Dear Healthcare Professional,

At MPR we strive to bring you important drug information in a concise and timely manner. In keeping with this goal, we are pleased to provide this PRESCRIBING ALERT with detailed information on Latuda® (lurasidone HCl) tablets, manufactured for Sunovion Pharmaceuticals Inc.

In June 2013, LATUDA was approved for the treatment of major depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and as adjunctive therapy with lithium or valproate.¹ LATUDA is taken once daily with food (at least 350 calories).¹ Efficacy as well as safety and tolerability of LATUDA was established in a 6-week monotherapy study and a 6-week adjunctive therapy study with lithium or valproate in adult patients with bipolar depression.¹ In these studies LATUDA was superior to placebo in reduction of depressive symptoms at Week 6.¹ Reduction of depressive symptoms were the primary and key secondary endpoints.¹

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

CONTRAINDICATIONS
LATUDA is contraindicated in the following:
• Known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone.
• Strong CYP3A4 inhibitors (e.g., ketoconazole)
• Strong CYP3A4 inducers (e.g., rifampin)

WARNINGS AND PRECAUTIONS
Cerebrovascular Adverse Reactions, Including Stroke: 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.
IMPORTANT SAFETY INFORMATION

Neuroleptic Malignant Syndrome (NMS): NMS, a potentially fatal symptom complex, has been reported with administration of antipsychotic drugs, including LATUDA. NMS can cause 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. Management should include immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems.

Tardive Dyskinesia (TD): TD is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can develop in patients with antipsychotic drugs. There is no known treatment for established cases of TD, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. The risk of developing TD 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. Given these considerations, LATUDA should be prescribed in a manner that is most likely to minimize the occurrence of TD. If signs and symptoms appear in a patient on LATUDA, drug discontinuation should be considered.

Metabolic Changes

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. 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 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.

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

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

Hyperprolactinemia: As with other drugs that antagonize dopamine D2 receptors, LATUDA elevates prolactin levels. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds.

In the short-term, placebo-controlled monotherapy study, the median change from baseline to endpoint in prolactin levels for LATUDA-treated females was 3.1 ng/mL and was 1.5 ng/mL for males. The proportion of female patients with prolactin elevations ≥5x ULN was 0.6% for LATUDA-treated patients versus 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥5x ULN was 0% for LATUDA-treated patients versus 0% for placebo-treated male patients.

(Important Safety Information continued on next page)
IMPORTANT SAFETY INFORMATION

In the short-term, placebo-controlled adjunctive therapy with lithium or valproate study, the median change from baseline to endpoint in prolactin levels for LATUDA-treated females was 3.2 ng/mL and was 2.4 ng/mL for males. The proportion of female patients with prolactin elevations ≥5x ULN was 0% for LATUDA-treated patients versus 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥5x ULN was 0% for LATUDA-treated patients versus 0% for placebo-treated male patients.

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. Patients with a preexisting low white blood cell count (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 a decline in WBC in the absence of other causative factors.

Orthostatic Hypotension and Syncope: LATUDA may cause orthostatic hypotension. Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension, in patients with known cardiovascular disease or history of cerebrovascular disease, and in patients who are antipsychotic-naïve.

Seizures: LATUDA should be used cautiously in patients with a history of seizures or with conditions that lower seizure threshold (e.g., Alzheimer’s dementia).

Potential for Cognitive and Motor Impairment: Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with LATUDA does not affect them adversely.

Body Temperature Regulation: 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.

Suicide: The possibility of 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.

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.

(Important Safety Information continued on next page)
ADVERSE REACTIONS
Commonly observed adverse reactions (≥5% incidence and at least twice the rate of placebo) for LATUDA were akathisia, extrapyramidal symptoms, and somnolence.

INDICATION
LATUDA is indicated for the treatment of major depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and as adjunctive therapy with lithium or valproate in adults.

Before prescribing LATUDA, please read the full Prescribing Information, including Boxed Warning.

More information about LATUDA is available in the current edition of MPR.

Sincerely,

Asha Gupta, PharmD
Clinical Communications Specialist
MPR Custom Programs

REFERENCE

LATUDA is a registered trademark of Dainippon Sumitomo Pharma Co., Ltd.
Sunovion Pharmaceuticals Inc. is a U.S. subsidiary of Dainippon Sumitomo Pharma Co., Ltd.
4/14 LAT967-13
**LATUDA has proven antidepressant efficacy and safety as monotherapy and as adjunctive therapy with lithium or valproate for adult patients with bipolar depression**

**IMPORTANT SAFETY INFORMATION**

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults taking antidepressants. Monitor for worsening and emergence of suicidal thoughts and behaviors. Increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack). Neuroleptic Malignant Syndrome: Manage with immediate discontinuation and close monitoring. Tardive Dyskinesia: Discontinue if clinically appropriate. 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. 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 typical antipsychotics. Weight Gain: Gain in body weight has been observed. Monitor weight. Hyperprolactinemia: Prolactin elevations may occur. 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. 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. Interactions: No dose adjustment necessary when used concomitantly with lithium or valproate. See Adults and Contraindications. Adverse Reactions: (incidence ≥5% and at least twice the rate of placebo) Akathisia, extrapyramidal symptoms, and somnolence. How Supplied: Tablets—Bottles of 30, 90, 500. Box of 100 (10 blister cards x 10 tablets)
Proven antidepressant efficacy as monotherapy

Patients were randomized to receive double-blind treatment with LATUDA 20–60 mg/day (n=166), 80–120 mg/day (n=169), or placebo (n=170) for 6 weeks.

LATUDA monotherapy was superior to placebo with a 44% greater reduction of MADRS total scores at Week 6 vs placebo. The high-dose range (80–120 mg/day) did not provide additional efficacy, on average, compared to the low-dose range (20–60 mg/day).

LATUDA was also proven superior to placebo in the key secondary endpoint measure of Clinical Global Impression-Bipolar Severity of Illness scale (CGI-BP-S).

Proven antidepressant efficacy as adjunctive therapy with lithium or valproate

Patients who had not adequately responded to ≥28 days of lithium or valproate were randomized to receive 6 weeks of double-blind adjunctive treatment with LATUDA (n=183) or placebo (n=165) added to therapeutic levels of either lithium or valproate.

LATUDA 20–120 mg/day as adjunctive therapy with lithium or valproate significantly reduced mean MADRS total scores at Week 6 vs placebo.

LATUDA was also proven superior to placebo in the key secondary endpoint measure of Clinical Global Impression-Bipolar Severity of Illness scale (CGI-BP-S).

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS
LATUDA is contraindicated in the following:

- Known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone.
- Strong CYP3A4 inhibitors (e.g., ketoconazole)
- Strong CYP3A4 inducers (e.g., rifampin)

Please see additional Important Safety Information, including Boxed Warning, on pages 7–8, and full Prescribing Information.
Safety and tolerability were evaluated in multiple bipolar depression studies for 6 weeks and 24 weeks.*

*At the end of 6 weeks, eligible patients from the bipolar depression clinical studies could continue into a 24-week, open-label extension study.

### MONOTHERAPY: ADVERSE REACTIONS OCCURRING IN ≥2% OF LATUDA-TREATED PATIENTS†‡

<table>
<thead>
<tr>
<th>Body system or organ class dictionary-derived term</th>
<th>Percentage of patients reporting reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=168)</td>
<td>LATUDA 20–60 mg (n=164)</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>8%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>4%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1%</td>
</tr>
<tr>
<td>Influenza</td>
<td>1%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Extrapyramidal symptoms‡</td>
<td>2%</td>
</tr>
<tr>
<td>Akathisia</td>
<td>2%</td>
</tr>
<tr>
<td>Somnolence§</td>
<td>7%</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>1%</td>
</tr>
</tbody>
</table>

†Adverse reactions in ≥2% of LATUDA-treated patients and occurring at greater incidence than in the placebo-treated patients in the 6-week, randomized, double-blind, placebo-controlled bipolar depression monotherapy study.

‡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.

### IMPORTANT SAFETY INFORMATION

**WARNINGS AND PRECAUTIONS**

**Cerebrovascular Adverse Reactions, Including Stroke:** 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.

Please see additional Important Safety Information, including **Boxed Warning**, on pages 7–8, and full Prescribing Information.
ADJUNCTIVE THERAPY: ADVERSE REACTIONS OCCURRING IN ≥2% OF LATUDA-TREATED PATIENTS.*

<table>
<thead>
<tr>
<th></th>
<th>Lithium/Valproate + Placebo (n=334)</th>
<th>Lithium/Valproate + LATUDA (n=360)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>10%</td>
<td>14%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>General disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight increased</td>
<td>&lt;1%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased appetite</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrapyramidal symptoms†</td>
<td>9%</td>
<td>14%</td>
</tr>
<tr>
<td>Somnolence‡</td>
<td>5%</td>
<td>11%</td>
</tr>
<tr>
<td>Akathisia</td>
<td>5%</td>
<td>11%</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restlessness</td>
<td>&lt;1%</td>
<td>4%</td>
</tr>
</tbody>
</table>

*Adverse reactions in ≥2% of LATUDA-treated patients and occurring at greater incidence than in the placebo-treated patients in the 6-week, randomized, double-blind, placebo-controlled bipolar depression adjunctive therapy studies.
†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.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Neuroleptic Malignant Syndrome (NMS): NMS, a potentially fatal symptom complex, has been reported with administration of antipsychotic drugs, including LATUDA. NMS can cause hyperpyrexia, muscle rigidity, altered mental state 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. Management should include immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems.

Tardive Dyskinesia (TD): TD is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can develop in patients with antipsychotic drugs. There is no known treatment for established cases of TD, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. The risk of developing TD 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. Given these considerations, LATUDA should be prescribed in a manner that is most likely to minimize the occurrence of TD. If signs and symptoms appear in a patient on LATUDA, drug discontinuation should be considered.

Please see additional Important Safety Information, including Boxed Warning, on pages 7–8, and full Prescribing Information.
Study discontinuation rates 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.1

* Data are from the 6-week, randomized, double-blind, placebo-controlled bipolar depression monotherapy study. Patients were randomized to flexibly dosed LATUDA 20–60 mg/day, LATUDA 80–120 mg/day, or placebo.

Mean changes in metabolic parameters4,8

Monotherapy: At Week 6, mean changes in metabolic parameters in patients who received placebo, LATUDA 20–60 mg/day, or LATUDA 80–120 mg/day, respectively:\n
- Total cholesterol: –3.2 mg/dL (n=147), 1.2 mg/dL (n=140), –4.6 mg/dL (n=144)
- Triglycerides: 6.0 mg/dL (n=147), 5.6 mg/dL (n=140), 0.4 mg/dL (n=144)
- Serum glucose: 1.8 mg/dL (n=148), –0.8 mg/dL (n=140), 1.8 mg/dL (n=143)

Adjunctive Therapy: At Week 6, mean changes in metabolic parameters in patients who received lithium/valproate plus placebo and lithium/valproate plus LATUDA 20–120 mg/day, respectively:\n
- Total cholesterol: –2.9 mg/dL (n=303), –3.1 mg/dL (n=321)
- Triglycerides: –4.6 mg/dL (n=303), 4.6 mg/dL (n=321)
- Serum glucose: –0.9 mg/dL (n=302), 1.2 mg/dL (n=319)

1 Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.
4 Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyphagia, and weakness.
8 Last observation carried forward (LOCF) analysis.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Metabolic Changes

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. 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 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.

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Monotherapy: Mean Weight Change*

- The proportion of patients with ≥7% weight gain (at Week 6 endpoint) was: 0.7% placebo vs 2.4% LATUDA.
  - At Week 24, mean weight change of –0.04 lb (–0.02 kg) was observed in patients who received LATUDA as monotherapy in the short-term study and continued in the uncontrolled, open-label extension study (n=130).

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

†At the end of 6 weeks, eligible patients from the bipolar depression clinical studies could continue into a 24-week, open-label extension study. Patients were started on LATUDA 60 mg/day and then flexibly dosed based on response to treatment.

Adjunctive Therapy: Mean Weight Change*

- The proportion of patients with ≥7% weight gain (at Week 6 endpoint) was: 0.3% placebo vs 3.1% LATUDA.
  - At Week 24, mean weight change of 2.82 lb (1.28 kg) was observed in patients who received LATUDA as adjunctive therapy in the short-term studies and continued in the uncontrolled, open-label extension study (n=86).

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IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Metabolic Changes

Dyslipidemia: Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. Weight Gain: Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

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CONTRAINDICATIONS
LATUDA is contraindicated in the following:

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Hyperprolactinemia: As with other drugs that antagonize dopamine D₂ receptors, LATUDA elevates prolactin levels. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds.

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In the short-term, placebo-controlled monotherapy study, the median change from baseline to endpoint in prolactin levels for LATUDA-treated females was 3.1 ng/mL and was 1.5 ng/mL for males. The proportion of female patients with prolactin elevations ≥5x ULN was 0.6% for LATUDA-treated patients versus 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥5x ULN was 0% for LATUDA-treated patients versus 0% for placebo-treated male patients.

In the short-term, placebo-controlled adjunctive therapy with lithium or valproate study, the median change from baseline to endpoint in prolactin levels for LATUDA-treated females was 3.2 ng/mL and was 2.4 ng/mL for males. The proportion of female patients with prolactin elevations ≥5x ULN was 0% for LATUDA-treated patients versus 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥5x ULN was 0% for LATUDA-treated patients versus 0% for placebo-treated male patients.

**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. Patients with a preexisting low white blood cell count (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 a decline in WBC in the absence of other causative factors.

**Orthostatic Hypotension and Syncope:** LATUDA may cause orthostatic hypotension. Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension, in patients with known cardiovascular disease or history of cerebrovascular disease, and in patients who are antipsychotic-naïve.

**Seizures:** LATUDA should be used cautiously in patients with a history of seizures or with conditions that lower seizure threshold (e.g., Alzheimer’s dementia).

**Potential for Cognitive and Motor Impairment:** Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with LATUDA does not affect them adversely.

**Body Temperature Regulation:** 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.

**Suicide:** The possibility of 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.

**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.

**ADVERSE REACTIONS**

Commonly observed adverse reactions (≥5% incidence and at least twice the rate of placebo) for LATUDA were akathisia, extrapyramidal symptoms, and somnolence.

**INDICATION**

LATUDA is indicated for the treatment of major depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and as adjunctive therapy with lithium or valproate in adults.

*Please see additional Important Safety Information, including Boxed Warning, on pages 7–8, and full Prescribing Information.*