Are You Up to Date?
Latest Guidance for Evidence-Based Treatment of Adults With Bipolar Depression

A Need for Guidance
Early and accurate diagnosis of the condition underlying depressive episodes is essential for appropriate treatment of patients. Specifically, it is important to recognize the depressive episodes associated with bipolar I disorder—which we also know as bipolar depression—and differentiate it from other forms of depression, such as those associated with general medical conditions, substance use, or major depressive disorder (MDD), according to Henry A. Nasrallah, MD.

Although no antidepressant is approved by the United States (US) Food and Drug Administration (FDA) as monotherapy for the treatment of bipolar disorder and there is limited evidence of efficacy, antidepressants are...
**AN EXPERT’S PERSPECTIVE**

**Commentary by Henry A. Nasrallah, MD**

As we learn more about the management of depressive episodes associated with bipolar I disorder, which is referred to as bipolar depression, we should factor this updated knowledge into our clinical decision-making. However, with a plethora of published information to sift through, how do health care professionals (HCPs) know where to begin? Treatment guidelines can serve as a good foundation, as long as we take into account that they are living and breathing documents that continuously evolve as new evidence emerges. When HCPs seek to apply guidelines to their practices, they should consider several factors, including the “up-to-dateness” of the recommendations, the reliability of their sources, and any therapeutic advances that have occurred since the last guidelines were published. For example, the latest American Psychiatric Association (APA) guideline for the treatment of patients with bipolar disorder was published 15 years ago (2002) and updated 12 years ago (2005), but the update is not considered a formal policy of the APA.  

In this newsletter, my colleagues and I provide a snapshot of the latest guidelines published between 2013 and 2016 for the management of bipolar depression, which is an important clinical distinction from unipolar depression (also known as major depressive disorder). Among other updates, additional atypical antipsychotics have been incorporated into these guidelines as treatment options for individuals with bipolar depression consistent with clinical trial data demonstrating the drugs’ efficacy and safety in this patient population. Because practice guidelines should reflect the latest advances in the management of bipolar depression, I encourage my HCP colleagues to ask the question, “Am I up to date?” as they weigh the options available for the evidence-based treatment of bipolar depression.

**References**


**Clay Jackson, MD, DipTh, FAAFP**

While there is growing consensus that, if possible, antidepressant monotherapy should be avoided for the treatment of bipolar depression, the role of antidepressants in conjunction with atypical antipsychotics or mood stabilizers remains unclear. To help shed some light on the issue, an ISBD task force released clinical recommendations specifically addressing antidepressant use in bipolar disorder, stating that antidepressant monotherapy in patients with bipolar I disorder should be avoided—a position consistent with the aforementioned practice guidelines.

Specifically, antidepressants should be avoided in patients with bipolar depression who have manic symptoms, psychomotor agitation, rapid cycling, or a history of antidepressant-induced mood elevation. Adjunctive antidepressants may be considered in carefully selected patients, including those with bipolar depression who have a history of positive response to this class of drugs.

Overall, the treatment of patients with bipolar depression can be challenging, in part because the number of approved treatment options for the disorder is limited and management requires careful contemplation of complex issues. Drs. Jackson, Nasrallah, and Snow, and Ms. Kraus conclude that when selecting treatment for an individual with bipolar depression, it is essential for health care professionals to take into consideration the evidence, guidelines, and recommendations, as well as the patient’s particular needs and preferences. Clinicians should refer to individual guidelines and recommendations for specific guidance.

Please see Brief Summary of full Prescribing Information, including Boxed Warning, on page S5.
LATUDA: A Treatment Option for Bipolar Depression in Adults

LATUDA is indicated in adults for the treatment of major depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and as adjunctive therapy with lithium or valproate. The efficacy of LATUDA was established in a 6-week monotherapy study and a 6-week adjunctive therapy study with lithium or valproate in adult patients with bipolar depression. The effectiveness of LATUDA has not been established for the treatment of mania associated with bipolar disorder.13

Each adult, phase 3, multicenter, randomized, double-blind, placebo-controlled clinical trial enrolled patients with major depressive episodes associated with bipolar I disorder, with or without rapid cycling, and without psychotic features. All psychotropic medications were tapered off, and patients were randomly assigned to a treatment group.14,15 Patients in the monotherapy study were randomized to flexibly dosed LATUDA 20-120 mg/day (N=169), or placebo (N=170).14 Patients in the adjunctive therapy study were randomized to flexibly dosed LATUDA 20-120 mg/day plus lithium or valproate (N=183) or placebo plus lithium or valproate (N=165).15 LATUDA dose adjustments within the assigned dosing range were permitted to optimize efficacy and tolerability. Study medication was taken once daily in the evening by mouth with a meal (eg, dinner) or within 30 minutes after eating.14,15

Efficacy in Adults

Efficacy was measured by the change from baseline to Week 6 in the Montgomery-Åsberg Depression Rating Scale (MADRS) score, the primary efficacy endpoint of the 2 trials. LATUDA monotherapy achieved a 44% greater reduction in MADRS score at Week 6 versus placebo (Figure 1).14 The mean decrease in MADRS score between baseline and Week 6 was 15.4 points for patients randomized to LATUDA 20-60 mg/day or 80-120 mg/day versus 10.7 points for patients randomized to placebo (P<.001).14 The higher dose range (80-120 mg/day) did not provide additional efficacy, on average, compared with the lower dose range (20-60 mg/day).13

With LATUDA as adjunctive therapy with lithium or valproate, the mean decrease in the MADRS score between baseline and Week 6 was 171 points for patients randomized to adjunctive LATUDA 20-120 mg/day versus 13.5 points for patients randomized to placebo (P<.01) (Figure 1).15

Safety and Tolerability in Adults

Adverse reactions occurring in at least 2% of patients in either LATUDA monotherapy group and at a greater incidence than placebo during acute therapy were nausea, akathisia, somnolence, dry mouth, extrapyramidal symptoms (EPS), diarrhea, anxiety, nasopharyngitis, back pain, vomiting, urinary tract infection, and influenza. Overall, in the combined LATUDA treatment groups, 6.0% (20/331) of patients discontinued treatment due to adverse reactions compared with 5.4% (9/168) of patients in the placebo group.13

The safety and tolerability of adjunctive LATUDA with lithium or valproate compared with placebo were examined in 2 short-term, randomized clinical trials of patients with bipolar depression. The adverse reactions that occurred in at least 2% of LATUDA-treated patients and at a greater incidence than placebo in the 2 studies combined were nausea, EPS, somnolence, akathisia, nasopharyngitis, vomiting, restlessness, fatigue, increased appetite, and increased weight. Overall, treatment was discontinued due to adverse reactions by 5.8% of patients (21/360) receiving LATUDA as adjunctive therapy with lithium or valproate and by 4.8% of patients (16/334) in the placebo group.13

Patients from both the LATUDA and placebo groups of the 6-week monotherapy and adjunctive therapy trials were eligible to continue into a 6-month, uncontrolled, open-label, flexible-dose extension study.13 The adverse reactions in at least 5% of patients who continued on LATUDA monotherapy in the longer-term study were headache, nausea, nasopharyngitis, akathisia, insomnia, and anxiety. Of those who continued on LATUDA adjunctive therapy plus lithium or valproate in the longer-term studies combined, 1.6% experienced parkinsonism, somnolence, akathisia, insomnia, anxiety, headache, and nausea.16

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular or cerebrovascular risk.13 Changes in weight and laboratory parameters during both the LATUDA short-term and longer-term trials were modest in comparison with those observed in patients treated with other antipsychotics.16

1The effectiveness of LATUDA for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies.
term monotherapy and adjunctive therapy studies are presented in Figure 2.\textsuperscript{12,16} Overall, the clinical trials demonstrated that at 6 weeks, metabolic changes were similar in the LATUDA and placebo groups,\textsuperscript{13,16} and at 24 weeks, no clinically significant changes in body weight or clinically relevant changes or shifts from open-label baseline in lipid parameters and glucose were observed.\textsuperscript{16}

For prolactin in the short-term monotherapy study, the median change in concentration was +1.7 ng/mL, +3.5 ng/mL, and +0.3 ng/mL for the low-dose LATUDA, high-dose LATUDA, and placebo groups, respectively, and -1.1 ng/mL for those who continued on LATUDA in the longer-term trial. In the short-term adjunctive therapy studies, the median change was +2.8 ng/mL in the LATUDA group and 0.0 ng/mL in the placebo group, and in the longer-term trial, it was -1.3 ng/mL in patients who continued on LATUDA.\textsuperscript{13,16}

Changes from baseline to endpoint in EPS, akathisia, and tardive dyskinesia were also evaluated in the LATUDA monotherapy and adjunctive therapy short-term and longer-term trials using the Simpson-Angus Scale (SAS), the Barnes Akathisia Scale (BAS), and the Abnormal Involuntary Movement Scale (AIMS), respectively. Categorical change was defined as a shift from normal at baseline to abnormal at study endpoint for the SAS, or as worsening from baseline to study endpoint for the BAS and AIMS. The mean change from baseline for LATUDA-treated patients was comparable to placebo on all 3 movement scales.\textsuperscript{13,16}

### References


### Abbreviations

- Li, lithium
- VPA, valproate

*Last observation carried forward.

\textsuperscript{1}Observed cases; patients who continued on LATUDA.

Safety population.

Notes: Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended. Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia, including polydipsia, polyuria, polyphagia, and weakness.
WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; AND SUICIDAL THOUGHTS AND BEHAVIORS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LATUDA is not approved for the treatment of patients with dementia-related psychosis.

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 episode associated with bipolar I disorder (bipolar depression).

CONTRAINDICATIONS
- Known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone.
- Strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, miltefraid, etc.).
- Strong CYP3A4 inducers (e.g., rifampin, avasimibe, St. John’s wort, phenytoin, carbamazepine, etc.).

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 lower 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>&lt;18</td>
<td>Increases Compared to Placebo</td>
</tr>
<tr>
<td>18-24</td>
<td>Decreases Compared to Placebo</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 regimen, including possibly discontinuing LATUDA, in patients whose depression is persistently worse, or who 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 a given dosage level, the rate of incidence of adverse events in an individual patient. Thus, it is not possible to predict in advance which patients in a given population may have a high risk of developing adverse reactions. Rather, the risk is dependent on the total dose of antipsychotic administered and the duration of treatment.

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

Hyperglycemia and Diabetes Mellitus
Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizoaffective disorder 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 glycemic control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes mellitus) 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.
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 7.

<table>
<thead>
<tr>
<th>Placebo</th>
<th>LATUDA 20 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change from Baseline (mg/dL)</td>
<td></td>
</tr>
<tr>
<td>n=303</td>
<td>n=321</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>-2.9</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-4.6</td>
</tr>
<tr>
<td>Proportion of Patients with Shifts</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (≥ 240 mg/dL)</td>
<td>5.7% (15/263)</td>
</tr>
<tr>
<td>Triglycerides (≥ 200 mg/dL)</td>
<td>8.6% (21/243)</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.

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 +3.2 (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 +2.09 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>Placebo (n=696)</th>
<th>LATUDA 20 to 80 mg/day (n=71)</th>
<th>LATUDA 80 mg/day (n=454)</th>
<th>LATUDA 120 mg/day (n=526)</th>
<th>LATUDA 160 mg/day (n=291)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change from Baseline (kg)</td>
<td>-0.02</td>
<td>-0.15</td>
<td>+0.22</td>
<td>+0.54</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>Placebo (n=111)</th>
<th>LATUDA 40 mg/day (n=109)</th>
<th>LATUDA 80 mg/day (n=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change from Baseline (kg)</td>
<td>+0.2</td>
<td>+0.3</td>
</tr>
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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).

Bipolar Depression

Adults

Monotherapy

Data from the adult short-term, flexible-dosed, placebo-controlled monotherapy bipolar depression studies are presented in Table 10. The mean change in weight gain was +0.29 kg for LATUDA-treated patients compared to -0.04 kg for placebo-treated patients. The proportion of patients with a ≥7% increase in body weight (at Endpoint) was 2.4% for LATUDA-treated patients and 0.7% for placebo-treated patients.

Table 10: Mean Change in Weight (kg) from Baseline in the Adult Monotherapy Bipolar Depression Study

<table>
<thead>
<tr>
<th>Placebo (n=151)</th>
<th>LATUDA 20 to 60 mg/day (n=143)</th>
<th>LATUDA 80 to 120 mg/day (n=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change from Baseline (kg)</td>
<td>-0.04</td>
<td>+0.56</td>
</tr>
</tbody>
</table>

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

Adjunctive Therapy with Lithium or Valproate

Data from the adult short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies are presented in Table 11. The mean change in weight gain was +0.11 kg for LATUDA-treated patients compared to +0.16 kg for placebo-treated patients. The proportion of patients with a ≥7% increase in body weight (at Endpoint) was 3.1% for LATUDA-treated patients and 0.3% for placebo-treated patients.

Table 11: Mean Change in Weight (kg) from Baseline in the Adult Adjunctive Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th>Placebo (n=307)</th>
<th>LATUDA 20 to 120 mg/day (n=327)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change from Baseline (kg)</td>
<td>+0.16</td>
</tr>
</tbody>
</table>

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

Pediatric Patients (10 to 17 years)

Data from the 6-week, placebo-controlled bipolar depression study in patients 10 to 17 years are presented in Table 12. The mean change in weight gain was +0.7 kg for LATUDA-treated patients compared to +0.5 kg for placebo-treated patients. The proportion of patients with a ≥7% increase in body weight (at Endpoint) was 4.0% for LATUDA-treated patients and 3.1% for placebo-treated patients.

Table 12: Mean Change in Weight (kg) from Baseline in the Bipolar Depression Study in Pediatric Patients (10 to 17 years)

<table>
<thead>
<tr>
<th>Placebo (n=170)</th>
<th>LATUDA 20 to 80 mg/day (n=175)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change from Baseline (kg)</td>
<td>+0.5</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, gynecometra, 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 tumorgenesis in humans, but the available evidence is too limited to be conclusive.
### Table 7: Change in Fasting Lipids in the Adult Adjunctive Therapy Bipolar Depression Studies

<table>
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<tr>
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### Schizophrenia

#### Adults

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<td>(n=484)</td>
</tr>
<tr>
<td>40 mg/ day</td>
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<td>(n=526)</td>
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<td>60 mg/ day</td>
<td>(n=526)</td>
<td>(n=291)</td>
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<tr>
<td>80 mg/ day</td>
<td>(n=291)</td>
<td>(n=114)</td>
</tr>
<tr>
<td>All Patients</td>
<td>-0.02</td>
<td>-0.15</td>
</tr>
<tr>
<td></td>
<td>+0.22</td>
<td>+0.54</td>
</tr>
<tr>
<td></td>
<td>+0.68</td>
<td>+0.60</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).

### Bipolar Depression

#### Adults

**Monotherapy**

Data from the adult short-term, flexible-dosed, placebo-controlled monotherapy bipolar depression study are presented in Table 10. The mean change in weight gain was +0.29 kg for LATUDA-treated patients compared to -0.04 kg for placebo-treated patients. The proportion of patients with ≥7% increase in body weight (at Endpoint) was 2.4% for LATUDA-treated patients and 0.7% for placebo-treated patients.

### Table 10: Mean Change in Weight (kg) 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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean Change from Baseline (mg/dL)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>(n=151)</td>
<td>(n=327)</td>
</tr>
<tr>
<td>20 to 60 mg/day</td>
<td>(n=111)</td>
<td>(n=296)</td>
</tr>
<tr>
<td>60 mg/day</td>
<td>(n=111)</td>
<td>(n=296)</td>
</tr>
<tr>
<td>All Patients</td>
<td>-0.04</td>
<td>+0.56</td>
</tr>
<tr>
<td></td>
<td>+0.29</td>
<td>+0.02</td>
</tr>
</tbody>
</table>

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

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

#### Adjunctive Therapy with Lithium or Valproate

Data from the adult short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies are presented in Table 11. The mean change in weight gain was +0.11 kg for LATUDA-treated patients compared to +0.16 kg for placebo-treated patients. The proportion of patients with ≥7% increase in body weight (at Endpoint) was 3.1% for LATUDA-treated patients and 0.3% for placebo-treated patients.

### Table 11: Mean Change in Weight (kg) 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><strong>Mean Change from Baseline (mg/dL)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>(n=303)</td>
<td>(n=170)</td>
</tr>
<tr>
<td>20 to 120 mg/day</td>
<td>(n=109)</td>
<td>(n=114)</td>
</tr>
<tr>
<td>60 mg/day</td>
<td>(n=109)</td>
<td>(n=114)</td>
</tr>
<tr>
<td>All Patients</td>
<td>+0.16</td>
<td>+0.11</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.

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

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

Data from the 6-week, placebo-controlled bipolar depression study in patients 10 to 17 years are presented in Table 12. The mean change in weight gain was +0.7 kg for LATUDA-treated patients compared to +0.5 kg for placebo-treated patients. The proportion of patients with ≥7% increase in body weight (at Endpoint) was 4.0% for LATUDA-treated patients and 5.3% for placebo-treated patients.

### Table 12: Mean Change in Weight (kg) 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><strong>Mean Change from Baseline (mg/dL)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>(n=170)</td>
<td>(n=175)</td>
</tr>
<tr>
<td>20 to 80 mg/day</td>
<td>(n=111)</td>
<td>(n=114)</td>
</tr>
<tr>
<td>80 mg/day</td>
<td>(n=111)</td>
<td>(n=114)</td>
</tr>
<tr>
<td>All Patients</td>
<td>+0.5</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 steroidsogenesis 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.

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, an increase in mammary gland neoplasia was observed in a carcinogenicity study conducted with lurasidone in rats and mice.
**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 14: 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>
<th>LATUDA 120 mg/ day</th>
<th>LATUDA 160 mg/ day</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>-1.9 (n=672)</td>
<td>-1.1 (n=70)</td>
<td>-1.4 (n=476)</td>
<td>-0.2 (n=495)</td>
<td>+3.3 (n=284)</td>
<td>+3.3 (n=115)</td>
</tr>
<tr>
<td>Females</td>
<td>-5.1 (n=203)</td>
<td>-0.7 (n=19)</td>
<td>-4.0 (n=148)</td>
<td>-0.2 (n=150)</td>
<td>+6.7 (n=70)</td>
<td>+7.1 (n=36)</td>
</tr>
<tr>
<td>Males</td>
<td>-1.3 (n=472)</td>
<td>-1.2 (n=51)</td>
<td>-0.7 (n=327)</td>
<td>-0.2 (n=545)</td>
<td>+3.1 (n=214)</td>
<td>+2.4 (n=79)</td>
</tr>
</tbody>
</table>

The proportion of patients with prolactin elevations ≥5× 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 ≥5× ULN was 5.7% for LATUDA-treated patients and 2.0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥5× ULN was 1.6% for LATUDA-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 15: 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 (n=103)</td>
<td>+0.75 (n=102)</td>
<td>+1.20 (n=99)</td>
</tr>
<tr>
<td>Females</td>
<td>+0.70 (n=39)</td>
<td>+0.60 (n=42)</td>
<td>+4.40 (n=33)</td>
</tr>
<tr>
<td>Males</td>
<td>0.00 (n=64)</td>
<td>+0.75 (n=60)</td>
<td>+1.00 (n=66)</td>
</tr>
</tbody>
</table>

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

**Bipolar Depression**

**Adults**

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

<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 (n=157)</td>
<td>+1.10 (n=165)</td>
</tr>
<tr>
<td>Females</td>
<td>+0.55 (n=78)</td>
<td>+2.50 (n=83)</td>
</tr>
<tr>
<td>Males</td>
<td>+0.50 (n=79)</td>
<td>+0.85 (n=82)</td>
</tr>
</tbody>
</table>

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

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

**Adjunctive Therapy with Lithium or Valproate**

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

**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 (n=157)</td>
<td>+1.10 (n=165)</td>
</tr>
<tr>
<td>Females</td>
<td>+0.55 (n=78)</td>
<td>+2.50 (n=83)</td>
</tr>
<tr>
<td>Males</td>
<td>+0.50 (n=79)</td>
<td>+0.85 (n=82)</td>
</tr>
</tbody>
</table>

The proportion of patients with prolactin elevations ≥5× ULN was 0% for LATUDA-treated patients and 0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥5× ULN was 0% for LATUDA-treated patients and 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥5× 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 +2.30 ng/mL. Median changes for prolactin are shown in Table 17.

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

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1000/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% (6/1508), 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 14.5% (31/214) of patients treated with LATUDA (15.5% LATUDA 40 mg and 13.5% LATUDA 80 mg/day) compared to 7.1% (8/112) of placebo patients.

Bipolar Depression

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

Adjunctive Therapy with Lithium or Valproate

In the adult short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies, somnolence was reported by 11.4% (41/366) 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.

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, obnubilation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuropsychiatric 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
• Neuropsychiatric 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 9.5% (134/1508) LATUDA-treated patients had 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:

The most common adverse reactions (incidence ≥ 5% 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 schizophrenia) 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) in which LATUDA was administered at daily doses ranging from 20 to 160 mg (n=1508).

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) in which LATUDA was administered at daily doses ranging from 20 to 160 mg (n=1508).

Table 19: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred During Acute Therapy (up to 6 weeks in patients with schizophrenia) in which LATUDA was administered at daily doses ranging from 20 to 160 mg (n=1508).

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 During Acute Therapy (up to 6 weeks in patients with bipolar depression) in which LATUDA was administered at daily doses ranging from 20 to 120 mg (n=331).

Table 19: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred During Acute Therapy (up to 6 weeks in patients with bipolar depression) in which LATUDA was administered at daily doses ranging from 20 to 120 mg (n=331).

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 akathisia and somnolence.

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

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 akathisia and somnolence.

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

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, torticolis, tremor, and trismus.

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

Dose-Related Adverse Reactions in the Monotherapy Study

In the adult short-term, placebo-controlled study (including lower and higher LATUDA dose ranges) 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 akathisia and somnolence.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 5.8% (21/360) LATUDA-treated patients and 4.8% (16/334) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.
Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients: Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in patients with bipolar depression) are shown in Table 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=354)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Nausea 10</td>
</tr>
<tr>
<td></td>
<td>Vomiting 1</td>
</tr>
<tr>
<td>General Disorders</td>
<td>Fatigue 1</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>Nasopharyngitis 2</td>
</tr>
<tr>
<td>Investigations</td>
<td>Weight Increased &lt;1</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Increased Appetite 1</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Extrapyramidal Symptoms* 9</td>
</tr>
<tr>
<td></td>
<td>Somnolence** 5</td>
</tr>
<tr>
<td></td>
<td>Akathisia 5</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Restlessness &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, 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, hypersonolence, 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/rhinorrhea (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: 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 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 6-Week Bipolar Depression Study in Pediatric Patients (10 to 17 years)

<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>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Nausea 6</td>
</tr>
<tr>
<td></td>
<td>Vomiting 4</td>
</tr>
<tr>
<td></td>
<td>Abdominal Pain Upper 2</td>
</tr>
<tr>
<td></td>
<td>Diarrhea 2</td>
</tr>
<tr>
<td></td>
<td>Abdominal Pain 1</td>
</tr>
<tr>
<td>General Disorders And Administration Site Conditions</td>
<td>Fatigue 2</td>
</tr>
<tr>
<td>Investigations</td>
<td>Weight Increased 2</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Decreased Appetite 2</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Somnolence* 6</td>
</tr>
<tr>
<td></td>
<td>Extrapyramidal symptoms** 5</td>
</tr>
<tr>
<td></td>
<td>Dizziness 5</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Insomnia 2</td>
</tr>
<tr>
<td></td>
<td>Abnormal Dreams 2</td>
</tr>
<tr>
<td></td>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer
* Somnolence includes adverse event terms: hypersomnia, hypersonolence, sedation, and somnolence.
** EPS includes adverse event terms: akathisia, cogwheel rigidity, dystonia, extrapyramidal disorder, joint stiffness, muscle rigidity, muscle spasms, 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 23.

Table 23: Incidence of EPS Compared to Placebo in Adult Schizophrenia Studies

<table>
<thead>
<tr>
<th>Body System or Organ Class</th>
<th>Placebo (N=708) (%): 20 mg/day (N=71), 40 mg/day (N=87), 80 mg/day (N=172)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LATUDA 80 mg/day (N=353): 120 mg/day (N=201), 160 mg/day (N=121)</td>
</tr>
<tr>
<td>All EPS events</td>
<td>9 21 23 39 20</td>
</tr>
<tr>
<td>All EPS events, excluding Akathisia/ Restlessness</td>
<td>6 11 12 22 13</td>
</tr>
<tr>
<td>Akathisia</td>
<td>3 6 11 12 22</td>
</tr>
<tr>
<td>Dystonia</td>
<td>&lt;1 0 4 5 7 2</td>
</tr>
<tr>
<td>Parkinsonism**</td>
<td>5 6 9 8 17 11</td>
</tr>
<tr>
<td>Restlessness</td>
<td>1 3 3 3 3</td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer
* Akathisia includes adverse event terms: akathisia, cogwheel rigidity, dystonia, extrapyramidal disorder, hyperkinesia, muscle rigidity, muscle spasms, oculogyric crisis, parkinsonism, tardive dyskinesia, and tremor.
** Parkinsonism includes adverse event terms: akathisia, cogwheel rigidity, dystonia, extrapyramidal disorder, hyperkinesia, 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. 1.6% 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>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>Dystonia</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 8.9% 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>20 to 60 mg/day (N=164) (%)</th>
<th>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>Parkinsonism**</td>
<td>0</td>
<td>0</td>
<td>2</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.

Adjunctive Therapy with Lithium or Valproate
In the adult short-term, placebo-controlled adjunctive therapy bipolar depression studies, for LATUDA-treated patients, the incidence of EPS, excluding akatishia 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=380) (%)</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>Parkinsonism**</td>
<td>&lt;1</td>
<td>1</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>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 hypersecretion</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 Dystinesia</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, cogwheel rigidity, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, parkinsonism, 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%).
Controlled studies appear in this listing; those occurring in 1/100 to 1/1000 patients frequency according to the following definitions: those occurring in at least 1/100 adults 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 AIDS (LATUDA, 3.4%; placebo, 1.2%).

**Adjunctive Therapy with Lithium or Valproate**

The mean change from baseline for LATUDA-treated adult patients for the SAS, BAS and AIMs was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients and placebo for the BAS (LATUDA, 8.7%; placebo, 2.1%), the SAS (LATUDA, 2.6%; placebo, 2.1%) and the AIDS (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 AIDS (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 according to the following definitions: those occurring in at least 1/100 patients (frequent) (only those not already listed in the tabulated results from placebo-controlled studies appear in this listing); those occurring in 1/100 to 1/1000 patients (infrequent); and those occurring in fewer than 1/1000 patients (rare).

**Blood and Lymphatic System Disorders:** Infrequent: anemia

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

**Ear and Labyrinth Disorders:** Infrequent: vertigo

**Eye Disorders:** Frequent: blurred vision

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

**General Disorders and Administrative Site Conditions:** Rare: sudden death

**Investigations:** Frequent: CPK increased

**Metabolism and Nutritional System Disorders:** Frequent: decreased appetite

**Musculoskeletal and Connective Tissue Disorders:** Rare: rhabdomyolysis

**Nervous System Disorders:** Infrequent: cerebrovascular accident, dysarthria

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

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

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

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

**Vascular Disorders:** Frequent: hypertension

**Clinical Laboratory Changes**

**Schizophrenia**

**Adults**

**Serum Creatinine:** In short-term, placebo-controlled trials, the mean change from Baseline in serum creatinine was +0.05 mg/dL for LATUDA-treated patients compared to +0.02 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 3.0% (43/1453) of LATUDA-treated patients and 1.6% (1/681) 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 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, adolescent schizophrenia study, the mean change from Baseline in serum creatinine was −0.009 mg/dL for LATUDA-treated patients compared to +0.017 mg/dL for placebo-treated patients. A creatinine shift from normal to high (based on the centralized laboratory definition) occurred in 7.2% (14/194) of LATUDA-treated patients and 2.9% (3/103) on placebo (Table 29).

**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=103)</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 +0.01 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% (3/112) of LATUDA-treated patients and 0.6% (1/162) on placebo (Table 30).

**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>
### Adjunctive Therapy with Lithium or Valproate

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

<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>
<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:**
  - Metabolism and Nutrition Disorders: Hyponatremia.
  - Hypersensitivity Reactions: Urticaria, throat swelling, tongue swelling, dyspnea, and rash.

### DRUG INTERACTIONS

#### Drugs Having Clinically Important Interactions with LATUDA

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Placebo (N=334)</th>
<th>LATUDA 20 to 120 mg/day (N=360)</th>
</tr>
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<tbody>
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<td>6.7%</td>
</tr>
</tbody>
</table>

#### Table 31: Serum Creatinine Shifts from Normal at Baseline to High at Study

**End-Point in the Adult Adjunctive Therapy Bipolar Depression Studies**

**Serum Creatinine Elevated**

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
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</tr>
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<tbody>
<tr>
<td>Serum Creatinine Elevated</td>
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</tr>
</tbody>
</table>

#### 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>

#### 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:** Diltiazem, atazanavir, erythromycin, fluconazole, verapamil

**Strong CYP3A4 Inducers**

- **Clinical Impact:** Concomitant use of LATUDA with strong CYP3A4 inducers decreased the exposure of lurasidone compared to the use of LATUDA alone.

- **Intervention:** LATUDA should not be used concomitantly with strong CYP3A4 inducers.

- **Examples:** Rifampin, voriconazole, 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

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

**Integrating drug PK**

- **Strong CYP3A4 Inhibitor**
  - Ketoconazole
  - Cmax
  - 400 mg/day
  - AUC

- **Moderate CYP3A4 Inhibitor**
  - Diltiazem
  - Cmax
  - 240 mg/day
  - AUC

- **Strong CYP3A4 Inducer**
  - Rifampin
  - Cmax
  - 600 mg/day
  - AUC

- **Lithium**
  - Cmax
  - 600 mg BID
  - AUC

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

**Integrating drug PK**

- **P-gp Substrates**
  - Diazinon
  - Cmax
  - 0.25 mg SD
  - AUC

- **CYP3A4 Substrates**
  - Midazolam
  - Cmax
  - 5 mg SD
  - AUC

- **Oral Contraceptive**
  - Ethinyl Estradiol
  - Cmax
  - AUC

- **Norethisterone**
  - Cmax
  - AUC

- **Lithium**
  - Cmax
  - 600mg BID
  - AUC

### USE IN SPECIFIC POPULATIONS

**Pregnancy**

**Risk Summary**

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/.
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.

Pediatric Patients

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

Figure 3: Impact of Other Patient Factors on LATUDA Pharmacokinetics

<table>
<thead>
<tr>
<th>PK</th>
<th>Fold 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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Population description</th>
<th>Gender</th>
<th>Cmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>AUC</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>Asian*</td>
<td>AUC</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.