Managing Multiple Comorbidities in Bipolar Disorder

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

INDICATIONS
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 in adults.

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

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

IMPORTANT SAFETY INFORMATION AND INDICATIONS FOR LATUDA
Suicidal Thoughts and Behaviors
Antidepressants increased the risk of suicidal thoughts and behaviors in patients aged 24 years and younger compared to placebo. Monitor for clinical worsening and emergence of suicidal thoughts and behavior. LATUDA is not approved for use in pediatric patients with depression.

A multidisciplinary panel of Clinical Experts contributed to the development of this 3-part newsletter series. Each issue explores strategies for the management of patients with bipolar disorder and features expert commentary from the psychiatry, primary care, or nurse-practitioner/physician-assistant perspective.

The Cost of Bipolar Disorder
Bipolar disorder is a serious psychiatric illness associated with a considerable medical and economic burden. In the United States (US), the estimated lifetime prevalence of bipolar disorder is 2% to 4%, with about 1% of US adults having a lifetime history of bipolar I disorder. It has been estimated that in 2009, the direct and indirect costs associated with bipolar disorder amounted to at least $151 billion in the US. In addition, costs for patients with comorbid medical, mental health, and substance use disorders may be 2 to 3 times those for patients without these comorbid conditions, with most of the increased cost going to medical services rather than to behavioral health care.

Medical comorbidities occur often in bipolar disorder. One study reviewed medical charts of 309 patients with bipolar disorder and found that 55% of patients had at least 1 comorbid medical condition, the most common being endocrine/metabolic disorders (23%) and vascular disease (21%).

Watch a video about the impact of lifestyle factors on adherence and outcomes.
MANAGING MULTIPLE COMORBIDITIES IN BIPOLAR DISORDER

AN EXPERT’S PERSPECTIVE

Commentary by James Sloan Manning, MD

The high prevalence rate of comorbid general medical conditions (GMCs) among patients with bipolar disorder has been well documented and illustrates the importance of integrating behavioral health and primary care services. Using data from the National Epidemiologic Survey on Alcohol and Related Conditions, Perron and colleagues reported that a diagnosis of bipolar I disorder was a significant risk factor for GMCs such as those noted in this newsletter. These comorbid GMCs added to physical, mental, and psychosocial disability, as measured by the 12-Item Short-Form Health Survey, Version 2. In addition, a meta-analysis of 2634 studies with 106,785 patients revealed that the estimated prevalence of unexplained somatic symptoms in patients with bipolar spectrum disorders was 47.8%—nearly double the rate of those in the general population. These data suggest important challenges to population-based health care, and there is a movement toward creating collaborative care models to meet these challenges. A review by Bradford and colleagues assessed models that integrated behavioral health and primary care services and found positive effects on prevention and management of chronic disease for patients with serious mental illness. Although more large trials are needed to confirm the effectiveness of those care models, creating an integrated, community-supported, chronic illness–focused, team-based care delivery system may help clinicians identify and track chronically ill patients and improve preventive care.

Furthermore, patient education on metabolic issues and risk factors, as well as incorporation of lifestyle interventions, such as healthy cooking classes, nutrition counseling, and exercise, into individualized treatment plans may also help mitigate the risk of comorbid GMCs.

In my opinion, by assuming that relapse and chronicity are realities of illness and acknowledging the impact that bipolar disorder and comorbid GMCs have on patient motivation and volition, clinicians may be able to improve the management and overall health of patients.

James Sloan Manning, MD

References

MONITORING METABOLIC RISK IN BIPOLAR DISORDER

In light of the increased risk for medical comorbidities in people with bipolar disorder, several guidelines recommend regular monitoring of metabolic parameters, including weight, body mass index, waist circumference, blood pressure, glucose, and lipids in this patient population.

Guidelines have been developed and published by the following organizations:
- British Association for Psychopharmacology (2016)
- Royal Australian and New Zealand College of Psychiatrists (2015)
- Canadian Network for Mood and Anxiety Treatment and the International Society for Bipolar Disorders (2013)

Although the suggested interval for the measurement of each parameter varies, all of the guidelines emphasize the importance of cardiometabolic monitoring in patients with bipolar disorder. Overall, health care professionals should consider physical health in their clinical assessment and treatment planning based on an individual’s specific needs and circumstances.

MONITORING METABOLIC RISK IN BIPOLAR DISORDER

Cardiovascular risk is increased in patients with bipolar disorder, even among those who are treatment naïve. The onset of cardiovascular disease (CVD) in patients with bipolar disorder occurs approximately 10 years earlier and with a mortality rate about twice that of the general population. Even among those who do not have CVD at baseline, the risk of developing new-onset CVD is more than twice that of matched control subjects or patients with major depressive disorder.

On average, patients with bipolar disorder die about 9 to 10 years earlier than the general population. Although some of this excess mortality is attributable to an increased risk of suicide, it is known that comorbid CVD contributes to greater mortality in this patient population.

Monitoring and Managing Metabolic Risks

As with CVD, patients with bipolar disorder are at risk of weight and body mass index (BMI) increases even when they are not overweight at baseline. Therefore, these individuals should receive regular monitoring of these and other metabolic parameters with the goal of identifying these trends before reaching diagnosable comorbidities. In fact, many clinical practice guidelines emphasize the importance of closely monitoring metabolic measures in patients with bipolar disorder. However, evidence suggests that these patients often fail to receive such routine preventive care. In the Understanding Patients’ Needs, Interactions, Treatment, and Expectations Global Survey, preventive care practices received by patients with bipolar disorder and schizophrenia were assessed. Researchers discovered that only about 30% of patients received appropriate weight and blood pressure monitoring, while only 20% underwent regular physical examinations.

To help ensure that patients with bipolar disorder receive the appropriate monitoring, follow-up, and preventive care, a collaborative and holistic approach, which includes a focus on lifestyle modifications and patient education, may be effective.

Mortality and Comorbid CVD

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To help ensure that patients with bipolar disorder receive the appropriate monitoring, follow-up, and preventive care, a collaborative and holistic approach, which includes a focus on lifestyle modifications and patient education, may be effective.
LATUDA: A Treatment Option for Bipolar Depression

LATUDA is indicated for the treatment of major depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and as adjunctive therapy with lithium or valproate. The efficacy of LATUDA was established in a 6-week monotherapy study and a 6-week adjunctive therapy study with lithium or valproate in adult patients with bipolar depression. The effectiveness of LATUDA has not been established for longer-term use (more than 6 weeks) or for the treatment of mania associated with bipolar disorder.1

Each phase 3, multicenter, randomized, double-blind, placebo-controlled clinical trial enrolled adult patients with major depressive episodes associated with bipolar I disorder, with or without rapid cycling, and without psychotic features. All psychotropic medications were tapered off, and patients were randomly assigned to a treatment group. Patients in the monotherapy study were randomized to flexibly dosed LATUDA 20-120 mg/day plus lithium or valproate (N=165). LATUDA monotherapy achieved a 44% greater reduction in MADRS score at Week 6 versus placebo (Figure 1).2 The mean decrease in MADRS score between baseline and Week 6 was 15.4 points for patients randomized to LATUDA 20-60 mg/day or 80-120 mg/day versus 10.7 points for patients randomized to placebo (P<.001).2 The higher dose range (80-120 mg/day) did not provide additional efficacy, on average, compared to the lower dose range (20-60 mg/day).21

With LATUDA as adjunctive therapy with lithium or valproate, the mean decrease in the MADRS score between baseline and Week 6 was 17.1 points for patients randomized to adjunctive LATUDA 20-120 mg/day versus 13.5 points for patients randomized to placebo (P<.01) (Figure 1).23

Safety and Tolerability

Adverse reactions occurring in at least 2% of patients in either LATUDA monotherapy group and at a greater incidence than placebo during acute therapy were nausea, akathisia, somnolence, dry mouth, extrapyramidal symptoms (EPS), diarrhea, anxiety, nasopharyngitis, back pain, vomiting, urinary tract infection, and influenza. Overall, in the combined LATUDA treatment groups, 6.0% (20/331) of patients discontinued treatment due to adverse reactions compared with 5.4% (9/168) of patients in the placebo group.21

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

Patients from both the LATUDA and placebo groups of the 6-week monotherapy and adjunctive therapy trials were eligible to continue into a 6-month, uncontrolled, open-label, flexible-dose extension study.21 The adverse reactions in at least 5% of patients who continued on LATUDA monotherapy in the longer-term study were headache, nausea, nasopharyngitis, akathisia, insomnia, and anxiety. Of those who continued on LATUDA adjunctive therapy plus lithium or valproate in the longer-term study, at least 5% experienced parkinsonism, somnolence, and at least 2% of LATUDA-treated patients experienced parkinsonism, somnolence, and dystonia.

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Efficacy

Efficacy was measured by the change from baseline to Week 6 in the Montgomery-Åsberg Depression Rating Scale (MADRS) score, the 2 trials’ primary efficacy endpoint. LATUDA monotherapy achieved a 44% greater reduction in MADRS score at Week 6 versus placebo (Figure 1).2 The mean decrease in MADRS score between baseline and Week 6 was 15.4 points for patients randomized to LATUDA 20-60 mg/day or 80-120 mg/day versus 10.7 points for patients randomized to placebo (P<.001).2 The higher dose range (80-120 mg/day) did not provide additional efficacy, on average, compared to the lower dose range (20-60 mg/day).21

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akathisia, insomnia, anxiety, headache, and nausea. 23,24 Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular or cerebrovascular risk. 21 Changes in weight and laboratory parameters during both the LATUDA short-term and longer-term monotherapy and adjunctive therapy studies are presented in Figure 2. 21,24 Overall, the clinical trials demonstrated that at 6 weeks, metabolic changes were similar in the LATUDA and placebo groups, 21 and at 24 weeks, no clinically significant changes in body weight or clinically relevant evolutions or shifts from open-label baseline in lipid parameters and glucose were observed. 24 For prolactin, in the short-term monotherapy study, the median change in concentration was +1.7 ng/mL, +3.5 ng/mL, and +0.3 ng/mL for the low-dose LATUDA, high-dose LATUDA, and placebo groups, respectively, and -1.1 ng/mL for those who continued on LATUDA in the longer-term trial. In the short-term adjunctive therapy studies, the median change was -2.8 ng/mL in the LATUDA group and 0.0 ng/mL in the placebo group, and in the longer-term trial, it was -1.3 ng/mL in patients who continued on LATUDA. 21,24

Changes from baseline to endpoint in EPS, akathisia, and tardive dyskinesia were also evaluated in the LATUDA monotherapy and adjunctive therapy short-term and longer-term trials using the Simpson-Angus Scale (SAS), the Barnes Akathisia Scale (BAS), and the Abnormal Involuntary Movement Scale (AIMS), respectively. Categorical change was defined as a shift from normal at baseline to abnormal at study endpoint for the SAS, or as worsening from baseline to study endpoint for the BAS and AIMS. The mean change from baseline for LATUDA-treated patients was comparable to placebo on all 3 movement scales. 21,24

Abbreviations: Li, lithium; VPA, valproate.
*Last observation carried forward.
†Observed cases; patients who continued on LATUDA.
‡Safety population.
§Notes: Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended. Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia, including polydipsia, polyuria, polyphagia, and weakness.

FIGURE 2. LATUDA MONOTHERAPY AND ADJUNCTIVE THERAPY: WEIGHT AND LABORATORY PARAMETERS

S4

Please see Brief Summary of full Prescribing Information, including Boxed Warning, on page S5.
LATUDA is not approved for use in pediatric patients with depression. It is unknown whether the risk of suicidal thoughts and behaviors in pediatric and young adult patients extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with MDD that antidepressants delay the recurrence of depression. Monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the health care provider. Consider changing the therapeutic regimen, including possibly discontinuing LATUDA, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

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

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

Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including LATUDA. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrythymia). 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 illnesses (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 toxicity, heat stroke, drug fever, and primary central nervous system pathology.

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

If a patient requires antipsychotic drug treatment recovery 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.

Tardive Dyskinesia

Tardive dyskinesia is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

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

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 is (1) known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on LATUDA, drug discontinuation should be considered. However, some patients may require treatment with LATUDA despite the presence of the syndrome.
Metabolic Changes
Atypical 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 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 ketoadiabetes 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 be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

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

Table 2: Change in Fasting Glucose in Adult Schizophrenia Studies

<table>
<thead>
<tr>
<th>Serum Glucose</th>
<th>Placebo</th>
<th>LATUDA 20 mg/day</th>
<th>LATUDA 40 mg/day</th>
<th>LATUDA 80 mg/day</th>
<th>LATUDA 120 mg/day</th>
<th>LATUDA 160 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change from Baseline (mg/dL)</td>
<td>n=650</td>
<td>n=71</td>
<td>n=78</td>
<td>n=506</td>
<td>n=283</td>
<td>n=113</td>
</tr>
<tr>
<td>Serum Glucose</td>
<td>-0.0</td>
<td>-0.6</td>
<td>+2.6</td>
<td>+0.4</td>
<td>+2.5</td>
<td>+2.5</td>
</tr>
</tbody>
</table>

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in glucose of +1.6 mg/dL at week 24 (n=335), +0.8 mg/dL at week 36 (n=299) and +2.3 mg/dL at week 52 (n=307).

Adolescents
In studies of adolescents and adults with schizophrenia, changes in fasting glucose were similar. In the short-term, placebo-controlled study of adolescents, fasting serum glucose mean values were +1.3 for placebo (n=95), +0.1 for 40 mg (n=90), and +1.8 for 80 mg (n=32).

Bipolar Disorder
Monotherapy
Data from the adult short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study are presented in Table 3.

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

<table>
<thead>
<tr>
<th>Serum Glucose</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>Mean Change from Baseline (mg/dL)</td>
<td>n=148</td>
<td>n=140</td>
<td>n=143</td>
</tr>
<tr>
<td>Serum Glucose</td>
<td>+1.8</td>
<td>-0.8</td>
<td>+1.8</td>
</tr>
</tbody>
</table>

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy in the short-term study and continued in the longer-term study, had a mean change in glucose of +1.2 mg/dL at week 24 (n=129).

Adjunctive Therapy with Lithium or Valproate
Data from the adult short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies are presented in Table 4.

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

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

Patients were randomized to flexibly dose 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=88).

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

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

Table 5: Change in Fasting Lipids in Adult Schizophrenia Studies

<table>
<thead>
<tr>
<th>Serum Glucose</th>
<th>Placebo</th>
<th>LATUDA 20 mg/day</th>
<th>LATUDA 40 mg/day</th>
<th>LATUDA 80 mg/day</th>
<th>LATUDA 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change from Baseline (mg/dL)</td>
<td>n=660</td>
<td>n=71</td>
<td>n=466</td>
<td>n=499</td>
<td>n=268</td>
</tr>
<tr>
<td>Serum Glucose</td>
<td>-0.9</td>
<td>+1.2</td>
<td>+14.3%</td>
<td>+10.1%</td>
<td>+10.5%</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 (n=356) 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.

Adolescents
In the adolescent short-term, placebo-controlled study, fasting serum cholesterol mean values were -9.6 for placebo (n=95), -4.4 for 40 mg (n=89), and +1.6 for 80 mg (n=92), and fasting serum triglyceride mean values were +0.1 for placebo (n=95), -0.6 for 40 mg (n=89), and +8.5 for 80 mg (n=92).

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

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

<table>
<thead>
<tr>
<th>Serum Glucose</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>Mean Change from Baseline (mg/dL)</td>
<td>n=147</td>
<td>n=140</td>
<td>n=144</td>
</tr>
<tr>
<td>Serum Glucose</td>
<td>+1.8</td>
<td>-0.8</td>
<td>+1.8</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 (n=130) and -1.0 (n=130) mg/dL at week 24, respectively.

Supplement to Current Psychiatry

S6
Adjunctive Therapy with Lithium or Valproate

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

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

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>LATUDA 20 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change from Baseline (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>-0.4</td>
<td>-0.2</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-0.2</td>
<td>-0.4</td>
</tr>
</tbody>
</table>

### Proportion of Patients with Shifts

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>LATUDA 20 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>1.3%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.3%</td>
<td>2.6%</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, longer-term bipolar depression studies, 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 -0.3 (n=88) and +5.9 (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

Adults

Data from short-term, placebo-controlled schizophrenia studies are presented in Table 8. The mean weight gain was +0.43 kg for LATUDA-treated patients compared to -0.02 kg for placebo-treated patients. Change in weight from baseline for olanzapine was +4.15 kg and for quetiapine extended-release was +2.09 kg in Studies 3 and 5, respectively. The proportion of patients with a ≥7% increase in body weight (at Endpoint) was 4.8% for LATUDA-treated patients versus 3.3% for placebo-treated patients.

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

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>LATUDA 20 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change from Baseline (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>-0.2</td>
<td>-0.1</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-0.2</td>
<td>+0.2</td>
</tr>
</tbody>
</table>

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in weight of -0.69 kg at week 24 (n=755), -0.59 kg at week 36 (n=443) and -0.72 kg at week 52 (n=377).

### Adolescents

Data from the short-term, placebo-controlled adolescent schizophrenia study are presented in Table 9. The mean weight gain was +0.5 kg for LATUDA-treated patients compared to +0.2 kg for placebo-treated patients. The proportion of patients with a ≥7% increase in body weight (at Endpoint) was 3.3% for LATUDA-treated patients versus 4.5% for placebo-treated patients.

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

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>LATUDA 20 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change from Baseline (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>-0.2</td>
<td>-0.1</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-0.2</td>
<td>+0.2</td>
</tr>
</tbody>
</table>

In the uncontrolled, longer-term schizophrenia studies, 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).

### Hyperprolactinemia

As with other drugs that antagonize dopamine D2 receptors, LATUDA elevates prolactin levels. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin 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.

### Schizophrenia

Adults

In short-term, placebo-controlled schizophrenia studies, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was +0.4 ng/mL and for placebo-treated patients was -1.9 ng/mL in the placebo-treated patients. The median change from baseline to endpoint for males was +0.5 ng/mL and for females was -0.2 ng/mL. Median changes for prolactin by dose are shown in Table 12.

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

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>LATUDA 20 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change from Baseline (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>-0.4</td>
<td>-0.2</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-0.2</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 weight of -0.02 kg at week 24 (n=130).

Adjunctive Therapy with Lithium or Valproate

Data from the adult short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies are presented in Table 11. The mean 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 11: Mean Change in Weight (kg) from Baseline in the Adult Adjunctive Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>LATUDA 20 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change from Baseline (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>+0.1</td>
<td>+0.1</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>+0.2</td>
<td>+0.2</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, 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).

### Table 12: Median Change in Prolactin (ng/mL) from Baseline in Adult Schizophrenia Studies

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>LATUDA 20 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Change from Baseline (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>-1.9</td>
<td>-1.1</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-1.1</td>
<td>-1.4</td>
</tr>
</tbody>
</table>

The proportion of patients with prolactin elevations ≥5x ULN was 1.6% versus 0.6% for placebo-treated male patients. For LATUDA-treated patients, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was -2.2 ng/mL at week 24 (n=357), -5.3 ng/mL at week 36 (n=190) and -6.7 ng/mL at week 52 (n=36).

### Schizophrenia

Adults

In short-term, placebo-controlled schizophrenia studies, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was +0.4 ng/mL and for placebo-treated patients was -1.9 ng/mL in the placebo-treated patients. The median change from baseline to endpoint for males was +0.5 ng/mL and for females was -0.2 ng/mL. Median changes for prolactin by dose are shown in Table 12.

### Table 12: Median Change in Prolactin (ng/mL) from Baseline in Adult Schizophrenia Studies

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>LATUDA 20 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Change from Baseline (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>-1.9</td>
<td>-1.1</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-1.1</td>
<td>-1.4</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 levels of -0.9 ng/mL at week 24 (n=357), -3.5 ng/mL at week 36 (n=190) and -2.2 ng/mL at week 52 (n=36).

### Adolescents

In the short-term, placebo-controlled adolescent schizophrenia study, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was +1.1 ng/mL and was +0.1 ng/mL for placebo-treated patients. For LATUDA-treated patients, the median change from baseline to endpoint for males was +1.0 ng/mL and for females was +2.6 ng/mL. Median changes for prolactin by dose are shown in Table 13.
The proportion of patients with prolactin elevations ≥5x ULN was 0.5% for LATUDA-treated patients versus 0.0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥5x ULN was 0% versus 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations 5x ULN was 0.6% versus 0.0% for placebo-treated male patients.

### Bipolar Depression

**Monotherapy**

The median change from baseline to endpoint in prolactin levels, in the adult short-term, placebo-controlled bipolar depression studies, was +1.7 ng/mL with LATUDA 20 to 60 mg/day and 80 to 120 mg/day, respectively compared to +0.3 ng/mL with placebo-treated patients. The median change from baseline to endpoint for males was +1.5 ng/mL and for females was +3.1 ng/mL. Median changes for prolactin by dose range are shown in Table 14.

**Adjunctive 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 ng/mL with LATUDA 20 to 60 mg/day and 80 to 120 mg/day, respectively compared to +0.3 ng/mL with placebo-treated patients. The median change from baseline to endpoint for males was +1.5 ng/mL and for females was +3.1 ng/mL. Median changes for prolactin by dose range are shown in Table 14.

The proportion of patients with prolactin elevations ≥5x ULN was 0.5% for LATUDA-treated patients versus 0.0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥5x ULN was 0% versus 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥5x ULN was 0% versus 0% for placebo-treated male patients.

### Schizophrenia

**Adults**

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

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

**Adolescents**

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

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

**Bipolar Depression**

**Monotherapy**

In the adult short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, there were no reported adverse events of orthostatic hypotension and syncope. Orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 0.6% with LATUDA 20 to 60 mg and 0.0% with LATUDA 80 to 120 mg compared to 0% with placebo.

**Adjunctive Therapy with Lithium or Valproate**

In the adult short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression 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.

**Falls**

LATUDA may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

**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 adult 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.

---

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

<table>
<thead>
<tr>
<th>Placebo</th>
<th>LATUDA 40 mg/day</th>
<th>LATUDA 80 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>+0.10 (n=103)</td>
<td>+0.75 (n=102)</td>
</tr>
<tr>
<td>Females</td>
<td>+0.70 (n=39)</td>
<td>+0.60 (n=42)</td>
</tr>
<tr>
<td>Males</td>
<td>+0.09 (n=64)</td>
<td>+0.75 (n=67)</td>
</tr>
</tbody>
</table>

The median change from baseline to endpoint for males was +1.5 ng/mL and for females was +3.1 ng/mL. Median changes from baseline to endpoint for males was +2.4 ng/mL and for females was +3.2 ng/mL.

### Table 14: Median Change in Prolactin (ng/mL) from Baseline in the Adult Monotherapy Bipolar Depression Study

<table>
<thead>
<tr>
<th>Placebo</th>
<th>LATUDA 20 to 60 mg/day</th>
<th>LATUDA 80 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>+0.3 (n=147)</td>
<td>+1.7 (n=140)</td>
</tr>
<tr>
<td>Females</td>
<td>+0.8 (n=82)</td>
<td>+7.8 (n=78)</td>
</tr>
<tr>
<td>Males</td>
<td>+0.4 (n=65)</td>
<td>+1.2 (n=62)</td>
</tr>
</tbody>
</table>

Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day, or placebo. The proportion of patients with prolactin elevations ≥5x upper limit of normal (ULN) was 0.6% 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% versus 0% for placebo-treated male patients.

### Table 15: Median Change in Prolactin (ng/mL) from Baseline in the Adult Adjunctive Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th>Placebo</th>
<th>LATUDA 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 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% versus 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥5x ULN was 0% versus 0% for placebo-treated male patients.

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

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

Adjunctive Therapy with Lithium or Valproate
In the adult short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression studies, no patient experienced seizures/convulsions.

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

Adults

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

Adolescents

In the short-term, placebo-controlled adolescent schizophrenia study, somnolence was reported by 14.5% (31/214) of patients treated with LATUDA (15.5% LATUDA 40 mg and 13.5% LATUDA 80 mg/day) compared to 7.1% (9/112) of placebo patients.

Bipolar Depression

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

Adjunctive Therapy with Lithium or Valproate
In the adult short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies, somnolence was reported by 11.4% (41/360) of patients treated with LATUDA 20-120 mg compared to 5.1% (17/334) of placebo patients.

Body Temperature Dysregulation
Disruption of the body’s ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing LATUDA for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Activation of Mania/Hypomania
Antidepressant treatment can increase the risk of developing a manic or hypomanic episode, particularly in patients with bipolar disorder. Monitor patients for the emergence of such episodes.

In the bipolar depression monotherapy and adjunctive therapy (with lithium or valproate) studies, less than 1% of subjects in the LATUDA and placebo groups developed manic or hypomanic episodes.

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

Neurological Adverse Reactions in Patients with Parkinson’s Disease or Dementia with Lewy Bodies

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

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
• Suicidal Thoughts and Behaviors
• Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-related Psychosis
• Neuropsychiatric Malignant Syndrome
• Tardive Dyskinesia
• Metabolic Changes
• Hyperprolactinemia
• Leukopenia, Neutropenia, and Agranulocytosis
• Orthostatic Hypotension and Syncope
• Falls
• Seizures

• Potential for Cognitive and Motor Impairment
• Body Temperature Dysregulation
• Activation of Mania/Hypomania
• Dysphagia
• Neurological Adverse Reactions in Patients with Parkinson’s Disease or Dementia with Lewy Bodies

Clinical Trials Experience

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

Adults

The information below is derived from an integrated clinical study database for LATUDA consisting of 3799 adult patients exposed to one or more doses of LATUDA for the treatment of schizophrenia and bipolar depression in placebo-controlled studies. This experience corresponds with a total experience of 1250.9 patient-years. A total of 1106 LATUDA-treated patients had at least 24 weeks and 371 LATUDA-treated patients had at least 92 weeks of exposure. Adverse events during exposure to study treatment were obtained by general inquiry and voluntarily reported adverse experiences, as well as results from physical examinations, vital signs, ECGs, weights and laboratory investigations. Adverse experiences were recorded by clinical investigators using their own terminology. In order to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

Schizophrenia

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

Commonly Observed Adverse Reactions:

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

Adverse Reactions Associated with Discontinuation of Treatment:

A total of 9.3% (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 did not occur) included acute dystonia (up to 6 weeks in patients with schizophrenia) 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 Adult Short-term Schizophrenia Studies

<table>
<thead>
<tr>
<th>Percentage of Patients Reporting Reaction</th>
<th>Body</th>
<th>Placebo</th>
<th>LATUDA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>System</td>
<td>(N=708)</td>
<td>20 mg/day</td>
</tr>
<tr>
<td>Class</td>
<td>(%)</td>
<td>(N=71)</td>
<td>(N=487)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>nausea</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>5</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Salivary</td>
<td>secretion</td>
<td>&lt;1</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>Back Pain</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Somnolence</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Akathisia</td>
<td>6</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Extrapyramidal Disorder**</td>
<td>6</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Delirium</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Depression</td>
<td>4</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Restlessness</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer

S9

Supplement to Current Psychiatry
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 60 mg, and 22.0% for LATUDA 120 mg). Akathisia was reported by 7.4% (9/121) of patients receiving 160 mg/day. Akathisia occurred in 3.0% of subjects receiving placebo. The frequency of extrapyramidal symptoms increased with dose up to 120 mg/day (5.6% for LATUDA 20 mg, 11.5% for LATUDA 40 mg, 11.9% for LATUDA 80 mg, and 22.0% for LATUDA 120 mg).

Bipolar Depression (Monotherapy)

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

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

Adverse Reactions Associated with Discontinuation of Treatment: A total of 6.0% (20/331) LATUDA-treated patients and 5.4% (9/168) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients:

Table 17: Adverse Reactions in 2% or More of LATUDA-Treated Patients

<table>
<thead>
<tr>
<th>Body System or Organ Class</th>
<th>Adverse Reaction</th>
<th>Placebo (N=168) (%)</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>Nausea</td>
<td>8 10 17 14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dry Mouth</td>
<td>4 6 4 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>2 2 6 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>2 5 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td>Nasopharyngitis</td>
<td>1 4 4 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Influenza</td>
<td>1 &lt;1 2 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urinary Tract Infection</td>
<td>&lt;1 2 1 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td>Back Pain</td>
<td>&lt;1 3 1 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td>Extrapyramidal Symptoms*</td>
<td>2 5 9 7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Akathisia</td>
<td>2 8 11 9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Somnolence**</td>
<td>7 7 14 11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td>Anxiety</td>
<td>1 4 5 4</td>
<td></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, globalex reflex abnormal, hypokinesia, muscle rigidity, oculogyric crisis, oromandibular dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and trismus.
** Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence.

Dose-Related Adverse Reactions in the Monotherapy Study:

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

Bipolar Depression

Adjunctive Therapy with Lithium or Valproate

The following findings are based on two adult short-term, placebo-controlled premarketing studies for bipolar depression in which LATUDA was administered at daily doses ranging from 20 to 120 mg as adjunctive therapy with lithium or valproate (n=360).

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

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

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

Table 18: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in the Adult Short-term Adjunctive Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th>Body System or Organ Class</th>
<th>Adverse Reaction</th>
<th>Placebo (N=334) (%)</th>
<th>LATUDA 20-120 mg/day (N=360) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td>Nausea</td>
<td>10 14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>1 4</td>
<td></td>
</tr>
<tr>
<td><strong>General Disorders</strong></td>
<td>Fatigue</td>
<td>1 3</td>
<td></td>
</tr>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td>Nasopharyngitis</td>
<td>2 4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infections and Infestations</td>
<td>&lt;1 3</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td>Weight Increased</td>
<td>1 3</td>
<td></td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td>Extrapyramidal Symptoms*</td>
<td>9 14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Somnolence**</td>
<td>5 11</td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td>Akathisia</td>
<td>5 11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Restlessness</td>
<td>&lt;1 4</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, globalex reflex abnormal, hypokinesia, muscle rigidity, oculogyric crisis, oromandibular dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and trismus.
** Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence.

Adolescents

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

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) in adolescent patients (13 to 17 years) treated with LATUDA were somnolence, nausea, akathisia, extrapyramidal symptoms (non-akathisia, 40mg only), vomiting, and rhinorrhea/rhinitis (80 mg only).

Adverse Reactions Associated with Discontinuation of Treatment: The incidence of discontinuation due to adverse reactions between LATUDA- and placebo-treated adolescent patients (13 to 17 years) was 4% and 8%, respectively.

Adverse Reactions Occurring at an Incidence of 2% or More 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 adolescent patients with schizophrenia) are shown in Table 19.
### Extrapyramidal Symptoms

#### Schizophrenia

**Adults**

In the short-term, placebo-controlled schizophrenia studies, for LATUDA-treated patients, the incidence of reported events related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness, was 13.5% 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 20.

#### Adolescents

In the short-term, placebo-controlled study of schizophrenia in adolescents, the incidence of EPS, excluding events related to akathisia, for LATUDA-treated patients was higher in the 40 mg (10%) and the 80 mg (7.7%) treatment groups vs. placebo (3.6%); and the incidence of akathisia-related events for LATUDA-treated patients was 6.9% versus 2.4% for placebo-treated patients. Incidence of EPS by dose is provided in Table 21.

<table>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>Placebo (N=708) (%)</th>
<th>LATUDA 20 mg/day (N=71) (%)</th>
<th>LATUDA 40 mg/day (N=487) (%)</th>
<th>LATUDA 80 mg/day (N=538) (%)</th>
<th>LATUDA 120 mg/day (N=291) (%)</th>
<th>LATUDA 160 mg/day (N=121) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All EPS events</td>
<td>9</td>
<td>10</td>
<td>21</td>
<td>23</td>
<td>39</td>
<td>20</td>
</tr>
<tr>
<td>All EPS events, excluding Akathisia/ Restlessness</td>
<td>6</td>
<td>6</td>
<td>11</td>
<td>12</td>
<td>22</td>
<td>13</td>
</tr>
<tr>
<td>Akathisia</td>
<td>3</td>
<td>6</td>
<td>11</td>
<td>12</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td>Dystonia*</td>
<td>&lt;1</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Parkinsonism**</td>
<td>5</td>
<td>6</td>
<td>9</td>
<td>8</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Restlessness</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer

**Table 20: Incidence of EPS Compared to Placebo in Adult Schizophrenia Studies**

### Bipolar Depression

#### Monotherapy

In the adult short-term, placebo-controlled monotherapy bipolar depression study, for LATUDA-treated patients, the incidence of reported events related to EPS, excluding akathisia and restlessness was 6.9% versus 2.4% for placebo-treated patients. The incidence of akathisia for LATUDA-treated patients was 9.4% versus 2.4% for placebo-treated patients. Incidence of EPS by dose groups is provided in Table 22.

#### Adjunctive Therapy with Lithium or Valproate

In the adult short-term, placebo-controlled adjunctive therapy bipolar depression studies, for LATUDA-treated patients, the incidence of EPS, excluding akathisia and restlessness, was 13.9% versus 8.7% for placebo. The incidence of akathisia for LATUDA-treated patients was 10.8% versus 4.8% for placebo-treated patients. Incidence of EPS is provided in Table 23.

<table>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>Placebo (N=334) (%)</th>
<th>LATUDA 20 to 120 mg/day (N=360) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All EPS events</td>
<td>13</td>
<td>24</td>
</tr>
<tr>
<td>All EPS events, excluding Akathisia/ Restlessness</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Akathisia</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Dystonia*</td>
<td>&lt;1</td>
<td>1</td>
</tr>
<tr>
<td>Parkinsonism**</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Restlessness</td>
<td>&lt;1</td>
<td>4</td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer

**Table 23: Incidence of EPS Compared to Placebo in the Adult Adjunctive Therapy Bipolar Depression Studies**
Schizophrenia

Adults

The mean change from baseline for LATUDA-treated patients for the SAS, BAS, and AIMS was comparable to placebo-treated patients, with the exception of the Barnes Akathisia Scale global score (LATUDA, 0.1; placebo, 0.0). The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 6.0%; placebo, 0.5%; p < 0.0001), the SAS (LATUDA, 5.9%; placebo, 2.3%) and the AIMS (LATUDA, 7.4%; placebo, 3.8%).

Adolescents

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

Bipolar Depression

Monotherapy

The mean change from baseline for LATUDA-treated adult patients for the SAS, BAS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients 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 adult patients for the SAS, BAS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients 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

Adolescents

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

Bipolar Depression

Monotherapy

In the adult 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 0.0% of subjects receiving placebo. No subject discontinued the clinical study due to dystonic events.

Adjunctive Therapy with Lithium or Valproate

In the adult short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression studies, dystonia occurred in 1.1% of LATUDA-treated subjects (0.1% LATUDA 40 mg and 1% LATUDA 80 mg) compared to 0% of patients receiving placebo. No patients discontinued the clinical study due to dystonic events.

Other Adverse Reactions Observed During the Premarketing Evaluation of LATUDA

Following is a list of adverse reactions reported by adult patients treated with LATUDA at multiple doses of ≥20 mg once daily within the premarketing database of 2903 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 18 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 1/100 to 1/1000 patients (infrequent); and those occurring in fewer than 1/1000 patients (rare).

Blood and Lymphatic System Disorders: Infrequent: anemia

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

Ear and Labyrinth Disorders: Infrequent: vertigo

Eye Disorders: Frequent: blurred vision

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

General Disorders and Administrative Site Conditions: Rare: sudden death

Investigations: Frequent: CPK increased

Metabolism and Nutritional System Disorders: Frequent: decreased appetite

Musculoskeletal and Connective Tissue Disorders: Rare: rhabdomyolysis

Nervous System Disorders: Infrequent: cerebrovascular accident, dysarthria

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

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

Serum Creatinine

Serum Creatinine: In short-term, placebo-controlled trials, the mean change from Baseline in serum creatinine was +0.05 mg/dL for LATUDA-treated patients compared to +0.02 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 3.0% (43/1453) of LATUDA-treated patients and 1.6% (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 24).

Table 24: Serum Creatinine Shifts from Normal to High at Study End-Point in Adult Schizophrenia Studies

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Placebo</th>
<th>LATUDA 20 mg/day</th>
<th>LATUDA 40 mg/day</th>
<th>LATUDA 80 mg/day</th>
<th>LATUDA 120 mg/day</th>
<th>LATUDA 160 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine Elevated</td>
<td>2%</td>
<td>1%</td>
<td>2%</td>
<td>5%</td>
<td>7%</td>
<td></td>
</tr>
</tbody>
</table>

Adolescents

Serum Creatinine: In the short-term, placebo-controlled, adolescent schizophrenia study, the mean change from Baseline in serum creatinine was –0.009 mg/dL for LATUDA-treated patients compared to +0.017 mg/dL for placebo-treated patients. A creatinine shift from normal to high (based on the centralized laboratory definition) occurred in 7.2% (14/194) of LATUDA-treated patients and 2.9% (3/103) on placebo (Table 25).

Table 25: Serum Creatinine Shifts from Normal to High at Study End-Point in the Adolescent Schizophrenia Study

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Placebo</th>
<th>LATUDA 40 mg/day</th>
<th>LATUDA 80 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine Elevated</td>
<td>2.9%</td>
<td>7.2%</td>
<td>7.2%</td>
</tr>
</tbody>
</table>

Bipolar Depression

Monotherapy

Serum Creatinine: In the adult short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, the mean change from Baseline in serum creatinine was +0.01 mg/dL for LATUDA-treated patients compared to –0.02 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 2.8% (9/322) of LATUDA-treated patients and 0.6% (1/162) on placebo (Table 26).

Table 26: Serum Creatinine Shifts from Normal to High at Study End-Point in the Adult Monotherapy Bipolar Depression Study

<table>
<thead>
<tr>
<th>Laboratory Parameter</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>Serum Creatinine Elevated</td>
<td>&lt;1%</td>
<td>2%</td>
<td>4%</td>
</tr>
</tbody>
</table>
Adjunctive Therapy with Lithium or Valproate
Serum Creatinine: In adult short-term, placebo-controlled premarketing adjunctive studies for bipolar depression, the mean change from Baseline in serum creatinine was +0.04 mg/dL for LATUDA-treated patients compared to -0.01 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 4.3% (15/360) of LATUDA-treated patients and 1.6% (5/334) on placebo (Table 27).

Table 27: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in the Adult Adjunctive Therapy Bipolar Depression Studies

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

Postmarketing Experience
The following adverse reactions have been identified during postapproval use of Latuda. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Hypersensitivity Reactions: Urticaria, throat swelling, tongue swelling, or establish a causal relationship to drug exposure.

DRUG INTERACTIONS

Drugs Having Clinically Important Interactions with LATUDA

Table 26: Clinically Important Drug Interactions with Latuda

**Strong CYP3A4 Inhibitors**

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

**Moderate CYP3A4 Inhibitors**

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

**Strong CYP3A4 Inducers**

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

**Moderate CYP3A4 Inducers**

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

**Drugs Having No Clinically Important Interactions with LATUDA**

Drugs Having No Clinically Important Interactions with LATUDA

Based on pharmacokinetic studies, no dosage adjustment of LATUDA is required when administered concomitantly with lithium, valproate, or substrates of P-gp or CYP3A4.

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

*INTERACTING DRUGS*  |  PK  | Field Change and 95% C.I.
--- | --- | ---
Ketoconazole 600 mg/day | Cmax | AUC |
Ritonavir 240 mg/day | Cmax | AUC |
Lithium 600 mg SID | Cmax | AUC |

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to LATUDA during pregnancy. For more information, contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit [https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/](https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/)

**Risk Summary**

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There are no studies of LATUDA use in pregnant women. The limited available data are not sufficient to inform a drug-associated risk of birth defects or miscarriage. In animal reproduction studies, no teratogenic effects were seen in pregnant rats and rabbits given lurasidone during the period of organogenesis at doses approximately 1.5- and 6-times, the maximum recommended human dose (MRHD) of 160 mg/day, respectively, based on mg/m² body surface area.

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

**Clinical Considerations**

Fetal/Neonatal Adverse Reactions

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

**Data**

Animal Data

Pregnant rats were treated with oral lurasidone at doses of 3, 10, and 25 mg/kg/day during the period of organogenesis. These doses are 0.2, 0.6, and 1.5 times the MRHD of 160 mg/day based on mg/m² body surface area. No teratogenic or embryo-fetal effects were observed up to 1.5 times the MRHD of 160 mg/day, based on mg/m². Pregnant rabbits were treated with oral lurasidone at doses of 2, 10, and 50 mg/kg/day during the period of organogenesis. These doses are 0.5, 2.4, and 12 times the MRHD of 160 mg/day based on mg/m². No teratogenic or embryo-fetal effects were observed up to 8 times the MRHD of 160 mg/day based on mg/m².

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

**Lactation**

**Risk Summary**

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

Schizophrenia

The safety and effectiveness of LATUDA 40-mg/day and 80-mg/day for the treatment of schizophrenia in adolescents (13 to 17 years) was established in a 6-week, placebo-controlled clinical study in 326 adolescent patients.

Depression

The safety and effectiveness of LATUDA have not been established in pediatric patients with depression.

Irritability Associated with Autistic Disorder

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

Efficacy was not demonstrated in a 6-week study evaluating LATUDA 20 mg/day and 60 mg/day for the treatment of pediatric patients 6 to 17 years of age with irritability associated with autistic disorder diagnosed by Diagnostic and Statistical Manual of Mental Disorders, 4th Ed., Text Revision (DSM-IV-TR) criteria. The primary objective of the study as measured by improvement from Baseline in the irritability subscale of the Aberrant Behavior Checklist (ABC) at Endpoint (Week 6) was not met. A total of 149 patients were randomized to LATUDA or placebo. Vomiting occurred at a higher rate than reported in other LATUDA studies (4/49 or 8% for 20 mg, 14/51 or 27% for 60 mg, and 2/49 or 4% for placebo), particularly in children age 6 to 12 (13 out of 18 patients on LATUDA with vomiting).

Juvenile animal studies

Adverse effects were seen on growth, physical and neurobehavioral development at doses as low as 0.2 times the MRHD based on mg/m². Lurasidone was orally administered to rats from postnatal days 21 through 91 (this period corresponds to childhood, adolescence, and young adulthood in humans) at doses of 3, 30, and 150 (males) or 300 (females) mg/kg/day which are 0.2 to 10 times (males) and 20 times (females) the maximum recommended adult human dose (MRHD) of 160 mg/day based on mg/m². The adverse effects included dose-dependent decreases in femoral length, bone mineral content, body and brain weights at 2 times the MRHD in both sexes, and motor hyperactivity at 0.2 and 2 times the MRHD in both sexes based on mg/m². In females, there was a delay in attainment of sexual maturity at 2 times the MRHD, associated with decreased serum estradiol. Mortality occurred in both sexes during early post-weaning period and some of the male weanlings died after only 4 treatments at doses as low as 2 times the MRHD based on mg/m². Histopathological findings included increased colloid in the thyroids and inflammation of the prostate in males at 10 times MRHD based on mg/m² and mammary gland hyperplasia, increased vaginal mucification, and increased ovarian atretic follicles at doses as low as 0.2 times the MRHD based on mg/m². Some of these findings were attributed to transiently elevated serum prolactin which was seen in both sexes at all doses. However, there were no changes at any dose level in reproductive parameters (fertility, conception indices, spermatogenesis, estrous cycle, gestation length, parturition, number of pups born). The no effect dose for neurobehavioral changes in males is 0.2 times the MRHD based on mg/m² and could not be determined in females. The no effect dose for growth and physical development in both sexes is 0.2 times the MRHD based on mg/m².

Geriatric Use

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

Elderly patients with dementia-related psychosis treated with LATUDA are at an increased risk of death compared to placebo. LATUDA is not approved for the treatment of patients with dementia-related psychosis.

Renal Impairment

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

Hepatic Impairment

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

Other Specific Populations

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

Studies in Specific Populations

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

Pediatric Patients

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

Figure 3: Impact of Other Patient Factors on LATUDA Pharmacokinetics

<table>
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<tr>
<th>PK</th>
<th>Change Relative to Reference</th>
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<tbody>
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<tr>
<td>PK</td>
<td>Change Relative to Reference</td>
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</tbody>
</table>

*Compared to Caucasian

DRUG ABUSE AND DEPENDENCE

Controlled Substance

LATUDA is not a controlled substance.

Abuse

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

OVERDOSE

Human Experience

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

Management of Overdosage

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