

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LATUDA safely and effectively. See full prescribing information for LATUDA.

LATUDA (lurasidone hydrochloride) tablets, for oral use  
Initial U.S. Approval: 2010

### WARNINGS:

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

See full prescribing information for complete boxed warning.

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.
- LATUDA is not approved for the treatment of patients with dementia-related psychosis (5.1).
- Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants (5.2)
- Monitor for worsening and emergence of suicidal thoughts and behaviors (5.2)

### RECENT MAJOR CHANGES

|   |        |
|---|--------|
| Boxed Warnings, Suicidal Thoughts and Behaviors (5.2)                 | 6/2013 |
| Indications and Usage, Bipolar Depression (1.2)                       | 6/2013 |
| Dosage and Administration, Bipolar Depression (2.1)                   | 6/2013 |
| Dosage Forms and Strengths (3)  | 7/2013 |
| Warnings and Precautions (5.2, 5.6, 5.7, 5.9, 5.10, 5.11, 5.13, 5.14) | 6/2013 |

### INDICATIONS AND USAGE

LATUDA is an atypical antipsychotic for the treatment of:

- Schizophrenia (1.1, 14.1)
- Depressive episodes associated with Bipolar I Disorder (bipolar depression), as monotherapy and as adjunctive therapy with lithium or valproate (1.2, 14.2).

### DOSAGE AND ADMINISTRATION

LATUDA should be taken with food (at least 350 calories). Administration with food substantially increases the absorption of LATUDA (2.3, 12.3).

| Indication               | Starting Dose | Recommended Dose        |
|--------------------------|---------------|-------------------------|
| Schizophrenia (2.1)      | 40 mg per day | 40 mg to 160 mg per day |
| Bipolar Depression (2.2) | 20 mg per day | 20 mg to 120 mg per day |

- **Moderate and Severe Renal Impairment:** Recommended starting dose is 20 mg per day, and the maximum recommended dose is 80 mg per day (2.4, 8.6).
- **Moderate and Severe Hepatic Impairment:** Recommended starting dose is 20 mg per day. The maximum recommended dose is 80 mg per day in moderate hepatic impairment and 40 mg per day in severe hepatic impairment (2.4, 8.6).
- **Concomitant Use of a Moderate CYP3A4 inhibitor (e.g., diltiazem):** LATUDA dose should be reduced to half of the original dose level. Recommended starting dose is 20 mg per day. Maximum recommended dose is 80 mg per day (2.5, 7.1)
- **Concomitant Use of a Moderate CYP3A4 Inducer:** It may be necessary to increase the dose of LATUDA (2.5, 7.1)

### DOSAGE FORMS AND STRENGTHS

Tablets: 20 mg, 40 mg, 60 mg, 80 mg and 120 mg (3)

### CONTRAINDICATIONS

- Known hypersensitivity to LATUDA or any components in the formulation (4).
- Concomitant use with a strong CYP3A4 inhibitor (e.g., ketoconazole) (2.5, 4, 7.1).
- Concomitant use with a strong CYP3A4 inducer (e.g., rifampin) (2.5, 4, 7.1).

### WARNINGS AND PRECAUTIONS

- **Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis:** Increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) (5.2).
- **Neuroleptic Malignant Syndrome:** Manage with immediate discontinuation and close monitoring (5.4).
- **Tardive Dyskinesia:** Discontinue if clinically appropriate (5.5).
- **Metabolic Changes:** Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain (5.6).
  - **Hyperglycemia and Diabetes Mellitus:** Monitor patients for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes.
  - **Dyslipidemia:** Undesirable alterations have been observed in patients treated with atypical antipsychotics.
  - **Weight Gain:** Gain in body weight has been observed. Monitor weight.
- **Hyperprolactinemia:** Prolactin elevations may occur (5.7).
- **Leukopenia, Neutropenia, and Agranulocytosis:** Perform complete blood counts (CBC) in patients with a pre-existing low white blood cell count (WBC) or a history of leukopenia or neutropenia. Consider discontinuing LATUDA if a clinically significant decline in WBC occurs in the absence of other causative factors (5.8).
- **Orthostatic Hypotension and Syncope:** Dizziness, tachycardia or bradycardia, and syncope may occur, especially early in treatment. In patients with known cardiovascular or cerebrovascular disease, and in antipsychotic-naïve patients, consider a lower starting dose and slower titration (5.9).

### ADVERSE REACTIONS

Commonly observed adverse reactions (incidence  $\geq$  5% and at least twice the rate for placebo) were (6.1):

- Schizophrenia: somnolence, akathisia, extrapyramidal symptoms, and nausea
- Bipolar depression: akathisia, extrapyramidal symptoms, and somnolence

To report SUSPECTED ADVERSE REACTIONS, contact Sunovion Pharmaceuticals Inc. at 1-877-737-7226 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Use LATUDA during pregnancy only if the potential benefit justifies the potential risk (8.1).
- **Nursing Mothers:** Discontinue drug or nursing, considering risk of drug discontinuation to the mother (8.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 7/2013

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**FULL PRESCRIBING INFORMATION: CONTENTS\***

**WARNING:**

**INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

**1 INDICATIONS AND USAGE**

- 1.1 Schizophrenia
- 1.2 Depressive Episodes Associated with Bipolar I Disorder

**2 DOSAGE AND ADMINISTRATION**

- 2.1 Schizophrenia
- 2.2 Depressive Episodes Associated with Bipolar I Disorder
- 2.3 Administration Instructions
- 2.4 Dose Modifications in Special Populations
- 2.5 Dose Modifications Due to Drug Interactions

**3 DOSAGE FORMS AND STRENGTHS**

**4 CONTRAINDICATIONS**

**5 WARNINGS AND PRECAUTIONS**

- 5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis
- 5.2 Suicidal Thoughts and Behaviors in Adolescents and Young Adults
- 5.3 Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis
- 5.4 Neuroleptic Malignant Syndrome
- 5.5 Tardive Dyskinesia
- 5.6 Metabolic Changes
- 5.7 Hyperprolactinemia
- 5.8 Leukopenia, Neutropenia and Agranulocytosis
- 5.9 Orthostatic Hypotension and Syncope
- 5.10 Seizures
- 5.11 Potential for Cognitive and Motor Impairment
- 5.12 Body Temperature Dysregulation
- 5.13 Suicide
- 5.14 Activation of Mania/Hypomania
- 5.15 Dysphagia
- 5.16 Neurological Adverse Reactions in Patients with Parkinson's Disease or Dementia with Lewy Bodies

**6 ADVERSE REACTIONS**

- 6.1 Clinical Trials Experience

**7 DRUG INTERACTIONS**

- 7.1 Potential for Other Drugs to Affect LATUDA
- 7.2 Potential for LATUDA to Affect Other Drugs

**8 USE IN SPECIFIC POPULATIONS**

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Other Patient Factors

**9 DRUG ABUSE AND DEPENDENCE**

- 9.1 Controlled Substance
- 9.2 Abuse

**10 OVERDOSAGE**

- 10.1 Human Experience
- 10.2 Management of Overdosage

**11 DESCRIPTION**

**12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

**13 NONCLINICAL TOXICOLOGY**

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

**14 CLINICAL STUDIES**

- 14.1 Schizophrenia
- 14.2 Depressive Episodes Associated with Bipolar I Disorder

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**17 PATIENT COUNSELING INFORMATION**

- 17.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis
- 17.2 Suicidal Thoughts and Behaviors; and Activation of Mania or Hypomania
- 17.3 Neuroleptic Malignant Syndrome
- 17.4 Metabolic Changes (Hyperglycemia and Diabetes Mellitus, Dyslipidemia, and Weight Gain)
- 17.5 Orthostatic Hypotension
- 17.6 Leukopenia/Neutropenia
- 17.7 Interference with Cognitive and Motor Performance
- 17.8 Pregnancy and Nursing
- 17.9 Concomitant Medication and Alcohol
- 17.10 Heat Exposure and Dehydration

\*Sections or subsections omitted from the Full Prescribing Information are not listed.

## 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)*].
- Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older [see *Warnings and Precautions (5.2)*].
- In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber [see *Warnings and Precautions (5.2)*].

## 1 INDICATIONS AND USAGE

### 1.1 Schizophrenia

LATUDA is indicated for the treatment of patients with schizophrenia.

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

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

### 1.2 Depressive Episodes Associated with Bipolar I Disorder

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

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

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

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

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Schizophrenia

The recommended starting dose of LATUDA is 40 mg once daily. Initial dose titration is not required. LATUDA has been shown to be effective in a dose range of 40 mg per day to 160 mg per day [see *Clinical Studies (14.1)*]. The maximum recommended dose is 160 mg per day.

### 2.2 Depressive Episodes Associated with Bipolar I Disorder

The recommended starting dose of LATUDA is 20 mg given once daily as monotherapy or as adjunctive therapy with lithium or valproate. Initial dose titration is not required. LATUDA has been shown to be effective in a dose range of 20 mg per day to 120 mg per day as monotherapy or as adjunctive therapy with lithium or valproate [see *Clinical Studies (14.2)*]. The maximum recommended dose, as monotherapy or as adjunctive therapy with lithium or valproate, is 120 mg per day. In the monotherapy study, the higher dose range (80 mg to 120 mg per day) did not provide additional efficacy, on average, compared to the lower dose range (20 to 60 mg per day) [see *Clinical Studies (14.2)*].

### 2.3 Administration Instructions

LATUDA should be taken with food (at least 350 calories). Administration with food substantially increases the absorption of LATUDA. Administration with food increases the AUC approximately 2-fold and increases the C<sub>max</sub> approximately 3-fold. In the clinical studies, LATUDA was administered with food [see *Clinical Pharmacology (12.3)*].

### 2.4 Dose Modifications in Special Populations

#### Renal Impairment

Dose adjustment is recommended in moderate (creatinine clearance: 30 to <50 mL/min) and severe renal impairment (creatinine clearance <30 mL/min) patients. The recommended starting dose is 20 mg per day. The dose in these patients should not exceed 80 mg per day [see *Use in Specific Populations (8.6)*].

#### Hepatic Impairment

Dose adjustment is recommended in moderate (Child-Pugh Score = 7 to 9) and severe hepatic impairment (Child-Pugh Score = 10 to 15) patients. The recommended starting dose is 20 mg per day. The dose in moderate hepatic impairment patients should not exceed 80 mg per day and the dose in severe hepatic impairment patients should not exceed 40 mg/day [see *Use in Specific Populations (8.6)*].

### 2.5 Dose Modifications Due to Drug Interactions

#### Concomitant Use with CYP3A4 Inhibitors

LATUDA should not be used concomitantly with a strong CYP3A4 inhibitor (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, etc.) [see *Contraindications (4)*].

If LATUDA is being prescribed and a moderate CYP3A4 inhibitor (e.g. diltiazem, atazanavir, erythromycin, fluconazole, verapamil etc.) is added to the therapy, the LATUDA dose should be reduced to half of the original dose level. Similarly, if a moderate CYP3A4 inhibitor is being

prescribed and LATUDA is added to the therapy, the recommended starting dose of LATUDA is 20 mg per day, and the maximum recommended dose of LATUDA is 80 mg per day [see *Contraindications (4); Drug Interactions (7.1)*].

Grapefruit and grapefruit juice should be avoided in patients taking LATUDA, since these may inhibit CYP3A4 and alter LATUDA concentrations [see *Drug Interactions (7.1)*].

#### Concomitant Use with CYP3A4 Inducers

LATUDA should not be used concomitantly with a strong CYP3A4 inducer (e.g., rifampin, avasimibe, St. John's wort, phenytoin, carbamazepine, etc.) [see *Contraindications (4); Drug Interactions (7.1)*]. If LATUDA is used concomitantly with a moderate CYP3A4 inducer, it may be necessary to increase the LATUDA dose after chronic treatment (7 days or more) with the CYP3A4 inducer.

### 3 DOSAGE FORMS AND STRENGTHS

LATUDA tablets are available in the following shape and color (Table 1) with respective one-sided debossing:

**Table 1: LATUDA Tablet Presentations**

| Tablet Strength | Tablet Color/Shape        | Tablet Markings |
|-----------------|---------------------------|-----------------|
| 20 mg           | white to off-white round  | L20             |
| 40 mg           | white to off-white round  | L40             |
| 60 mg           | white to off white oblong | L60             |
| 80 mg           | pale green oval           | L80             |
| 120 mg          | white to off-white oval   | L120            |

### 4 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.) [see *Drug Interactions (7.1)*].
- Strong CYP3A4 inducers (e.g., rifampin, avasimibe, St. John's wort, phenytoin, carbamazepine, etc.) [see *Drug Interactions (7.1)*].

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks),

largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6- to 1.7-times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to 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 antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

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

Table 2

| Age Range | Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated |
|-----------|---|
|           | Increases Compared to Placebo   |
| <18       | 14 additional cases   |
| 18-24     | 5 additional cases  |
|           | Decreases Compared to Placebo   |
| 25-64     | 1 fewer case  |
| ≥65       | 6 fewer cases   |

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

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

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

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

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

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

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

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

### **5.4 Neuroleptic Malignant Syndrome**

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including LATUDA.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. It is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, 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 after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. If reintroduced, the patient should be carefully monitored, since recurrences of NMS have been reported.

### **5.5 Tardive Dyskinesia**

Tardive dyskinesia is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients 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 ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with 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*

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in [Table 3](#).

**Table 3: Change in Fasting Glucose in Schizophrenia Studies**

|  | LATUDA           |                 |                   |                  |                   |                 |
|--|------------------|-----------------|-------------------|------------------|-------------------|-----------------|
|  | Placebo          | 20 mg/day       | 40 mg/day         | 80 mg/day        | 120 mg/day        | 160 mg/day      |
| <b>Mean Change from Baseline (mg/dL)</b>                                 |                  |                 |                   |                  |                   |                 |
|  | <b>n=680</b>     | <b>n=71</b>     | <b>n=478</b>      | <b>n=508</b>     | <b>n=283</b>      | <b>n=113</b>    |
| Serum Glucose  | -0.0             | -0.6            | +2.6              | -0.4             | +2.5              | +2.5            |
| <b>Proportion of Patients with Shifts to <math>\geq 126</math> mg/dL</b> |                  |                 |                   |                  |                   |                 |
| Serum Glucose<br>( $\geq 126$ mg/dL)                                     | 8.3%<br>(52/628) | 11.7%<br>(7/60) | 12.7%<br>(57/449) | 6.8%<br>(32/472) | 10.0%<br>(26/260) | 5.6%<br>(6/108) |

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in glucose of +1.8 mg/dL at week 24 (n=355), +0.8 mg/dL at week 36 (n=299) and +2.3 mg/dL at week 52 (n=307).

#### *Bipolar Depression*

##### *Monotherapy*

Data from the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study are presented in [Table 4](#).

**Table 4: Change in Fasting Glucose in the Monotherapy Bipolar Depression Study**

|  | LATUDA          |                 |                  |
|--|-----------------|-----------------|------------------|
|  | Placebo         | 20 to 60 mg/day | 80 to 120 mg/day |
| <b>Mean Change from Baseline (mg/dL)</b>                                 |                 |                 |                  |
|  | <b>n=148</b>    | <b>n=140</b>    | <b>n=143</b>     |
| Serum Glucose  | +1.8            | -0.8            | +1.8             |
| <b>Proportion of Patients with Shifts to <math>\geq 126</math> mg/dL</b> |                 |                 |                  |
| Serum Glucose<br>( $\geq 126$ mg/dL)                                     | 4.3%<br>(6/141) | 2.2%<br>(3/138) | 6.4%<br>(9/141)  |

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 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 short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies are presented in [Table 5](#).

**Table 5: Change in Fasting Glucose in the Adjunctive Therapy Bipolar Depression Studies**

|  | LATUDA          |                  |
|--|-----------------|------------------|
|  | Placebo         | 20 to 120 mg/day |
| <b>Mean Change from Baseline (mg/dL)</b>                                 |                 |                  |
|  | <b>n=302</b>    | <b>n=319</b>     |
| Serum Glucose  | -0.9            | +1.2             |
| <b>Proportion of Patients with Shifts to <math>\geq 126</math> mg/dL</b> |                 |                  |
| Serum Glucose ( $\geq 126$ mg/dL)  | 1.0%<br>(3/290) | 1.3%<br>(4/316)  |

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=88).

#### Dyslipidemia

Undesirable 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 6](#).

**Table 6: Change in Fasting Lipids in Schizophrenia Studies**

|   | LATUDA            |                 |                   |                  |                   |                 |
|---|-------------------|-----------------|-------------------|------------------|-------------------|-----------------|
|   | Placebo           | 20 mg/day       | 40 mg/day         | 80 mg/day        | 120 mg/day        | 160 mg/day      |
| <b>Mean Change from Baseline (mg/dL)</b>  |                   |                 |                   |                  |                   |                 |
|   | <b>n=660</b>      | <b>n=71</b>     | <b>n=466</b>      | <b>n=499</b>     | <b>n=268</b>      | <b>n=115</b>    |
| Total Cholesterol                         | -5.8              | -12.3           | -5.7              | -6.2             | -3.8              | -6.9            |
| Triglycerides                             | -13.4             | -29.1           | -5.1              | -13.0            | -3.1              | -10.6           |
| <b>Proportion of Patients with Shifts</b> |                   |                 |                   |                  |                   |                 |
| Total Cholesterol ( $\geq 240$ mg/dL)     | 5.3%<br>(30/571)  | 13.8%<br>(8/58) | 6.2%<br>(25/402)  | 5.3%<br>(23/434) | 3.8%<br>(9/238)   | 4.0%<br>(4/101) |
| Triglycerides ( $\geq 200$ mg/dL)         | 10.1%<br>(53/526) | 14.3%<br>(7/49) | 10.8%<br>(41/379) | 6.3%<br>(25/400) | 10.5%<br>(22/209) | 7.0%<br>(7/100) |

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.

## Bipolar Depression

### Monotherapy

Data from the short-term, flexible-dosed, placebo-controlled, monotherapy bipolar depression study are presented in [Table 7](#).

**Table 7: Change in Fasting Lipids in the Monotherapy Bipolar Depression Study**

|   | LATUDA          |                   |                  |
|---|-----------------|-------------------|------------------|
|   | Placebo         | 20 to 60 mg/day   | 80 to 120 mg/day |
| <b>Mean Change from Baseline (mg/dL)</b>  |                 |                   |                  |
|   | <b>n=147</b>    | <b>n=140</b>      | <b>n=144</b>     |
| Total cholesterol                         | -3.2            | +1.2              | -4.6             |
| Triglycerides                             | +6.0            | +5.6              | +0.4             |
| <b>Proportion of Patients with Shifts</b> |                 |                   |                  |
| Total cholesterol<br>(≥ 240 mg/dL)        | 4.2%<br>(5/118) | 4.4%<br>(5/113)   | 4.4%<br>(5/114)  |
| Triglycerides<br>(≥ 200 mg/dL)            | 4.8%<br>(6/126) | 10.1%<br>(12/119) | 9.8%<br>(12/122) |

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 total cholesterol and triglycerides of -0.5 (n=130) and -1.0 (n=130) 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 studies are presented in [Table 8](#).

**Table 8: Change in Fasting Lipids in the Adjunctive Therapy Bipolar Depression Studies**

|   | LATUDA           |                  |
|---|------------------|------------------|
|   | Placebo          | 20 to 120 mg/day |
| <b>Mean Change from Baseline (mg/dL)</b>  |                  |                  |
|   | <b>n=303</b>     | <b>n=321</b>     |
| Total cholesterol                         | -2.9             | -3.1             |
| Triglycerides                             | -4.6             | +4.6             |
| <b>Proportion of Patients with Shifts</b> |                  |                  |
| Total cholesterol<br>(≥ 240 mg/dL)        | 5.7%<br>(15/263) | 5.4%<br>(15/276) |

|                                | Placebo                                  | LATUDA<br>20 to 120 mg/day |
|--------------------------------|--|----------------------------|
|                                | <b>Mean Change from Baseline (mg/dL)</b> |                            |
| Triglycerides<br>(≥ 200 mg/dL) | 8.6%<br>(21/243)                         | 10.8%<br>(28/260)          |

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

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA, as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study, had a mean change in total cholesterol and triglycerides of -0.9 (n=88) and +5.3 (n=88) mg/dL at week 24, respectively.

### Weight Gain

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

### Schizophrenia

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in [Table 9](#). 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 [see *Clinical Studies (14.1)*], respectively. The proportion of patients with a ≥ 7% increase in body weight (at Endpoint) was 4.8% for LATUDA-treated patients versus 3.3% for placebo-treated patients.

**Table 9: Mean Change in Weight (kg) from Baseline in Schizophrenia Studies**

|              | LATUDA             |                     |                      |                      |                       |                       |
|--------------|--------------------|---------------------|----------------------|----------------------|-----------------------|-----------------------|
|              | Placebo<br>(n=696) | 20 mg/day<br>(n=71) | 40 mg/day<br>(n=484) | 80 mg/day<br>(n=526) | 120 mg/day<br>(n=291) | 160 mg/day<br>(n=114) |
| All Patients | -0.02              | -0.15               | +0.22                | +0.54                | +0.68                 | +0.60                 |

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in weight of -0.69 kg at week 24 (n=755), -0.59 kg at week 36 (n=443) and -0.73 kg at week 52 (n=377).

### Bipolar Depression

#### Monotherapy

Data from the short-term, flexible-dosed, placebo-controlled monotherapy bipolar depression study are presented in [Table 10](#). 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 10: Mean Change in Weight (kg) from Baseline in the Monotherapy Bipolar Depression Study**

|              | LATUDA             |                            |                             |
|--------------|--------------------|----------------------------|-----------------------------|
|              | Placebo<br>(n=151) | 20 to 60 mg/day<br>(n=143) | 80 to 120 mg/day<br>(n=147) |
| All Patients | -0.04              | +0.56                      | +0.02                       |

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

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

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

Data from the short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies are presented in Table 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  $\geq 7\%$  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 Adjunctive Therapy Bipolar Depression Studies**

|              | LATUDA             |                             |
|--------------|--------------------|-----------------------------|
|              | Placebo<br>(n=307) | 20 to 120 mg/day<br>(n=327) |
| All Patients | +0.16              | +0.11                       |

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<sub>2</sub> receptors, LATUDA elevates prolactin levels.

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

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

between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

### *Schizophrenia*

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

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

|              | LATUDA          |                |                 |                 |                 |                 |
|--------------|-----------------|----------------|-----------------|-----------------|-----------------|-----------------|
|              | Placebo         | 20 mg/day      | 40 mg/day       | 80 mg/day       | 120 mg/day      | 160 mg/day      |
| All Patients | -1.9<br>(n=672) | -1.1<br>(n=70) | -1.4<br>(n=476) | -0.2<br>(n=495) | +3.3<br>(n=284) | +3.3<br>(n=115) |
| Females      | -5.1<br>(n=200) | -0.7<br>(n=19) | -4.0<br>(n=149) | -0.2<br>(n=150) | +6.7<br>(n=70)  | +7.1<br>(n=36)  |
| Males        | -1.3<br>(n=472) | -1.2<br>(n=51) | -0.7<br>(n=327) | -0.2<br>(n=345) | +3.1<br>(n=214) | +2.4<br>(n=79)  |

The proportion of patients with prolactin elevations  $\geq 5\times$  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  $\geq 5\times$  ULN was 5.7% for LATUDA-treated patients versus 2.0% for placebo-treated female patients. The proportion of male patients with prolactin elevations  $\geq 5\times$  ULN was 1.6% versus 0.6% for placebo-treated male patients.

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

### *Bipolar Depression*

#### *Monotherapy*

The median change from baseline to endpoint in prolactin levels, in the short-term, flexible-dosed, placebo-controlled monotherapy bipolar depression study, was +1.7 ng/mL and +3.5 ng/mL with LATUDA 20 to 60 mg/day and 80 to 120 mg/day, respectively compared to +0.3 ng/mL with placebo-treated patients. The median change from baseline to endpoint for males was +1.5 ng/mL and for females was +3.1 ng/mL. Median changes for prolactin by dose range are shown in [Table 13](#).

**Table 13: Median Change in Prolactin (ng/mL) from Baseline in the Monotherapy Bipolar Depression Study**

|              | LATUDA          |                 |                  |
|--------------|-----------------|-----------------|------------------|
|              | Placebo         | 20 to 60 mg/day | 80 to 120 mg/day |
| All Patients | +0.3<br>(n=147) | +1.7<br>(n=140) | +3.5<br>(n=144)  |
| Females      | 0.0<br>(n=82)   | +1.8<br>(n=78)  | +5.3<br>(n=88)   |
| Males        | +0.4<br>(n=65)  | +1.2<br>(n=62)  | +1.9<br>(n=56)   |

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  $\geq 5x$  upper limit of normal (ULN) was 0.4% for LATUDA-treated patients versus 0.0% for placebo-treated patients. The proportion of female patients with prolactin elevations  $\geq 5x$  ULN was 0.6% for LATUDA-treated patients versus 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations  $\geq 5x$  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 monotherapy in the short-term and continued in the longer-term study, had a median change in prolactin of -1.15 ng/mL at week 24 (n=130).

*Adjunctive Therapy with Lithium or Valproate*

The median change from baseline to endpoint in prolactin levels, in the short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies was +2.8 ng/mL with LATUDA 20 to 120 mg/day compared to 0.0 ng/mL with placebo-treated patients. The median change from baseline to endpoint for males was +2.4 ng/mL and for females was +3.2 ng/mL. Median changes for prolactin across the dose range are shown in [Table 14](#).

**Table 14: Median Change in Prolactin (ng/mL) from Baseline in the Adjunctive Therapy Bipolar Depression Studies**

|              | LATUDA          |                  |
|--------------|-----------------|------------------|
|              | Placebo         | 20 to 120 mg/day |
| All Patients | 0.0<br>(n=301)  | +2.8<br>(n=321)  |
| Females      | +0.4<br>(n=156) | +3.2<br>(n=162)  |
| Males        | -0.1<br>(n=145) | +2.4<br>(n=159)  |

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  $\geq 5x$  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  $\geq 5x$  ULN was 0% for LATUDA-treated patients versus 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations  $\geq 5x$  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).

## 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  $< 1000/\text{mm}^3$ ) should discontinue LATUDA and have their WBC followed until recovery.

## 5.9 Orthostatic Hypotension and Syncope

LATUDA may cause orthostatic hypotension and syncope, perhaps due to its  $\alpha 1$ -adrenergic receptor antagonism. Associated adverse reactions can include dizziness, lightheadedness, tachycardia, and bradycardia. Generally, these risks are greatest at the beginning of treatment and during dose escalation. Patients at increased risk of these adverse reactions or at increased risk of developing complications from hypotension include those with dehydration, hypovolemia, treatment with antihypertensive medication, history of cardiovascular disease (e.g., heart failure, myocardial infarction, ischemia, or conduction abnormalities), history of cerebrovascular disease, as well as patients who are antipsychotic-naïve. In such patients, consider using a lower starting dose and slower titration, and monitor orthostatic vital signs.

Orthostatic hypotension, as assessed by vital sign measurement, was defined by the following vital sign changes:  $\geq 20$  mm Hg decrease in systolic blood pressure and  $\geq 10$  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% (1/708)] and syncope [0.1% (2/1508), 0% (0/708)].

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

## *Bipolar Depression*

### *Monotherapy*

In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, there were no reported adverse events of orthostatic hypotension and syncope.

Orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 0.6% with LATUDA 20 to 60 mg and 0.6% with LATUDA 80 to 120 mg compared to 0% with placebo.

### *Adjunctive Therapy with Lithium or Valproate*

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

## **5.10 Seizures**

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

### *Schizophrenia*

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

## *Bipolar Depression*

### *Monotherapy*

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

### *Adjunctive Therapy with Lithium or Valproate*

In the short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression studies, no patient experienced seizures/convulsions.

## **5.11 Potential for Cognitive and Motor Impairment**

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

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

### *Schizophrenia*

In short-term, placebo-controlled schizophrenia studies, somnolence was reported by 17.0% (256/1508) of patients treated with LATUDA (15.5% LATUDA 20 mg, 15.6% LATUDA 40 mg, 15.2% LATUDA 80 mg, 26.5% LATUDA 120 mg and 8.3% 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% (41/360) of patients treated with LATUDA 20-120 mg compared to 5.1% (17/334) of placebo patients.

## **5.12 Body Temperature Dysregulation**

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing LATUDA for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration [*see Patient Counseling Information (17.9)*].

## **5.13 Suicide**

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

### *Schizophrenia*

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

### *Bipolar Depression*

#### *Monotherapy*

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

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

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

## **5.14 Activation of Mania/Hypomania**

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

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

### **5.15 Dysphagia**

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

### **5.16 Neurological Adverse Reactions in Patients with Parkinson's Disease or Dementia with Lewy Bodies**

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

## **6 ADVERSE REACTIONS**

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis [*see Boxed Warning and Warnings and Precautions (5.1)*]
- Suicidal Thoughts and Behaviors [*see Boxed Warning and Warnings and Precautions (5.2)*]
- Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-related Psychosis [*see Warnings and Precautions (5.23)*]
- Neuroleptic Malignant Syndrome [*see Warnings and Precautions (5.4)*]
- Tardive Dyskinesia [*see Warnings and Precautions (5.5)*]
- Metabolic Changes (Hyperglycemia and Diabetes Mellitus, Dyslipidemia, and Weight Gain) [*see Warnings and Precautions (5.6)*]
- Hyperprolactinemia [*see Warnings and Precautions (5.7)*]
- Leukopenia, Neutropenia, and Agranulocytosis [*see Warnings and Precautions (5.8)*]
- Orthostatic Hypotension and Syncope [*see Warnings and Precautions (5.9)*]
- Seizures [*see Warnings and Precautions (5.10)*]
- Potential for Cognitive and Motor Impairment [*see Warnings and Precautions (5.11)*]
- Body Temperature Dysregulation [*see Warnings and Precautions (5.12)*]
- Suicide [*see Warnings and Precautions (5.13)*]
- Activation of Mania/Hypomania [*see Warnings and Precautions (5.14)*]
- Dysphagia [*see Warnings and Precautions (5.15)*]
- 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 3799 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  $\geq$  5% and at least twice the rate of placebo) in patients treated with LATUDA were somnolence, akathisia, extrapyramidal symptoms, and nausea.

*Adverse Reactions Associated with Discontinuation of Treatment:* A total of 9.5% (143/1508) LATUDA-treated patients and 9.3% (66/708) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

*Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients:* Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in patients with schizophrenia) are shown in [Table 15](#).

**Table 15: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in Short-term Schizophrenia Studies**

| Body System or Organ Class                                     | Percentage of Patients Reporting Reaction |                               |                                |                                |                                 |                                 |    |
|--|---|-------------------------------|--------------------------------|--------------------------------|---------------------------------|---------------------------------|----|
|  | Placebo<br>(N=708)<br>(%)                 | LATUDA                        |                                |                                |                                 |                                 |    |
|  |   | 20<br>mg/day<br>(N=71)<br>(%) | 40<br>mg/day<br>(N=487)<br>(%) | 80<br>mg/day<br>(N=538)<br>(%) | 120<br>mg/day<br>(N=291)<br>(%) | 160<br>mg/day<br>(N=121)<br>(%) |    |
| <b>Gastrointestinal Disorders</b>                              |   |                               |                                |                                |                                 |                                 |    |
| Nausea   | 5   | 11                            | 10                             | 9                              | 13                              | 7                               | 10 |
| Vomiting   | 6   | 7                             | 6                              | 9                              | 9                               | 7                               | 8  |
| Dyspepsia  | 5   | 11                            | 6                              | 5                              | 8                               | 6                               | 6  |
| Salivary<br>Hypersecretion                                     | <1  | 1                             | 1                              | 2                              | 4                               | 2                               | 2  |
| <b>Musculoskeletal and<br/>Connective Tissue<br/>Disorders</b> |   |                               |                                |                                |                                 |                                 |    |
| Back Pain  | 2   | 0                             | 4                              | 3                              | 4                               | 0                               | 3  |
| <b>Nervous System<br/>Disorders</b>                            |   |                               |                                |                                |                                 |                                 |    |
| Somnolence*  | 7   | 15                            | 16                             | 15                             | 26                              | 8                               | 17 |
| Akathisia  | 3   | 6                             | 11                             | 12                             | 22                              | 7                               | 13 |
| Extrapyramidal<br>Disorder**                                   | 6   | 6                             | 11                             | 12                             | 22                              | 13                              | 14 |
| Dizziness  | 2   | 6                             | 4                              | 4                              | 5                               | 6                               | 4  |
| <b>Psychiatric Disorders</b>                                   |   |                               |                                |                                |                                 |                                 |    |
| Insomnia   | 8   | 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, 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 7.4% (9/121) of patients receiving 160 mg/day. Akathisia occurred in 3.0% of subjects receiving placebo. The frequency of extrapyramidal symptoms increased with dose up to 120 mg/day (5.6% for LATUDA 20 mg, 11.5% for LATUDA 40 mg, 11.9% for LATUDA 80 mg, and 22.0% for LATUDA 120 mg).

### ***Bipolar Depression (Monotherapy)***

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

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

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

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

| Body System or Organ Class<br>Dictionary-derived Term  | Percentage of Patients Reporting Reaction |   |  |                                 |
|--|---|---|--|---------------------------------|
|  | Placebo<br>(N=168)<br>(%)                 | LATUDA<br>20-60<br>mg/day<br>(N=164)<br>(%) | LATUDA<br>80-120<br>mg/day<br>(N=167)<br>(%) | All<br>LATUDA<br>(N=331)<br>(%) |
| <b>Gastrointestinal Disorders</b>                      |   |   |  |                                 |
| Nausea   | 8   | 10  | 17   | 14                              |
| Dry Mouth  | 4   | 6   | 4  | 5                               |
| Vomiting   | 2   | 2   | 6  | 4                               |
| Diarrhea   | 2   | 5   | 3  | 4                               |
| <b>Infections and Infestations</b>                     |   |   |  |                                 |
| Nasopharyngitis  | 1   | 4   | 4  | 4                               |
| Influenza  | 1   | <1  | 2  | 2                               |
| Urinary Tract Infection                                | <1  | 2   | 1  | 2                               |
| <b>Musculoskeletal and Connective Tissue Disorders</b> |   |   |  |                                 |
| Back Pain  | <1  | 3   | <1   | 2                               |
| <b>Nervous System Disorders</b>                        |   |   |  |                                 |
| Extrapyramidal Symptoms*                               | 2   | 5   | 9  | 7                               |
| Akathisia  | 2   | 8   | 11   | 9                               |
| Somnolence**   | 7   | 7   | 14   | 11                              |
| <b>Psychiatric Disorders</b>                           |   |   |  |                                 |
| Anxiety  | 1   | 4   | 5  | 4                               |

Note: Figures rounded to the nearest integer

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

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

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

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

***Bipolar Depression***

***Adjunctive Therapy with Lithium or Valproate***

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

*Commonly Observed Adverse Reactions:* The most common adverse reactions (incidence  $\geq$  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 17](#).

**Table 17: 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**

| Body System or Organ Class<br>Dictionary-derived Term | Percentage of Patients Reporting Reaction |  |
|---|---|--|
|   | Placebo<br>(N=334)<br>(%)                 | LATUDA<br>20 to 120 mg/day<br>(N=360)<br>(%) |
| <b>Gastrointestinal Disorders</b>                     |   |  |
| Nausea  | 10  | 14   |
| Vomiting  | 1   | 4  |
| <b>General Disorders</b>                              |   |  |
| Fatigue   | 1   | 3  |
| <b>Infections and Infestations</b>                    |   |  |
| Nasopharyngitis                                       | 2   | 4  |
| <b>Investigations</b>                                 |   |  |
| Weight Increased                                      | <1  | 3  |
| <b>Metabolism and Nutrition Disorders</b>             |   |  |
| Increased Appetite                                    | 1   | 3  |
| <b>Nervous System Disorders</b>                       |   |  |
| Extrapyramidal Symptoms*                              | 9   | 14   |
| Somnolence**  | 5   | 11   |
| Akathisia   | 5   | 11   |
| <b>Psychiatric Disorders</b>                          |   |  |
| Restlessness  | <1  | 4  |

Note: Figures rounded to the nearest integer

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

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

## Extrapyramidal Symptoms

### *Schizophrenia*

In the short-term, placebo-controlled schizophrenia studies, for LATUDA-treated patients, the incidence of reported events related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness, was 13.5% versus 5.8% for placebo-treated patients. The incidence of akathisia for LATUDA-treated patients was 12.9% versus 3.0% for placebo-treated patients. Incidence of EPS by dose is provided in [Table 18](#).

**Table 18: Incidence of EPS Compared to Placebo in Schizophrenia Studies**

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

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 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 19](#).

**Table 19: Incidence of EPS Compared to Placebo in the Monotherapy Bipolar Depression Study**

| Adverse Event Term                                     | LATUDA                    |                                   |                                    |
|--|---------------------------|-----------------------------------|------------------------------------|
|  | Placebo<br>(N=168)<br>(%) | 20 to 60 mg/day<br>(N=164)<br>(%) | 80 to 120 mg/day<br>(N=167)<br>(%) |
| All EPS events   | 5                         | 12                                | 20                                 |
| All EPS events,<br>excluding<br>Akathisia/Restlessness | 2                         | 5                                 | 9                                  |
| Akathisia  | 2                         | 8                                 | 11                                 |
| Dystonia*  | 0                         | 0                                 | 2                                  |
| Parkinsonism**   | 2                         | 5                                 | 8                                  |
| Restlessness   | <1                        | 0                                 | 3                                  |

Note: Figures rounded to the nearest integer

\* Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus

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

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

In the 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 20](#).

**Table 20: Incidence of EPS Compared to Placebo in the Adjunctive Therapy Bipolar Depression Studies**

| <b>Adverse Event Term</b>                                       | <b>Placebo<br/>(N=334)<br/>(%)</b> | <b>LATUDA<br/>20 to 120 mg/day<br/>(N=360)<br/>(%)</b> |
|---|------------------------------------|--|
| <b>All EPS events</b>   | <b>13</b>                          | <b>24</b>  |
| <b>All EPS events,<br/>excluding<br/>Akathisia/Restlessness</b> | <b>9</b>                           | <b>14</b>  |
| Akathisia   | 5                                  | 11   |
| Dystonia*   | <1                                 | 1  |
| Parkinsonism**  | 8                                  | 13   |
| Restlessness  | <1                                 | 4  |

Note: Figures rounded to the nearest integer

\* Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus

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

In the short-term, placebo-controlled schizophrenia and bipolar depression studies, data was objectively collected on the Simpson Angus Rating Scale (SAS) for extrapyramidal symptoms (EPS), the Barnes Akathisia Scale (BAS) for akathisia and the Abnormal Involuntary Movement Scale (AIMS) for dyskinesias.

#### *Schizophrenia*

The mean change from baseline for LATUDA-treated patients for the SAS, BAS and AIMS was comparable to placebo-treated patients, with the exception of the Barnes Akathisia Scale global score (LATUDA, 0.1; placebo, 0.0). The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 14.4%; placebo, 7.1%), the SAS (LATUDA, 5.0%; placebo, 2.3%) and the AIMS (LATUDA, 7.4%; placebo, 5.8%).

#### *Bipolar Depression*

##### *Monotherapy*

The mean change from baseline for LATUDA-treated patients for the SAS, BAS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 8.4%; placebo, 5.6%), the SAS (LATUDA, 3.7%; placebo, 1.9%) and the AIMS (LATUDA, 3.4%; placebo, 1.2%).

##### *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 0.8% of subjects receiving placebo. Seven subjects (0.5%, 7/1508) discontinued clinical trials due to dystonic events – four were receiving LATUDA 80 mg/day and three were receiving LATUDA 120 mg/day.

### *Bipolar Depression*

#### *Monotherapy*

In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, dystonia occurred in 0.9% of LATUDA-treated subjects (0.0% and 1.8% for LATUDA 20 to 60 mg/day and LATUDA 80 to 120 mg/day, respectively) compared to 0.0% of subjects receiving placebo. No subject discontinued the clinical study due to dystonic events.

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

In the 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  $\geq 20$  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 15](#) 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*

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

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

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

*Vascular Disorders: **Frequent:** hypertension*

### Clinical Laboratory Changes

#### Schizophrenia

*Serum Creatinine:* In short-term, placebo-controlled trials, the mean change from Baseline in serum creatinine was +0.05 mg/dL for LATUDA-treated patients compared to +0.02 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 3.0% (43/1453) of LATUDA-treated patients 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 21).

**Table 21: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in Schizophrenia Studies**

| Laboratory Parameter      | Placebo (N=708) | LATUDA 20 mg/day (N=71) | LATUDA 40 mg/day (N=487) | LATUDA 80 mg/day (N=538) | LATUDA 120 mg/day (N=291) | LATUDA 160 mg/day (N=121) |
|---------------------------|-----------------|-------------------------|--------------------------|--------------------------|---------------------------|---------------------------|
| Serum Creatinine Elevated | 2%              | 1%                      | 2%                       | 2%                       | 5%                        | 7%                        |

#### 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% (9/322) of LATUDA-treated patients and 0.6% (1/162) on placebo (Table 22).

**Table 22: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in a Monotherapy Bipolar Depression Study**

| Laboratory Parameter      | Placebo<br>(N=168) | LATUDA<br>20 to 60 mg/day<br>(N=164) | LATUDA<br>80 to 120 mg/day<br>(N=167) |
|---------------------------|--------------------|--------------------------------------|---------------------------------------|
| Serum Creatinine Elevated | <1%                | 2%                                   | 4%                                    |

#### *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 23).

**Table 23: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in the Adjunctive Therapy Bipolar Depression Studies**

| Laboratory Parameter      | Placebo<br>(N=334) | LATUDA<br>20 to 120 mg/day<br>(N=360) |
|---------------------------|--------------------|---------------------------------------|
| Serum Creatinine Elevated | 2%                 | 4%                                    |

## 7 DRUG INTERACTIONS

### 7.1 Potential for Other Drugs to Affect LATUDA

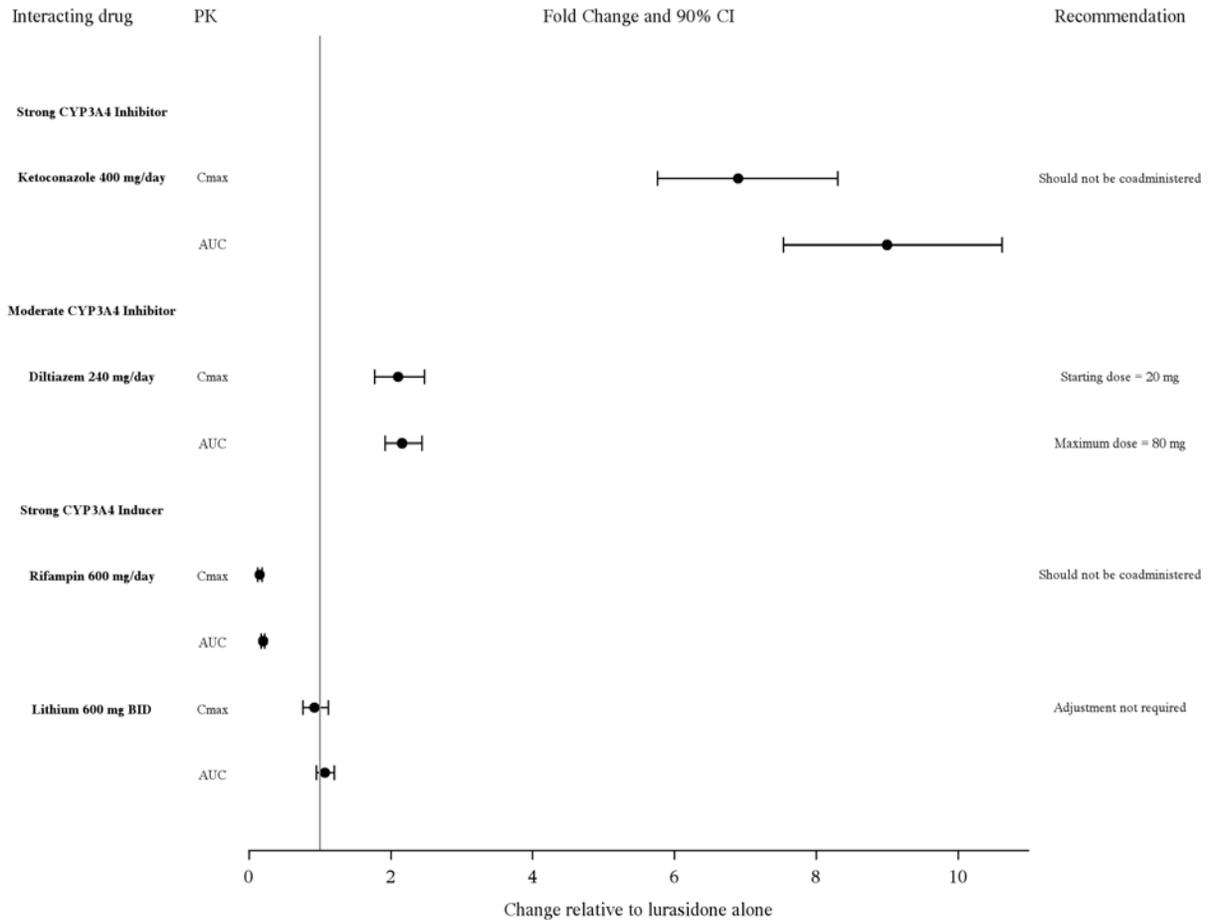
LATUDA is predominantly metabolized by CYP3A4. LATUDA should not be used concomitantly with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, etc.) or strong CYP3A4 inducers (e.g., rifampin, avasimibe, St. John's wort, phenytoin, carbamazepine, etc.) [see *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 moderate CYP3A4 inducer, it may be necessary to increase the LATUDA dose [see *Dosage and Administration* (2.5)].

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

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

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

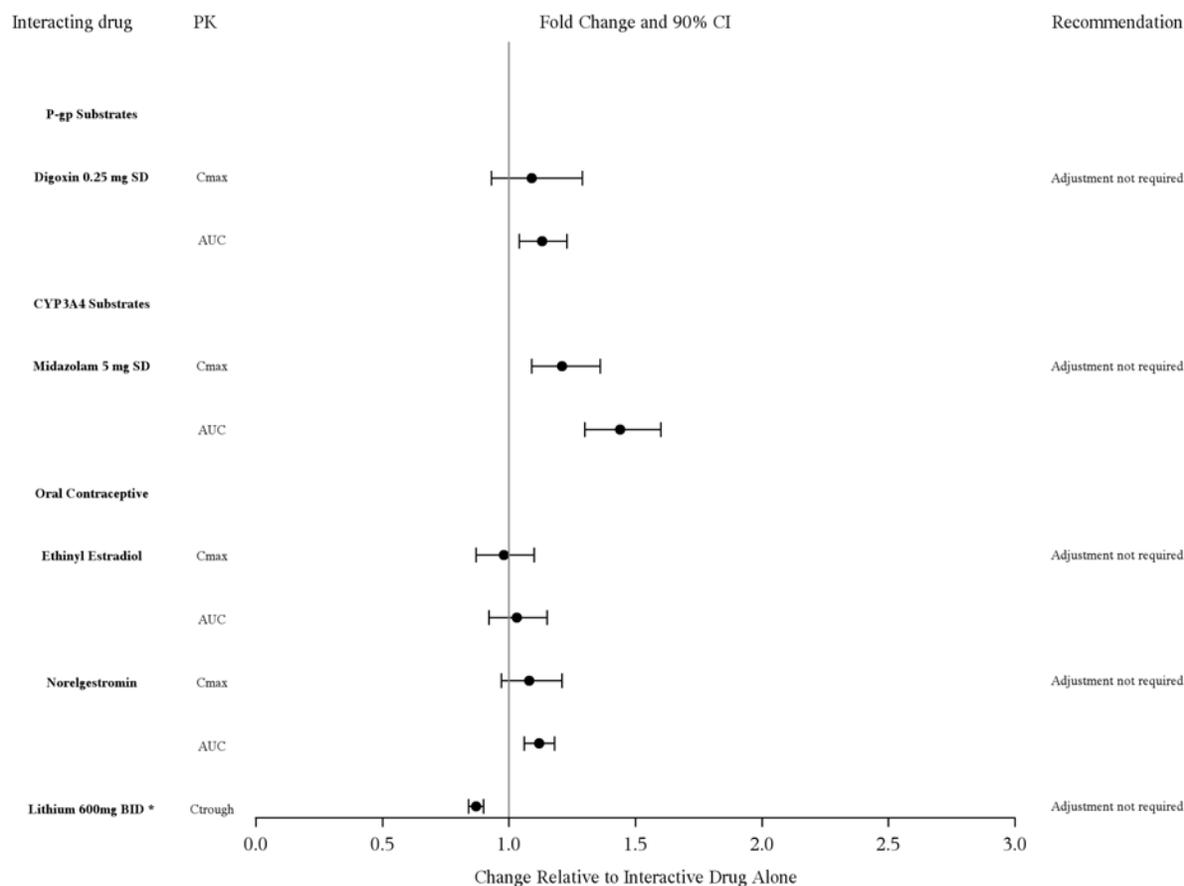
**Figure 1: Impact of Other Drugs on LATUDA Pharmacokinetics**



## 7.2 Potential for LATUDA to Affect Other Drugs

No dose 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**



\* Steady state lithium C<sub>trough</sub> 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, hypertonia, 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/m<sup>2</sup> 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/m<sup>2</sup> 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**

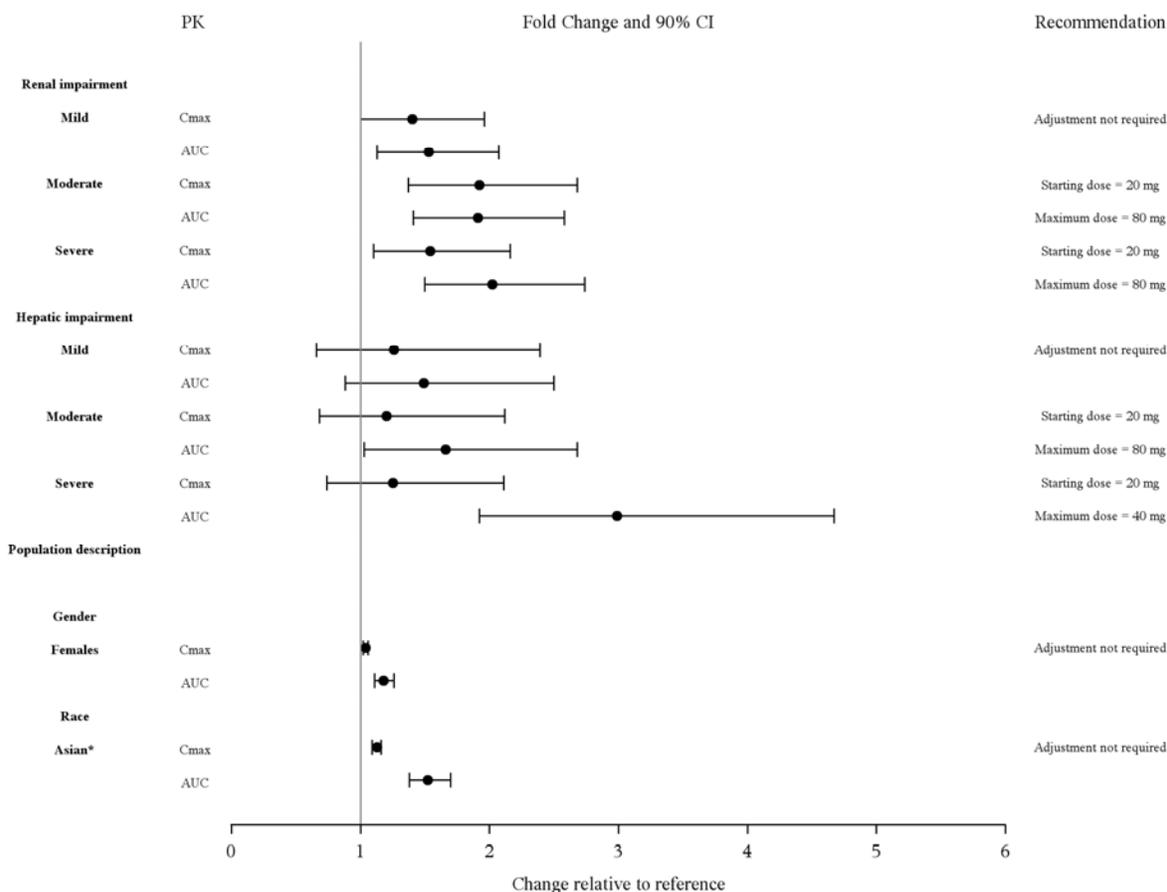
Clinical studies with LATUDA did not include sufficient numbers of patients aged 65 and older to determine whether or not they respond differently from younger patients. In elderly patients with psychosis (65 to 85), LATUDA concentrations (20 mg/day) were similar to those in young subjects. It is unknown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



\* Compare to Caucasian

## 9 DRUG ABUSE AND DEPENDENCE

### 9.1 Controlled Substance

LATUDA is not a controlled substance.

### 9.2 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).

## 10 OVERDOSAGE

### 10.1 Human Experience

In premarketing clinical studies, accidental or intentional overdose 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.

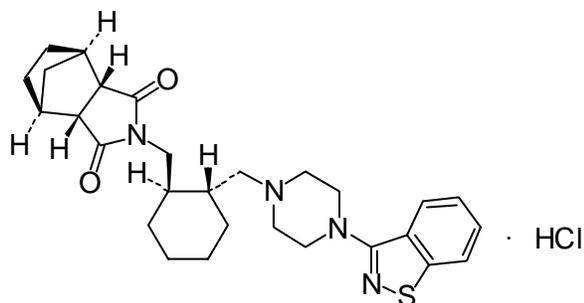
The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

## 11 DESCRIPTION

LATUDA is an atypical antipsychotic belonging to the chemical class of benzisothiazol derivatives.

Its chemical name is (3*aR*,4*S*,7*R*,7*aS*)-2-{(1*R*,2*R*)-2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-ylmethyl] cyclohexylmethyl}hexahydro-4,7-methano-2*H*-isindole-1,3-dione hydrochloride. Its molecular formula is C<sub>28</sub>H<sub>36</sub>N<sub>4</sub>O<sub>2</sub>S·HCl and its molecular weight is 529.14.

The chemical structure is:



Lurasidone hydrochloride is a white to off-white powder. It is very slightly soluble in water, practically insoluble or insoluble in 0.1 N HCl, slightly soluble in ethanol, sparingly soluble in methanol, practically insoluble or insoluble in toluene and very slightly soluble in acetone.

LATUDA tablets are intended for oral administration only. Each tablet contains 20 mg, 40 mg, 60 mg, 80 mg, or 120 mg of lurasidone hydrochloride.

Inactive ingredients are mannitol, pregelatinized starch, croscarmellose sodium, hypromellose, magnesium stearate, Opadry<sup>®</sup> and carnauba wax. Additionally, the 80 mg tablet contains yellow ferric oxide and FD&C Blue No. 2 Aluminum Lake.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The mechanism of action of LATUDA in the treatment of schizophrenia and bipolar depression is unknown. However, its efficacy in schizophrenia and bipolar depression could be mediated through a combination of central dopamine Type 2 (D<sub>2</sub>) and serotonin Type 2 (5HT<sub>2A</sub>) receptor antagonism.

### 12.2 Pharmacodynamics

LATUDA is an antagonist with high affinity binding at the dopamine D<sub>2</sub> receptors (K<sub>i</sub>=1 nM) and the 5-hydroxytryptamine (5-HT, serotonin) receptors 5-HT<sub>2A</sub> (K<sub>i</sub>=0.5 nM) and 5-HT<sub>7</sub> (K<sub>i</sub>=0.5 nM) receptors. It also binds with moderate affinity to the human  $\alpha_{2C}$  adrenergic receptors (K<sub>i</sub>=11 nM), is a partial agonist at serotonin 5-HT<sub>1A</sub> (K<sub>i</sub>=6.4 nM) receptors, and is an antagonist at the  $\alpha_{2A}$  adrenergic receptors (K<sub>i</sub>=41 nM). LATUDA exhibits little or no affinity for histamine H<sub>1</sub> and muscarinic M<sub>1</sub> receptors (IC<sub>50</sub> > 1,000 nM).

#### *ECG Changes*

The effects of LATUDA on the QTc interval were evaluated in a randomized, double-blind, multiple-dose, parallel-dedicated thorough QT study in 43 patients with schizophrenia or schizoaffective disorder, who were treated with LATUDA doses of 120 mg daily, 600 mg daily and completed the study. The maximum mean (upper 1-sided, 95% CI) increase in baseline-adjusted QTc intervals based on individual correction method (QTcI) was 7.5 (11.7) ms and 4.6 (9.5) ms, for the 120 mg and 600 mg dose groups respectively, observed at 2 to 4 hours after dosing. In this study, there was no apparent dose (exposure)-response relationship.

In short-term, placebo-controlled studies in schizophrenia and bipolar depression, no post-baseline QT prolongations exceeding 500 msec were reported in patients treated with LATUDA or placebo.

### 12.3 Pharmacokinetics

The activity of LATUDA is primarily due to the parent drug. The pharmacokinetics of LATUDA is dose-proportional within a total daily dose range of 20 mg to 160 mg. Steady-state concentrations of LATUDA are reached within 7 days of starting LATUDA.

Following administration of 40 mg of LATUDA, the mean (%CV) elimination half-life was 18 (7) hours.

*Absorption and Distribution:* LATUDA is absorbed and reaches peak serum concentrations in approximately 1-3 hours. It is estimated that 9-19% of an administered dose is absorbed.

Following administration of 40 mg of LATUDA, the mean (%CV) apparent volume of distribution was 6173 (17.2) L. LATUDA is highly bound (~99%) to serum proteins.

In a food effect study, LATUDA mean  $C_{max}$  and AUC were about 3-times and 2-times, respectively, when administered with food compared to the levels observed under fasting conditions. LATUDA exposure was not affected as meal size was increased from 350 to 1000 calories and was independent of meal fat content [see *Dosage and Administration (2.3)*].

In clinical studies, establishing the safety and efficacy of LATUDA, patients were instructed to take their daily dose with food [see *Dosage and Administration (2.3)*].

*Metabolism and Elimination:* LATUDA is metabolized mainly via CYP3A4. The major biotransformation pathways are oxidative *N*-dealkylation, hydroxylation of norbornane ring, and *S*-oxidation. LATUDA is metabolized into two active metabolites (ID-14283 and ID-14326) and two major non-active metabolites (ID-20219 and ID-20220). Based on *in vitro* studies, LATUDA is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP4A11, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 enzymes. Because LATUDA is not a substrate for CYP1A2, smoking is not expected to have an effect on the pharmacokinetics of LATUDA.

Total excretion of radioactivity in urine and feces combined was approximately 89%, with about 80% recovered in feces and 9% recovered in urine, after a single dose of [ $^{14}$ C]-labeled LATUDA.

Following administration of 40 mg of LATUDA, the mean (%CV) apparent clearance was 3902 (18.0) mL/min.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

*Carcinogenesis:* LATUDA increased incidences of malignant mammary gland tumors and pituitary gland adenomas in female mice orally dosed with 30, 100, 300, or 650 mg/kg/day. The lowest dose produced plasma levels (AUC) approximately equal to those in humans receiving the MRHD of 160 mg/day. No increases in tumors were seen in male mice up to the highest dose tested, which produced plasma levels (AUC) 14-times those in humans receiving the MRHD.

LATUDA increased the incidence of mammary gland carcinomas in female rats orally dosed at 12 and 36 mg/kg/day: the lowest dose; 3 mg/kg/day is the no-effect dose which produced plasma levels (AUC) 0.4-times those in humans receiving the MRHD. No increases in tumors were seen in male rats up to the highest dose tested, which produced plasma levels (AUC) 6-times those in humans receiving the MRHD.

Proliferative and/or neoplastic changes in the mammary and pituitary glands of rodents have been observed following chronic administration of antipsychotic drugs and are considered to be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated pituitary or mammary gland tumors in rodents to humans is unknown [see *Warnings and Precautions (5.7)*].

*Mutagenesis:* LATUDA did not cause mutation or chromosomal aberration when tested *in vitro* and *in vivo*. LATUDA was negative in the Ames gene mutation test, the Chinese Hamster Lung (CHL) cells, and in the *in vivo* mouse bone marrow micronucleus test up to 2000 mg/kg (61 times the MRHD of 160 mg/kg based on  $\text{mg}/\text{m}^2$  body surface area).

*Impairment of Fertility:* Estrus cycle irregularities were seen in rats orally administered LATUDA at 1.5, 15 and 150 mg/kg/day for 15 consecutive days prior to mating, during the

mating period, and through day 7 of gestation. The no-effect dose is 0.1 mg/kg which is approximately 0.006-times the MRHD of 160 mg/day based on body surface area. Fertility was reduced only at the highest dose, which was reversible after a 14-day drug-free period. The no-effect dose for reduced fertility was 15 mg/kg, which is approximately equal to the MRHD based on body surface area.

LATUDA had no effect on fertility in male rats treated orally with LATUDA for 64 consecutive days prior to mating and during the mating period at doses up to 150 mg/kg/day (9-times the MRHD based on mg/m<sup>2</sup> body surface area).

## **14 CLINICAL STUDIES**

### **14.1 Schizophrenia**

The efficacy of LATUDA for the treatment of schizophrenia was established in five short-term (6-week), placebo-controlled studies in adult patients (mean age of 38.4 years, range 18-72) who met DSM-IV criteria for schizophrenia. An active-control arm (olanzapine or quetiapine extended-release) was included in two studies to assess assay sensitivity.

Several instruments were used for assessing psychiatric signs and symptoms in these studies:

1. Positive and Negative Syndrome Scale (PANSS), is a multi-item inventory of general psychopathology used to evaluate the effects of drug treatment in schizophrenia. PANSS total scores may range from 30 to 210.
2. Brief Psychiatric Rating Scale derived (BPRSd), derived from the PANSS, is a multi-item inventory primarily focusing on positive symptoms of schizophrenia, whereas the PANSS includes a wider range of positive, negative and other symptoms of schizophrenia. The BPRSd consists of 18 items rated on a scale of 1 (not present) to 7 (severe). BPRSd scores may range from 18 to 126.
3. The Clinical Global Impression severity scale (CGI-S) is a clinician-rated scale that measures the subject's current illness state on a 1- to 7-point scale.

The endpoint associated with each instrument is change from baseline in the total score to the end of week 6. These changes are then compared to placebo changes for the drug and control groups.

The results of the studies follow:

1. Study 1: In a 6-week, placebo-controlled trial (N=145) involving two fixed doses of LATUDA (40 or 120 mg/day), both doses of LATUDA at Endpoint were superior to placebo on the BPRSd total score, and the CGI-S.
2. Study 2: In a 6-week, placebo-controlled trial (N=180) involving a fixed dose of LATUDA (80 mg/day), LATUDA at Endpoint was superior to placebo on the BPRSd total score, and the CGI-S.
3. Study 3: In a 6-week, placebo- and active-controlled trial (N=473) involving two fixed doses of LATUDA (40 or 120 mg/day) and an active control (olanzapine), both LATUDA doses and the active control at Endpoint were superior to placebo on the PANSS total score, and the CGI-S.

4. Study 4: In a 6-week, placebo-controlled trial (N=489) involving three fixed doses of LATUDA (40, 80 or 120 mg/day), only the 80 mg/day dose of LATUDA at Endpoint was superior to placebo on the PANSS total score, and the CGI-S.
5. Study 5: In a 6-week, placebo- and active-controlled trial (N=482) involving two fixed doses of LATUDA (80 or 160 mg/day) and an active control (quetiapine extended-release), both LATUDA doses and the active control at Endpoint were superior to placebo on the PANSS total score, and the CGI-S.

Thus, the efficacy of LATUDA at doses of 40, 80, 120 and 160 mg/day has been established (Table 24).

**Table 24: Primary Efficacy Results for Studies in Schizophrenia (BPRSd or PANSS Scores)**

| Study                           | Treatment Group  | Primary Efficacy Measure: BPRSd |                                   |   |
|---------------------------------|--|---------------------------------|-----------------------------------|---|
|                                 |  | Mean Baseline Score (SD)        | LS Mean Change from Baseline (SE) | Placebo-subtracted Difference <sup>a</sup> (95% CI) |
| 1                               | LATUDA (40 mg/day)*                                    | 54.2 (8.8)                      | -9.4 (1.6)                        | -5.6 (-9.8, -1.4)                                   |
|                                 | LATUDA (120 mg/day)*                                   | 52.7 (7.6)                      | -11.0 (1.6)                       | -6.7 (-11.0, -2.5)                                  |
|                                 | Placebo  | 54.7 (8.1)                      | -3.8 (1.6)                        | --  |
| 2                               | LATUDA (80 mg/day)*                                    | 55.1 (6.0)                      | -8.9 (1.3)                        | -4.7 (-8.3, -1.1)                                   |
|                                 | Placebo  | 56.1 (6.8)                      | -4.2 (1.4)                        | --  |
| Primary Efficacy Measure: PANSS |  |                                 |                                   |   |
| 3                               | LATUDA (40 mg/day)*                                    | 96.6 (10.7)                     | -25.7 (2.0)                       | -9.7 (-15.3, -4.1)                                  |
|                                 | LATUDA (120 mg/day)*                                   | 97.9 (11.3)                     | -23.6 (2.1)                       | -7.5 (-13.4, -1.7)                                  |
|                                 | Olanzapine (15 mg/day)* <sup>b</sup>                   | 96.3 (12.2)                     | -28.7 (1.9)                       | -12.6 (-18.2, -7.9)                                 |
|                                 | Placebo  | 95.8 (10.8)                     | -16.0 (2.1)                       | --  |
| 4                               | LATUDA (40 mg/day)                                     | 96.5 (11.5)                     | -19.2 (1.7)                       | -2.1 (-7.0, 2.8)                                    |
|                                 | LATUDA (80 mg/day)*                                    | 96.0 (10.8)                     | -23.4 (1.8)                       | -6.4 (-11.3, -1.5)                                  |
|                                 | LATUDA (120 mg/day)                                    | 96.0 (9.7)                      | -20.5 (1.8)                       | -3.5 (-8.4, 1.4)                                    |
|                                 | Placebo  | 96.8 (11.1)                     | -17.0 (1.8)                       | --  |
| 5                               | LATUDA (80 mg/day)*                                    | 97.7 (9.7)                      | -22.2 (1.8)                       | -11.9 (-16.9, -6.9)                                 |
|                                 | LATUDA (160 mg/day)*                                   | 97.5 (11.8)                     | -26.5 (1.8)                       | -16.2 (-21.2, -11.2)                                |
|                                 | Quetiapine Extended-release (600 mg/day)* <sup>b</sup> | 97.7 (10.2)                     | -27.8 (1.8)                       | -17.5 (-22.5, -12.4)                                |
|                                 | Placebo  | 96.6 (10.2)                     | -10.3 (1.8)                       | --  |

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval, unadjusted for multiple comparisons.

<sup>a</sup> Difference (drug minus placebo) in least-squares mean change from baseline.

<sup>b</sup> Included for assay sensitivity.

\* Doses statistically significantly superior to placebo.

Examination of population subgroups based on age (there were few patients over 65), gender and race did not reveal any clear evidence of differential responsiveness.

## 14.2 Depressive Episodes Associated with Bipolar I Disorder

### *Monotherapy*

The efficacy of LATUDA, as monotherapy, was established in a 6-week, multicenter, randomized, double-blind, placebo-controlled study of adult patients (mean age of 41.5 years, range 18 to 74) who met DSM-IV-TR criteria for major depressive episodes associated with bipolar I disorder, with or without rapid cycling, and without psychotic features (N=485). Patients were randomized to one of two flexible-dose ranges of LATUDA (20 to 60 mg/day, or 80 to 120 mg/day) or placebo.

The primary rating instrument used to assess depressive symptoms in this study was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale with total scores ranging from 0 (no depressive features) to 60 (maximum score). The primary endpoint was the change from baseline in MADRS score at Week 6. The key secondary instrument was the Clinical Global Impression-Bipolar-Severity of Illness scale (CGI-BP-S), a clinician-rated scale that measures the subject's current illness state on a 7-point scale, where a higher score is associated with greater illness severity.

For both dose groups, LATUDA was superior to placebo in reduction of MADRS and CGI-BP-S scores at Week 6. The primary efficacy results are provided in [Table 25](#). The high dose range (80 to 120 mg per day) did not provide additional efficacy on average, compared to the low dose range (20 to 60 mg per day).

### *Adjunctive Therapy with Lithium or Valproate*

The efficacy of LATUDA, as an adjunctive therapy with lithium or valproate, was established in a 6-week, multicenter, randomized, double-blind, placebo-controlled study of adult patients (mean age of 41.7 years, range 18 to 72) who met DSM-IV-TR criteria for major depressive episodes associated with bipolar I disorder, with or without rapid cycling, and without psychotic features (N=340). Patients who remained symptomatic after treatment with lithium or valproate were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo.

The primary rating instrument used to assess depressive symptoms in this study was the MADRS. The primary endpoint was the change from baseline in MADRS score at Week 6. The key secondary instrument was the CGI-BP-S scale.

LATUDA was superior to placebo in reduction of MADRS and CGI-BP-S scores at Week 6, as an adjunctive therapy with lithium or valproate ([Table 25](#)).

**Table 25: Primary Efficacy Results for Studies in Depressive Episodes Associated with Bipolar I Disorder (MADRS Scores)**

| Study                    | Treatment Group                                | Primary Efficacy Measure: MADRS |                                   |   |
|--------------------------|--|---------------------------------|-----------------------------------|---|
|                          |  | Mean Baseline Score (SD)        | LS Mean Change from Baseline (SE) | Placebo-subtracted Difference <sup>a</sup> (95% CI) |
| Monotherapy study        | LATUDA (20-60 mg/day)*                         | 30.3 (5.0)                      | -15.4 (0.8)                       | -4.6 (-6.9, -2.3)                                   |
|                          | LATUDA (80-120 mg/day)*                        | 30.6 (4.9)                      | -15.4 (0.8)                       | -4.6 (-6.9, -2.3)                                   |
|                          | Placebo  | 30.5 (5.0)                      | -10.7 (0.8)                       | --  |
| Adjunctive Therapy study | LATUDA (20-120 mg/day)* + lithium or valproate | 30.6 (5.3)                      | -17.1 (0.9)                       | -3.6 (-6.0, -1.1)                                   |
|                          | Placebo + lithium or valproate                 | 30.8 (4.8)                      | -13.5 (0.9)                       | --  |

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval, unadjusted for multiple comparisons.

<sup>a</sup> Difference (drug minus placebo) in least-squares mean change from baseline. \* Treatment group statistically significantly superior to placebo.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

LATUDA tablets are white to off-white, round (20 mg or 40 mg), white to off-white, oblong (60 mg), pale green, oval (80 mg) or white to off-white, oval (120 mg) and identified with strength-specific one-sided debossing, “L20” (20 mg), “L40” (40 mg), “L80” (80 mg) or “L120” (120 mg). Tablets are supplied in the following strengths and package configurations (Table 26):

**Table 26: Package Configuration for LATUDA Tablets**

| Tablet Strength | Package Configuration  | NDC Code                                    |
|-----------------|--|---|
| 20 mg           | Bottles of 30  | 63402-302-30                                |
|                 | Bottles of 90  | 63402-302-90                                |
|                 | Bottles of 500   | 63402-302-50                                |
|                 | Box of 100 (Hospital Unit Dose)<br>10 blister cards, 10 tablets each | 63402-302-10 Carton<br>63402-302-01 Blister |
| 40 mg           | Bottles of 30  | 63402-304-30                                |
|                 | Bottles of 90  | 63402-304-90                                |
|                 | Bottles of 500   | 63402-304-50                                |
|                 | Box of 100 (Hospital Unit Dose)<br>10 blister cards, 10 tablets each | 63402-304-10 Carton<br>63402-304-01 Blister |
| 60 mg           | Bottles of 30  | 63402-306-30                                |
|                 | Bottles of 90  | 63402-306-90                                |
|                 | Bottles of 500   | 63402-306-50                                |
|                 | Box of 100 (Hospital Unit Dose)<br>10 blister cards, 10 tablets each | 63402-306-10 Carton<br>63402-306-01 Blister |
| 80 mg           | Bottles of 30  | 63402-308-30                                |
|                 | Bottles of 90  | 63402-308-90                                |
|                 | Bottles of 500   | 63402-308-50                                |
|                 | Box of 100 (Hospital Unit Dose)<br>10 blister cards, 10 tablets each | 63402-308-10 Carton<br>63402-308-01 Blister |
| 120 mg          | Bottles of 30  | 63402-312-30                                |
|                 | Bottles of 90  | 63402-312-90                                |
|                 | Bottles of 500   | 63402-312-50                                |
|                 | Box of 100 (Hospital Unit Dose)<br>10 blister cards, 10 tablets each | 63402-312-10 Carton<br>63402-312-01 Blister |

### Storage

Store LATUDA tablets at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F) [*See USP Controlled Room Temperature*].

## **17 PATIENT COUNSELING INFORMATION**

Physicians are advised to discuss with patients for whom they prescribe LATUDA all relevant safety information including, but not limited to, the following:

### **17.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis**

Advise patients and caregivers that elderly patients with dementia-related psychoses treated with atypical antipsychotic drugs are at increased risk of death compared with placebo. LATUDA is not approved for elderly patients with dementia-related psychosis [*see Boxed Warning; Warnings and Precautions (5.1)*].

### **17.2 Suicidal Thoughts and Behaviors; and Activation of Mania or Hypomania**

Educate patients, families, and caregivers about the risk of suicidal thoughts and behaviors with antidepressant treatment, as well as the risk of mania and hypomania. Advise them about monitoring for the emergence of suicidal thoughts and behavior, manic/hypomanic symptoms, irritability, agitation, or unusual changes in behavior. Instruct patients, families, and caregivers to report such symptoms to the healthcare provider [*see Warnings and Precautions (5.2 and 5.14)*].

### **17.3 Neuroleptic Malignant Syndrome**

Advise patients and caregivers that a potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs. Signs and symptoms of NMS include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia) [*see Warnings and Precautions (5.4)*].

### **17.4 Metabolic Changes (Hyperglycemia and Diabetes Mellitus, Dyslipidemia, and Weight Gain)**

Educate patients and caregivers about the risk of metabolic changes and the need for specific monitoring. The risks include hyperglycemia and diabetes mellitus, dyslipidemia, weight gain, and cardiovascular reactions. Educate patients and caregivers about the symptoms of hyperglycemia (high blood sugar) and diabetes mellitus (e.g., polydipsia, polyuria, polyphagia, and weakness). Monitor all patients for these symptoms. Patients who are diagnosed with diabetes or have risk factors for diabetes (obesity, family history of diabetes) should have their fasting blood glucose monitored before beginning treatment and periodically during treatment. Patients who develop symptoms of hyperglycemia should have assessments of fasting glucose. Clinical monitoring of weight is recommended [*see Warnings and Precautions (5.6)*].

### **17.5 Orthostatic Hypotension**

Educate patients about the risk of orthostatic hypotension, particularly at the time of initiating treatment, re-initiating treatment, or increasing the dose [*see Warnings and Precautions (5.9)*].

## 17.6 Leukopenia/Neutropenia

Advise patients with a pre-existing low WBC or a history of drug-induced leukopenia/neutropenia that they should have their CBC monitored while taking LATUDA [see *Warnings and Precautions (5.8)*].

## 17.7 Interference with Cognitive and Motor Performance

Caution patients about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that LATUDA therapy does not affect them adversely [see *Warnings and Precautions (5.11)*].

## 17.8 Pregnancy and Nursing

Instruct patients to notify their physician if they become pregnant or intend to become pregnant during therapy with LATUDA [see *Use in Specific Populations (8.1)*].

## 17.9 Concomitant Medication and Alcohol

Instruct patients to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, because there is a potential for drug interactions. Advise patients to avoid alcohol while taking LATUDA [see *Drug Interactions (7)*].

## 17.10 Heat Exposure and Dehydration

Educate patients regarding appropriate care in avoiding overheating and dehydration [see *Warnings and Precautions (5.12)*].



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.

Revised: Month Year

901456RXX

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**Medication Guide**  
**LATUDA (luh-TOO-duh)**  
**(lurasidone hydrochloride)**  
**Tablets**

**What is the most important information I should know about LATUDA?**

**LATUDA may cause serious side effects, including:**

- 1. Increased risk of death in elderly people who are confused, have memory loss and have lost touch with reality (dementia-related psychosis).** Medicines like LATUDA can increase the risk of death in elderly people who are confused, have memory loss and have lost touch with reality (dementia-related psychosis). LATUDA should not be used to treat people with dementia-related psychosis.
- 2. Increased risk of suicidal thoughts or actions (antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions).**
  - **Talk to your, or your family member's, healthcare provider about:**
    - all risks and benefits of treatment with antidepressant medicines.
    - all treatment choices for depression or other serious mental illness.
  - **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
  - **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) depression, bipolar illness (also called manic-depressive illness), or a history of suicidal thoughts or actions.
  - **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
    - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
    - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
    - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

**Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:**

- thoughts about suicide or dying
- attempts to commit suicide

- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

### What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to your healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

### What is LATUDA?

LATUDA is a prescription medicine used to treat adults with:

- schizophrenia
- depressive episodes associated with bipolar I disorder, alone or with lithium or valproate

It is not known if LATUDA is safe and effective in children.

### Who should not take LATUDA?

#### Do not take LATUDA if you:

- are allergic to lurasidone hydrochloride or any of the ingredients in LATUDA. See the end of this Medication Guide for a complete list of ingredients in LATUDA.

- are taking certain other medicines called CYP3A4 inhibitors or inducers including ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, rifampin, avasimibe, St. John's wort, phenytoin, or carbamazepine. Ask your healthcare provider if you are not sure if you are taking any of these medicines.

### **What should I tell my healthcare provider before taking LATUDA?**

#### **Before you take LATUDA, tell your healthcare provider if you:**

- have or have had diabetes or high blood sugar in you or your family. Your healthcare provider should check your blood sugar before you start LATUDA and also during therapy.
- have or have had high levels of total cholesterol, triglycerides or LDL-cholesterol or low levels of HDL-cholesterol
- have or have had low or high blood pressure
- have or have had low white blood cell count
- have or have had seizures
- have or have had abnormal thyroid tests
- have or have had high prolactin levels
- have or have had heart problems
- have or have had liver problems
- have or have had any other medical conditions
- are pregnant or plan to become pregnant. It is not known if LATUDA will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if LATUDA passes into your breast milk. You and your healthcare provider should decide if you will take LATUDA or breastfeed. You should not do both.

**Tell the healthcare provider about all the medicines that you take or recently have taken** including prescription medicines, over-the-counter medicines, herbal supplements and vitamins.

LATUDA and other medicines may affect each other causing serious side effects. LATUDA may affect the way other medicines work, and other medicines may affect how LATUDA works.

Especially tell your healthcare provider if you take or plan to take medicines for:

- depression
- high blood pressure
- Parkinson's disease
- trouble sleeping
- abnormal heart beats or rhythm
- epilepsy
- inflammation
- psychosis

Know the medicines you take. Keep a list of your medicines to show your healthcare provider and pharmacist when you get a new medicine.

### **How should I take LATUDA?**

- Take LATUDA exactly as your healthcare provider tells you to take it. Do not change the dose yourself.
- Take LATUDA by mouth, with food (at least 350 calories).
- If you take too much LATUDA, call your healthcare provider or poison control center at 1-800-222-1222 right away, or go to the nearest hospital emergency room.

### **What should I avoid while taking LATUDA?**

- Avoid eating grapefruit or drinking grapefruit juice while you take LATUDA since these can affect the amount of LATUDA in the blood. Do not drive, operate machinery, or do other dangerous activities until you know how LATUDA affects you. LATUDA may make you drowsy.
- Avoid getting overheated or dehydrated.
  - Do not over-exercise.
  - In hot weather, stay inside in a cool place if possible.
  - Stay out of the sun. Do not wear too much or heavy clothing.
  - Drink plenty of water.
- Do not drink alcohol while taking LATUDA. It may make some side effects of LATUDA worse.

### **What are possible side effects of LATUDA?**

#### **LATUDA can cause serious side effects, including:**

- **See “What is the most important information I should know about LATUDA?”**
- **stroke that can lead to death can happen in elderly people with dementia who take medicines like LATUDA**
- **neuroleptic malignant syndrome (NMS)**. NMS is a rare but very serious condition that can happen in people who take antipsychotic medicines, including LATUDA. NMS can cause death and must be treated in a hospital. Call your healthcare provider right away if you become severely ill and have some or all of these symptoms:
  - high fever
  - excessive sweating
  - rigid muscles
  - confusion
  - changes in your breathing, heartbeat, and blood pressure
- **movements you cannot control in your face, tongue, or other body parts (tardive dyskinesia)**. These may be signs of a serious condition. Tardive dyskinesia may not go away, even if you stop taking LATUDA. Tardive dyskinesia may also start after you stop taking LATUDA.

- **high blood sugar (hyperglycemia).** High blood sugar can happen if you have diabetes already or if you have never had diabetes. High blood sugar could lead to:
  - build-up of acid in your blood due to ketones (ketoacidosis)
  - coma
  - death

Increases in blood sugar can happen in some people who take LATUDA. Extremely high blood sugar can lead to coma or death. If you have diabetes or risk factors for diabetes (such as being overweight or a family history of diabetes) your healthcare provider should check your blood sugar before you start LATUDA and during therapy.

**Call your healthcare provider** if you have any of these symptoms of high blood sugar (hyperglycemia) while taking LATUDA:

- feel very thirsty
  - need to urinate more than usual
  - feel very hungry
  - feel weak or tired
  - feel sick to your stomach
  - feel confused, or your breath smells fruity
- **high fat levels in your blood (increased cholesterol and triglycerides).** High fat levels may happen in people treated with LATUDA. You may not have any symptoms, so your healthcare provider may decide to check your cholesterol and triglycerides during your treatment with LATUDA.
  - **increase in weight (weight gain).** Weight gain has been reported in patients taking medicines like LATUDA. You and your healthcare provider should check your weight regularly. Talk to your healthcare provider about ways to control weight gain, such as eating a healthy, balanced diet, and exercising.
  - **increases in prolactin levels.** Your healthcare provider may do blood tests to check your prolactin levels.
  - **low white blood cell count**
  - **decreased blood pressure (orthostatic hypotension),** including lightheadedness or fainting caused by a sudden change in heart rate and blood pressure when rising too quickly from a sitting or lying position.
  - **seizures**
  - **difficulty swallowing**

**The most common side effects of LATUDA include:**

- sleepiness or drowsiness
- restlessness and feeling like you need to move around (akathisia)
- difficulty moving, slow movements, muscle stiffness, or tremor
- nausea

These are not all the possible side effects of LATUDA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

### **How should I store LATUDA?**

- Store LATUDA tablets at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep LATUDA and all medicines out of the reach of children.

### **General information about the safe and effective use of LATUDA.**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use LATUDA for a condition for which it was not prescribed. Do not give LATUDA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about LATUDA. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about LATUDA that is written for health professionals.

For more information, go to [www.LATUDA.com](http://www.LATUDA.com) or call 1-888-394-7377.

### **What are the ingredients in LATUDA?**

**Active ingredient:** lurasidone hydrochloride

**Inactive ingredients:** mannitol, pregelatinized starch, croscarmellose sodium, hypromellose, magnesium stearate, Opadry® and carnauba wax. Additionally, the 80 mg tablet contains yellow ferric oxide and FD&C Blue No. 2 Aluminum Lake

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured for:

Sunovion Pharmaceuticals Inc.

Marlborough, MA 01752 USA

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