Major depressive episodes associated with bipolar I disorder (bipolar depression) present several important challenges in psychiatry practice. Patients with bipolar disorder are more likely to present with depressive symptoms,1 and over the long-term course of the disease they typically spend much more time with depression than mania.2 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.3 Although the risk of mania is reduced by adding a mood stabilizer,4 the randomized, double-blind, placebo-controlled Systematic Treatment Enhancement Program for Bipolar Disorder (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.5

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.

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Majordepressive episodes associated with bipolar I disorder (bipolar depression) present several important challenges in psychiatry practice. Patients with bipolar disorder are more likely to present with depressive symptoms,1 and over the long-term course of the disease they typically spend much more time with depression than mania.2 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.3 Although the risk of mania is reduced by adding a mood stabilizer,4 the randomized, double-blind, placebo-controlled Systematic Treatment Enhancement Program for Bipolar Disorder (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.5
PATIENT PROFILE: MEGHAN*

Meghan is a 35-year-old mother of 2 children who was diagnosed with major depressive episodes associated with bipolar I disorder (bipolar depression) approximately 3 months ago and is now returning to her psychiatrist for a follow-up visit 10 weeks after beginning treatment with a mood stabilizer.

According to her history, Meghan first sought treatment for depression from a primary care physician (PCP) 4 years ago, shortly after her wedding. At the time, Meghan reported feeling “really down” and “depressed” in college and recounted several episodes of insomnia, anxiety, and low energy. She told her PCP that her symptoms had abruptly worsened after her wedding and that she had trouble getting out of bed, had little appetite, and had lost a significant amount of weight. The PCP diagnosed Meghan with major depressive disorder 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 4 months ago, Meghan again sought treatment for depression from a different PCP. With her 2 children in school, Meghan had recently returned to work as a waitress. In addition to her depressed mood, she reported feeling irritable, overwhelmed on the job, and angry with her husband. Meghan's PCP prescribed a serotonin-norepinephrine reuptake inhibitor, and, based on recent changes in insurance coverage, Meghan was able to take the medication as prescribed. She experienced rapid improvement in her depressive symptoms within the first 3 or 4 days of treatment, but she also reported increasing anxiety, agitation, and sleep difficulty. At a follow-up visit 2 weeks after beginning treatment, Meghan exhibited a markedly increased rate of speech, and she talked in great detail about plans to quit her job and start her own investment company (for which she has no training or experience), and mentioned that she planned to remortgage her house for start-up funds. Meghan's PCP became concerned that Meghan might be experiencing a medication-induced manic episode. He asked Meghan to discontinue the antidepressant and referred her to a psychiatrist for additional evaluation and treatment.

At her first visit with the psychiatrist, Meghan was tearful and showed signs of psychomotor retardation. She complained of significant sleep difficulties and problems dealing with stresses of her marriage and her recent return to work. Meghan's psychiatrist administered the Mood Disorder Questionnaire (MDQ), a screening tool that can help identify individuals with a lifetime history of mania.1 Meghan's MDQ screening result was positive. Following a complete review of history and clinical assessment, Meghan's psychiatrist diagnosed her with bipolar I disorder. The psychiatrist started Meghan on monotherapy with the mood stabilizer valproate. Meghan's psychiatrist also conducted a baseline assessment of depressive symptoms using the Patient Health Questionnaire-9 (PHQ-9), a patient-rated scale that tracks the 9 DSM-5 symptoms of a major depressive episode.2,3 He further conducted periodic assessments with the PHQ-9 after treatment initiation to track Meghan's progress. Finally, the psychiatrist performed serum valproate assessments 2, 4, and 8 weeks after titration to ensure adequate dosing. The psychiatrist assesses Meghan 10 weeks after she initiated valproate and confirms that she is not currently manic. However, Meghan continues to experience residual depressive symptoms. Along with her current mood stabilizer, her psychiatrist decides to add adjunctive 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. The psychiatrist also works closely with Meghan's PCP to monitor her mood symptoms and potential adverse effects associated with her pharmacotherapy for bipolar depression.

* Hypothetical case representing a fictional patient.

**References**


Despite the limitations of antidepressant therapy in this patient population, patients with bipolar disorder are often treated using complex polypharmacy regimens that may include mood stabilizers, atypical antipsychotics, and antidepressants. In the STEP-BD study, more than 60% of patients with bipolar disorder were on medication regimens that included 2 or more agents, and 18% were using 4 or more medications.4

Patients who begin pharmacotherapy for bipolar depression require careful monitoring to evaluate control of mood symptoms. Considering the time constraints that are typical in clinical practice, patient-rated scales may be more practical than clinician-rated instruments.7 Alternatively, some clinicians may prefer to use the Clinical Global Impression of Severity (CGI-S) or Improvement (CGI-I), simple scales that quantify patient progress.8 Simply asking patients to identify the 2 or 3 symptoms that they find most troubling can provide an individualized assessment of treatment response. These symptoms can be documented, and frequency and severity may be assessed at each subsequent visit.9

Several studies have also examined the impact of collaborative treatment approaches in which patient care is managed by a multidisciplinary treatment team that may include psychiatrists, other mental health professionals, nurse coordinators, and primary care physicians.9,10 Collaborative care models have been shown to produce several beneficial outcomes in patients with bipolar disorder in comparison with usual care, including reduced time spent in mood episodes9 and a faster rate of decline in depressive symptoms over time.11 Collaborative care may also help better control chronic comorbid general medical conditions (eg, hypertension).10

**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. The results of this pivotal trial were published in the February 2014 issue of The American Journal of Psychiatry. 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 (eg, dinner) or within 30 minutes after eating.

**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. The MADRS is a 10-item, clinician-rated scale with total scores ranging from 0 to 60. At Week 6, LATUDA added to lithium or valproate was associated with statistically significantly greater reduction from baseline MADRS total score than was placebo added to lithium or valproate (-17.1 vs -13.5 points; P<.01). LATUDA was also associated with significantly greater reduction in the key secondary endpoint of Clinical Global Impression-Bipolar Version-Severity scale score. 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. 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. 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 in body weight of at least 70% was noted for 3.1% of patients who received LATUDA versus 0.3% of patients who received placebo. 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. 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.

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. Extrapyramidal symptoms, akathisia, and tardive dyskinesia were examined using the Simpson-Angus Scale, the Barnes Akathisia Scale (BAS), and the Barnes Akathisia Scale (BAS), and the Barnes Akathisia Scale (BAS), and the Barnes Akathisia Scale (BAS), and the Barnes Akathisia Scale (BAS), and the Barnes Akathisia Scale (BAS), and the Barnes Akathisia Scale (BAS), and the Barnes Akathisia Scale (BAS), and the Barnes Akathisia Scale (BAS), and the Barnes Akathisia Scale (BAS), and the Barnes Akathisia Scale (BAS).
AN EXPERT’S PERSPECTIVE

Case Commentary by Henry A. Nasrallah, MD

The case history of Meghan* illustrates several recurrent themes in some patients with bipolar depression, including: 1) the age of onset; 2) the delay in receiving treatment due to coverage-related issues; and 3) the diagnosis of unipolar depression based on presenting symptoms, leading to the prescribing of a monotherapy antidepressant (selective serotonin reuptake inhibitor); 4) the exquisite vulnerability of bipolar disorder to stress—even during a happy event—which can trigger symptoms; and 5) the prescribing of a serotonin-norepinephrine reuptake inhibitor antidepressant to a patient experiencing a mixed state of depression, anger, and irritability, which may contribute to a switch to mania, which is what happened to Meghan when she developed rapid speech, impulsivity (ie, quitting her job), and grandiosity (ie, planning to start an investment business for which she has no training or experience).

Fortunately, Meghan’s PCP recognized the serious switch to mania and referred her to a psychiatrist, who started her on a mood stabilizer (valproate). When Meghan’s depression persisted 10 weeks later, the psychiatrist prescribed LATUDA, an agent approved by the United States Food and Drug Administration for major depressive episodes associated with bipolar I disorder (bipolar depression), which in conjunction with her mood stabilizer may help to manage Meghan’s bipolar depression.

A theme that emerges in Meghan’s case is the importance of a collaborative relationship between the PCP and the psychiatrist. This is the optimal model for the care of all psychiatric patients.

*Hypothetical case representing a fictional patient.

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 associated with antipsychotic use in children aged 12 and under [see Warnings and Precautions (5.2)].
- In patients of all ages who are started on antidepressant therapy, monitor closely for worsening of symptoms and for emergence of suicidal thoughts and behavior. Advise families and caregivers of the need for close observation and communication with the prescriber [see Warnings and Precautions (5.2)].

INDICATIONS AND USAGE

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.

CONTRAINDICATIONS

- Known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone [see Adverse Reactions (6.1)].
- Strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, etc.).
- Strong CYP3A4 inducers (e.g., rifampin, avasimibe, St. John’s wort, phenytoin, carbamazepine, etc.) [see Drug Interactions (7.1)].

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 2.6% 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 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 placebo in children aged 6 and under; however, 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 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.

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></td>
<td>Increases Composed to Placebo</td>
</tr>
<tr>
<td>&lt;18</td>
<td>14 additional cases</td>
</tr>
<tr>
<td>18-24</td>
<td>5 additional cases</td>
</tr>
<tr>
<td>25-64</td>
<td>1 fewer case</td>
</tr>
<tr>
<td>≥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 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 emerging suicidal 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 symptoms (EPS) or other atypical neuroleptic symptoms. The diagnostic evaluation of NMS should include laboratory tests for: (a) electrolyte abnormalities; (b) evidence of central anticholinergic symptoms and signs (e.g., urinary retention, vaginitis); and (c) evidence of systemic infection.

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

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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 ketoadosis 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 association between 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 antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Schizophrenia

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 2.

Table 2: Change in Fasting Glucose in Schizophrenia Studies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Change from Baseline (mg/dL)</th>
<th>n=660</th>
<th>n=71</th>
<th>n=466</th>
<th>n=699</th>
<th>n=288</th>
<th>n=115</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Total Cholesterol</td>
<td>-5.8</td>
<td>-12.3</td>
<td>-5.7</td>
<td>-6.2</td>
<td>-3.8</td>
<td>-6.9</td>
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<tr>
<td></td>
<td>Triglycerides</td>
<td>-13.4</td>
<td>-26.1</td>
<td>-5.1</td>
<td>-13.0</td>
<td>-3.1</td>
<td>-10.6</td>
</tr>
<tr>
<td>LATUDA 20 to 60 mg/day</td>
<td>Total Cholesterol</td>
<td>5.3%</td>
<td>13.8%</td>
<td>6.2%</td>
<td>5.3%</td>
<td>3.8%</td>
<td>4.0%</td>
</tr>
<tr>
<td></td>
<td>Triglycerides</td>
<td>-10.1</td>
<td>-14.3</td>
<td>-10.8</td>
<td>-6.3</td>
<td>10.3%</td>
<td>7.0%</td>
</tr>
<tr>
<td>LATUDA 80 to 120 mg/day</td>
<td>Total Cholesterol</td>
<td>3.8%</td>
<td>10.1%</td>
<td>6.3%</td>
<td>4.3%</td>
<td>9.8%</td>
<td>12.1%</td>
</tr>
<tr>
<td></td>
<td>Triglycerides</td>
<td>4.6%</td>
<td>10.1%</td>
<td>6.3%</td>
<td>4.3%</td>
<td>9.8%</td>
<td>12.1%</td>
</tr>
</tbody>
</table>

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>Mean Change from Baseline (mg/dL)</th>
<th>n=302</th>
<th>n=319</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Serum Glucose</td>
<td>-0.7</td>
<td>+1.2</td>
</tr>
<tr>
<td>LATUDA 20 to 120 mg/day</td>
<td>Serum Glucose</td>
<td>1.0%</td>
<td>1.3%</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 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

Unacceptable 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>Treatment</th>
<th>Mean Change from Baseline (mg/dL)</th>
<th>n=660</th>
<th>n=71</th>
<th>n=466</th>
<th>n=699</th>
<th>n=288</th>
<th>n=115</th>
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<tr>
<td>Placebo</td>
<td>Total Cholesterol</td>
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<td>-4.6</td>
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<td></td>
<td>Triglycerides</td>
<td>+6.0</td>
<td>+5.6</td>
<td>+0.4</td>
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<td></td>
</tr>
<tr>
<td>LATUDA 20 to 60 mg/day</td>
<td>Total Cholesterol</td>
<td>-2.9</td>
<td>+1.2</td>
<td>-4.6</td>
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</tr>
<tr>
<td></td>
<td>Triglycerides</td>
<td>+6.0</td>
<td>+5.6</td>
<td>+0.4</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>LATUDA 80 to 120 mg/day</td>
<td>Total Cholesterol</td>
<td>-2.9</td>
<td>+1.2</td>
<td>-4.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Triglycerides</td>
<td>+6.0</td>
<td>+5.6</td>
<td>+0.4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 mg/dL and -15.1 mg/dL (n=577) mg/dL at week 24, -3.1 mg/dL and -4.8 mg/dL (n=303) mg/dL at week 36 and -2.5 mg/dL (n=307) mg/dL at week 52, respectively.

Bipolar Depression

Monotherapy

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

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Change from Baseline (mg/dL)</th>
<th>n=147</th>
<th>n=144</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Total Cholesterol</td>
<td>-2.9</td>
<td>+1.2</td>
</tr>
<tr>
<td></td>
<td>Triglycerides</td>
<td>-6.3</td>
<td>+0.4</td>
</tr>
<tr>
<td>LATUDA 20 to 60 mg/day</td>
<td>Total Cholesterol</td>
<td>-2.9</td>
<td>+1.2</td>
</tr>
<tr>
<td></td>
<td>Triglycerides</td>
<td>-6.3</td>
<td>+0.4</td>
</tr>
<tr>
<td>LATUDA 80 to 120 mg/day</td>
<td>Total Cholesterol</td>
<td>-2.9</td>
<td>+1.2</td>
</tr>
<tr>
<td></td>
<td>Triglycerides</td>
<td>-6.3</td>
<td>+0.4</td>
</tr>
</tbody>
</table>

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy in the short-term and continued in the longer-term study had a mean change in total cholesterol and triglycerides of -0.5 mg/dL and -1.0 mg/dL at week 24, respectively.

Adjunctive Therapy with Lithium or Valproate

Data from the short-term, flexible-dosed, placebo-controlled, adjunctive therapy bipolar depression study are presented in Table 7.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Change from Baseline (mg/dL)</th>
<th>n=303</th>
<th>n=321</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Total Cholesterol</td>
<td>-1.0</td>
<td>-3.1</td>
</tr>
<tr>
<td></td>
<td>Triglycerides</td>
<td>-1.0</td>
<td>-3.1</td>
</tr>
<tr>
<td>LATUDA 20 to 60 mg/day</td>
<td>Total Cholesterol</td>
<td>-1.0</td>
<td>-3.1</td>
</tr>
<tr>
<td></td>
<td>Triglycerides</td>
<td>-1.0</td>
<td>-3.1</td>
</tr>
<tr>
<td>LATUDA 80 to 120 mg/day</td>
<td>Total Cholesterol</td>
<td>-1.0</td>
<td>-3.1</td>
</tr>
<tr>
<td></td>
<td>Triglycerides</td>
<td>-1.0</td>
<td>-3.1</td>
</tr>
</tbody>
</table>
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 median mean weight was -0.43 kg for LATUDA-treated patients compared to -0.02 kg for placebo-treated patients. Change in weight from baseline for diazinane was +4.15 kg and for quetiapine extended-release was +2.09 kg in Studies 3 and 5 [see Clinical Studies (14.1)]; for quetiapine. The proportion of patients with a ≥ 7% increase in body weight (at Endpoint) was 4.8% for LATUDA-treated patients versus 3.6% for placebo-treated patients.

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

<table>
<thead>
<tr>
<th>Placebo (n=868)</th>
<th>20 mg/day (n=71)</th>
<th>40 mg/day (n=84)</th>
<th>60 mg/day (n=526)</th>
<th>80 mg/day (n=78)</th>
<th>120 mg/day (n=231)</th>
<th>160 mg/day (n=114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>-0.02</td>
<td>-0.15</td>
<td>+0.22</td>
<td>+0.54</td>
<td>+0.68</td>
<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>Placebo (n=151)</th>
<th>20 to 60 mg/day (n=143)</th>
<th>80 to 120 mg/day (n=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>-0.04</td>
<td>+0.56</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).

Adjuvant Therapy with Lithium or Valproate
Data from the short-term, flexible-dosed, placebo-controlled adjuvant 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 Adjuvant Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th>Placebo (n=307)</th>
<th>20 to 120 mg/day (n=327)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>+0.16</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 D_{2} 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 mg/dL 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>Placebo</th>
<th>20 mg/day</th>
<th>40 mg/day</th>
<th>LATUDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>-1.9 (n=672)</td>
<td>-1.1 (n=740)</td>
<td>-1.4 (n=476)</td>
</tr>
<tr>
<td>Females</td>
<td>-5.1 (n=203)</td>
<td>-0.7 (n=169)</td>
<td>-0.1 (n=148)</td>
</tr>
<tr>
<td>Males</td>
<td>-2.3 (n=472)</td>
<td>-0.1 (n=51)</td>
<td>+0.1 (n=327)</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 0.0% 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 ng/mL at week 36 (n=190) and -2.2 mg/mL at week 52 (n=307).

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

<table>
<thead>
<tr>
<th>Placebo</th>
<th>20 to 60 mg/day</th>
<th>80 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>+0.3 (n=67)</td>
<td>+0.1 (n=60)</td>
</tr>
<tr>
<td>Females</td>
<td>+0.0 (n=62)</td>
<td>+1.6 (n=79)</td>
</tr>
<tr>
<td>Males</td>
<td>+0.4 (n=60)</td>
<td>+1.2 (n=62)</td>
</tr>
</tbody>
</table>

The proportion of patients with prolactin elevations ≥ 5x upper limit of normal (ULN) was 0.6% for LATUDA-treated patients 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 median change in prolactin of -1.15 mg/mL at week 24 (n=130).

Adjuvant Therapy with Lithium or Valproate
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/mL with LATUDA 20 to 60 mg/day and 80 to 120 mg/day, respectively compared to +0.3 mg/mL with placebo-treated patients. The median change from baseline to endpoint for males was +1.5 mg/mL and for females was +3.1 mg/mL. Median changes for prolactin by dose range are shown in Table 12.

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

<table>
<thead>
<tr>
<th>Placebo</th>
<th>20 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>0.0 (n=301)</td>
</tr>
<tr>
<td>Females</td>
<td>+0.4 (n=156)</td>
</tr>
<tr>
<td>Males</td>
<td>-0.1 (n=145)</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.

The proportion of patients with prolactin elevations ≥ 5x upper limit of normal (ULN) was 0.0% for LATUDA-treated patients versus 0.0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥ 5x ULN was 0.6% for LATUDA-treated patients versus 0.0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥ 5x 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 with either lithium or valproate, in the short-term and continued in the longer-term study, had a median change in prolactin of -2.3 mg/mL at week 24 (n=88).

5.8 Leukopenia, Neutropenia and Agranulocytosis
Leukopenia/neutropenia has been reported during treatment with antipsychotic agents. Agranulocytosis (including fatal cases) has been reported with other agents in the class.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug-induced leukopenia/neutropenia should have their 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 in infection and treated promptly if such symptoms or signs or development of 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.

Orthonystic 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 [0.3% (5/1508), 0.1% (1/7080) and syncope [0.1% (2/1508), 0% (0/7080)]

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% (1/7080) 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 a thermal 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 (5.16)]
- 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)]
- Neuroleptic Prolactinemia [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

5.6 Adverse Reactions

In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, 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.
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>Percentage of Patients Reporting Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=708)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>5</td>
</tr>
<tr>
<td>Salivary Hypersalivation</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Musculoskeletal and Connective Tissue Disorders

| Back Pain                  | 2                         | 0                | 4                | 3                | 4                | 0                | 3            |

Nervous System Disorders

| Somnolence*                | 7                         | 15               | 16               | 15               | 26               | 8                | 17           |
| Akathisia                  | 3                         | 6                | 11               | 12               | 22               | 7                | 13           |
| Extrapyramidal Disorder** | 6                         | 6                | 11               | 12               | 22               | 13               | 14           |
| Dizziness                  | 2                         | 6                | 4                | 4                | 5                | 6                | 4            |

Psychiatric Disorders

| Insomnia                   | 6                         | 8                | 10               | 11               | 9                | 7                | 10           |
| Agitation                  | 4                         | 10               | 7                | 3                | 6                | 5                | 5            |
| Anxiety                    | 4                         | 3                | 6                | 4                | 7                | 3                | 5            |
| Restlessness               | 1                         | 1                | 3                | 1                | 3                | 2                | 2            |

Note: Figures rounded to the nearest integer

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

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

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 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, 12.3% for LATUDA 80 mg, and 22.0% for LATUDA 120 mg). 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 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, 12.3% for LATUDA 80 mg, and 22.0% for LATUDA 120 mg). 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, 12.3% for LATUDA 80 mg, and 22.0% for LATUDA 120 mg).

Bipolar Depression

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 Monotherapy

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 4.6% (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>Percentage of Patients Reporting Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=334)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
</tr>
<tr>
<td>General Disorders</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
</tr>
<tr>
<td>Weight Increased</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
</tr>
<tr>
<td>Increased Appetite</td>
<td>1</td>
</tr>
</tbody>
</table>

Nervous System Disorders

| Extrapyramidal Symptoms*   | 9                         | 14                           | 14                           |                     |
| Somnolence**               | 5                         | 11                           | 11                           |                     |
| Akathisia                  | 5                         | 11                           | 11                           |                     |
| Psychiatric Disorders      |                           |                             |                             |                     |
| Restlessness               | <1                        | 4                            | 4                            |                     |
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 (N=711)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All EPS events</td>
<td>10 20 21 23 39 20</td>
<td>13 22 14 12 22 13</td>
</tr>
<tr>
<td>All EPS events, excluding Akathisia/Restlessness</td>
<td>&lt;1 0 4 5 7 2</td>
<td></td>
</tr>
<tr>
<td>Akathisia</td>
<td>3 6 11 12 22 7</td>
<td></td>
</tr>
<tr>
<td>Dystonia</td>
<td>&lt;1 0 4 5 7 2</td>
<td></td>
</tr>
<tr>
<td>Parkinsonism**</td>
<td>5 6 9 8 17 11</td>
<td></td>
</tr>
<tr>
<td>Restlessness</td>
<td>1 4 3 1 3 2</td>
<td></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 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 EPS 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=164) (%)</th>
<th>LATUDA (N=167)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All EPS events</td>
<td>5 12 20</td>
<td></td>
</tr>
<tr>
<td>All EPS events, excluding Akathisia/Restlessness</td>
<td>2 5 9</td>
<td></td>
</tr>
<tr>
<td>Akathisia</td>
<td>2 8 11</td>
<td></td>
</tr>
<tr>
<td>Dystonia</td>
<td>0 0 0</td>
<td></td>
</tr>
<tr>
<td>Parkinsonism**</td>
<td>2 5 8</td>
<td></td>
</tr>
<tr>
<td>Restlessness</td>
<td>0 1 3</td>
<td></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

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 1.8% for LATUDA 20 to 60 mg/day and LATUDA 80 to 120 mg/day, respectively) compared to 0.8% of subjects receiving placebo. Seven subjects (0.5%, 7/1500) 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 1.6% for LATUDA 20 to 60 mg/day and LATUDA 80 to 120 mg/day, respectively) compared to 0.8% of subjects receiving placebo. No subject discontinued the clinical study due to dystonic events.

Adjunctive Therapy with Lithium or Valproate

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

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 the following order of decreasing frequency:

2. Cardiac Disorders: Infrequent: tachycardia, atrial fibrillation, tachycardia
3. Ear and Labyrinth Disorders: Infrequent: vertigo
4. Gastrointestinal Disorders: Infrequent: abdominal pain, diarrhea
5. General Disorders and Administrative Site Conditions: Rare: anemia
6. Genetic Disorders: Infrequent: diabetes mellitus
8. Hematopoietic and lymphoid disorders: Infrequent: anemia
9. Hypertension: Infrequent: hypertension
11. Obsessive-Compulsive Disorder: Infrequent: abnormal dreams, panic attack, sleep disorder
12. Renal and Urinary Disorders: Infrequent: renal failure
13. Reproductive and Breast Disorders: Infrequent: amenorrhea, dysmenorrhea
15. Skin and Subcutaneous Tissue Disorders: Frequent: rash, pruritus
16. Vascular Disorders: Frequent: hypertension

Clinical Laboratory Changes

Schizophrenia

The mean change from baseline for LATUDA-treated patients for the BAS, SAS 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%).

Adjunctive Therapy with Lithium or Valproate

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, 8.7%; placebo, 2.1%), the SAS (LATUDA, 2.8%; placebo, 2.1%) and the AIMS (LATUDA, 2.8%; placebo, 0.6%).

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 0.6% of subjects receiving placebo. Seven subjects (0.5%, 7/1500) discontinued clinical trials due to dystonic events – four were receiving LATUDA 80 mg/day and three were receiving LATUDA 120 mg/day.

Blood and Lymphatic System Disorders: Infrequent: anemia
Cardiac Disorders: Frequent: tachycardia, atrial fibrillation, tachycardia
Ear and Labyrinth Disorders: Infrequent: vertigo
Eye Disorders: Frequent: blurred vision
Gastrointestinal Disorders: Infrequent: 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: abnormal dreams, panic attack, sleep disorder
Renal and Urinary Disorders: Infrequent: dysuria, 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-

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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% (N=22) of LATUDA-treated patients and 0.6% (N=16) 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=194)</th>
<th>LATUDA 80 to 120 mg/day (N=567)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine Elevated</td>
<td>&lt;1%</td>
<td>2%</td>
<td>4%</td>
</tr>
</tbody>
</table>

**Adjunctive Therapy with Lithium or Valproate**

Serum Creatinine: In 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 CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, memantine, etc.) or moderate CYP3A4 inducers (e.g., rifampin, avasimibe, St. John’s wort, phenytoin, carbamazepine, etc.). LATUDA should be used with caution with strong CYP3A4 inducers (e.g., diltiazem, atazanavir, erythromycin, fluconazole, verapamil, etc.) (see Contraindications (4)). The LATUDA dose should be reduced to half of the original level when used concomitantly with moderate inhibitors of CYP3A4 (e.g., diltiazem, atazanavir, erythromycin, fluconazole, verapamil, etc.). If LATUDA is used concomitantly with a strong CYP3A4 inhibitor or inducer, it may be necessary to increase the LATUDA dose (see Dosing 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 Dosing and Administration (2.5)).

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

<table>
<thead>
<tr>
<th>Interacting drug</th>
<th>PK Parameter</th>
<th>Fold Change and 90% CI</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP3A4 Inhibitor</td>
<td>Cmax</td>
<td>Should not be coadministered</td>
<td></td>
</tr>
<tr>
<td>Ketoconazole 400 mg/day</td>
<td>AUC</td>
<td>Should not be coadministered</td>
<td></td>
</tr>
<tr>
<td>Moderate CYP3A4 Inhibitor</td>
<td>Cmax</td>
<td>Should not be coadministered</td>
<td></td>
</tr>
<tr>
<td>Diltiazem 240 mg/day</td>
<td>AUC</td>
<td>Should not be coadministered</td>
<td></td>
</tr>
<tr>
<td>Strong CYP3A4 Inducer</td>
<td>Cmax</td>
<td>Should not be coadministered</td>
<td></td>
</tr>
<tr>
<td>Ritonavir 600 mg/day</td>
<td>AUC</td>
<td>Should not be coadministered</td>
<td></td>
</tr>
<tr>
<td>Lithium 600 mg BID</td>
<td>AUC</td>
<td>Should not be coadministered</td>
<td></td>
</tr>
</tbody>
</table>

**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**

<table>
<thead>
<tr>
<th>Interacting drug</th>
<th>PK Parameter</th>
<th>Fold Change and 90% CI</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-gp Substrates</td>
<td>Cmax</td>
<td>Adjustment not required</td>
<td></td>
</tr>
<tr>
<td>Digoxin 0.25 mg SD</td>
<td>AUC</td>
<td>Adjustment not required</td>
<td></td>
</tr>
<tr>
<td>CYP3A4 Substrates</td>
<td>Cmax</td>
<td>Adjustment not required</td>
<td></td>
</tr>
<tr>
<td>Midazolam 5 mg SD</td>
<td>AUC</td>
<td>Adjustment not required</td>
<td></td>
</tr>
<tr>
<td>Oral Contraceptive</td>
<td>Cmax</td>
<td>Adjustment not required</td>
<td></td>
</tr>
<tr>
<td>Ethylx Extratol</td>
<td>AUC</td>
<td>Adjustment not required</td>
<td></td>
</tr>
<tr>
<td>Noradrenergic</td>
<td>Cmax</td>
<td>Adjustment not required</td>
<td></td>
</tr>
<tr>
<td>Lithium 600mg BID*</td>
<td>Cmax</td>
<td>Adjustment not required</td>
<td></td>
</tr>
</tbody>
</table>

* Steady state lithium serum 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, hyperpyrexia, 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>Patient Factor</th>
<th>PK Parameter</th>
<th>Change Relative to Reference</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal impairment</td>
<td>Cmax, AUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>Cmax, AUC</td>
<td>Adjusted not required</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Cmax, AUC</td>
<td>Starting dose = 20 mg</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>Cmax, AUC</td>
<td>Maximum dose = 80 mg</td>
<td></td>
</tr>
<tr>
<td>Hepatic impairment</td>
<td>Cmax, AUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>Cmax, AUC</td>
<td>Adjusted not required</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Cmax, AUC</td>
<td>Starting dose = 20 mg</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>Cmax, AUC</td>
<td>Maximum dose = 80 mg</td>
<td></td>
</tr>
<tr>
<td>Population description</td>
<td>Cmax, AUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Cmax, AUC</td>
<td>Adjusted not required</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>Cmax, AUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>Cmax, AUC</td>
<td>Adjusted not required</td>
<td></td>
</tr>
<tr>
<td>Asian*</td>
<td>Cmax, AUC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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.

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**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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