoid eating grapefruit or drinking grapefruit juice during treatment with LATUDA. Grapefruit and grapefruit juice may affect the amount of LATUDA in your blood.
- Do not become too hot or dehydrated during treatment with LATUDA.
- Do not exercise too much.
- In hot weather, stay inside in a cool place if possible.
- Stay out of the sun.
- Do not wear too much clothing or heavy clothing.
- Drink plenty of water.

What are the possible side effects of LATUDA?

LATUDA may cause serious side effects, including:

- See “What is the most important information I should know about LATUDA?”
- Stroked (cerebrovascular problems) in elderly people with dementia-related psychosis that can lead to death.
- Neuroleptic malignant syndrome (NMS) a serious condition that can lead to death. Call your healthcare provider or go to the nearest hospital emergency room right away if you have some or all of the following signs and symptoms of NMS:
  - high fever
  - stiff muscles
  - confusion
  - increased sweating
  - changes in your breathing, heart rate, and blood pressure
- are breastfeeding or plan to breastfeed. It is not known if LATUDA passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with LATUDA.
- are pregnant or plan to become pregnant. It is not known if LATUDA will harm your unborn baby. Talk to your healthcare provider about the risk to your unborn baby if you take LATUDA during pregnancy.
- have or have had kidney or liver problems
- have or have had seizures
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○ Tell your healthcare provider if you become pregnant or think you are pregnant during treatment with LATUDA.
○ If you become pregnant during treatment with LATUDA, talk to your healthcare provider about registering with the National Pregnancy Registry for Atypical Antipsychotics. You can register by calling 1-866-961-2388 or go to http://womenmentalhealth.org/clincial-and-researchprograms/pregnancyregistry/.

How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?

- Pay close attention to any changes, especially sudden changes in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
- Call a healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
- Keep all follow-up visits with the healthcare provider as scheduled. Call a healthcare provider between visits as needed, especially if you have concerns about symptoms.

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

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

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- have or have had low white blood cell count
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  - Do not exercise too much.
  - In hot weather, stay inside in a cool place if possible.
  - Stay out of the sun.
  - Do not wear too much clothing or heavy clothing.
  - Drink plenty of water.

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- Neuroleptic malignant syndrome (NMS) a serious condition that can lead to death. Call your healthcare provider or go to the nearest hospital emergency room right away if you have some or all of the following signs and symptoms of NMS:
  - high fever
  - stiff muscles
  - confusion
  - increased sweating
  - changes in your breathing, heart rate, and blood pressure
• Uncontrolled body movements (tardive dyskinesia). LATUDA may cause movements that you cannot control in your face, tongue, or other body parts. Tardive dyskinesia may not go away, even if you stop taking LATUDA. Tardive dyskinesia may also start after you stop taking LATUDA.

• Problems with your metabolism such as:
  ○ high blood sugar (hyperglycemia) and diabetes. Increases in blood sugar can happen in some people who take LATUDA. Extremely high blood sugar can lead to coma or death. If you have diabetes or risk factors for diabetes (such as being overweight or a family history of diabetes), your healthcare provider should check your blood sugar before you start and during treatment with LATUDA.

  Call your healthcare provider if you have any of these symptoms of high blood sugar during treatment with LATUDA:
  • feel very thirsty
  • need to urinate more than usual
  • feel very hungry
  • feel weak or tired
  • feel sick to your stomach
  • feel confused, or your breath smells fruity
  ○ increased fat levels (cholesterol and triglycerides) in your blood.
  ○ weight gain. You and your healthcare provider should check your weight regularly during treatment with LATUDA.

  • Increased prolactin levels in your blood (hyperprolactinemia). Your healthcare provider may do blood tests to check your prolactin levels during treatment with LATUDA. Tell your healthcare provider if you have any of the following signs and symptoms of hyperprolactinemia:

    Females:
    ○ absence of your menstrual cycle
    ○ secretion of breast milk when you are not breastfeeding

    Males:
    ○ problems getting or maintaining an erection (erectile dysfunction)
    ○ enlargement of breasts (gynecomastia)

  • Low white blood cell count. Your healthcare provider may do blood tests during the first few months of treatment with LATUDA.

  • Decreased blood pressure (orthostatic hypotension). You may feel lightheaded or faint when you rise too quickly from a sitting or lying position.

  • Falls. LATUDA may make you sleepy or dizzy, may cause a decrease in your blood pressure when changing position (orthostatic hypotension), and can slow your thinking and motor skills which may lead to falls that can cause fractures or other injuries.

  • Seizures (convulsions)

  • Problems controlling your body temperature so that you feel too warm. See “What should I avoid while taking LATUDA?”

  • Mania or hypomania (manic episodes) in people with a history of bipolar disorder. Symptoms may include:
    ○ greatly increased energy
    ○ severe problems sleeping
    ○ racing thoughts
    ○ reckless behavior
    ○ unusually grand ideas
    ○ excessive happiness or irritability
    ○ talking more or faster than usual

  • Difficulty swallowing

The most common side effects of LATUDA include:

• Adults with schizophrenia:
  ○ sleepiness or drowsiness
  ○ restlessness and feeling like you need to move around (akathisia)
  ○ difficulty moving, slow movements, muscle stiffness, or tremor
  ○ nausea

• Children 13 to 17 years of age with schizophrenia:
  ○ sleepiness or drowsiness
  ○ nausea
  ○ restlessness and feeling like you need to move around (akathisia)
  ○ difficulty moving, slow movements, muscle stiffness, or tremor
  ○ runny nose
  ○ vomiting

• Adults with bipolar depression:
  ○ restlessness and feeling like you need to move around (akathisia)
  ○ difficulty moving, slow movements, muscle stiffness, or tremor
  ○ sleepiness or drowsiness

• Children 10 to 17 years of age with bipolar depression:
  ○ nausea
  ○ weight gain
  ○ problems sleeping (insomnia)

These are not all of the possible side effects of LATUDA. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store LATUDA?
• Store LATUDA tablets at room temperature between 68°F to 77°F (20°C to 25°C).
• Keep LATUDA and all medicines out of the reach of children.

General information about the safe and effective use of LATUDA. Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use LATUDA for a condition for which it was not prescribed. Do not give LATUDA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about LATUDA that is written for health professionals.

What are the ingredients in LATUDA?
Active ingredient: lurasidone hydrochloride
Inactive ingredients: 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

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Manufactured for:
Sunovion Pharmaceuticals Inc. Marlborough, MA 01752 USA
LATUDA is a registered trademark of Sumitomo Dainippon Pharma Co. Ltd.; Sunovion Pharmaceuticals Inc. is a U.S. subsidiary of Sumitomo Dainippon Pharma Co. Ltd.
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For more information, go to www.LATUDA.com or call 1-888-394-7377.

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