Bipolar Depression: The Search for Diagnosis and Treatment

Maj or depressive episodes associated with bipolar I disorder (bipolar depression) can be difficult to diagnose, which can prove challenging for clinicians and frustrating for patients. Patients can wait up to 10 years or longer from the time of symptom onset to receiving an accurate diagnosis. According to one study, patients undergo a mean of 3.5 differential diagnoses and see 4 healthcare professionals before finally receiving a diagnosis of bipolar disorder. Misdiagnosis is a frequent challenge. In a study of patients in a community sample who screened positive for bipolar disorder, nearly half (49%) had previously received no diagnosis, and nearly a third (31.2%) had received an incorrect diagnosis of major depressive disorder. Only 19.8% received a diagnosis of bipolar disorder. Consistent with this finding, unipolar depression, at 60%, is the most common misdiagnosis among patients later diagnosed with bipolar disorder. Anxiety disorder is the second most common misdiagnosis, at 26%.
Jane is a 30-year-old elementary school teacher who has been referred to a psychiatric nurse practitioner (NP) by her primary care provider after she expressed frustration with her lack of response to antidepressant therapy as prescribed by a previous psychiatrist. When asked how she is doing in general, she responds that this year has been tough. When urged for specifics, Jane divulges that she has experienced on-and-off bouts of depression for about 10 years. Jane complains that she has low energy and has had increasing difficulty coping with the demands of her job, which she used to love. Part of Jane’s frustration with her previous psychiatric provider is that she is tired of trying one antidepressant after another.

Jane’s psychiatric NP uses the Patient Health Questionnaire–9 item (PHQ-9)\(^1\) to screen her for depression and the Mood Disorder Questionnaire (MDQ)\(^2\) to screen for a lifetime history of mania. The results of the MDQ point to a history of manic episodes, but more information is required. The psychiatric NP conducts a full diagnostic interview with Jane to come to a definitive diagnosis. Jane denies feeling “unusually good” in the past. With her permission, the psychiatric NP speaks with Jane’s husband to gather collateral information to supplement the full diagnostic interview. Jane’s husband reveals that Jane has had several periods of unusual behavior in the past, during which time she was uncharacteristically short tempered and jeopardized the couple’s finances with impulsive decisions. On the basis of the PHQ-9, the MDQ, the full diagnostic interview, and collateral information, the psychiatric NP diagnoses Jane with bipolar I disorder and initiates therapy with a mood stabilizer.

Jane returns for an office visit 3 weeks after starting the mood stabilizer for an assessment of her symptoms. Despite the mood stabilizer, she continues to complain of finding little enjoyment in her daily activities. She relates that she has been taking the medication as prescribed. Jane returns for a second follow-up 3 weeks later, reporting that her depressive symptoms have still not improved since she began the medication. Plasma levels obtained at this time confirm treatment adherence.

The psychiatric NP keeps Jane on the mood stabilizer, and after discussing all available treatment options with her, decides to add Lratuda\(^3\) (lurasidone HCl) for the treatment of her major depressive episodes associated with bipolar I disorder (bipolar depression).

One difficulty in diagnosing bipolar disorder is that affected patients are more likely to present with depressive symptoms than with symptoms of hypomania or mania.\(^4\) Over the long-term course of the disease they typically spend more than two-thirds of their symptomatic time with depression as opposed to mania.\(^5\)

As a result, in clinical practice, antidepressants are frequently used for the treatment of bipolar depression.\(^6\) However, in patients with bipolar depression, antidepressant treatment is associated with a risk of medication-induced switch to mania or hypomania. For example, a study of antidepressant use in patients with depressive episodes associated with bipolar disorder found that 24.4% switched to mania, hypomania, or a mixed state during antidepressant treatment.\(^6\) Although the risk of mania is reduced by adding a mood stabilizer,\(^7\) the randomized, double-blind, placebo-controlled Systematic Treatment Enhancement Program for Bipolar Disorder, or STEP-BD, study found that the combination of an antidepressant and a mood stabilizer was not more likely to improve depressive symptoms than a mood stabilizer alone.\(^8\)

**LATUDA: A Treatment Option for Bipolar Depression**

The efficacy of LATUDA for the adjunctive treatment of bipolar depression was evaluated in a phase 3, randomized, multicenter, double-blind, placebo-controlled clinical trial of 348 patients with bipolar I disorder.\(^9\) The results of this pivotal trial were published in the February 2014 issue of The American Journal of Psychiatry.\(^9\) All psychotropic medications other than lithium or valproate were tapered off during the screening phase, and a therapeutic range of lithium (0.6-1.2 mEq/L) or valproate (50-125 µg/mL) was maintained for at least 28 days. The patients were then randomized to receive flexibly dosed adjunctive LATUDA 20 mg/day to 120 mg/day plus lithium or valproate (n=183) or placebo plus lithium or valproate (n=165) for 6 weeks. Study medication was taken once daily in the evening by mouth with a meal (e.g., dinner) or within 30 minutes after eating.\(^9\)

**Short-term Efficacy**

**Figure 1** shows the improvement in depressive symptoms for the LATUDA and placebo groups from baseline...
to Week 6 as measured using the Montgomery-Åsberg Depression Rating Scale (MADRS) total score, which was the study’s primary efficacy endpoint.9 The MADRS is a 10-item, clinician-rated scale with total scores ranging from 0 to 60. At Week 6, Latuda® (lurasidone HCl) added to lithium or valproate was associated with statistically significantly greater reduction from baseline MADRS total score than was placebo added to lithium or valproate (−17.1 vs −13.5 points; P<.01). LATUDA was also associated with significantly greater reduction in the key secondary endpoint of the Clinical Global Impression-Bipolar Version-Severity scale score.10

**Short-term Safety**

The safety of LATUDA as adjunctive therapy with lithium or valproate was also established in a second short-term, randomized, placebo-controlled study for bipolar depression. Together, these 2 studies enrolled 360 patients who received LATUDA at daily doses of 20 mg to 120 mg as adjunctive therapy with lithium or valproate.10 Adverse events that occurred in at least 2% of LATUDA-treated patients and more often than in the placebo group are shown in `Figure 2`.10

In the 2 short-term studies of LATUDA as adjunctive therapy, the mean increase in body weight from baseline to Week 6 was 0.2 pounds for patients who received LATUDA plus lithium or valproate versus 0.4 pounds for patients who received placebo plus lithium or valproate. An increase of body weight of at least 7.0% was noted for 3.1% of patients who received LATUDA versus 0.3% of patients who received placebo.10 Patients in the LATUDA group exhibited a mean increase in blood glucose concentration of 1.2 mg/dL, compared with a mean decrease of 0.9 mg/dL for patients who received placebo.10 Total cholesterol concentration decreased by a mean of 3.1 mg/dL in the LATUDA group versus a decrease of 2.9 mg/dL in the placebo group. The mean triglyceride concentration increased by 4.6 mg/dL in the LATUDA group and decreased by 4.6 mg/dL in the placebo group.10

In these 2 studies, the median prolactin concentration increased by 2.8 ng/mL between baseline and Week 6 for patients in the LATUDA group and remained unchanged for patients in the placebo group. For male patients, the change from baseline to Week 6 was +2.4 ng/mL with LATUDA and −0.1 ng/mL with placebo; for female patients, the median change from baseline was +3.2 ng/mL with LATUDA versus +0.4 ng/mL with placebo.10

Extrapyramidal symptoms (EPS), akathisia, and tardive dyskinesia were examined using the Simpson-Angus Scale, the Barnes Akathisia Scale (BAS), and the Abnormal Involuntary Movement Scale (AIMS), respectively. A shift from normal at baseline to abnormal at Week 6 (or at last observation carried forward for patients who discontinued prematurely) was noted for 2.8% of patients who received LATUDA plus lithium or valproate versus 2.1% of patients receiving placebo plus lithium or valproate. On the BAS, worsening from baseline to endpoint was noted for 8.7% versus 2.1% of patients who received LATUDA or placebo, respectively, whereas on the AIMS, worsening from baseline was noted for 2.8% of patients who received LATUDA versus 0.6% of those receiving placebo.10 EPS observed during the 6-week study included akathisia (11% vs 5% for LATUDA and placebo groups, respectively), dystonia (1% vs <1%), parkinsonism (13% vs 8%), and restlessness (4% vs <1%).10

**Figure 1. Primary Efficacy Endpoint: MADRS Score**

Baseline mean = 30.6

<table>
<thead>
<tr>
<th>Reduction in severity of depression</th>
<th>Time (Weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-13.5</td>
<td>6</td>
</tr>
<tr>
<td>-17.1</td>
<td>6</td>
</tr>
</tbody>
</table>

**Figure 2. Adverse Reactions in ≥2% of LATUDA-Treated Patients and at Greater Incidence Than Placebo**

Abbreviations: EPS, extrapyramidal symptoms; Li, lithium; VPA, valproate. Note: Figures rounded to the nearest integer.

* EPS includes bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, gait abnormal, hyperkinesia, muscle rigidity, oculogyric crisis, oremandibular dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticolis, tremor, and trismus.

† Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence.
AN EXPERT’S PERSPECTIVE

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

Unfortunately, it is not uncommon for individuals with bipolar disorder to go undiagnosed or misdiagnosed for long periods of time. When Jane* presents to her psychiatric NP, her primary complaint is her depression, and we know that she is tired of trying one antidepressant after another. This account of failed antidepressant therapy is a red flag that the patient may have bipolar disorder. She has not expressed any symptoms other than those of a depressive nature thus far, which can mask the need to investigate further into her history. In fact, I would urge primary care and psychiatric providers to rule out bipolar disorder in any patient who presents with depressive symptoms to help prevent a misdiagnosis and possible inappropriate treatment. A straight forward way to do that is via screening tools, such as the MDO, which screens for a lifetime history of mania. This tool can provide feedback to the patient, who may start to recognize his or her symptoms through the screening tools. Following a positive screen, assessment of mood symptoms using the DSM-5 criteria and asking about sudden switches in mood over time is important. It is also helpful to ask the patient to cite any previous diagnoses, as patients are not always sure of their diagnostic history. Asking specifically about a family history of bipolar disorder in first- and second-degree relatives may help to confirm a diagnosis of heritable bipolar disorder.

JANE’s denial of feeling “unusually good” in the past is not as much a denial as it is a lack of self-awareness and insight. To gain insight from an outside source, the psychiatric NP speaks with Jane’s husband. If Jane had not been willing to include her husband in the conversation, the psychiatric NP could have asked Jane, “Has your family ever mentioned that you were acting out of character?” An account of family members’ responses could provide additional clues into Jane’s own bipolar symptoms.

Once Jane is diagnosed with bipolar I disorder, she begins therapy with a mood stabilizer. It is important to follow up—even by phone—to make sure her depression does not get any worse. As with any medication, if there is no improvement, a change in dose or treatment may be warranted. In this case, after 6 weeks, the psychiatric NP adds Latuda® (lurasidone HCl) to the mood stabilizer to treat Jane’s bipolar depression.

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

* Hypothetical case representing a fictional patient.

Longer-term Safety

Patients with bipolar depression who completed the two 6-week trials of LATUDA as adjunctive therapy with lithium or valproate were eligible to continue into a 6-month, uncontrolled, open-label, flexible-dose extension study. Eligible patients who received placebo in the short-term studies were switched to LATUDA in the longer-term extension study. Adverse events that occurred in at least 5% of patients who continued on LATUDA adjunctive therapy plus lithium or valproate (n=254) included parkinsonism (14.2%), somnolence (9.1%), akathisia (8.7%), insomnia (71%), nausea (5.5%), and headache (5.5%). Changes in weight and laboratory parameters from open-label baseline to Week 24 were as follows: mean change in weight, 1.7 pounds; mean change in glucose, −0.5 mg/dL; mean change in cholesterol, 0.4 mg/dL; mean change in triglycerides, 1.6 mg/dL; and median change in prolactin levels, −1.3 ng/dL.11

* The effectiveness of LATUDA for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies.

References


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

1.1 Schizophrenia
LATUDA is indicated for the treatment of patients with schizophrenia.

The efficacy of LATUDA in schizophrenia was established in five 6-week controlled studies of adult patients with schizophrenia [see Clinical Studies (14.1)].

The effectiveness of LATUDA for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient [see Dosage and Administration (2)].

1.2 Depressive Episodes Associated with Bipolar I Disorder
Monotherapy: LATUDA is indicated as monotherapy for the treatment of patients with major depressive episodes associated with bipolar I disorder (bipolar depression). The efficacy of LATUDA was established in a 6-week monotherapy study in adult patients with bipolar depression [see Clinical Studies (14.2)].

Adjunctive Therapy with Lithium or Valproate: LATUDA is indicated as adjunctive therapy with either lithium or valproate for the treatment of patients with major depressive episodes associated with bipolar I disorder (bipolar depression). The efficacy of LATUDA as adjunctive therapy was established in a 6-week study in adult patients with bipolar depression who were treated with lithium or valproate [see Clinical Studies (14.2)].

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

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

4 CONTRAINDICATIONS

• Known hypersensitivity to lisuride HCI or any components in the formulation. Angioedema has been observed with lisuride [see Adverse Reactions (6.1)].

• Strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, etc.).

• Strong CYP3A4 inducers (e.g., rifampin, St. John’s wort, phenytoin, carbamazepine, etc.) [see Drug Interactions (7.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of 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 2.5% 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 in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. LATUDA is not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning].

5.2 Suicidal Thoughts and Behaviors in Adolescents and Young Adults

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with short-term use of antidepressants in adults aged >24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk of differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

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

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient’s presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidal thoughts and behaviors, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for LATUDA should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

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

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

5.4 Neuroleptic Malignant Syndrome

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

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

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

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. If reintroduced, the patient should be carefully monitored, since recurrences of NMS have been reported.

5.5 Tardive Dyskinesia

Tardive dyskinesia is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which
Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study, had a mean change in glucose of +1.7 mg/dL at week 24 (=0.85).

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

Schizophrenia

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 5.

Table 5: Change in Fasting Lipids in Schizophrenia Studies

<table>
<thead>
<tr>
<th>LATUDA</th>
<th>Placebo</th>
<th>20 to 60 mg/day</th>
<th>40 to 120 mg/day</th>
<th>80 mg/day</th>
<th>120 mg/day</th>
<th>160 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Glucose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(≥ 240 mg/dL)</td>
<td>1.3%</td>
<td>1.0%</td>
<td>0.6%</td>
<td>0.5%</td>
<td>0.4%</td>
<td>0.3%</td>
</tr>
<tr>
<td>(≥ 126 mg/dL)</td>
<td>1.3%</td>
<td>1.0%</td>
<td>0.6%</td>
<td>0.5%</td>
<td>0.4%</td>
<td>0.3%</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 monotherapy in the short-term study and continued in the longer-term study, had a mean change in total cholesterol and triglycerides of -3.8 mg/dL and -15.1 (95% CI) mg/dL at week 24, -3.1 (95% CI) mg/dL at week 36 and -2.5 (95% CI) mg/dL at week 52, respectively.

Adjunctive Therapy with Lithium or Valproate

Data from the short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies are presented in Table 4.

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

<table>
<thead>
<tr>
<th>LATUDA</th>
<th>Placebo</th>
<th>20 to 120 mg/day</th>
<th>Mean Change from Baseline (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Glucose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(≥ 126 mg/dL)</td>
<td>1.3%</td>
<td>1.0%</td>
<td>0.6%</td>
</tr>
<tr>
<td>(≥ 126 mg/dL)</td>
<td>1.3%</td>
<td>1.0%</td>
<td>0.6%</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 5.3 (n=88) mg/dL at week 24, respectively.

Weight Gain

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

Schizophrenia

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 diazepam was +4.15 kg and for quetiapine extended-release was +2.09 kg in Studies 3 and 5 [see Clinical Studies (14.3)]; the proportion of patients with a ≥ 7% increase in body weight (at Endpoint) was 4.8% for LATUDA-treated patients versus 3.0% for placebo-treated patients.

Table 8: Mean Change in Weight (kg) from Baseline in Schizophrenia Studies

<table>
<thead>
<tr>
<th></th>
<th>LATUDA (n=88)</th>
<th>20 mg/day (n=71)</th>
<th>40 mg/day (n=84)</th>
<th>60 mg/day (n=52)</th>
<th>80 mg/day (n=29)</th>
<th>100 mg/day (n=14)</th>
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<tbody>
<tr>
<td>Change in Weight (kg)</td>
<td>-0.02</td>
<td>-0.15</td>
<td>+0.22</td>
<td>+0.54</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 -0.89 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

Monotherapy

Data from the short-term, flexible-dosed, placebo-controlled monotherapy bipolar depression study are presented in Table 9. The mean 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 versus 0.7% for placebo-treated patients.

Table 9: Mean Change in Weight (kg) from Baseline in the Monotherapy Bipolar Depression Study

<table>
<thead>
<tr>
<th></th>
<th>LATUDA (n=151)</th>
<th>20 to 60 mg/day (n=143)</th>
<th>80 to 120 mg/day (n=147)</th>
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<tbody>
<tr>
<td>Change in Weight (kg)</td>
<td>-0.04</td>
<td>+0.06</td>
<td>+0.02</td>
</tr>
</tbody>
</table>

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

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

Adjunctive Therapy with Lithium or Valproate

Data from the short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies are presented in Table 10. The mean 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 versus 0.3% for placebo-treated patients.

Table 10: Mean Change in Weight (kg) from Baseline in the Adjunctive Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th></th>
<th>LATUDA (n=307)</th>
<th>20 to 120 mg/day (n=327)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Weight (kg)</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).

5.7 Hyperprolactinemia

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

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotroph secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds. Long-standing hyperprolactinemia, when associated with hypogonadism, may lead to decreased bone density in both female and male patients. [see Adverse Reactions (6)]

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in a LATUDA carcinogenicity study conducted in rats and mice [see Nonclinical Toxicology (13)]. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

Schizophrenia

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 11.

Table 11: Median Change in Prolactin (ng/mL) from Baseline in Schizophrenia Studies

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=672)</th>
<th>20 mg/day (n=174)</th>
<th>40 mg/day (n=148)</th>
<th>60 mg/day (n=146)</th>
<th>80 mg/day (n=150)</th>
<th>LATUDA (n=520)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Prolactin (ng/mL)</td>
<td>-1.9</td>
<td>-1.4</td>
<td>-0.2</td>
<td>+3.3</td>
<td>+3.3</td>
<td></td>
</tr>
</tbody>
</table>

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

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

Bipolar Depression

Monotherapy

The median change from baseline to endpoint in prolactin levels, in the 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 12.

Table 12: Median Change in Prolactin (ng/mL) from Baseline in the Monotherapy Bipolar Depression Study

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=307)</th>
<th>20 to 60 mg/day (n=140)</th>
<th>80 to 120 mg/day (n=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Prolactin (ng/mL)</td>
<td>+0.3</td>
<td>+1.7</td>
<td>+3.3</td>
</tr>
</tbody>
</table>

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

The median change from baseline to endpoint in prolactin levels, in the 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 across the dose range are shown in Table 13.

Table 13: Median Change in Prolactin (ng/mL) from Baseline in the Adjunctive Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=307)</th>
<th>20 to 120 mg/day (n=196)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Prolactin (ng/mL)</td>
<td>0.0</td>
<td>+2.8</td>
</tr>
</tbody>
</table>

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

The proportion of patients with prolactin elevations ≥ 5× upper limit of normal (ULN) was 0.4% for LATUDA-treated patients versus 0.0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥ 5× ULN was 0.6% for LATUDA-treated patients versus 0.0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥ 5× ULN was 0.0% versus 0.0% 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 mean change in prolactin of +1.15 mg/mL at week 24 (n=130).

Adjunctive Therapy with Lithium or Valproate

The median change from baseline to endpoint in prolactin levels, in the 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 13.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and LATUDA should be discontinued at the first sign of decline in WBC, in the absence of other causative factors.
Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1000/mm³) should discontinue LATUDA and have their WBC followed until recovery.

5.9 Orthostatic Hypotension and Syncope
LATUDA may cause orthostatic hypotension and syncope, perhaps due to its α1-adrenergic receptor antagonism. Associated adverse reactions can include dizziness, lightheadedness, tachycardia, and syncope. Generally, the 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 slowly titrating, 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
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 10.3% (5/1508), 0.1% (1/708) and syncope 0.1% (2/1508), 0% (0/708).

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

Bipolar Depression
Monotherapy
In the 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 0.1% with LATUDA 20 to 120 mg compared to 0.9% with placebo.

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

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

Bipolar Depression
Monotherapy
In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, no patient experienced seizures/convulsions.

Adjunctive Therapy with Lithium or Valproate
In the short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression therapy study, 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.

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

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

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

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

5.12 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 prescribeing LATUDA for patients who will be experiencing conditions that may contribute to temperature elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration [see Patient Counseling Information (7.9)].

5.13 Suicide
The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. Prescriptions for LATUDA should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Schizophrenia
In short-term, placebo-controlled schizophrenia studies, the incidence of treatment-emergent suicidal ideation was 0.4% (6/1508) for LATUDA-treated patients compared to 0.8% (6/708) on placebo. No suicide attempts or completed suicides were reported in these studies.

Bipolar Depression
Monotherapy
In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, the incidence of treatment-emergent suicidal ideation was 0.0% (0/331) with LATUDA-treated patients compared to 0.0% (0/168) with placebo-treated patients. No suicide attempts or completed suicides were reported in this study.

Adjunctive Therapy with Lithium or Valproate
In the short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression studies, the incidence of treatment-emergent suicidal ideation was 1.1% (4/360) for LATUDA-treated patients compared to 0.3% (1/334) on placebo. No suicide attempts or completed suicides were reported in these studies.

5.14 Activation of Mania/Hypomania
Antidepressant treatment can increase the risk of developing a manic or hypomanic episode, particularly in patients with bipolar disorder. Monitor patients for the emergence of such episodes. In the bipolar depression monotherapy and adjunctive therapy (with lithium or valproate) studies, less than 1% of subjects in the LATUDA and placebo groups developed manic or hypomanic episodes.

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

5.16 Neurological Adverse Reactions in Patients with Parkinson’s Disease or Dementia with Lewy Bodies
Patients with Parkinson’s Disease or Dementia with Lewy Bodies are reported to have an increased sensitivity to antipsychotic medication. Manifestations of this increased sensitivity include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome.

6. ADVERSE REACTIONS
The following adverse reactions are discussed in more detail in other sections of the labeling:

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis [see Boxed Warning and Warnings and Precautions (5.1)]
- Suicidal Thoughts and Behaviors [see Boxed Warning and Warnings and Precautions (5.2)]
- Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-related Psychosis [see Warnings and Precautions (5.23)]
- Neuroleptic Malignant Syndrome [see Warnings and Precautions (5.4)]
- Tardive Dyskinesia [see Warnings and Precautions (5.5)]
- Metabolic Changes (Hyperglycemia and Diabetes Mellitus, Dyslipidemia, and Weight Gain) [see Warnings and Precautions (5.6)]
- Extrapyramidal Reactions [see Warnings and Precautions (5.7)]
- Leukopenia, Neutropenia, and Agranulocytosis [see Warnings and Precautions (5.8)]
- Orthostatic Hypotension and Syncope [see Warnings and Precautions (5.9)]
- Seizures [see Warnings and Precautions (5.10)]
- Potential for Cognitive and Motor Impairment [see Warnings and Precautions (5.11)]
- Body Temperature Dysregulation [see Warnings and Precautions (5.12)]
- Suicide [see Warnings and Precautions (5.23)]
- Activation of Mania/Hypomania [see Warnings and Precautions (5.14)]
- Dysphagia [see Warnings and Precautions (5.15)]
- Neurological Adverse Reactions in Patients with Parkinson’s Disease or Dementia with Lewy Bodies [see Warnings and Precautions (5.16)]

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

The information below is derived from an integrated clinical study database for LATUDA consisting of 37/99 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 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% (143/1508) LATUDA-treated patients and 9.3% (66/708) of placebo-treated patients discontinued due to

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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 14.

Table 14: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in Short-term Schizophrenia Studies

<table>
<thead>
<tr>
<th>Body System or Organ Class</th>
<th>Placebo (N=2170) (%)</th>
<th>LATUDA 20 to 60 mg/day (N=667) (%)</th>
<th>LATUDA 80-120 mg/day (N=167) (%)</th>
<th>All LATUDA (N=331) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>5</td>
<td>11</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
<td>7</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>5</td>
<td>11</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
<td>7</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>Back Pain</td>
<td>2 0 4 3 4 0 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>11</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Back Pain</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Dizziness</td>
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<td>6</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>11</td>
<td>10</td>
<td>7</td>
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<tr>
<td>Nervous System Disorders</td>
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<td>Nausea</td>
<td>6</td>
<td>11</td>
<td>10</td>
<td>7</td>
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<tr>
<td>Dizziness</td>
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<td>Psychiatric Disorders</td>
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</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>11</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td>6</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
| Dose-Related Adverse Reactions in the Schizophrenia Studies

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

The following findings are based on the 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%, 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 15.

Table 15: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in a Short-term Monotherapy Bipolar Depression Study

<table>
<thead>
<tr>
<th>Body System or Organ Class</th>
<th>Placebo (N=188) (%)</th>
<th>LATUDA 20 to 60 mg/day (N=164) (%)</th>
<th>LATUDA 80-120 mg/day (N=167) (%)</th>
<th>All LATUDA (N=331) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>10</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4</td>
<td>6</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>10</td>
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<td>Vomiting</td>
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<tr>
<td>Diarrhea</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Psychiatric Disorders</td>
<td></td>
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</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>10</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4</td>
<td>6</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer

**Dose-Related Adverse Reactions in the Monotherapy Study:**

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

**Bipolar Depression (Adjunctive Therapy with Lithium or Valproate)**

The following findings are based on two 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 16.

Table 16: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in the Short-term Adjunctive Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th>Body System or Organ Class</th>
<th>Placebo (N=334) (%)</th>
<th>LATUDA 20 to 120 mg/day (N=360) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
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<tr>
<td>Nausea</td>
<td>10</td>
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<tr>
<td>Diarrhea</td>
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<td>6</td>
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<tr>
<td>Nervous System Disorders</td>
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<td></td>
</tr>
<tr>
<td>Akathisia</td>
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<td>4</td>
</tr>
<tr>
<td>Somnolence**</td>
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<tr>
<td>Psychiatric Disorders</td>
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<tr>
<td>Anxiety</td>
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<td>4</td>
</tr>
<tr>
<td>Somnolence**</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer

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

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

Schizophrenia

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% versus 5.8% for placebo-treated patients. The incidence of akathisia for LATUDA-treated patients was 12.9% versus 3.0% for placebo-treated patients. Incidence of EPS by dose is provided in Table 17.

Table 17: Incidence of EPS Compared to Placebo in Schizophrenia Studies

<table>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>Placebo (N=708) (%)</th>
<th>LATUDA 20 to 120 mg/day (N=164) (%)</th>
<th>LATUDA 60 to 120 mg/day (N=167) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All EPS events</td>
<td>10 21 23 39 20</td>
<td>6 12 22 13</td>
<td></td>
</tr>
<tr>
<td>All EPS, excluding Akathisia/Restlessness</td>
<td>6 11 12 22 7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer

Akathisia

There was no evidence of an increase in the incidence of akathisia for LATUDA-treated patients versus placebo.

Dystonia

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

Parkinsonism

Restlessness

Bipolar Depression

Monotherapy

In the short-term, placebo-controlled monotherapy bipolar depression study, for LATUDA-treated patients, the incidence of reported events related to EPS, excluding akathisia and restlessness was 6.9% versus 2.4% for placebo-treated patients. The incidence of akathisia for LATUDA-treated patients was 9.4% versus 2.4% for placebo-treated patients. Incidence of EPS by dose groups is provided in Table 18.

Table 18: Incidence of EPS Compared to Placebo in the Monotherapy Bipolar Depression Study

<table>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>Placebo (N=168) (%)</th>
<th>LATUDA 20 to 60 mg/day (N=164) (%)</th>
<th>LATUDA 60 to 120 mg/day (N=167) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All EPS events</td>
<td>5 12 20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All EPS, excluding Akathisia/Restlessness</td>
<td>2 5 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akathisia</td>
<td>2 6 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dystonia*</td>
<td>0 0 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parkinsonism**</td>
<td>2 5 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restlessness</td>
<td>&lt;1 1 3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer

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

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

Adjunctive Therapy with Lithium or Valporate

In the short-term, placebo-controlled adjunctive therapy bipolar depression studies, dystonia occurred in 0.9% of LATUDA-treated subjects (0.0% and 1.0% for LATUDA 10 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.

Adverse Reactions Observed During the Premarketing Evaluation of LATUDA

Following is a list of adverse reactions reported by patients treated with LATUDA at multiple doses ≥ 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 14 or those that appear elsewhere in the LATUDA label are not included. Although the reactions reported occurred during treatment with LATUDA, they were not necessarily caused by it.

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 1/1000 to 1/100 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: Frequent: cerebrovascular accident, dysarthria

Psychiatric Disorders: Infrequent: abnormally deep, panic attack, sleep disorder

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

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

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

Vascular Disorders: Frequent: hypertension

Clinical Laboratory Changes

Schizophrenia

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 versus 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%).

Bipolar Depression

Monotherapy

The mean change from baseline for LATUDA-treated 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 versus placebo for the BAS (LATUDA, 8.4%; placebo, 5.6%), the SAS (LATUDA, 3.7%; placebo, 1.9%) and the AIMS (LATUDA, 3.4%; placebo, 1.2%).

Adverse Effect of 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

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.

Bipolar Depression

Monotherapy

In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, dystonia occurred in 0.9% of LATUDA-treated subjects (0.0% and 1.0% 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.

Other Adverse Reactions Observed During the Premarketing Evaluation of LATUDA

Following is a list of adverse reactions reported by patients treated with LATUDA at multiple doses ≥ 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 14 or those that appear elsewhere in the LATUDA label are not included. Although the reactions reported occurred during treatment with LATUDA, they were not necessarily caused by it.

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 1/1000 to 1/100 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: Frequent: cerebrovascular accident, dysarthria

Psychiatric Disorders: Infrequent: abnormally deep, panic attack, sleep disorder

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

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

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

Vascular Disorders: Frequent: hypertension

Clinical Laboratory Changes

Schizophrenia
treated patients and 1.6% (11/681) on placebo. The threshold for high creatinine value varied from > 0.79 to > 1.3 mg/dL based on the centralized laboratory definition for each study (Table 20).

Table 20: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in 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=627)</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>

**Bipolar Depression**

**Monotherapy**

Serum Creatinine: In the 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% (17/622) of LATUDA-treated patients and 0.8% (17/162) on placebo (Table 21).

Table 21: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in a Monotherapy Bipolar Depression Study

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Placebo (N=168)</th>
<th>LATUDA 20 to 60 mg/day (N=104)</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>

**Depression**

**Adjunctive to Lithium or Valproate**

Serum Creatinine: In 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 22).

Table 22: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in the Adjunctive Therapy Bipolar Depression Studies

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

**7 DRUG INTERACTIONS**

**7.1 Potential for Other Drugs to Affect LATUDA**

LATUDA is predominantly metabolized by CYP3A4. LATUDA should not be used concomitantly with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, etc.) or strong CYP3A4 inducers (e.g., rifampin, avasimibe, St. John’s wort, phenytoin, carbamazepine, etc.). LATUDA concentrations were not affected by lurasidone, and lurasidone concentrations were not affected by valproate. A dedicated drug-drug interaction study has not been conducted with valproate and LATUDA.

**7.2 Potential for LATUDA to Affect Other Drugs**

No adjustment is needed for lithium, substrates of P-gp, CYP3A4 (Figure 2) or valproate when coadministered with LATUDA.

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

Interacting drug PK

<table>
<thead>
<tr>
<th>P-gp Substrates</th>
<th>Cmax</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dipotassium 0.25 mg SD</td>
<td>Adjustment not required</td>
<td></td>
</tr>
<tr>
<td>CYP3A4 Substrates</td>
<td>Cmax</td>
<td>AUC</td>
</tr>
<tr>
<td>Midazolam 5 mg SD</td>
<td>Adjustment not required</td>
<td></td>
</tr>
<tr>
<td>Oral Contraceptive</td>
<td>Cmax</td>
<td>AUC</td>
</tr>
<tr>
<td>Ethylmorphine</td>
<td>Adjustment not required</td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Cmax</td>
<td>AUC</td>
</tr>
<tr>
<td>Lithium 600mg BID</td>
<td>Cmax</td>
<td>AUC</td>
</tr>
</tbody>
</table>

7.3 Use in Specific Populations

8.1 Pregnancy

Pregnancy Category B

**Risk Summary**

There are no adequate and well-controlled studies of LATUDA use in pregnant women. Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypotonia, hypotension, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

LATUDA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Human Data**

Safe use of LATUDA during pregnancy or lactation has not been established; therefore, use of LATUDA in pregnancy, in nursing mothers, or in women of childbearing potential requires that the benefits of treatment be weighed against the possible risks to mother and child.

**Animal Data**

No adverse developmental effects were observed in a study in which pregnant rats were given lurasidone during the period of organogenesis and continuing through weaning at doses up to 10 mg/kg/day, which is approximately half of the maximum recommended human dose (MRHD) of 160 mg/day based on mg/m² body surface area.

No teratogenic effects were seen in studies in which pregnant rats and rabbits were given lurasidone during the period of organogenesis at doses up to 25 and 50 mg/kg/day, respectively. These doses are 1.5- and 6-times, in rats and rabbits, respectively, the MRHD of 160 mg/day based on mg/m² body surface area.

8.2 Nursing Mothers

LATUDA was excreted in milk of rats during lactation. It is not known whether LATUDA or its metabolites are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, considering the risk of drug discontinuation to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

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

Elderly patients with dementia-related psychosis treated with LATUDA are at an increased risk of death compared to placebo. LATUDA is not approved for the treatment of patients with dementia-related psychosis (see Boxed Warning).
### 8.6 Other Patient Factors

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

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

<table>
<thead>
<tr>
<th>Renal impairment</th>
<th>Cmax</th>
<th>AUC</th>
<th>Adjustment</th>
<th>Starting dose</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td></td>
<td></td>
<td>not required</td>
<td>20 mg</td>
<td>80 mg</td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td></td>
<td>not required</td>
<td>20 mg</td>
<td>80 mg</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
<td>20 mg</td>
<td>40 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepatic impairment</th>
<th>Cmax</th>
<th>AUC</th>
<th>Adjustment</th>
<th>Starting dose</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td></td>
<td></td>
<td>not required</td>
<td>20 mg</td>
<td>80 mg</td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
<td>20 mg</td>
<td>80 mg</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
<td>20 mg</td>
<td>40 mg</td>
</tr>
</tbody>
</table>

Population description

- **Gender**
  - Females
    - Cmax
    - AUC
    - Adjustment not required
  - Race
    - Asian
    - Cmax
    - AUC
    - Adjustment not required

*Compare to Caucasian

### 10 OVERDOSE

#### 10.1 Human Experience

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

#### 10.2 Management of Overdosage

Consult a Certified Poison Control Center for up-to-date guidance and advice. There is no specific antidote to LATUDA, therefore, appropriate supportive measures should be instituted and close medical supervision and monitoring should continue until the patient recovers. Consider the possibility of multiple-drug overdose.

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.