

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

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

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).

RECENT MAJOR CHANGES

Dosage and Administration, Schizophrenia (2.1) 04/2012
Dosage and Administration, Dose Modifications in Special Populations (2.3) 04/2012

INDICATIONS AND USAGE

LATUDA is an atypical antipsychotic indicated for the treatment of patients with schizophrenia (1). Efficacy was established in five 6-week controlled studies of adult patients with schizophrenia (14.1).

DOSAGE AND ADMINISTRATION

- The recommended starting dose of LATUDA is 40 mg once daily (2.1).
- The maximum recommended dose is 160 mg once daily (2.1).
- LATUDA should be taken with food (2.2).
- **Moderate and severe renal impairment:** Recommended starting dose is 20 mg and the maximum recommended dose is 80 mg (2.3).
- **Moderate and severe hepatic impairment:** Recommended starting dose is 20 mg. The maximum recommended dose is 80 mg in moderate hepatic impairment and 40 mg in severe hepatic impairment (2.3).
- **Concomitant use with a moderate CYP3A4 inhibitor (e.g., diltiazem):** Recommended starting dose is 20 mg and the maximum recommended dose is 80 mg (2.4, 7.1)

DOSAGE FORMS AND STRENGTHS

Tablets: 20 mg, 40 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) (4, 7.1)
- Concomitant use with a strong CYP3A4 inducer (e.g., rifampin) (4, 7.1).

WARNINGS AND PRECAUTIONS

- **Cerebrovascular Adverse Reactions:** An increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) has been seen in elderly patients with dementia-related psychoses treated with atypical antipsychotic drugs (5.2).
- **Neuroleptic Malignant Syndrome:** Manage with immediate discontinuation and close monitoring (5.3).
- **Tardive Dyskinesia:** Discontinue if clinically appropriate (5.4).
- **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 (5.5).
 - **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; clinical monitoring of weight is recommended.
- **Hyperprolactinemia:** Prolactin elevations may occur (5.6).
- **Leukopenia, Neutropenia, and Agranulocytosis:** have been reported with antipsychotics. Patients with a pre-existing low white blood cell count (WBC) or a history of leukopenia/neutropenia: Monitor complete blood count (CBC) frequently during the first few months of therapy and discontinue LATUDA at the first sign of a decline in WBC in the absence of other causative factors (5.7).
- **Orthostatic Hypotension and Syncope:** Dizziness, tachycardia or bradycardia, and syncope may occur, especially early in treatment. Use with caution in patients with known cardiovascular or cerebrovascular disease, and in antipsychotic-naïve patients (5.8).

ADVERSE REACTIONS

Commonly observed adverse reactions (incidence $\geq 5\%$ and at least twice the rate for placebo) included somnolence, akathisia, nausea and parkinsonism (6.1).

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.

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

Revised: 12/2012

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

FULL PRESCRIBING INFORMATION

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

1 INDICATIONS AND USAGE

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)*].

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/day to 160 mg/day [see *Clinical Studies (14.1)*]. The maximum recommended dose is 160 mg/day.

2.2 Administration Instructions

LATUDA should be taken with food (at least 350 calories) [see *Clinical Pharmacology (12)*].

2.3 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. The dose in these patients should not exceed 80 mg/day [see *Use in Specific Populations (8)*].

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. The dose in moderate hepatic impairment patients should not exceed 80 mg/day and the dose in severe hepatic impairment patients should not exceed 40 mg/day [see *Use in Specific Populations (8)*].

2.4 Dose Modifications Due to Drug Interactions

Concomitant Use with Potential CYP3A4 Inhibitors

The recommended starting dose is 20 mg/day. The dose of LATUDA should not exceed 80 mg/day in combination with a moderate CYP3A4 inhibitor such as diltiazem. LATUDA should not be used in combination with a strong CYP3A4 inhibitor (e.g., ketoconazole) [see *Contraindications (4)*; *Drug Interactions (7.1)*].

Concomitant Use with Potential CYP3A4 Inducers

LATUDA should not be used in combination with a strong CYP3A4 inducer (e.g., rifampin) [see *Contraindications (4)*; *Drug Interactions (7.1)*].

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

Tablet Strength	Tablet Color/Shape	Tablet Markings
80 mg	pale green oval	L80
120 mg	white to off-white oval	L120

4 CONTRAINDICATIONS

LATUDA is contraindicated in the following:

- Any patient with a known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone [see *Adverse Reactions (6.1)*].
- Concomitant use with strong CYP3A4 inhibitors (e.g., ketoconazole) [see *Drug Interactions (7.1)*].
- Concomitant use with strong CYP3A4 inducers (e.g., rifampin) [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 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)*].

5.3 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 creatinine 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.

5.4 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.

5.5 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and 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.

Pooled data from short-term, placebo-controlled studies are presented in [Table 2](#).

Table 2: Change in Fasting Glucose

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

In the uncontrolled, longer-term 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).

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. Pooled data from short-term, placebo-controlled studies are presented in [Table 3](#).

Table 3: Change in Fasting Lipids

	LATUDA					
	Placebo	20 mg/day	40 mg/day	80 mg/day	120 mg/day	160 mg/day
Mean Change from Baseline (mg/dL)						
	n=660	n=71	n=466	n=499	n=268	n=115
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
Proportion of Patients with Shifts						
Total Cholesterol (≥ 240 mg/dL)	5.3% (30/571)	13.8% (8/58)	6.2% (25/402)	5.3% (23/434)	3.8% (9/238)	4.0% (4/101)
Triglycerides (≥ 200 mg/dL)	10.1% (53/526)	14.3% (7/49)	10.8% (41/379)	6.3% (25/400)	10.5% (22/209)	7.0% (7/100)

In the uncontrolled, longer-term 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.

Weight Gain

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

Pooled data from short-term, placebo-controlled studies are presented in [Table 4](#). 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 4: Mean Change in Weight (kg) from Baseline

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

In the uncontrolled, longer-term 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).

5.6 Hyperprolactinemia

As with other drugs that antagonize dopamine D₂ 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)].

In short-term, placebo-controlled 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 5.

Table 5: Median Change in Prolactin (ng/mL) from Baseline

	LATUDA					
	Placebo	20 mg/day	40 mg/day	80 mg/day	120 mg/day	160 mg/day
All Patients	-1.9 (n=672)	-1.1 (n=70)	-1.4 (n=476)	-0.2 (n=495)	3.3 (n=284)	3.3 (n=115)
Females	-5.1 (n=200)	-0.7 (n=19)	-4.0 (n=149)	-0.2 (n=150)	6.7 (n=70)	7.1 (n=36)
Males	-1.3 (n=472)	-1.2 (n=51)	-0.7 (n=327)	-0.2 (n=345)	3.1 (n=214)	2.4 (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 $\geq 5x$ ULN was 5.7% for LATUDA-treated patients versus 2.0% for placebo-treated female patients. The proportion of male patients with prolactin elevations $\geq 5x$ ULN was 1.6% versus 0.6% for placebo-treated male patients.

In the uncontrolled longer-term 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).

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.

5.7 Leukopenia, Neutropenia and Agranulocytosis

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

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and LATUDA should be discontinued at the first sign of decline in WBC, in the absence of other causative factors.

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1000/mm³) should discontinue LATUDA and have their WBC followed until recovery.

5.8 Orthostatic Hypotension and Syncope

LATUDA may cause orthostatic hypotension, perhaps due to its α 1-adrenergic receptor antagonism. The incidence of orthostatic hypotension and syncope events from short-term, placebo-controlled 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)]. Assessment of orthostatic hypotension was defined by vital sign changes (≥ 20 mm Hg decrease in systolic blood pressure and ≥ 10 bpm increase in pulse from sitting to standing or supine to standing positions). In short-term clinical trials, orthostatic hypotension 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.

Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications), and in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction, ischemia, or conduction abnormalities), or cerebrovascular disease.

5.9 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.

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

5.10 Potential for Cognitive and Motor Impairment

LATUDA, like other antipsychotics, has the potential to impair judgment, thinking or motor skills.

In short-term, placebo-controlled trials, 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. In these short-term trials, somnolence included: hypersomnia, hypersomnolence, sedation and somnolence.

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.

5.11 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 [*see Patient Counseling Information (17.9)*].

5.12 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.

In short-term, placebo-controlled studies in patients with schizophrenia, 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.

5.13 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.

5.14 Use in Patients with Concomitant Illness

Clinical experience with LATUDA in patients with certain concomitant illnesses is limited [*see Clinical Pharmacology (12.3)*].

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.

LATUDA has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical trials. Because of the risk of orthostatic hypotension with LATUDA, caution should be observed in patients with known cardiovascular disease [*see Warnings and Precautions (5.8)*].

6 ADVERSE REACTIONS

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

- Use in Elderly Patients with Dementia-Related Psychosis [*see Boxed Warning and Warnings and Precautions (5.1)*]
- Cerebrovascular Adverse Reactions, Including Stroke [*see Warnings and Precautions (5.2)*]

- Neuroleptic Malignant Syndrome [see Warnings and Precautions (5.3)]
- Tardive Dyskinesia [see Warnings and Precautions (5.4)]
- Hyperglycemia and Diabetes Mellitus [see Warnings and Precautions (5.5)]
- Hyperprolactinemia [see Warnings and Precautions (5.6)]
- Leukopenia, Neutropenia, and Agranulocytosis [see Warnings and Precautions (5.7)]
- Orthostatic Hypotension and Syncope [see Warnings and Precautions (5.8)]
- Seizures [see Warnings and Precautions (5.9)]
- Potential for Cognitive and Motor Impairment [see Warnings and Precautions (5.10)]
- Body Temperature Regulation [see Warnings and Precautions (5.11)]
- Suicide [see Warnings and Precautions (5.12)]
- Dysphagia [see Warnings and Precautions (5.13)]

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 a clinical study database for LATUDA consisting of 2905 patients with schizophrenia exposed to one or more doses with a total experience of 985.3 patient-years. Of these patients, 1508 participated in short-term, placebo-controlled schizophrenia studies with doses of 20 mg, 40 mg, 80 mg, 120 mg or 160 mg once daily. A total of 769 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.

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, nausea and parkinsonism.

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 6](#).

Table 6: 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 Dictionary-derived Term	Percentage of Patients Reporting Reaction	
	Placebo (N=708)	All LATUDA (N=1508)
Gastrointestinal Disorders		
Nausea	5	10
Vomiting	6	8
Dyspepsia	5	6
Salivary Hypersecretion	<1	2
Musculoskeletal and Connective Tissue Disorders		
Back Pain	2	3
Nervous System Disorders		
Somnolence*	7	17
Akathisia	3	13
Parkinsonism**	5	10
Dizziness	2	4
Dystonia***	<1	4
Psychiatric Disorders		
Insomnia	8	10
Agitation	4	5
Anxiety	4	5
Restlessness	1	2

Note: Figures rounded to the nearest integer

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

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

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

Dose-Related Adverse Reactions

In pooled data from the short-term, placebo-controlled, fixed-dose studies, there were no dose-related adverse reactions (greater than 5% incidence) in patients treated with LATUDA across the 20 mg/day to 160 mg/day dose range. However, the frequency of akathisia increased with dose up to 120 mg/day (5.6% LATUDA 20 mg, 10.7% LATUDA 40 mg, 12.3% LATUDA 80 mg, 22.0% 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.

Extrapyramidal Symptoms

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 7.

Table 7: Incidence of EPS Compared to Placebo

Adverse Event Term	LATUDA					
	Placebo (N=709) (%)	20 mg/day (N=71) (%)	40 mg/day (N=487) (%)	80 mg/day (N=538) (%)	120 mg/day (N=291) (%)	160 mg/day (N=121) (%)
All EPS events	9	10	21	23	39	20
All EPS events, excluding 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

In the short-term, placebo-controlled schizophrenia studies, data was objectively collected on the Simpson Angus Rating Scale for extrapyramidal symptoms (EPS), the Barnes Akathisia Scale (for akathisia) and the Abnormal Involuntary Movement Scale (for dyskinesias). The mean change from baseline for LATUDA-treated patients 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%) and the SAS (LATUDA, 5.0%; placebo, 2.3%).

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.

In the short-term, placebo-controlled clinical trials, 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.

Other Adverse Reactions Observed During the Premarketing Evaluation of LATUDA

Following is a list of adverse reactions reported by patients treated with LATUDA at multiple doses of ≥ 20 mg once daily during any phase of a study within the database of 2905 patients. 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 6 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

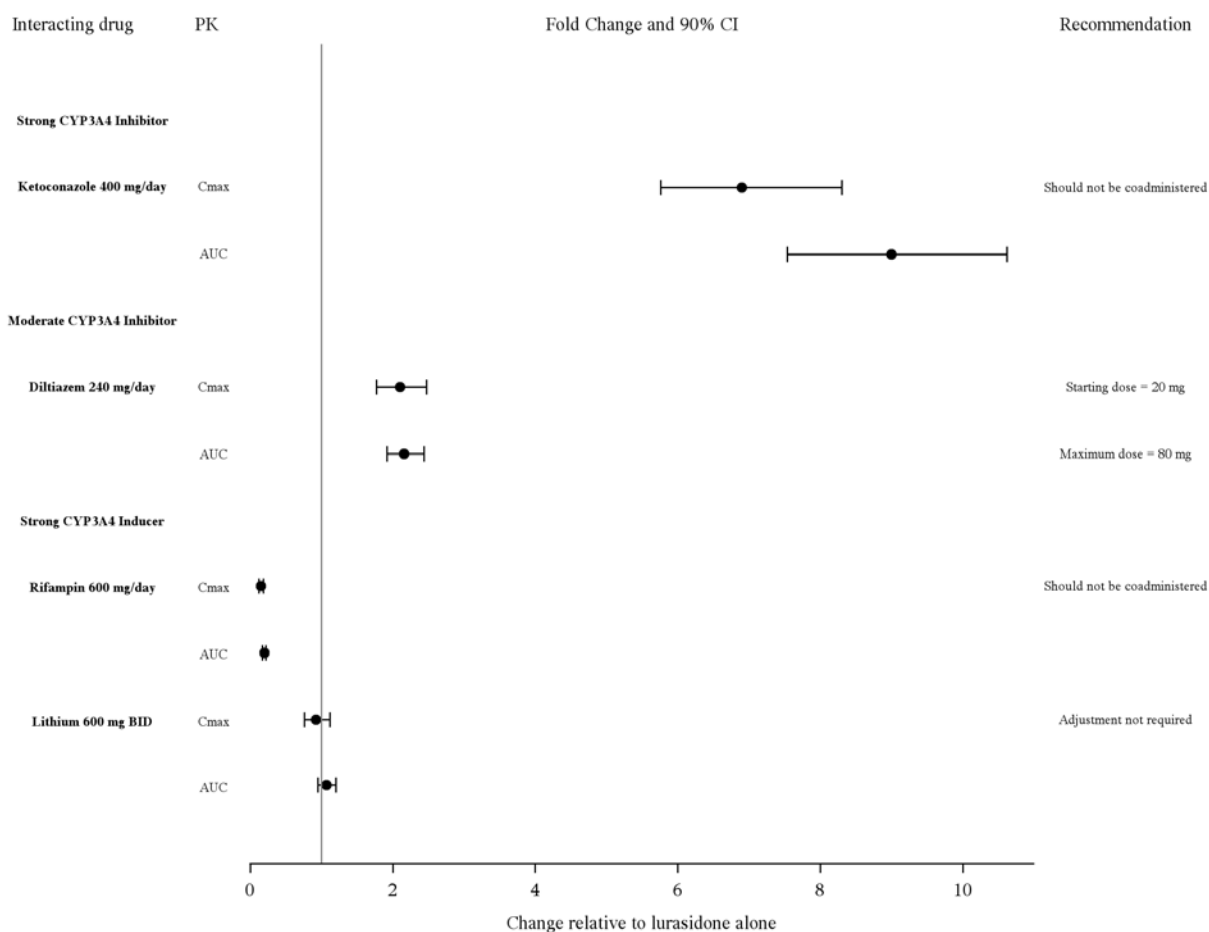
Vascular Disorders: **Frequent:** hypertension

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect LATUDA

LATUDA is predominantly metabolized by CYP3A4. LATUDA should not be used in combination with strong inhibitors or inducers of this enzyme [see *Contraindications (4)*] and dose should be limited when used in combination with moderate inhibitors of CYP3A4 [see *Dosage and Administration (2.4)*]. No dose adjustment is needed with concomitant use of lithium (see [Figure 1](#)).

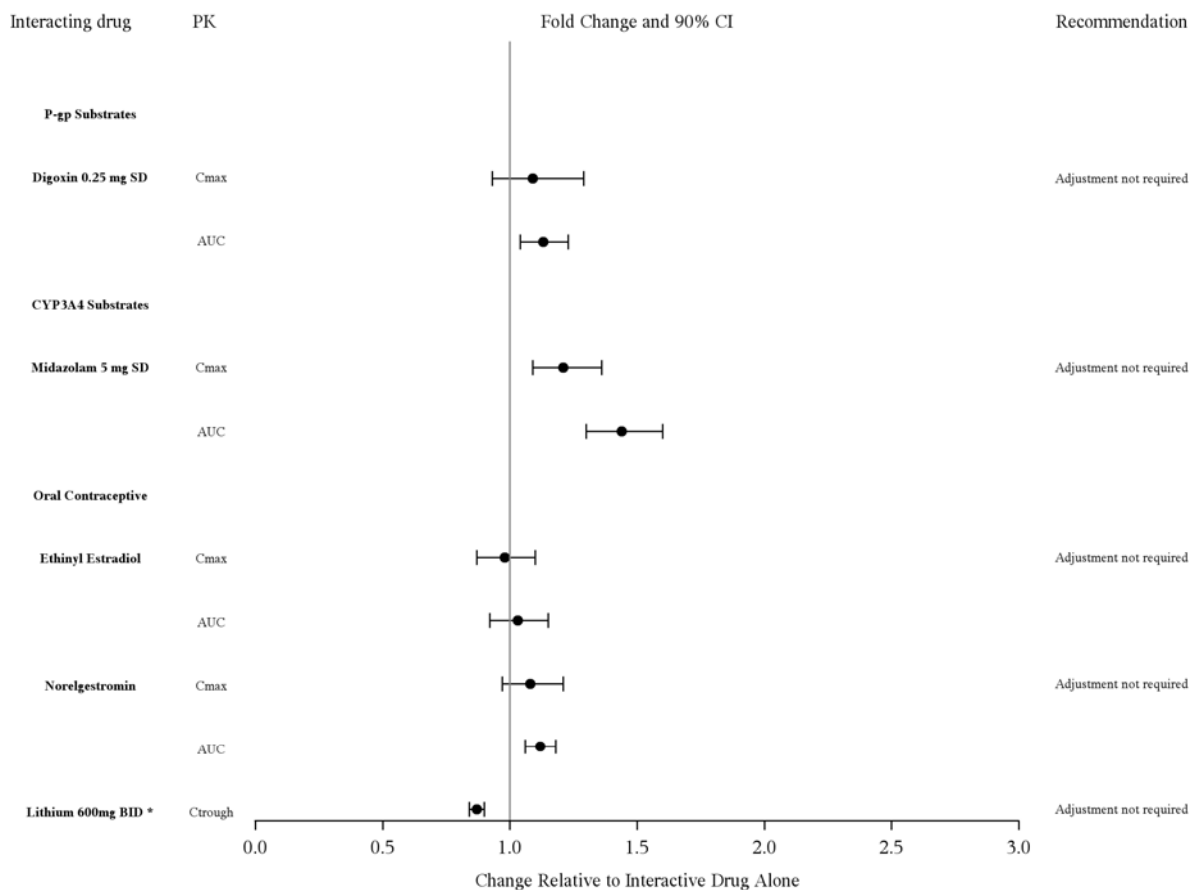
Figure 1: Impact of Other Drugs on LATUDA Pharmacokinetics



7.2 Potential for LATUDA to Affect Other Drugs

No adjustment is needed on the dose of lithium, or substrates of P-gp or CYP3A4 when coadministered with LATUDA (Figure 2).

Figure 2: Impact of LATUDA on Other Drugs



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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category B

LATUDA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects

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.

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 seen in a study in which pregnant rats were given LATUDA during the period of organogenesis and continuing through weaning at doses up to 10 mg/kg/day; this dose is approximately half of the MRHD based on body surface area.

No teratogenic effects were seen in studies in which pregnant rats and rabbits were given LATUDA 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 maximum recommended human dose (MRHD) of 160 mg/day based on 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 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

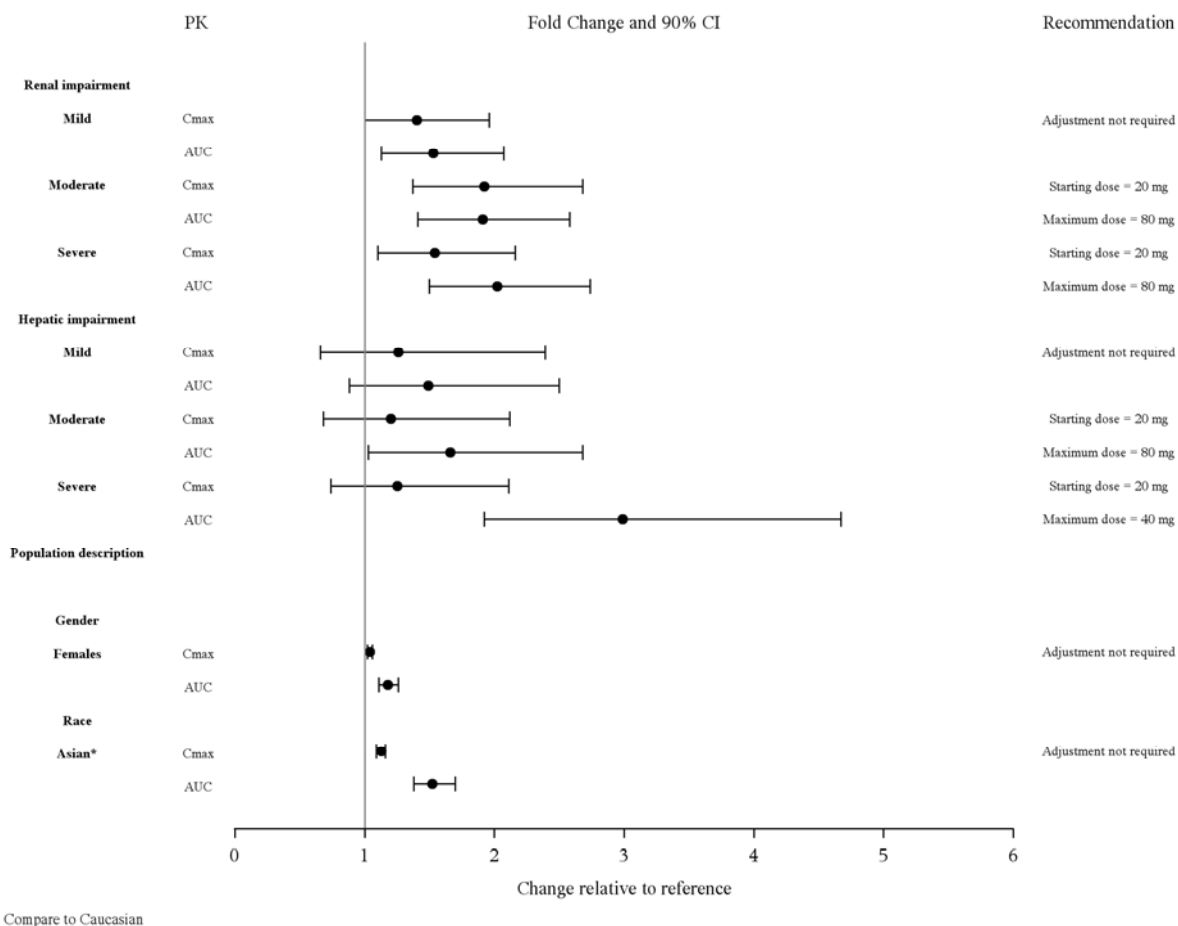
Clinical studies of LATUDA in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 and older to determine whether or not they respond differently from younger patients. In elderly patients with psychosis (65 to 85), LATUDA concentrations (20 mg/day) were similar to those in young subjects [*see Clinical Pharmacology (12.3)*]. No dose adjustment is necessary in elderly patients ([Figure 2](#)).

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



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 involving 2905 patients, 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.

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.

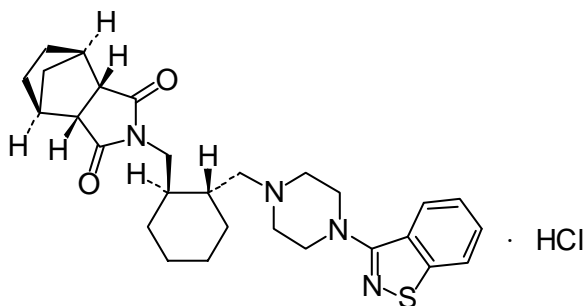
The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

11 DESCRIPTION

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

Its chemical name is (3a*R*,4*S*,7*R*,7a*S*)-2-[(1*R*,2*R*)-2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-ylmethyl] cyclohexylmethyl] hexahydro-4,7-methano-2*H*-isoindole-1,3-dione hydrochloride. Its molecular formula is C₂₈H₃₆N₄O₂S·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, 80 mg, or 120 mg of lurasidone hydrochloride.

Inactive ingredients are 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Although the mechanism of action of LATUDA is unknown, the efficacy of LATUDA in schizophrenia could be mediated through a combination of central dopamine Type 2 (D₂) and serotonin Type 2 (5HT_{2A}) receptor antagonism.

12.2 Pharmacodynamics

LATUDA is an antagonist with high affinity binding at the dopamine D₂ receptors (K_i=0.994 nM) and the 5-hydroxytryptamine (5-HT, serotonin) receptors 5-HT_{2A} (K_i=0.47 nM) and 5-HT₇ (K_i=0.495 nM) receptors. It also binds with moderate affinity at the human α_{2C} adrenergic receptors (K_i=10.8 nM), is a partial agonist at serotonin 5-HT_{1A} (K_i=6.38 nM) receptors, and is an antagonist at the α_{2A} adrenergic receptors (K_i=40.7 nM). LATUDA exhibits little or no affinity for histamine H₁ and muscarinic M₁ receptors (IC₅₀ > 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, no post-baseline QT prolongations exceeding 500 msec were reported in patients treated with LATUDA or placebo.

Changes in Laboratory Tests

There were no clinically important differences between LATUDA and placebo in mean change from baseline to endpoint in routine hematology, urinalysis, or serum chemistry.

Creatinine: In short-term, placebo-controlled trials, the mean change from Baseline in 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 [*see Dose Modifications in Special Populations (2.3); Use in Specific Populations (8)*].

Transaminases: The mean changes in AST and ALT for LATUDA- and placebo-treated patients were similar. The proportion of patients with transaminases (AST and ALT) elevations ≥ 3 -times ULN was similar for all LATUDA-treated patients (0.6% and 0.8%, respectively) to placebo-treated patients (0.9% and 1.0%, respectively).

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* (2.2)].

In clinical studies, establishing the safety and efficacy of LATUDA, patients were instructed to take their daily dose with food [see *Dosage and Administration* (2.2)].

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 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 (5.6)*].

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/day based on 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 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. 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. 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. 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. 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. 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. 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 8).

Table 8: Summary of Results for Primary Efficacy Endpoints

Study Number	Primary Endpoint	LS Mean (SE) ^a Difference from Placebo in Change from Baseline					
		LATUDA				Olanzapine	Quetiapine Extended-Release
		40 mg/day	80 mg/day	120 mg/day	160 mg/day	15 mg/day	600 mg/day
1	BPRSd	-5.6* (2.1)	-	-6.7* (2.2)	-	-	-
2	BPRSd	-	-4.7* (1.8)	-	-	-	-
3	PANSS	-9.7* (2.9)	-	-7.5* (3.0)	-	-12.6** (2.8)	-
4	PANSS	-2.1 (2.5)	-6.4* (2.5)	-3.5 (2.5)	-	-	-
5	PANSS	-	-11.9* (2.6)	-	-16.2* (2.5)	-	-17.5** (2.6)

* adjusted p-value ≤0.05

** non-adjusted p-value ≤0.05

^a Least Squares Mean (Standard Error)

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.

16 HOW SUPPLIED/STORAGE AND HANDLING

LATUDA tablets are white to off-white, round (20 mg or 40 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 9):

Table 9: 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) 10 blister cards, 10 tablets each	63402-302-10 Carton 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) 10 blister cards, 10 tablets each	63402-304-10 Carton 63402-304-01 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) 10 blister cards, 10 tablets each	63402-308-10 Carton 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) 10 blister cards, 10 tablets each	63402-312-10 Carton 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

Patients and caregivers should be advised 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 Neuroleptic Malignant Syndrome

Patients and caregivers should be counseled 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 (5.3)*].

17.3 Hyperglycemia and Diabetes Mellitus

Patients should be aware of the symptoms of hyperglycemia (high blood sugar) and diabetes mellitus. Patients who are diagnosed with diabetes, those with risk factors for diabetes, or those that develop these symptoms during treatment should have their blood glucose monitored at the beginning of and periodically during treatment [see *Warnings and Precautions (5.5)*].

17.4 Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, particularly at the time of initiating treatment, re-initiating treatment, or increasing the dose [see *Warnings and Precautions (5.8)*].

17.5 Leukopenia/Neutropenia

Patients with a pre-existing low WBC or a history of drug-induced leukopenia/neutropenia should be advised that they should have their CBC monitored while taking LATUDA [see *Warnings and Precautions (5.7)*].

17.6 Interference with Cognitive and Motor Performance

Patients should be cautioned 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 (5.10)*].

17.7 Pregnancy and Nursing

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

17.8 Concomitant Medication and Alcohol

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions. Patients should be advised to avoid alcohol while taking LATUDA [see *Drug Interactions (7)*].

17.9 Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration [see *Warnings and Precautions (5.11)*].



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Revised: December 2012

901456R07

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