Bipolar depression: A Collaborative Approach to Care

Please see Brief Summary of full Prescribing Information, including Boxed Warning, on page S5.

INDICATIONS
LATUDA is indicated for monotherapy treatment of adult and pediatric patients (10 to 17 years) with major depressive episode associated with bipolar I disorder (bipolar depression) and adjunctive treatment with lithium or valproate in adult patients with bipolar depression.

The effectiveness of LATUDA for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

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

IMPORTANT SAFETY INFORMATION FOR LATUDA
Suicidal Thoughts and Behaviors
Antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adults in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors.

Bipolar disorder is characterized by fluctuations between hypomania, depression, or mania, though depressive episodes represent the most common symptomatic status associated with bipolar disorder. Individuals with bipolar disorder have higher rates of metabolic syndrome relative to age- and gender-matched healthy comparison subjects. The prevalence of metabolic syndrome affects the risk of cardiovascular disease morbidity and mortality in these individuals. In fact, comorbid cardiovascular disease is a greater contributor to mortality than is suicide in patients with bipolar disorder.

The onset of cardiovascular disease is also seen up to a decade earlier in this patient population, suggesting that close monitoring of cardiometabolic parameters is helpful for overall patient management. While being aware of these cardiovascular risk factors in individuals with bipolar disorder is important, psychiatric providers are not always able to serve as both specialists in mental health and as clinicians who follow their patients’ physical health;
PATIENT PROFILE: DAVE*

Dave is a 47-year-old obese information technology specialist who was diagnosed with bipolar I disorder 15 years ago. He has been seeing a new psychiatric nurse practitioner (NP) for the past few months. Dave is currently taking an atypical antipsychotic and a mood stabilizer—the same regimen that a psychiatrist prescribed 5 years ago. At a recent visit to the psychiatric NP, Dave states that he had initially improved when on the regimen, but lately, he is depressed, and his wife thinks he seems sad.

Dave’s wife, who accompanied him to the appointment, confirms that he had improved when he started his medication regimen, explaining that he had regained interest in spending time with his friends. However, she states that, more recently, he seems to be unengaged and unhelpful with tasks at home or on errands with the kids, which is creating strain in their marriage. She says that she does not believe his current therapy is working anymore. In reply, Dave acknowledges that he sometimes lacks the motivation to do things his wife asks him to do, adding that “no one understands [him].” When asked how work is going, he responds that he does well with his “actual job” but sometimes takes too long filling out paperwork.

The psychiatric NP delves into Dave’s treatment and medical history. Dave’s initial treatment for bipolar I disorder at the time of diagnosis was a first-generation antipsychotic and a mood stabilizer. Although Dave has not experienced a manic episode since his diagnosis, he has had several major depressive episodes, marked by overeating and lethargy. He has gained weight, which contributes to his lack of energy and interest in getting out of the house. His previous psychiatrist subsequently switched Dave to a different atypical antipsychotic. However, at this visit, Dave reports a worsening in depressive symptoms and “not enough energy” to follow an exercise regimen.

While noting Dave’s history, the psychiatric NP observes that Dave was breathing heavily and sweating during the first portion of the appointment after walking up a short flight of stairs. The psychiatric NP takes Dave’s pulse and blood pressure and measures his weight and waist circumference, keeping in mind that individuals with bipolar disorder are at higher risk for metabolic abnormalities and cardiovascular disease, compared with the general population.1 Further, weight gain and undesirable alterations in lipids have been observed with atypical antipsychotic use; patients treated with atypical antipsychotics should be monitored for unfavorable changes in metabolic parameters. The psychiatric NP talks to Dave about the importance of managing his physical health and arranges to work with a primary care colleague to monitor and address Dave’s cardiometabolic risk factors.

Noting Dave’s persistent depressive symptoms, the psychiatric NP decides to keep Dave on his current mood stabilizer and switch his atypical antipsychotic to Latuda® (lurasidone HCI) for the treatment of his major depressive episodes associated with bipolar I disorder (bipolar depression).

Before Dave and his wife leave the office, the psychiatric NP expresses that Dave and his entire family can be involved in improving their lifestyle, starting with simple dietary changes, and reiterates that atypical antipsychotics can cause unfavorable weight and metabolic changes. If necessary, referral to a nutritionist can provide additional knowledge and support. Increased activity is an important lifestyle modification, as well; family participation in activities, such as a nature walk or bike ride, can offer rewards beyond those of physical well-being.

* Hypothetical case representing a fictional patient.

Reference

LATUDA: A Treatment Option for Bipolar Depression
The efficacy of LATUDA for the adjunctive treatment of bipolar depression was evaluated in a phase 3, randomized, multicenter, double-blind, placebo-controlled clinical trial of 348 patients with bipolar I disorder.2 The results of this pivotal trial were published in the February 2014 issue of The American Journal of Psychiatry.2 All psychotropic medications other than lithium or valproate were tapered off during the screening phase, and a therapeutic range of lithium (0.6-1.2 mEq/L) or valproate (50-125 μg/mL) was maintained for at least 28 days. The patients were then randomized to receive flexibly dosed adjunctive Latuda® (lurasidone HCI)
20 mg/day to 120 mg/day plus lithium or valproate (n=183) or placebo plus lithium or valproate (n=165) for 6 weeks. Study medication was taken once daily in the evening by mouth with a meal (eg, dinner) or within 30 minutes after eating.7

**Short-term Efficacy**

**Figure 1** shows the improvement in depressive symptoms for the LATUDA and placebo groups from baseline to Week 6 as measured using the Montgomery-Asberg Depression Rating Scale (MADRS) score, which was the study’s primary efficacy endpoint.** The MADRS is a 10-item, clinician-rated scale with scores ranging from 0 to 60.7 At Week 6, LATUDA added to lithium or valproate was associated with statistically significantly greater reduction from baseline MADRS total score than was placebo added to lithium or valproate (−17.1 vs −13.5 points; P<.01). LATUDA was also associated with significantly greater reduction in the key secondary endpoint of the Clinical Global Impression-Bipolar Version-Severity scale score.2

**Short-term Safety**

The safety of LATUDA as adjunctive therapy with lithium or valproate was also established in a second short-term, randomized, placebo-controlled study for bipolar depression. Together, these 2 studies enrolled 360 patients who received LATUDA at daily doses of 20 mg to 120 mg as adjunctive therapy with lithium or valproate.7 Adverse events that occurred in at least 2% of LATUDA-treated patients and more often than in the placebo group are shown in **Figure 2.**7 In the 2 short-term studies of LATUDA as adjunctive therapy, the mean increase in body weight from baseline to Week 6 was 0.2 pounds for patients who received LATUDA plus lithium or valproate versus 0.4 pounds for patients who received placebo plus lithium or valproate. An increase of body weight of at least 7% was noted for 3.1% of patients who received LATUDA versus 0.3% of patients who received placebo.7 Patients in the LATUDA group exhibited a mean increase in blood glucose concentration of 1.2 mg/dL, compared with a mean decrease of 0.9 mg/dL for patients who received placebo.7 Total cholesterol concentration decreased by a mean of 3.1 mg/dL in the LATUDA group versus a decrease of 2.9 mg/dL in the placebo group. The mean triglyceride concentration increased by 4.6 mg/dL in the LATUDA group and decreased by 4.6 mg/dL in the placebo group.7

In these 2 studies, the median prolactin concentration increased by 2.8 ng/mL between baseline and Week 6 for patients in the LATUDA group and remained unchanged for patients in the placebo group. For male patients, the median change from baseline to Week 6 was +2.4 ng/mL with LATUDA and −0.1 ng/mL with placebo; for female patients, the median change from baseline was +3.2 ng/mL with LATUDA versus +0.4 ng/mL with placebo.7

Extrapyramidal symptoms (EPS), akathisia, and tardive dyskinesia were examined using the Simpson-Angus Scale, the Barnes Akathisia Scale (BAS), and the Abnormal Involuntary Movement Scale (AIMS), respectively. A shift from normal at baseline to abnormal at Week 6 (or at last observation carried forward for patients who discontinued prematurely) was noted for 2.8% of patients who received Latuda® (lurasidone HCl) plus lithium
AN EXPERT’S PERSPECTIVE

Case Commentary by Diane Snow, PhD, APRN, PMHNP-BC, FAANP, FIAAN

The first step in a comprehensive follow-up by the primary care clinician would be to run a standard lab workup to assess a new baseline of values, including, but not limited to: thyroid, cholesterol, and triglycerides. These values can provide a point of reference for ongoing appointments. Next, the clinician should delve into the patient’s sleep habits, which could be affecting his motivation and energy levels. If Dave’s sleep habits do require further investigation, the clinician may take this opportunity to refer Dave to a sleep laboratory or another health care professional.

To address Dave’s physical health, the psychiatric NP or primary care clinician should discuss basic lifestyle modifications (ie, dietary change, increase in exercise) with Dave and his wife. Keeping family members active in the discussion and treatment plan can be valuable, as they can provide support and serve as another perspective on a patient’s health status and overall functioning.

Collaboration should continue between the psychiatric NP and primary care clinician as these health care providers track Dave’s progress in regards to his depressive symptoms and results from his periodic physical exams.

Improvements of any kind—no matter how big or small—can help the patient, so working with Dave while incorporating changes agreed upon by him and his wife can be a good start toward improving overall health practice.

Diane Snow, PhD, APRN, PMHNP-BC, FAANP, FIAAN

*Hypothetical case representing a fictional patient.

References

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

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.

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.

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 effect. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

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

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

Metabolic Changes

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

Hyperglycemia and Diabetes Mellitus

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

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

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

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. 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.

Suicidal Thoughts and Behaviors

Antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adults in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors.

**INDICATIONS AND USAGE**

LATUDA is indicated for:

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

**CONTRAINDICATIONS**

- Known hypersensitivity to lurasidone HCl or any components in the formulation.
- Treatment of adult and adolescent patients (13 to 17 years) with schizophrenia.
- Indication for suicide risk reduction with adult and pediatric patients (10 to 17 years) with major depressive episode associated with bipolar I disorder (bipolar depression).

**WARNINGS AND PRECAUTIONS**

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.

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 1.

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 1: 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></td>
<td>Increases Compared to Placebo</td>
</tr>
<tr>
<td>&lt;18</td>
<td>14 additional patients</td>
</tr>
<tr>
<td>18-24</td>
<td>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.

*Note: Read the full Prescribing Information before prescribing LATUDA.*
### Table 2: Change in Fasting Glucose in Adult Schizophrenia Studies

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo</th>
<th>LATUDA 20 mg/day</th>
<th>LATUDA 80 mg/day</th>
<th>LATUDA 120 mg/day</th>
<th>LATUDA 160 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change from Baseline (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=680</td>
<td>n=517</td>
<td>n=508</td>
<td>n=283</td>
<td>n=113</td>
<td></td>
</tr>
<tr>
<td>Serum Glucose</td>
<td>-0.0</td>
<td>-0.6</td>
<td>+2.6</td>
<td>-0.4</td>
<td>+2.5</td>
</tr>
</tbody>
</table>

 Patients were randomized to flexibly dosed LATUDA 20 mg/day, LATUDA 80 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 +1.0 mg/dL; 45% of placebo (n=130) and +1.0 mg/dL (n=130) at week 24, respectively.

### Table 3: Change in Fasting Glucose in the Adult Monotherapy Bipolar Depression Study

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo</th>
<th>LATUDA 20 mg/day</th>
<th>LATUDA 80 mg/day</th>
<th>LATUDA 120 mg/day</th>
<th>LATUDA 160 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change from Baseline (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=148</td>
<td>n=140</td>
<td>n=143</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Glucose</td>
<td>+1.8</td>
<td>-0.8</td>
<td>+1.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

 Patients were randomized to flexibly dosed LATUDA 20 mg/day, LATUDA 80 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 +1.0 mg/dL, +1.8 mg/dL for 80 mg/day (n=92).

### Table 4: Change in Fasting Glucose in the Adult Adjunctive Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo</th>
<th>LATUDA 20 mg/day</th>
<th>LATUDA 80 mg/day</th>
<th>LATUDA 120 mg/day</th>
<th>LATUDA 160 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change from Baseline (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=302</td>
<td>n=319</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Glucose</td>
<td>-0.9</td>
<td>+1.2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

 Patients were randomized to flexibly dosed LATUDA 20 mg/day or placebo.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as adjunctive therapy with 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).
Adjuuctive Therapy with Lithium or Valproate

Data from the adult short-term, flexible-dosed, placebo-controlled, adjuuctive therapy bipolar depression studies are presented in Table 9.

Table 9: Mean Change in Weight (kg) from Baseline in the Adolescent

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Change from Baseline (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Total cholesterol: -2.9, Triglycerides: -4.6</td>
</tr>
<tr>
<td>LATUDA 20 to 120 mg/day</td>
<td>Total cholesterol: -3.1, Triglycerides: +4.6</td>
</tr>
</tbody>
</table>

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

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

Pediatric Patients (10 to 17 years)

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

Weight Gain

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

Schizophrenia

Adults

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 8. The mean weight gain was +0.43 kg for LATUDA-treated patients compared to +0.02 kg for placebo-treated patients. Change in weight from baseline for olanzapine was +4.15 kg and for quetiapine extended-release was +2.03 kg in Studies 3 and 5, 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 8: Mean Change in Weight (kg) from Baseline in Adult Schizophrenia Studies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo 20 mg/day (n=696)</th>
<th>LATUDA 20 mg/day (n=848)</th>
<th>LATUDA 80 mg/day (n=526)</th>
<th>LATUDA 120 mg/day (n=291)</th>
<th>LATUDA 160 mg/day (n=114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>-0.02</td>
<td>-0.15</td>
<td>+0.22</td>
<td>+0.54</td>
<td>+0.68</td>
</tr>
</tbody>
</table>

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 9. 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 9: Mean Change in Weight (kg) from Baseline in the Adolescent Schizophrenia Study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo 40 mg/day (n=111)</th>
<th>LATUDA 40 mg/day (n=108)</th>
<th>LATUDA 80 mg/day (n=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>+0.2</td>
<td>+0.3</td>
<td>+0.7</td>
</tr>
</tbody>
</table>

Hyperprolactinemia

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

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecostasia, 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.

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. 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 13.

Table 13: Median Change in Prolactin (ng/mL) from Baseline in the Adolescent Schizophrenia Studies

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>LATUDA 20 mg/day</th>
<th>LATUDA 40 mg/day</th>
<th>LATUDA 80 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>-1.9</td>
<td>-1.1</td>
<td>-1.4</td>
<td>-0.2</td>
</tr>
<tr>
<td>(n=672)</td>
<td>(n=70)</td>
<td>(n=476)</td>
<td>(n=501)</td>
<td>(n=495)</td>
</tr>
<tr>
<td>Females</td>
<td>-5.1</td>
<td>-0.7</td>
<td>-4.0</td>
<td>-0.2</td>
</tr>
<tr>
<td>(n=200)</td>
<td>(n=19)</td>
<td>(n=149)</td>
<td>(n=150)</td>
<td>(n=150)</td>
</tr>
<tr>
<td>Males</td>
<td>-1.3</td>
<td>-1.2</td>
<td>-0.7</td>
<td>-0.2</td>
</tr>
<tr>
<td>(n=472)</td>
<td>(n=51)</td>
<td>(n=327)</td>
<td>(n=345)</td>
<td>(n=345)</td>
</tr>
</tbody>
</table>

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

In the uncontrolled longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a median change in prolactin of -0.9 ng/mL at week 24 (n=357), -5.3 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 14.

Table 14: Median Change in Prolactin (ng/mL) from Baseline in the Adolescent Schizophrenia Study

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>LATUDA 40 mg/day</th>
<th>LATUDA 80 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>+0.10</td>
<td>+0.75</td>
<td>+1.20</td>
</tr>
<tr>
<td>(n=103)</td>
<td>(n=102)</td>
<td>(n=99)</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>+0.70</td>
<td>+0.60</td>
<td>+4.40</td>
</tr>
<tr>
<td>(n=39)</td>
<td>(n=42)</td>
<td>(n=33)</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.00</td>
<td>+0.75</td>
<td>+1.00</td>
</tr>
<tr>
<td>(n=64)</td>
<td>(n=63)</td>
<td>(n=65)</td>
<td></td>
</tr>
</tbody>
</table>

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

Bipolar Depression

Adults

Monotherapy

The median change from baseline to endpoint in prolactin levels, in the adult short-term, flexible-dosed, placebo-controlled monotherapy bipolar depression study, was +1.7 ng/mL and +3.5 ng/mL with LATUDA 20 to 60 mg/day and 80 to 120 mg/day, respectively compared to +0.3 ng/mL with placebo-treated patients. The median change from baseline to endpoint for males was +1.5 ng/mL and for females was +3.1 ng/mL. Median changes for prolactin by dose range are shown in Table 15.

Table 15: Median Change in Prolactin (ng/mL) from Baseline in the Adult Monotherapy Bipolar Depression Study

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>LATUDA 20 to 60 mg/day</th>
<th>LATUDA 80 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>+0.3</td>
<td>+1.7</td>
<td>+3.5</td>
</tr>
<tr>
<td>(n=147)</td>
<td>(n=140)</td>
<td>(n=144)</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>0.0</td>
<td>+1.8</td>
<td>+5.3</td>
</tr>
<tr>
<td>(n=82)</td>
<td>(n=78)</td>
<td>(n=88)</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>+0.4</td>
<td>+1.2</td>
<td>+1.9</td>
</tr>
<tr>
<td>(n=85)</td>
<td>(n=82)</td>
<td>(n=56)</td>
<td></td>
</tr>
</tbody>
</table>

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

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

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

Adjunctive Therapy with Lithium or Valproate

The median change from baseline to endpoint in prolactin levels, in the adult short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies was +2.8 ng/mL with LATUDA 20 to 120 mg/day compared to 0.0 ng/mL with placebo-treated patients. The median change from baseline to endpoint for males was +2.4 ng/mL and for females was +3.2 ng/mL. Median changes for prolactin across the dosing range are shown in Table 16.

Table 16: Median Change in Prolactin (ng/mL) from Baseline in the Adult Adjunctive Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>LATUDA 20 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>0.0</td>
<td>+2.8</td>
</tr>
<tr>
<td>(n=301)</td>
<td>(n=321)</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>+0.4</td>
<td>+3.2</td>
</tr>
<tr>
<td>(n=156)</td>
<td>(n=162)</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>-0.1</td>
<td>+2.4</td>
</tr>
<tr>
<td>(n=145)</td>
<td>(n=159)</td>
<td></td>
</tr>
</tbody>
</table>

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

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

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

Pediatric Patients (10 to 17 years)

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

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

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>LATUDA 20 to 80 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>+0.50</td>
<td>+1.10</td>
</tr>
<tr>
<td>(n=157)</td>
<td>(n=165)</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>+0.55</td>
<td>+2.50</td>
</tr>
<tr>
<td>(n=78)</td>
<td>(n=83)</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>+0.50</td>
<td>+0.85</td>
</tr>
<tr>
<td>(n=79)</td>
<td>(n=82)</td>
<td></td>
</tr>
</tbody>
</table>

Patients with severe neutropenia (absolute neutrophil count < 1000/mm³) should discontinue LATUDA and have their WBC followed until recovery.

The proportion of patients with prolactin elevations ≥5x upper limit of normal (ULN) was 0.0% for LATUDA-treated patients and 0.6% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥5x ULN was 0.6% for LATUDA-treated patients and 1.3% for placebo-treated female patients. No male patients in the placebo or LATUDA treatment groups had prolactin elevations ≥5x ULN.

Leukopenia, Neutropenia and Agranulocytosis

Leukopenia/neutropenia has been reported during treatment with antipsychotic agents. Agranulocytosis (including fatal cases) has been reported with other agents in the class. Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug-induced leukopenia/neutropenia should have their WBC followed until recovery. Patients with severe neutropenia (absolute neutrophil count < 1000/mm³) should discontinue LATUDA and have their WBC followed until recovery.
Orthostatic Hypotension and Syncope
LATUDA may cause orthostatic hypotension and syncope, perhaps due to its α1-adrenergic receptor antagonism. Associated adverse reactions can include dizziness, lightheadedness, tachycardia, and bradycardia. Generally, these risks are greatest at the beginning of treatment and during dose escalation. Patients at increased risk of these adverse reactions or at increased risk of developing complications from hypotension include those with dehydration, hypovolemia, treatment with antihypertensive medication, history of cardiovascular disease (e.g., heart failure, myocardial infarction, ischemia, or conduction abnormalities), history of cerebrovascular disease, as well as patients who are antipsychotic-naïve. In such patients, consider using a lower starting dose and slower titration, and monitor orthostatic vital signs.

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

Schizophrenia

Adults

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

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

Adolescents

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

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

Bipolar Depression

Adults

Monotherapy

In the adult short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, there were no reported adverse events of orthostatic hypotension and syncope. Orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 0.6% with LATUDA 20 to 60 mg and 0.6% with LATUDA 80 to 120 mg compared to 0% with placebo.

Adjunctive Therapy with Lithium or Valproate

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

Pediatric Patients (10 to 17 years)

In the 6-week, placebo-controlled bipolar depression study in pediatric patients 10 to 17 years, 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.

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.

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.

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.

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.

ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of this Brief Summary:

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis
- Suicidal Thoughts and Behaviors
- Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-related Psychosis
- Neuroleptic Malignant Syndrome
- Tardive Dyskinesia
- Metabolic Changes
- Hyperprolactinemia
- Leukopenia, Neutropenia, and Agranulocytosis
- Orthostatic Hypotension and Syncope
- Falls
- Seizures
- Potential for Cognitive and Motor Impairment
- Body Temperature Dysregulation
- Activation of Mania/Hypomania
- Dysphagia
- Neurological Adverse Reactions in Patients with Parkinson’s Disease or Dementia with Lewy Bodies
Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

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

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

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

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

Adverse Reactions Associated with Discontinuation of Treatment: A total of 14.1% (413/300) LATUDA-treated patients and 9.3% (66/708) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients: Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in patients with bipolar depression) are shown in Table 18.

Table 18: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred during Acute Therapy (up to 6 weeks in patients with schizophrenia) are shown rounded to the nearest percent and LATUDA incidence greater than placebo) that 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.

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

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence ≥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 19.

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

<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=334) LATUDA 20 to 120 mg/day</td>
</tr>
<tr>
<td></td>
<td>(N=369)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>10%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14%</td>
</tr>
<tr>
<td>General Disorders</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1%</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>3%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2%</td>
</tr>
<tr>
<td>Investigations</td>
<td>4%</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
</tr>
<tr>
<td>Increased Appetite</td>
<td>1%</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
</tr>
<tr>
<td>Extrapyramidal Symptoms*</td>
<td>9%</td>
</tr>
<tr>
<td>Somnolence**</td>
<td>14%</td>
</tr>
<tr>
<td>Akathisia</td>
<td>5%</td>
</tr>
<tr>
<td>Restlessness</td>
<td>11%</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
</tr>
<tr>
<td>Restlessness</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer
* Extrapyramidal symptoms include adverse event terms: bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, gait abnormality, hypokinesia, muscle rigidity, oculogyric crisis, oromandibular dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and tardive dyskinesia.
** Somnolence includes adverse event terms: hypersomnia, hyposomnolence, sedation, and somnolence.

Adolescents

Schizophrenia

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

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) in adolescent patients (13 to 17 years) treated with LATUDA were somnolence, nausea, akathisia, extrapyramidal symptoms (non-akathisia, 40 mg only), vomiting, and rhinorrhea/rihthritis (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 6%, respectively.

Supplement to Clinician Reviews - S11
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 24.

Table 24: Incidence of EPS Compared to Placebo in the Adolescent Schizophrenia Study

<table>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>Placebo (N=112) (%)</th>
<th>LATUDA 40 mg/day (N=110) (%)</th>
<th>LATUDA 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, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus.
** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor.

Bipolar Depression
Adults
Monotherapy
In the adult short-term, placebo-controlled monotherapy bipolar depression study, for LATUDA-treated patients, the incidence of reported events related to EPS, excluding akathisia and restlessness was 6.9% and 2.4% for placebo-treated patients. The incidence of akathisia for LATUDA-treated patients was 9.4% and 2.4% for placebo-treated patients. Incidence of EPS by dose groups is provided in Table 25.

Table 25: 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>
<tr>
<td>Akathisia</td>
<td>2</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Dystonia*</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Parkinsonism**</td>
<td>2</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Restlessness</td>
<td>&lt;1</td>
<td>0</td>
<td>3</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, glabellar reflex abnormal, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor.

Adjuvantive Therapy with Lithium or Valproate
In the adult short-term, placebo-controlled adjutantive therapy bipolar depression studies, for LATUDA-treated patients, the incidence of EPS, excluding akathisia and restlessness, was 13.9% and 8.7% for placebo. The incidence of akathisia for LATUDA-treated patients was 10.8% and 4.8% for placebo-treated patients. Incidence of EPS is provided in Table 26.

Table 26: 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>Akathisia</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Parkinsonism**</td>
<td>&lt;1</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, torticollis, and trismus.
** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor.

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

Pediatric Patients (10 to 17 years)
In the 6-week, placebo-controlled study of bipolar depression in pediatric patients 10 to 17 years, the incidence of EPS, excluding events related to akathisia, for LATUDA-treated patients was similar in the LATUDA 20 to 80 mg/day (3.4%) treatment group vs. placebo (3.5%); and the incidence of akathisia-related events for LATUDA-treated patients was 2.9% vs. 3.5% for placebo-treated patients. Incidence of EPS by dose is provided in Table 27.

Table 27: 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>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>Salivation</td>
<td>&lt;1</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 include adverse event terms: akathisia, cogwheel rigidity, dyskinesia, dystonia, hyperkinesia, joint stiffness, muscle rigidity, muscle spasms, musculoskeletal stiffness, oculogyric crisis, parkinsonism, tardive dyskinesia, and tremor.
** Parkinsonism includes adverse event terms: bradykinesia, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, parkinsonism, and psychomotor retardation.
*** Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus.

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

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

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Bipolar Depression

**Adults**

**Monotherapy**

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

**Adjunctive Therapy with Lithium or Valproate**

The mean change from baseline for LATUDA-treated adult patients for the SAS, BAS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients and placebo for the BAS (LATUDA, 8.4%; placebo, 2.1%), the SAS (LATUDA, 2.8%; placebo, 2.1%) and the AIMS (LATUDA, 2.8%; placebo, 0.6%).

**Pediatric Patients (10 to 17 years)**

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

Dystonia

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

Schizophrenia

**Adults**

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

**Adolescents**

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

Bipolar Depression

**Adults**

**Monotherapy**

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

**Adjunctive Therapy with Lithium or Valproate**

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

**Pediatric Patients (10 to 17 years)**

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

Other Adverse Reactions Observed During the Premarking Evaluation of LATUDA

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

Reactions are further categorized by organ class and listed in order of decreasing frequency compared to placebo-treated patients. The reactions in this list are not intended to mean that those occurring in at least 1/100 patients (frequent) (only those not already listed in the tabulated results from placebo-controlled studies appear in this listing); those occurring in 1/100 to 1/1000 patients (infrequent); and those occurring in fewer than 1/1000 patients (rare).

Table 28: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in Adult Schizophrenia Studies

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Placebo (N=708)</th>
<th>LATUDA 20 mg/ day (N=71)</th>
<th>LATUDA 40 mg/ day (N=487)</th>
<th>LATUDA 80 mg/ day (N=538)</th>
<th>LATUDA 120 mg/ day (N=291)</th>
<th>LATUDA 160 mg/ day (N=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine Elevated</td>
<td>2%</td>
<td>1%</td>
<td>2%</td>
<td>2%</td>
<td>5%</td>
<td>7%</td>
</tr>
</tbody>
</table>

**Adolescents**

Serum Creatinine: In the short-term, placebo-controlled trials, the mean change from Baseline in serum creatinine was +0.05 mg/dL for LATUDA-treated patients compared to +0.02 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 3.0% (43/1453) of LATUDA-treated patients and 1.6% (11/681) on placebo. The threshold for high creatinine value varied from > 0.79 to > 1.3 mg/dL, based on the centralized laboratory definition for each study (Table 28).

Table 29: 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=169)</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

**Adults**

**Monotherapy**

Serum Creatinine: In the adult short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, the mean change from Baseline in serum creatinine was −0.09 mg/dL for LATUDA-treated patients compared to +0.017 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 7.2% (14/194) of LATUDA-treated patients and 2.9% (3/103) on placebo (Table 29).

Table 30: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in the Adult Monotherapy Bipolar Depression Study

<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>
Adjuv tive Therapy with Lithium or Valproate

Serum Creatinine: In adult short-term, placebo-controlled premarketing adjunctive studies for bipolar depression, the mean change from Baseline in serum creatinine was +0.04 mg/dL for LATUDA-treated patients compared to -0.01 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 4.3% (15/360) of LATUDA-treated patients and 1.6% (5/334) on placebo (Table 31).

Table 31: 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 the 6-week, placebo-controlled bipolar depression study in pediatric patients 10 to 17 years, the mean change from Baseline in serum creatinine was +0.021 mg/dL for LATUDA-treated patients compared to +0.009 mg/dL for placebo-treated patients. A creatinine shift from normal to high (based on the centralized laboratory definition) occurred in 6.7% (11/163) of LATUDA-treated patients and 4.5% (7/155) on placebo (Table 32).

Table 32: 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>

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.

**DRUG INTERACTIONS**

**Drugs Having Clinically Important Interactions with LATUDA**

Table 33: Clinically Important Drug Interactions with LATUDA

**Strong CYP3A4 Inhibitors**

- **Clinical Impact:** Concomitant use of LATUDA with strong CYP3A4 inhibitors increased the exposure of lurasidone compared to the use of LATUDA alone.
- **Intervention:** LATUDA should not be used concomitantly with strong CYP3A4 inhibitors.
- **Examples:** Ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil

**Moderate CYP3A4 Inhibitors**

- **Clinical Impact:** Concomitant use of LATUDA with moderate CYP3A4 inhibitors increased the exposure of lurasidone compared to the use of LATUDA alone.
- **Intervention:** LATUDA dose should be reduced to half of the original level when used concomitantly with moderate inhibitors of CYP3A4.
- **Examples:** Dillazem, atazanavir, erythromycin, fluconazole, verapamil

**Strong CYP3A4 Inducers**

- **Clinical Impact:** Concomitant use of LATUDA with strong CYP3A4 inducers decreased the exposure of lurasidone compared to the use of LATUDA alone.
- **Intervention:** LATUDA should not be used concomitantly with strong CYP3A4 inducers.
- **Examples:** Rifampin, aminosidine, St. John’s Wort, phenytoin, carbamazepine

**Moderate CYP3A4 Inducers**

- **Clinical Impact:** Concomitant use of LATUDA with moderate CYP3A4 inducers decreased the exposure of lurasidone compared to the use of LATUDA alone.
- **Intervention:** LATUDA dose should be increased when used concomitantly with moderate inducers of CYP3A4.
- **Examples:** Bosentan, efavirenz, etravirine, modafinil, nafcillin

**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.

**Drug Interaction Studies**

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

Figure 1: Impact of Other Drugs on LATUDA Pharmacokinetics

![Figure 1: Impact of Other Drugs on LATUDA Pharmacokinetics](image)

**USE IN SPECIFIC POPULATIONS**

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

Fetal/Neonatal Adverse Reactions

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

Data

Animal Data

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

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

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

Lactation

Risk Summary

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

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

Bipolar Depression

The safety and effectiveness of LATUDA 20 to 80 mg/day for the treatment of bipolar depression in pediatric patients (10 to 17 years) was established in a 6-week, placebo-controlled clinical study in 347 pediatric patients. The safety and effectiveness of LATUDA has not been established in pediatric patients less than 10 years of age with bipolar depression.

Irritability Associated with Autistic Disorder

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

Efficacy was not demonstrated in a 6-week study evaluating LATUDA 20 mg/day and 60 mg/day for the treatment of pediatric patients 6 to 17 years of age with irritability associated with autistic disorder diagnosed by Diagnostic and Statistical Manual of Mental Disorders, 4th Ed., Text Revision (DSM-IV-TR) criteria. The primary objective of the study as measured by improvement from Baseline in the irritability subscale of the aberrant behavior checklist (ABC) at Endpoint (Week 6) was not met. A total of 149 patients were randomized to LATUDA or placebo. Vomiting occurred at a higher rate than reported in other LATUDA studies (4/49 or 8% for 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 and brain weights at 2 times the MRHD in both sexes, and motor hyperactivity at 0.2 and 2 times the MRHD in both sexes based on mg/m². In females, there was a delay in attainment of sexual maturity at 2 times the MRHD, associated with decreased serum estradiol. Mortality occurred in both sexes during early post-weaning period and some of the male weanlings died after only 4 treatments at doses as low as 2 times the MRHD based on mg/m².

Histopathological findings included increased colloid in the thyroids and inflammation of the prostate in males at 10 times MRHD based on mg/m² and mammary gland hyperplasia, increased vaginal mucification, and increased ovarian atretic follicles at doses as low as 0.2 times the MRHD based on mg/m². Some of these findings were attributed to transiently elevated serum prolactin which was seen in both sexes at all doses. However, there were no changes at any dose level in reproductive parameters (fertility, conception indices, spermatogenesis, estrous cycle, gestation length, parturition, number of pups born). The no effect dose for neurobehavioral changes in males is 0.2 times the MRHD based on mg/m² and could not be determined in females. The no effect dose for growth and physical development in both sexes is 0.2 times the MRHD based on mg/m².

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.

Renal Impairment

Reduce the maximum recommended dosage in patients with moderate or severe renal impairment (ClCr<50 mL/minute). Patients with impaired renal function (ClCr<50 mL/minute) had higher exposure to lurasidone than patients with normal renal function. Greater exposure may increase the risk of LATUDA-associated adverse reactions.

Hepatic Impairment

Reduce the maximum recommended dosage in patients with moderate to severe hepatic impairment (Child-Pugh score >7). Patients with moderate to severe hepatic impairment (Child-Pugh score >7) generally had higher exposure to lurasidone than patients with normal hepatic function. Greater exposure may increase the risk of LATUDA-associated adverse reactions.

Other Specific Populations

No dosage adjustment for LATUDA is required on the basis of a patient’s sex, race, or smoking status.

Studies in Specific Populations

The effect of intrinsic patient factors on the pharmacokinetics of LATUDA is presented in Figure 3.

Pediatic Patients

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

Figure 3: Impact of Other Patient Factors on LATUDA Pharmacokinetics

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

*Compare to Caucasian
DRUG ABUSE AND DEPENDENCE

Controlled Substance
LATUDA is not a controlled substance.

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

OVERDOSAGE

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

Management of Overdosage
No specific antidotes for LATUDA are known. In managing overdose, provide supportive care, including close medical supervision and monitoring, and consider the possibility of multiple drug involvement. If an overdose occurs, consult a Certified Poison Control Center (1-800-222-1222 or www.poison.org). Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with an acute overdose of LATUDA. Similarly, the alpha-blocking properties of bretylium might be additive to those of LATUDA, resulting in problematic hypotension.

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

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

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

Manufactured for:
Sunovion Pharmaceuticals Inc. Marlborough, MA 01752 USA
For Customer Service, call 1-888-394-7377.
For Medical Information, call 1-800-739-0565.
To report suspected adverse reactions, call 1-877-737-7226.

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