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A Clinical Expert Approach to the Management of Bipolar Depression in Primary Care

A 3-PART NEWSLETTER SERIES

THIRD IN A SERIES OF 3 NEWSLETTERS

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Bipolar Depression in Primary Care:
A Multidisciplinary Approach

INDICATIONS AND USAGE
LATUDA is indicated for 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 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. The efficacy of LATUDA in the treatment of mania associated with bipolar disorder has not been established.

IMPORTANT SAFETY INFORMATION AND INDICATIONS FOR LATUDA
Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older. In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber. LATUDA is not approved for use in patients under the age of 18 years.

Major depressive episodes associated with bipolar I disorder (bipolar depression) present several important challenges in primary care. Approximately 10% of patients in the primary care setting who are receiving antidepressants for depression have symptoms that may suggest undiagnosed bipolar disorder. Recognizing patients with bipolar depression is especially important because antidepressant use in patients with bipolar disorder is associated with a possible risk of medication-induced mania or hypomania. For example, a study of antidepressant use in patients with depressive episodes associated with bipolar disorder found that 24.4% transitioned to mania, hypomania, or a mixed state during antidepressant treatment. Treatment responses that suggest a possible diagnosis of bipolar depression include a rapid onset of improvement or “activating” side effects (eg, anxiety, insomnia, agitation). Diagnosis and treatment may also be complicated by
PATIENT PROFILE: MEGHAN*

Meghan is a 35-year-old mother of 2 children who lives in a rural area with limited access to healthcare specialists. She has recently begun pharmacotherapy for major depressive episodes associated with bipolar I disorder (bipolar depression) in a patient-centered medical home (PCMH).

Meghan first saw a PCP for her depressive symptoms 4 years ago. Meghan said that she had been struggling with depression “for years,” but because she lived in a small, rural community, she was not comfortable seeking help. Meghan said that she often felt “really down” and “depressed” as early as college and experienced frequent episodes of insomnia, anxiety, and low energy. Despite her reservations about being treated for a mood disorder, Meghan felt she had to seek help because her depressive symptoms had recently become worse. Her PCP diagnosed her with major depressive disorder (MDD) and prescribed a selective serotonin reuptake inhibitor, but Meghan never took the medication because she did not have health insurance with prescription medication coverage.

About 2 years ago, Meghan’s health insurance plan changed, and she joined the PCMH. She developed an excellent relationship with the family physician and nurse practitioner (NP) whom she usually sees for her primary care needs. Four months ago, Meghan told her NP about her previous diagnosis of MDD and asked about potential treatment options. With her 2 children now in school, Meghan had recently returned to work as a waitress. However, in addition to her ongoing problems with depressed mood, she reported feeling irritable, overwhelmed on the job, and angry with her husband.

Meghan’s NP prescribed a serotonin-norepinephrine reuptake inhibitor, and Meghan began taking the medication as prescribed. The following week during a telephone follow-up, she reported rapid improvement in her depressive symptoms within the first 3 or 4 days of treatment, but she also reported increasing anxiety, agitation, concentration and attention difficulties at work, and sleep disturbances. Meghan was urged to come in the following day and exhibited a markedly increased rate of speech. She talked in great detail about plans to quit her job and start her own investment company (for which she had no training or experience), and she mentioned that she planned to remortgage her house for start-up funds. Meghan’s NP became concerned that Meghan might be experiencing a medication-induced manic episode. Meghan was immediately referred to the psychiatrist attached to the PCMH for additional evaluation and treatment.

At this time, the psychiatrist reviews Meghan’s history and symptoms and agrees that her response to antidepressant medication is suggestive of a medication-induced manic episode. A complete diagnostic interview confirms a diagnosis of bipolar I disorder, and the psychiatrist recommends that Meghan begin monotherapy with the atypical antipsychotic LATUDA, which is indicated for treatment of major depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and as adjunctive therapy with lithium or valproate. Meghan agrees to try this new treatment, and her PCMH assigns Meghan to a case manager, who will help monitor her symptoms and coordinate visits with her psychiatrist, NP, and family physician. Meghan’s treatment plan includes regular assessment of depressive symptoms, adverse events, weight and body mass index (BMI), lipids, and serum glucose. Meghan is overweight, with a BMI of 29.8 kg/m², so her psychiatrist and NP encourage her to try to achieve a healthier body weight. The NP offers to refer Meghan to nutrition counseling services offered through the PCMH.

* Hypothetical case representing a fictional patient.
with lithium or valproate in adult patients with bipolar depression. The effectiveness of LATUDA has not been established for longer-term use (more than 6 weeks) or for the treatment of mania associated with bipolar disorder.13

The results of a phase 3, randomized, multicenter, double-blind, placebo-controlled clinical trial that examined the efficacy and safety of LATUDA monotherapy for patients with bipolar I depression were published in the February 2014 issue of *The American Journal of Psychiatry.*14 Adult patients (N=505) with major depressive episodes associated with bipolar I disorder, with or without rapid cycling, and without psychotic features, were evaluated for eligibility.14 All psychotropic medications were tapered off, and patients were randomly assigned to 1 of 3 treatment groups: flexibly dosed LATUDA 20-60 mg/day (N=168), flexibly dosed LATUDA 80-120 mg/day (N=169), or placebo (N=170).14 LATUDA dosing adjustments were permitted for patients in both LATUDA groups to optimize efficacy and tolerability.14 Study medication was taken once daily in the evening by mouth with a meal (eg, dinner) or within 30 minutes at eating.14

**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.14

The MADRS is a 10-item, clinician-rated scale with total scores ranging from 0 to 60.13 At Week 6, LATUDA 20-60 mg/day and 80-120 mg/day were associated with statistically significant improvement in MADRS score from baseline to the 6-week endpoint than placebo (-15.4 for both LATUDA treatment groups vs -10.7 for the placebo group; *P*<.001 for each LATUDA group vs placebo).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

**Short-term Safety**

Figure 2 shows the incidence of adverse reactions occurring in ≥2% of patients in either LATUDA group and at greater incidence than placebo during acute therapy (up to 6 weeks in patients with bipolar depression).13 Treatment was discontinued prematurely due to adverse events in 20 of 331 patients (6.0%) who received LATUDA 20-120 mg/day, and in 9/168 patients (5.4%) who received placebo.13

In the short-term study of LATUDA monotherapy, the mean change in body weight from baseline to Week 6 was +1.2 pounds for patients who received LATUDA 20-60 mg/day, 0.0 pounds for patients who received LATUDA 80-120 mg/day, and -0.1 pound for patients who received placebo.13 Increase of body weight of at least 7% was noted for 2.4% of patients who received LATUDA versus 0.7% of patients who received placebo.13 Changes in fasting glucose and lipids for the LATUDA and placebo groups are shown in the Table.13

The median prolactin concentration increased by 1.7 ng/mL for the LATUDA 20-60 mg group, 3.5 ng/mL for the LATUDA 80-120 mg group, and...
initial diagnosis of MDD appeared reasonable at the time, for patients with suspected MDD, particularly those with markers of a bipolar disorder, such as Meghan’s onset of symptoms and irritability, further assessment might have led to the bipolar I diagnosis, even before the initial trial of medication. Screening tools, such as the Composite International Diagnostic Interview 3.0 and the Mood Disorder Questionnaire, can be efficient screening approaches that are feasible for use by non-psychiatric staff in a PCMH. If the initial suspicion of a bipolar diagnosis is strong or suggestive, assessment by the psychiatrist who collaborates with the PCMH is indicated.

Meghan benefited from the timely follow-up the PCMH provided. Early phone calls can be very beneficial. For instance, a brief phone call by support staff 2 to 3 days after a visit in which treatment is initiated can prompt 3 questions: “Did you get the prescription filled? Have you started taking the medication? Do you have any concerns we need to address today?” Such a call by her prior PCP could have identified that cost was a barrier in initiating recommended treatment. A call 7 to 10 days after treatment initiation could query treatment adherence, response, and/or potential side effects. The call between Meghan and the PCMH identified the aberrant treatment response leading to initiation of urgent intervention and possibly preventing a catastrophic outcome for Meghan and her family.

In many regions of the country, and particularly in rural communities, psychiatrists are a scarce resource. Fortunately, some such communities have close-knit medical professional communities making cross-practice collaboration possible. The PCMH also provides a natural setting in which to integrate the management of bipolar I disorder and other mental illnesses with care of chronic medical conditions. In Meghan’s case, by intervening to help her control her weight, the PCMH could potentially prevent the development of diabetes, cardiovascular disease, and knee or hip osteoarthritis. Furthermore, as expanded insurance coverage is leading to an influx of patients seeking care, many of whom have had limited opportunities to access helpful treatment in the past, the PCMH provides a strategy to efficiently manage demand that otherwise might overwhelm practices, particularly in rural and other underserved communities.

Larry Culpepper, MD, MPH

References
BRIEF SUMMARY OF LATUDA FULL PRESCRIBING INFORMATION

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

• Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death [see Warnings and Precautions (5.1)].

• LATUDA is not approved for use in patients with dementia-related psychosis [see Warnings and Precautions (5.1)].

• Antipsychotic drugs, including LATUDA, increase the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older [see Warnings and Precautions (5.2)].

• In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber [see Warnings and Precautions (5.2)].

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 lisuridine HCl or any components in the formulation. Angioedema has been observed with lisuridine [see Adverse Reactions (6.1)].

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

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

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. 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 antipsychotic drugs 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 antidepressant use 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 a 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.

Table 1

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;19</td>
<td>Increases Compared to Placebo</td>
</tr>
<tr>
<td>18-24</td>
<td>14 additional cases</td>
</tr>
<tr>
<td>25-64</td>
<td>5 additional cases</td>
</tr>
<tr>
<td>&gt;65</td>
<td>Decreases Compared to Placebo</td>
</tr>
<tr>
<td>25-64</td>
<td>1 fewer case</td>
</tr>
<tr>
<td>&gt;65</td>
<td>6 fewer cases</td>
</tr>
</tbody>
</table>

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 several 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, impulsiveness, 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, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic syndrome, drug fever, and acute 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 may develop tardive dyskinesia. Both short-term and long-term treatment of psychotic patients with antipsychotic drugs is associated with an increased risk of developing tardive dyskinesia.

The risk of developing tardive dyskinesia is increased in patients treated for a long period of time. The risk may be reduced when treatment is discontinued. However, tardive dyskinesia may not resolve following discontinuation of the drug.
patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

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

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

5.6 Metabolic Changes

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

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoadiposis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Because LATUDA was not marketed at the time these studies were performed, it is not known if LATUDA is associated with this increased risk.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment.

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As with other antipsychotic drugs, a clinically significant weight gain may occur in some patients treated with LATUDA. In controlled clinical trials of up to 1 year duration, weight gain was observed in a dose-dependent manner in patients treated with LATUDA. Therefore, weight gain should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and polyuria should undergo fasting blood glucose testing. In some cases, hyperglycemia has been associated with ketoacidosis or hyperosmolar coma.

Atypical antipsychotic drugs have been associated with metabolic changes that may increase

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study, had a mean change in glucose of +1.7 mg/dL at week 24 (n=89).

Dyslipidemia

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

Schizophrenia

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

5.7 Adverse Reactions

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in total cholesterol and triglycerides of -3.8 (n=336) and -15.1 (n=357) mg/dL at week 24, -3.1 (n=303) and -4.8 (n=303) mg/dL at week 36 and -2.5 (n=307) and -6.9 (n=307) mg/dL at week 52, respectively.

Bipolar Depression

Monotherapy

Data from the short-term, flexible-dosed, placebo-controlled monotherapy bipolar depression studies are presented in Table 7.

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>Treatment</th>
<th>Placebo</th>
<th>LATUDA 20 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Glucose</td>
<td>Mean</td>
<td>Change from Baseline</td>
</tr>
<tr>
<td></td>
<td>(mg/dL)</td>
<td>(mg/dL)</td>
</tr>
<tr>
<td>Placebo</td>
<td>n=302</td>
<td>-0.1</td>
</tr>
<tr>
<td>LATUDA 20 to 120 mg/day</td>
<td>n=319</td>
<td>+1.2</td>
</tr>
</tbody>
</table>

Proportion of Patients with Shifts to ≥ 126 mg/dL

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

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study, had a mean change in glucose of +1.7 mg/dL at week 24 (n=89).

Table 5: Change in Fasting Lipids in Schizophrenia Studies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>LATUDA 20 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Glucose</td>
<td>Mean</td>
<td>Change from Baseline</td>
</tr>
<tr>
<td></td>
<td>(mg/dL)</td>
<td>(mg/dL)</td>
</tr>
<tr>
<td>Placebo</td>
<td>n=660</td>
<td>-0.6</td>
</tr>
<tr>
<td>LATUDA 20 to 120 mg/day</td>
<td>n=115</td>
<td>+1.7</td>
</tr>
</tbody>
</table>

Total Cholesterol

Triglycerides

Proportion of Patients with Shifts

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study, had a mean change in glucose of +1.7 mg/dL at week 24 (n=89).

Table 6: Change in Fasting Lipids in the Monotherapy Bipolar Depression Study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>LATUDA 20 to 60 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Glucose</td>
<td>Mean</td>
<td>Change from Baseline</td>
</tr>
<tr>
<td></td>
<td>(mg/dL)</td>
<td>(mg/dL)</td>
</tr>
<tr>
<td>Placebo</td>
<td>n=167</td>
<td>-0.3</td>
</tr>
<tr>
<td>LATUDA 20 to 60 mg/day</td>
<td>n=144</td>
<td>+0.4</td>
</tr>
</tbody>
</table>

Total Cholesterol

Triglycerides

Proportion of Patients with Shifts

Table 7: Change in Fasting Lipids in the Adjunctive Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>LATUDA 20 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Glucose</td>
<td>Mean</td>
<td>Change from Baseline</td>
</tr>
<tr>
<td></td>
<td>(mg/dL)</td>
<td>(mg/dL)</td>
</tr>
<tr>
<td>Placebo</td>
<td>n=303</td>
<td>-0.6</td>
</tr>
<tr>
<td>LATUDA 20 to 120 mg/day</td>
<td>n=321</td>
<td>+1.8</td>
</tr>
</tbody>
</table>

Total Cholesterol

Triglycerides

Proportion of Patients with Shifts

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy in the short-term and continued in the longer-term study had a mean change in total cholesterol and triglycerides of -0.5 (n=110) and -1.0 (n=110) mg/dL at week 24, respectively. Adjunctive Therapy with Lithium or Valproate

Data from the short-term, flexible-dosed, placebo-controlled, monotherapy bipolar depression study are presented in Table 6.

Table 8: Change in Fasting Lipids in the Monotherapy Bipolar Depression Study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>LATUDA 20 to 60 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Glucose</td>
<td>Mean</td>
<td>Change from Baseline</td>
</tr>
<tr>
<td></td>
<td>(mg/dL)</td>
<td>(mg/dL)</td>
</tr>
<tr>
<td>Placebo</td>
<td>n=167</td>
<td>-0.3</td>
</tr>
<tr>
<td>LATUDA 20 to 60 mg/day</td>
<td>n=144</td>
<td>+0.4</td>
</tr>
</tbody>
</table>

Total Cholesterol

Triglycerides

Proportion of Patients with Shifts

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy in the short-term and continued in the longer-term study had a mean change in total cholesterol and triglycerides of -0.5 (n=110) and -1.0 (n=110) mg/dL at week 24, respectively.
In the uncontrolled, open-label, long-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 mmol/L 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 (14.1)]; respectively. 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>Group</th>
<th>Baseline Weight</th>
<th>Week 24 Weight</th>
<th>Week 52 Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=696)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 mg/day (n=71)</td>
<td>-0.02</td>
<td>+0.56</td>
<td>+0.68</td>
</tr>
<tr>
<td>40 mg/day (n=84)</td>
<td>-0.15</td>
<td>+0.22</td>
<td>+0.68</td>
</tr>
<tr>
<td>60 mg/day (n=80)</td>
<td>+0.02</td>
<td>+0.54</td>
<td>+0.66</td>
</tr>
<tr>
<td>80 mg/day (n=526)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>120 mg/day (n=281)</td>
<td>-0.3</td>
<td>+0.7</td>
<td></td>
</tr>
<tr>
<td>160 mg/day (n=114)</td>
<td>-0.2</td>
<td>-0.07</td>
<td>-0.37</td>
</tr>
<tr>
<td>Placebo (n=151)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 to 60 mg/day (n=78)</td>
<td>-0.02</td>
<td>+0.56</td>
<td>+0.68</td>
</tr>
<tr>
<td>80 to 120 mg/day (n=73)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In the uncontrolled, long-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>Group</th>
<th>Baseline Weight</th>
<th>Week 24 Weight</th>
<th>Week 52 Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=307)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 to 60 mg/day (n=143)</td>
<td>-0.04</td>
<td>+0.56</td>
<td>+0.02</td>
</tr>
<tr>
<td>80 to 120 mg/day (n=147)</td>
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<tr>
<td>Placebo (n=62)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>20 to 60 mg/day (n=36)</td>
<td>-0.02</td>
<td>+0.56</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 as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, long-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>Group</th>
<th>Baseline Weight</th>
<th>Week 24 Weight</th>
<th>Week 52 Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=151)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 to 60 mg/day (n=143)</td>
<td>-0.04</td>
<td>+0.56</td>
<td>+0.02</td>
</tr>
<tr>
<td>80 to 120 mg/day (n=147)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

In the uncontrolled, long-term bipolar depression studies (primarily open-label extension studies), LATUDA was associated with a mean change in weight from baseline to endpoint for males was +0.5 ng/mL and +3.5 mg/kg with LATUDA 20 to 60 mg/day and 80 to 120 mg/day, respectively compared to +0.3 mg/kg with placebo-treated patients. The median change from baseline to endpoint for males was +1.5 ng/mL and for females was +3.1 mg/kg. Median changes for prolactin by dose range are shown in Table 12.

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo</th>
<th>LATUDA 20 to 60 mg/day</th>
<th>LATUDA 80 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=696)</td>
<td>-0.2</td>
<td>+0.56</td>
<td>+0.68</td>
</tr>
<tr>
<td>20 mg/day (n=71)</td>
<td>-0.15</td>
<td>+0.22</td>
<td>+0.68</td>
</tr>
<tr>
<td>40 mg/day (n=84)</td>
<td>+0.02</td>
<td>+0.54</td>
<td>+0.66</td>
</tr>
<tr>
<td>60 mg/day (n=80)</td>
<td>-0.3</td>
<td>+0.7</td>
<td></td>
</tr>
<tr>
<td>80 mg/day (n=526)</td>
<td>-0.2</td>
<td>-0.07</td>
<td></td>
</tr>
<tr>
<td>120 mg/day (n=281)</td>
<td>-0.2</td>
<td>-0.07</td>
<td></td>
</tr>
<tr>
<td>160 mg/day (n=114)</td>
<td>-0.2</td>
<td>-0.07</td>
<td></td>
</tr>
</tbody>
</table>

The proportion of patients with prolactin elevations ≥ 5x 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 ≥ 5x ULN was 5.7% for LATUDA-treated patients versus 2.0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥ 5x 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 mg/kg with LATUDA 20 to 60 mg/day and 80 to 120 mg/day, respectively compared to +0.3 mg/kg with placebo-treated patients. The median change from baseline to endpoint for males was +1.5 ng/mL and for females was +3.1 mg/kg. 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>Group</th>
<th>Placebo</th>
<th>LATUDA 20 to 60 mg/day</th>
<th>LATUDA 80 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=151)</td>
<td>0.0</td>
<td>+2.8</td>
<td>+5.3</td>
</tr>
<tr>
<td>20 to 60 mg/day (n=78)</td>
<td>0.0</td>
<td>+2.8</td>
<td>+5.3</td>
</tr>
<tr>
<td>80 to 120 mg/day (n=73)</td>
<td>0.0</td>
<td>+2.8</td>
<td>+5.3</td>
</tr>
</tbody>
</table>

Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day, or placebo as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, long-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 Hypoprothrombinemia
As with other drugs that antagonize dopamine D2 receptors, LATUDA elevates prolactin levels.

Hypoprothrombinemia 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 hypoprothrombinemia, 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 mg/mL and for females was -0.2 ng/mL. Median changes for prolactin by dose are shown in Table 11.

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 blurred vision. 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 slow 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
In the incidence of orthostatic hypotension and syncope reported as adverse events from short-term, placebo-controlled schizophrenia studies was (LATUDA incidence, placebo incidence): orthostatic hypotension 0.3% (5/1508), 0.1% (1/708) and syncope [0.1% (2/1508), 0% (0/708)]. In short-term schizophrenia clinical studies, orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 0.8% with LATUDA 40 mg, 2.1% with LATUDA 80 mg, 1.7% with LATUDA 120 mg and 0.8% with LATUDA 160 mg compared to 0.7% with placebo.

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 0.6% 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 short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression therapy studies, there were no reported adverse events of orthostatic hypotension and syncope. Orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 1.1% with LATUDA 20 to 120 mg compared to 0.9% with placebo.

5.10 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 studies, no patient experienced seizures/convulsions.

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 9.3% LATUDA 160 mg/day) compared to 7.1% (50/708) of placebo patients.

Bipolar Depression
Monotherapy
In the 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 short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies, somnolence was reported by 11.4% (41/369) 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 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 [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% (4/369) 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 (5.3)]
- 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)]
- Acute Angle-closure Glaucoma [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 (5.13)]
- Activation of Mania/Hypomania [see Warnings and Precautions (5.14)]
- Dysphagia [see Warnings and Precautions (5.15)]
- Neuropsychiatric 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
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% of 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>Percentage of Patients Reporting Reaction</th>
<th>Body System or Organ Class</th>
<th>Placebo (N=710) (%)</th>
<th>20 mg/day (N=771) (%)</th>
<th>40 mg/day (N=843) (%)</th>
<th>60 mg/day (N=938) (%)</th>
<th>80 mg/day (N=291) (%)</th>
<th>120 mg/day (N=291) (%)</th>
<th>All LATUDA (N=1658) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>11</td>
<td>10</td>
<td>9</td>
<td>9</td>
<td>13</td>
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<td>10</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
<td>7</td>
<td>6</td>
<td>9</td>
<td>9</td>
<td>7</td>
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<tr>
<td>Diarrhea</td>
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<td>11</td>
<td>6</td>
<td>5</td>
<td>6</td>
<td>8</td>
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<td>6</td>
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<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
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</tr>
<tr>
<td>Back Pain</td>
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<td>4</td>
<td>3</td>
<td>4</td>
<td>0</td>
<td>3</td>
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<tr>
<td><strong>Psychiatric Disorders</strong></td>
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</tr>
<tr>
<td>Insomnia</td>
<td>2</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>4</td>
<td>3</td>
<td>7</td>
<td>3</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restlessness</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td></td>
<td></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, hypnorsomnia, sedation, and somnolence

Dose-Related Adverse Reactions in the Monotherapy Study:

In the short-term, placebo-controlled study (involving lower and higher LATUDA dose range) [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

Adjuvant 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 adjuvant 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>Percentage of Patients Reporting Reaction</th>
<th>Body System or Organ Class</th>
<th>Placebo (N=334) (%)</th>
<th>LATUDA 20-60 mg/day (N=164) (%)</th>
<th>LATUDA 80-120 mg/day (N=167) (%)</th>
<th>All LATUDA (N=331) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</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, hypnorsomnia, sedation, and somnolence

<table>
<thead>
<tr>
<th>Percentage of Patients Reporting Reaction</th>
<th>Body System or Organ Class</th>
<th>Placebo (N=188) (%)</th>
<th>LATUDA 20-60 mg/day (N=184) (%)</th>
<th>LATUDA 80-120 mg/day (N=167) (%)</th>
<th>All LATUDA (N=331) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></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>
<td>14</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>4</td>
<td>6</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td>4</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, hypnorsomnia, sedation, and somnolence

In the short-term, placebo-controlled study (involving lower and higher LATUDA dose range) [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.
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</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=71)</td>
<td>20 mg/day</td>
</tr>
<tr>
<td>All EPS events</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>All EPS events, excluding Akathisia</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

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

Bipolar Disorder

Adjunctive Therapy with Lithium or Valproate

In the short-term, placebo-controlled adjunctive therapy bipolar depression studies, dystonia occurred in 0.9% of LATUDA-treated subjects (0.0% and 1.6% for LATUDA 20 to 60 mg/day and LATUDA 80 to 120 mg/day, respectively) compared to 0.6% of subjects receiving placebo. Seven subjects (0.5%, 7/1508) discontinued clinical trials due to dystonic events – four were receiving LATUDA 80 mg/day and three were receiving LATUDA 120 mg/day.

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 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 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 first degree, angina pectoris, bradycardia
Ear and Labyrinth Disorders: Infrequent: vertigo
Eye Disorders: Frequent: blurred vision
Gastrointestinal Disorders: Frequent: abdominal pain, diarrhea; Infrequent: gastritis
General Disorders and Administrative Site Conditions: Rare: sudden death
Investigations: Frequent: CPK increased
Metabolism and Nutritional System Disorders: Frequent: decreased appetite
Musculoskeletal and Connective Tissue Disorders: Rare: rhabdomyolysis
Nervous System Disorders: Infrequent: cerebrovascular accident, dysarthria
Psychiatric Disorders: Infrequent: abnormal dreams, panic attack, sleep disorder
Renal and Urinary Disorders: Infrequent: dysuria; Rare: renal failure
Reproductive System and Breast Disorders: Infrequent: amenorrhea, dysmenorrhea; Rare: breast enlargement, breast pain, galactorrhea, erectile dysfunction
Skin and Subcutaneous Tissue Disorders: Frequent: rash, pruritus; Rare: angioedema
Vascular Disorders: Frequent: hypertension
Clinical Laboratory Changes

Schizophrenia

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 versus placebo in 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, 5.6%).
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=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>2%</td>
<td>1%</td>
<td>2%</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 +0.03 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% (8/282) of LATUDA-treated patients and 0.6% (1/162) 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=314)</th>
<th>LATUDA 20 to 120 mg/day (N=360)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine Elevated</td>
<td>&lt;1%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Adjunctive Therapy with Lithium or Valproate

Serum Creatinine: In short-term, placebo-controlled monotherapy 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% (15/350) of LATUDA-treated patients and 3.5% (5/143) 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=360)</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.). If LATUDA is used concomitantly with a strong CYP3A4 inhibitor (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, etc.) or strong CYP3A4 inducer (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, etc.), the original level when used concomitantly with moderate inhibitors of CYP3A4 (e.g., diltiazem, verapamil, etc.) or strong CYP3A4 inducers (e.g., rifampin, avasimibe, St. John’s wort, phenytoin, carbamazepine, etc.) should be reduced to half of the original level when used concomitantly with moderate inhibitors of CYP3A4 (e.g., diltiazem, atazanavir, erythromycin, fluorconazole, verapamil, etc.). If LATUDA is used concomitantly with a moderate CYP3A4 inducer, it may be necessary to increase the LATUDA dose (see Dosage and Administration (2.5)).

Lithium: It is not necessary to adjust the LATUDA dose when used concomitantly with lithium (Figure 1).

Valproate: It is not necessary to adjust the LATUDA dose when used concomitantly with valproate. A dedicated drug-drug interaction study has not been conducted with valproate and LATUDA. Based on pharmacokinetic data from the bipolar depression studies valproate levels were not affected by lurasidone, and lurasidone concentrations were not affected by valproate.

Grapefruit: Grapefruit and grapefruit juice should be avoided in patients taking LATUDA, since these may inhibit CYP3A4 and alter LATUDA concentrations (see Dosage and Administration (2.5)).

Figure 1: Impact of Other Drugs on LATUDA Pharmacokinetics

Interacting drug PK | Cmax | AUC | Recommendation
--- | --- | --- | ---
Strong CYP3A4 Inhibitor | | | Should not be coadministered
Ketoconazole 400 mg/day | Cmax | | Should not be coadministered
AUC |
Moderate CYP3A4 Inhibitor | | | Should not be coadministered
Diltiazem 240 mg/day | Cmax | | Should not be coadministered
AUC |
Strong CYP3A4 Inducer | | | Should not be coadministered
Ritonavir 600 mg/day | Cmax | | Should not be coadministered
AUC |
Lithium 600 mg BID | Cmax | | Adjustment not required
AUC |

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 | Fold Change and 90% CI | Recommendation
--- | --- | ---
P-gp Substrates | | Adjusted not required
Diphenhydramine 0.25 mg SD | Cmax | | Adjusted not required
AUC |
CYP3A4 Substrates | | Adjusted not required
Midazolam 5 mg SD | Cmax | | Adjusted not required
AUC |
Oral Contraceptive | | Adjusted not required
Ethyl Estradiol | Cmax | | Adjusted not required
AUC |
Norethisterone | Cmax | | Adjusted not required
AUC |
Lithium 600mg BID | Cmax | | Adjusted not required
AUC |

* Steady state lithium trough on Day 4 vs Day 8 when lithium was coadministered with lurasidone at steady state

8 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, hyperonia, hypotonia, 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.

8.3 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>PK</th>
<th>Cmax</th>
<th>AUC</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal impairment</td>
<td>Mild</td>
<td>Cmax</td>
<td>Adjustment not required</td>
</tr>
<tr>
<td>Severe</td>
<td>Cmax</td>
<td>AUC</td>
<td>Starting dose = 20 mg</td>
</tr>
<tr>
<td>Moderate</td>
<td>Cmax</td>
<td>AUC</td>
<td>Maximum dose = 80 mg</td>
</tr>
<tr>
<td>Hepatic impairment</td>
<td>Mild</td>
<td>Cmax</td>
<td>Adjustment not required</td>
</tr>
<tr>
<td>Severe</td>
<td>Cmax</td>
<td>AUC</td>
<td>Starting dose = 20 mg</td>
</tr>
<tr>
<td>Moderate</td>
<td>Cmax</td>
<td>AUC</td>
<td>Maximum dose = 80 mg</td>
</tr>
<tr>
<td>Population description</td>
<td>Gender</td>
<td>Cmax</td>
<td>Adjustment not required</td>
</tr>
<tr>
<td>Race</td>
<td>Cmax</td>
<td>AUC</td>
<td>Starting dose = 20 mg</td>
</tr>
<tr>
<td>Asian*</td>
<td>Cmax</td>
<td>AUC</td>
<td>Maximum dose = 40 mg</td>
</tr>
</tbody>
</table>

*Compare to Caucasian

10 OVERDOSAGE

10.1 Human Experience

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

10.2 Management of Overdosage

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.

Manufactured for:
Sunovion Pharmaceuticals Inc.
Marlborough, MA 01752 USA

For Customer Service, call 1-888-394-7377.
For Medical Information, call 1-800-739-0565.
To report suspected adverse reactions, call 1-877-737-7226.

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