FULL PRESCRIBING INFORMATION

LATUDA*

(lurasidone hydrochloride)

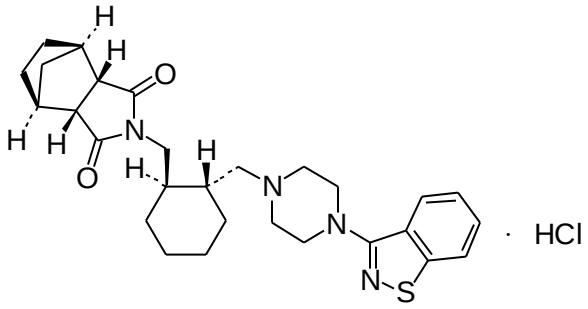
Tablets

1. 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 $C_{28}H_{36}N_4O_2S \cdot HCl$ 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 and 80 mg of lurasidone hydrochloride.

Inactive ingredients are mannitol, pregelatinized starch, croscarmellose sodium, hypromellose, magnesium stearate, Opadry® (contains hypromellose, titanium dioxide and polyethylene glycol 8000) and carnauba wax. Additionally, the 80 mg tablet contains yellow ferric oxide and FD&C Blue No. 2 Aluminum Lake.

2 CLINICAL PHARMACOLOGY

2.1 Mechanism of Action

The mechanism of action of lurasidone in the treatment of schizophrenia and bipolar depression is unclear. However, its efficacy in schizophrenia and bipolar depression could be mediated through a combination of central dopamine D2 and serotonin Type 2 (5-HT2A) receptor antagonism.

2.2 Pharmacodynamics

In vitro receptor binding studies revealed that LATUDA is an antagonist with high affinity at dopamine D_2 receptors (K*i* = 0.994 nM) and the 5-hydroxytryptamine (5-HT, serotonin) receptors 5-HT_{2A} (K*i* = 0.47 nM) and 5-HT_7 (*Ki* = 0.495 nM), is an antagonist with moderate affinity for α_{2C} adrenergic receptors (K*i* = 10.8 nM), is a partial agonist at serotonin 5-HT_{1A} (*Ki* = 6.38 nM) receptors, an antagonist at α_{2A} (K*i* = 40.7 nM) and α_1 (K*i* = 47.9 nM) adrenergic receptors. LATUDA exhibits little or no affinity for histamine H_1 and muscarinic M_1 receptors (IC_{50} >1,000 nM).

ECG Changes

Electrocardiogram (ECG) measurements were taken at various time points during the LATUDA clinical trial program. No post-baseline QT prolongations exceeding 500 msec were reported in patients treated with LATUDA. Within a subset of patients defined as having an increased cardiac risk, no potentially important changes in ECG parameters were observed. No cases of torsade de pointes or other severe cardiac arrhythmias were observed in the pre-marketing clinical program.

The effects of LATUDA on the QT/QTc interval were evaluated in a dedicated QT study involving 87 clinically stable patients with schizophrenia or schizoaffective disorder, who were treated with LATUDA doses of 120 mg daily, 600 mg daily, or ziprasidone 160 mg daily. Holter monitor-derived electrocardiographic assessments were obtained over an eight hour period at baseline and steady state. No patients treated with LATUDA experienced QTc increases > 60 msec from baseline, nor did any patient experience a QTc of > 500 msec.

2.3 Pharmacokinetics

Adult

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 the mean (%CV) elimination half-life was 18 (7) hours.

Children and Adolescents

The pharmacokinetics of LATUDA, in pediatric patients 6-17 years of age, was similar to those in adults. There were no clinically relevant differences between genders in the pharmacokinetics of LATUDA in patients with schizophrenia, bipolar depression, autism, or other psychiatric disorders.

Absorption

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.

In a food effect study, LATUDA mean Cmax 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.

Distribution

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.

Metabolism and Elimination

LATUDA is metabolised mainly via CYP3A4. The major biotransformation pathways are oxidative N-dealkylation, hydroxylation of norbornane ring, and S-oxidation. LATUDA is metabolized into two non-major active metabolites (ID-14283 and ID-14326) and two major non-active metabolites (ID-20219 and ID-20220).

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.

3 USE IN SPECIFIC POPULATIONS

3.1 Pregnancy

Pregnancy Category B: In animal studies, no teratogenic or other adverse effects on fetuses were observed in studies in which LATUDA was administered during the period of organogenesis to rats and rabbits at oral doses up to 25 and 50 mg/kg/day, corresponding to 1.5 and 6 times, respectively, the MRHD based on body surface area. No effects on delivery or pup development were observed in rats given LATUDA from early gestation to weaning at oral doses up to 10 mg/kg/day (about half the MRHD based on body surface area). There are no adequate and well-controlled studies in pregnant women.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with LATUDA. LATUDA should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

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.

3.2. 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.

3.3 Pediatric Use

Schizophrenia

The safety and effectiveness of LATUDA has not been established in pediatric patients less than 13 years of age with schizophrenia.

Bipolar Depression

The safety and effectiveness of LATUDA 20 to 80 mg/day for the treatment of bipolar depression in pediatric patients (10 to 17 years) was evaluated in a 6-week, placebo-controlled clinical study in 347 pediatric patients.

The safety and effectiveness of LATUDA has not been established in pediatric patients less than 13 years of age with bipolar depression.

Irritability Associated with Autistic Disorder

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

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

In a long-term, open-label study that enrolled pediatric patients (age 6 to 17 years) with schizophrenia, bipolar depression, or autistic disorder from three short-term, placebo-controlled trials, 54% (378/701) received lurasidone for 104 weeks. There was one adverse event in this trial that was considered possibly drug-related and has not been reported in adults receiving lurasidone: a 10-year-old male experienced a prolonged, painful erection, consistent with priapism, that led to treatment discontinuation.

In this trial, the mean increase in height from open-label baseline to Week 104 was 4.94 cm. To adjust for normal growth, z-scores were derived (measured in standard deviations [SD]), which normalize for the natural growth of children and adolescents by comparisons to age- and sex-matched population standards. A z-score change <0.5 SD is considered not clinically significant. In this trial, the mean change in height z-score from open-label baseline to Week 104 was +0.05 SD, indicating minimal deviation from the normal growth curve.

3.4 Geriatric Use

No dose adjustment is necessary in elderly patients. 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.

Dosing recommendations for older patients with normal renal function (CrCl ≥80 ml/min) are the same as for adults with normal renal function. However, as older patients may have diminished renal function, dose adjustments may be required according to their renal function status (see “Patients with renal impairment”). Renal function and cardiovascular status should be assessed prior to commencing treatment with LATUDA.

4 DRUG INTERACTIONS

4.1 Potential for Other Drugs to Affect LATUDA

LATUDA is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP4A11, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 enzymes. This suggests that an interaction of LATUDA with drugs that are inhibitors or inducers of these enzymes is unlikely.

LATUDA is predominantly metabolized by CYP3A4; interaction of LATUDA with strong and moderate inhibitors or inducers of this enzyme has been observed (Table 1). LATUDA should not be used in combination with strong CYP3A4 inhibitors (e.g., ketoconazole) or strong CYP3A4 inducers (e.g., rifampin).

Lithium: It is not necessary to adjust the LATUDA dose when used in combination with lithium (Table 1).

Given the primary central nervous system effects of lurasidone, LATUDA should be used with caution in combination with other centrally acting drugs and alcohol. Grapefruit and grapefruit juice inhibits CYP3A4 and may increase the serum levels of LATUDA. It should not be taken with LATUDA.

Table 1: Summary of Effect of Coadministered Medicines on Exposure to LATUDA in Healthy Subjects or Patients with Schizophrenia

Coadministered Medicine	**Dose Schedule**		**Effect on LATUDA Pharmacokinetics**		**Recommendation**
	Coadministered Medicine	**LATUDA**	**Cmax**	**AUC**	
Ketoconazole (strong CYP3A4 inhibitor)	400 mg/day for 7 days	10 mg single dose	6.8-fold increase	9.3-fold increase	Coadministration of LATUDA is contraindicated
Diltiazem (moderate CYP3A4 inhibitor)	240 mg/day for 5 days	20 mg single dose	2.1-fold increase	2.2-fold increase	LATUDA dose should not exceed 80 mg/day if coadministered
Rifampin (strong CYP3A4 inducer)	600 mg/day for 8 days	40 mg single dose	85% decrease	82-83% decrease	Coadministration of LATUDA is contraindicated
Lithium	600 mg BID for 8 days	120 mg/day for 8 days	92%[a]	107%[a]	No LATUDA dose adjustment required.

[a]Ratio of geometric least squares means (LATUDA + lithium/LATUDA)

4.2 Potential for LATUDA to Affect Other Drugs

Digoxin (P-gp substrate): Coadministration of LATUDA (120 mg/day) at steady state with a single dose of digoxin (0.25 mg) increased C_{max} and $AUC_{(0-24)}$ for digoxin by approximately 9% and 13%, respectively relative to digoxin alone. Digoxin dose adjustment is not required when coadministered with LATUDA.

Lithium: Coadministration of LATUDA (120 mg/day) and lithium (1200 mg/day) at steady state resulted in comparable mean lithium C_{max} values on Day 4 (0.65 mmol/L) and Day 8 (0.75 mmol/L) and maintenance of the therapeutic range for lithium (0.6 to 1.2 mmol/L). No adjustment of lithium dose is required when coadministered with LATUDA.

Midazolam (CYP3A4 substrate): Coadministration of LATUDA (120 mg/day) at steady state with a single dose of 5 mg midazolam increased midazolam C_{max} and $AUC_{(0-24)}$ by approximately 21% and 44%, respectively relative to midazolam alone. Midazolam dose adjustment is not required when coadministered with LATUDA.

Oral Contraceptive (estrogen/progesterone): Coadministration of LATUDA (40 mg/day) at steady state with an oral contraceptive (OC) containing ethinyl estradiol and norelgestimate resulted in equivalent $AUC_{(0-24)}$ and C_{max} of ethinyl estradiol and norelgestromin relative to OC administration alone. Also, sex hormone binding globulin levels were not meaningfully affected by coadministration of LATUDA and OC. Dose adjustment of OC dose is not required when coadministered with LATUDA.

5 CLINICAL STUDIES

5.1 Schizophrenia

Adult

Short-term Studies

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 2).

An analysis of patients with a ≥30% reduction from baseline PANSS score (clinical response analysis) was performed in three of these studies. The placebo response rate was around 35% across the studies and the response rates for LATUDA 40 mg, 80 mg, and 120 mg were all around 50%, giving a 15% difference in response rates from placebo and a NNT of 6.7 for one patient to achieve a clinically significant improvement. One study assessed efficacy of the 160 mg dose and 120 patients were given this dose. The response rate for 160 mg LATUDA was 63%, a NNT of approximately 3.6. There was limited evidence of dose response for doses between 40 mg and 80 mg.

Table 2: 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[a] (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)*[b]	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)*[b]	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.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
[b] 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.

Long-term Studies

Long-term maintenance efficacy of LATUDA (40 to 160 mg) was demonstrated in a 12 month non-inferiority trial with quetiapine extended release (XR) (200 to 800 mg once daily). LATUDA was non-inferior to quetiapine XR in time to relapse of schizophrenia. LATUDA had a small increase from baseline to Month 12 in body weight and body mass index (Mean (SD): 0.73 (3.36) kg and 0.28 (1.17) kg/m^2, respectively) compared to quetiapine XR (1.23 (4.56) kg and 0.45 (1.63) kg/m^2, respectively). Overall, LATUDA had a negligible effect on weight and other metabolic parameters including total cholesterol, triglycerides, and glucose levels.

In a long-term safety study, clinically stable patients were treated using 40 to 120 mg LATUDA or 2 to 6 mg risperidone. In this study, the rate of relapse over a 12-month period was 20% for LATUDA and 16% for risperidone. This difference neared, but did not reach, statistical significance.

In a long-term study designed to assess the maintenance of effect, LATUDA was more effective than placebo in maintaining symptom control and delaying relapse of schizophrenia. After having been treated for an acute episode and stabilized for a minimum of 12 weeks with LATUDA, patients were then randomized in a double-blind manner to either continue on LATUDA or on placebo until they experienced a relapse in schizophrenia symptoms. In the primary analysis of time to relapse in which patients that withdrew without relapse were censored at the time of withdrawal, patients on LATUDA showed a significantly longer time to relapse compared with patients on placebo (p=0.039). The Kaplan-Meier estimates of the probability of relapse at Week 28 were 42.2% for LATUDA and 51.2% for placebo. The probability of all-cause discontinuation at Week 28 were 58.2% for LATUDA and 69.9% for placebo (p=0.072).

Adolescents

The efficacy of LATUDA in the treatment of schizophrenia in adolescent patients (13 to 17 years of age) was evaluated in one 6-week, placebo-controlled study of patients (N=327) who met DSM-IV criteria for schizophrenia. Both the 80 mg and 40 mg doses of LA demonstrated superiority over placebo on the PANSS total score after 6 weeks of double-blind treatment (Table 3).

Table 3: Summary of Results for Primary Efficacy Endpoints

Primary Endpoint	**LS Mean (SE)a Difference from Placebo in Change from Baseline**	
	LATUDA	
	40 mg/day	**80 mg/day**
PANSS	-8.0 (2.21)*	-7.7 (2.22)*

*adjusted p-value ≤0.001
non-adjusted p-value ≤0.05
[a] Least Squares Mean (Standard Error)
PANSS: Positive and Negative Syndrome Scale

A 104-week open-label uncontrolled extension study (Study D1050302) was designed to evaluate the long-term safety, tolerability, and effectiveness of flexibly dosed lurasidone (20, 40, 60 or 80 mg/day) in pediatric subjects who completed a 6-week double-blind, placebo-controlled treatment period in preceding studies of three indications. Only results for 271 subjects with schizophrenia who enrolled from Study D1050301 are hereinafter presented. Of these, 213 subjects (78.6%), 186 subjects (68.6%) completed through 28 and 52 weeks, and 156 (57.6%) subjects completed 104 weeks of treatment period.
For PANSS total score, the mean baseline (± SD) in Study D1050301 and Study D1050302 were 93.5 ± 11.01 and 76.0 ± 17.72, respectively; the mean change (± SD) from baseline of Study D1050301 was -29.2 ± 14.73 at Week 28 and decreased further to -32.4 ± 14.61 at Week 52 and -34.3 ± 16.32 at Week 104.
Mean change (± SD) from baseline of Study D1050302 was -11.9 ± 13.74 at Week 28, -15.6 ± 14.97 at Week 52, -18.4 ± 16.73 at Week 104.

5.2 Bipolar Depression

Adults

Short-term Studies

Monotherapy

The efficacy of LATUDA, as monotherapy, was established in a 6-week, 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 depressive episodes associated with bipolar I disorder, with or without rapid cycling, and without psychotic features. Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 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 mean change from baseline in MADRS total 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 (Table 4). Change in quality of life was measured by the Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) total score at Week 6. There was no adjustment for multiplicity for this endpoint. The LS mean change in Q-LES-Q-SF total score from baseline was 19.3 in the Latuda 20-60 mg/day dose group, 19.8 in the Latuda 80-120 mg/day dose group, and 12.8 in the placebo group.

Adjunctive Therapy

The efficacy of LATUDA, as an adjunctive therapy to lithium or valproate, was established in a 6-week, 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 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 mean change from baseline in MADRS total 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 as an adjunctive therapy to lithium or valproate at Week 6 (Table 4). Change in quality of life was measured by the Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) total score at Week 6. There was no adjustment for multiplicity for this endpoint. The LS mean change in Q-LES-Q-SF total score form baseline was 22.2 in the Latuda (20-120 mg/day) + lithium or valproate dose group and 15.9 in the placebo + lithium or valproate group.

Table 4: Summary of Efficacy Results for Primary and Key Secondary Endpoints in Bipolar Depression Studies

	LS Mean (SE)[a] Difference from Placebo in Change from Baseline		
	Monotherapy study		**Adjunctive study**
	LATUDA	LATUDA	LATUDA

	20 to 60 mg/day	80 to 120 mg/day	20 to 120 mg/day + lithium or valproate
Primary Endpoint MADRS	-4.6* (1.2)	-4.6* (1.2)	-3.6* (1.3)
Key Secondary Endpoint CGI-BP-S	-0.7* (0.1)	-0.6* (0.1)	-0.4* (0.2)

* multiplicity adjusted p-value ≤0.01 compared to placebo group
[a] Least Squares Mean (Standard Error)

Pediatric Patients

The efficacy of LATUDA was established in a 6-week, multicenter, randomized, double-blind, placebo-controlled study of pediatric (10 to 17 years) who met DSM-5 criteria for a major depressive episode associated with bipolar I disorder, with or without rapid cycling, and without psychotic features (N=343). Patients were randomized to flexibly dosed LATUDA 20 to 80 mg/day or placebo.

The primary rating scale used to assess depressive symptoms in this study was the Children's Depression Rating Scale, Revised (CDRS-R) total score. The primary endpoint was the change from baseline in CDRS-R score at Week 6. The key secondary endpoint was the change from baseline in CGI-BP-S depression score.

LATUDA was superior to placebo in reduction of CDRS-R total score and CGI-BP-S depression score at Week 6. The primary efficacy results are provided in Table 5.

Table 5: Primary Efficacy Results for the Study in Depressive Episode Associated with Bipolar I Disorder (CDRS-R Total Score) in Pediatric Patients (10 to 17 years)

Treatment Group	Primary Efficacy Measure: CDRS-R		
	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
LATUDA (20 to 80 mg/day)*	59.2 (8.24)	-21.0 (1.06)	-5.7 (-8.4,-3.0)
Placebo	58.6 (8.26)	-15.3 (1.08)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval, unadjusted for multiple comparisons.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
* Treatment group statistically significantly superior to placebo.

6. INDICATIONS AND USAGE

LATUDA is indicated for:

• Treatment of adult and adolescent patients age 13 to 17 years with schizophrenia.

• Monotherapy treatment of adult and pediatric patients (13 to 17 years) with major depressive episode associated with bipolar I disorder (bipolar depression).

• Adjunctive treatment with lithium or valproate in adult patients with major depressive episode associated with bipolar I disorder (bipolar depression).

7. CONTRAINDICATIONS

LATUDA is contraindicated in any patient with a known hypersensitivity to lurasidone HCl or any components in the formulation.

LATUDA is contraindicated with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, and voriconazole) and strong CYP3A4 inducers (e.g., rifampin, St. John's wort, phenytoin, and carbamazepine).

8 WARNINGS AND PRECAUTIONS

8.1 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.

8.2 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

8.3 Extrapyramidal Symptoms (EPS)

Medicinal products with dopamine receptor antagonistic properties have been associated with extrapyramidal adverse reactions including rigidity, tremors, mask-like face, dystonias, drooling of saliva, drooped posture and abnormal gait. In placebo controlled clinical studies in adult patients with schizophrenia there was an increased occurrence of EPS following treatment with LATUDA compared to placebo.

8.4 Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS), characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels, has been reported in association with administration of antipsychotic drugs, including LATUDA.

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

8.5 Tardive Dyskinesia

Tardive dyskinesia is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can develop in patients treated with antipsychotic drugs, including lurasidone. 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.

8.6 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 < $1000/mm^3$) should discontinue LATUDA and have their WBC followed until recovery.

8.7 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. 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.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients 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.

Dyslipidemia

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

Schizophrenia

Adults

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 6.

Table 6: Change in Fasting Lipids in Adult Schizophrenia Studies

		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 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.

In long-term controlled studies, the rate of markedly abnormal metabolic parameters was similar between LATUDA, risperidone, and quetiapine XR. For patients given any dose of LATUDA, the rate of shift from normal to high total cholesterol was 2.2% and triglycerides was 6.2%.

Adolescents

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

Bipolar Depression

Adults

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**
Mean Change from Baseline (mg/dL)			
	n=147	**n=140**	**n=144**
Total cholesterol	-3.2	1.2	-4.6
Triglycerides	6.0	5.6	0.4
Proportion of Patients with Shifts			
Total cholesterol (≥ 240 mg/dL)	4.2% (5/118)	4.4% (5/113)	4.4% (5/114)
Triglycerides (≥ 200 mg/dL)	4.8% (6/126)	10.1% (12/119)	9.8% (12/122)

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy in the short-term and continued in the longer-term study had a mean change in total cholesterol and triglycerides of -0.5 mg/dL (n=130) and -1.0 mg/dL (n=130) at week 24, respectively.

Adjunctive Therapy with Lithium or Valproate

Data from the short-term, flexible-dosed, placebo-controlled, adjunctive therapy bipolar depression study are presented in Table 8.

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

	Placebo	LATUDA 20 to 120 mg/day
Mean Change from Baseline (mg/dL)		
	n=303	**n=321**
Total cholesterol	-2.9	-3.1
Triglycerides	-4.6	+4.6
Proportion of Patients with Shifts		
Total cholesterol (≥ 240 mg/dL)	5.7% (15/263)	5.4% (15/276)
Triglycerides (≥ 200 mg/dL)	8.6% (21/243)	10.8% (28/260)

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.

Pediatric Patients (10 to 17 years)

In the short-term, placebo-controlled bipolar depression study with pediatric patients 10 to 17 years, mean change in fasting cholesterol was -6.3 mg/dL for LATUDA 20 to 80 mg/day (n=144) and -1.4 mg/dL for placebo (n=145), and mean change in fasting triglyceride was -7.6 mg/dL for LATUDA 20 to 80 mg/day (n=144) and +5.9 mg/dL for placebo (n=145).

Weight Gain

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

Schizophrenia

Adults

The mean weight gain was 0.43 kg for LATUDA-treated patients compared to 0.02 kg for placebo-treated patients. 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.

Bipolar Depression

Adults

Monotherapy

The mean change in 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 and 0.7% for placebo-treated patients.

Adjunctive Therapy with Lithium or Valproate

The mean change in weight gain was +0.11 kg for LATUDA-treated patients compared to +0.16 kg for placebo-treated patients. The proportion of patients with a ≥7% increase in body weight (at Endpoint) was 3.1% for LATUDA-treated patients and 0.3% for placebo-treated patients.

Pediatric Patients (10-17 years)

The mean change in weight gain was +0.7 kg for LATDUA-treated patients compared to +0.5 kg for placebo-treated patients. The proportion of patients with a ≥7% increase in body weight (at Endpoint) was 4.0% for LATUDA-treated patients and 5.3% for placebo-treated patients.

8.8 Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 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. Premenopausal women who develop secondary amenorrhoea of greater than six months duration should receive appropriate preventative therapy to avoid hypooestrogenic bone loss.

Schizophrenia

Adults

In short-term, placebo-controlled schizophrenia studies, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was +0.4 ng/mL and 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.

Bipolar Depression

Adults

Monotherapy

The median change from baseline to endpoint in prolactin levels, in the adult 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.

Adjunctive Therapy with Lithium or Valproate

The median change from baseline to endpoint in prolactin levels, in the adult 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.

Pediatric Patients (10 to 17 years)

In the 6-week, placebo-controlled bipolar depression study with pediatric patients 10 to 17 years, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was +1.10 ng/mL and was +0.50 ng/mL for placebo-treated patients. For LATUDA-treated patients, the median change from baseline to endpoint for males was +0.85 ng/mL and for females was +2.50 ng/mL.

8.9 Orthostatic Hypotension, Syncope, and Cardiovascular Disease

LATUDA may cause orthostatic hypotension, perhaps due to its α1-adrenergic receptor antagonism. Caution should be exercised when LATUDA is prescribed in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction, ischemia, or conduction abnormalities), cerebrovascular disease, conditions that predispose the patient to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications) or family history of QT prolongation, hypokalaemia, and in concomitant use with other medicinal products thought to prolong the QT interval. Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

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. Due to the risk of orthostatic hypotension with LATUDA, caution should be observed in patients with known cardiovascular disease.

8.10 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.

8.11 Potential for Cognitive and Motor Impairment

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

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

8.12. Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicinal products. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with LATUDA and preventive measures undertaken.

8.13. 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.

8.14 Suicide

Antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adult patients. Closely monitor for clinical worsening and emergence of suicidal thoughts and behaviors.

Depressive episodes are associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission of depression occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. In addition to depressive episodes associated with bipolar disorder, depression may be co-morbid with schizophrenia.

Schizophrenia is also associated with an increased risk of suicide-related events, and thus close supervision and appropriate clinical management of high risk patients should accompany drug therapy.

Patients with a history of suicide-related events are also known to be at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

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.

8.15. Dysphagia

Oesophageal 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.

9. 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:

9.1. Increased Mortality in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled studies with similar atypical antipsychotics in elderly subjects with dementia-related psychosis, there was a higher incidence of fatalities compared to placebo-treated subjects. Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death compared to placebo. A meta-analysis of seventeen placebo-controlled trials with dementia-related behavioural disorders showed a risk of death in the drug-treated patients of between 1.6- to 1.7-times that seen in placebo-treated patients. The clinical studies included in the meta-analysis were undertaken with olanzapine, aripiprazole, risperidone, and quetiapine. Over the course of these studies, averaging about ten weeks in duration, the rate of death in drug-treated patients was about 4.5%, compared to a rate of approximately 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. LATUDA is not approved for elderly patients with dementia-related psychosis or behavioural disorders.

9.2. 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).

9.3. 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.

9.4. Orthostatic Hypotension

Educate patients about the risk of orthostatic hypotension, particularly at the time of initiating treatment, re-initiating treatment, or increasing the dose.

9.5. 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.

9.6. 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.

9.7. Pregnancy and Nursing

Instruct patients to notify their physician if they become pregnant or intend to become pregnant during therapy with LATUDA.

9.8. 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.

10 NONCLINICAL TOXICOLOGY

10.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

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.

Mutagenicity

LATUDA did not cause mutation or chromosomal aberration when tested *in vitro* and *in vivo* test battery. 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 which is 61 times the MRHD of 160 mg/day based on mg/m^2 body surface area.

Reproductive and Developmental Toxicity

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 gestation day 7. No effect was seen at the lowest dose of 0.1 mg/kg which is approximately 0.006 times the MRHD of 160 mg/day based on mg/m^2. 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 approximately equal to the MRHD based on mg/m^2.

LATUDA had no effect on fertility in male rats treated orally for 64 consecutive days prior to mating and during the mating period at doses up to 9 times the MRHD based on mg/m^2.

Pregnant rats were treated with oral LATUDA at doses of 3, 10, and 25 mg/kg/day during the period of organogenesis. These doses are 0.2, 0.6, and 1.5 times the MRHD of 160 mg/day based on mg/m^2 body surface area. No teratogenic or embryo-fetal effects were observed up to 1.5 times the MHRD of 160 mg/day, based on mg/m^2.

Pregnant rabbits were treated with oral LATUDA at doses of 2, 10, and 50 mg/kg/day during the period of organogenesis. These doses are 0.2, 1.2 and 6 times the MRHD of 160 mg/day based on mg/m^2. No teratogenic or embryo-fetal effects were observed up to 6 times the MHRD of 160 mg/day based on mg/m^2.

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

In juvenile animal studies, adverse effects were seen on growth, physical and neurobehavioral development at doses as low as 0.2 times the MRHD based on mg/m^2. LATUDA was orally administered to rats from postnatal days 21 through 91 (this period corresponds to childhood, adolescence, and young adulthood in humans) at doses of 3, 30, and 150 (males) or 300 (females) mg/kg/day which are 0.2 to 10 times (males) and 20 times (females) the maximum recommended adult human dose (MRHD) of 160 mg/day based on mg/m^2. The adverse effects included dose-dependent decreases in femoral length, bone mineral content, body and brain weights at 2 times the MRHD in both sexes, and motor hyperactivity at 0.2 and 2 times the MRHD in both sexes based on mg/m^2. In females, there was a delay in attainment of sexual maturity at 2 times the MRHD, associated with decreased serum estradiol. Mortality occurred in both sexes during early post-weaning period and some of the male weanlings died after only 4 treatments at doses as low as 2 times the MRHD based on mg/m^2. Histopathological findings included increased colloid in the thyroids and inflammation of the prostate in males at 10 times MRHD based on mg/m^2 and mammary

gland hyperplasia, increased vaginal mucification, and increased ovarian atretic follicles at doses as low as 0.2 times the MRHD based on mg/m^2. Some of these findings were attributed to transiently elevated serum prolactin which was seen in both sexes at all doses. However, there were no changes at any dose level in reproductive parameters (fertility, conception indices, spermatogenesis, estrous cycle, gestation length, parturition, number of pups born). The no effect dose for neurobehavioral changes in males is 0.2 times the MHRD based on mg/m^2 and could not be determined in females. The no effect dose for growth and physical development in both sexes is 0.2 times the MRHD based on mg/m^2.

11. ADVERSE REACTIONS

Schizophrenia

Adults

Summary of the safety profile

The safety of LATUDA has been evaluated at doses of 20 to 160 mg in clinical studies in patients with schizophrenia treated for up to 52 weeks and in the post marketing setting. The most common adverse drug reactions (ADRs) (≥10%) were akathisia and somnolence, which were dose related up to 120 mg daily.

Tabulated summary of adverse reactions

Adverse drug reactions (ADRs) based upon pooled data are shown by system, organ class and by preferred term are listed in Table 9. The incidence of ADRs reported in clinical trials is tabulated by frequency category. The following terms and frequencies are applied: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 9:

System Organ Class	Very Common	Common	Uncommon	Rare	Frequency not known
Infections and infestations			Nasopharyngitis		
Blood and lymphatic system disorders				Eosinophilia	Leukopenia**** Neutropenia**** Anemia****
Immune system disorders		hypersensitivity			

System Organ Class	Very Common	Common	Uncommon	Rare	Frequency not known
Metabolism and nutrition disorders		Weight increased	Decreased appetite Blood glucose increased Hyponatraemia		
Psychiatric disorders		Insomnia Agitation Anxiety Restlessness	Nightmare Catatonia		Suicidal behaviour**** Panic attack**** Sleep disorder****
Nervous system disorders	Akathisia Somnolence*	Parkinsonism** Dizziness Dystonia*** Dyskinesia	Lethargy Dysarthria Tardive dyskinesia	Neuroleptic malignant syndrome (NMS)	Convulsion****
Eye disorders			Blurred vision		
Ear and labyrinth disorders					Vertigo****
Cardiac disorders			Tachycardia		Angina**** AV block first degree**** Bradycardia****
Vascular disorders			Hypertension Hypotension Orthostatic hypotension Hot flush Blood pressure increased		
Gastrointestinal disorders		Nausea Vomiting Dyspepsia Salivary hypersecretion Dry mouth Upper abdominal pain Stomach discomfort	Flatulence		Diarrhoea**** Dysphagia**** Gastritis****
Hepatobiliary disorders			Alanine aminotransferase increased		
Skin and subcutaneous tissue disorders		Rash Pruritus	Hyperhidrosis	Angioedema	Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders		Musculoskeletal stiffness Blood creatine phosphokinase increase	Joint stiffness Myalgia Neck pain Back pain	Rhabdomyolysis	

System Organ Class	Very Common	Common	Uncommon	Rare	Frequency not known
Renal and urinary disorders		Serum creatinine increased	Dysuria		Renal failure****
Pregnancy, puerperium and perinatal conditions					Drug withdrawal syndrome neonatal (see 4.6)
Reproductive system and breast disorders			Blood prolactin increased		Breast enlargement**** Breast pain**** Galactorrhoea**** Erectile dysfunction**** Amenorrhoea**** Dysmenorrhoea****
General disorders and administration site conditions		Fatigue	Gait disturbance		Sudden death attributable to underlying cardiovascular disease observed during the clinical development programme****

*Somnolence includes adverse reaction terms: hypersomnia, hypersomnolence, sedation, and somnolence
**Parkinsonism includes adverse reaction terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor
***Dystonia includes adverse reaction terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus.
****ADRs noted in Phase 2 and 3 controlled and uncontrolled studies; however, the incidence of occurrence for these are too low to estimate frequencies.

Adolescents

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

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

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

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

Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6-weeks in adolescent patients with schizophrenia) are shown in Table 10

Table 10: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in the Adolescent Short-term Schizophrenia Study

	Percentage of Patients Reporting Reaction			
Body System or Organ Class Dictionary-derived Term	**Placebo (N=112)**	**LATUDA 40 mg/day (N=110)**	**LATUDA 80 mg/day (N=104)**	**All LATUDA (N=214)**
Gastrointestinal Disorders				
Nausea	3	13	14	14
Vomiting	2	8	6	8
Diarrhea	1	3	5	4
Dry Mouth	0	2	3	2
Infections and Infestations				
Viral Infection**	6	11	10	10
Rhinitis***	2	<1	8	4
Oropharyngeal pain	0	<1	3	2
Tachycardia	0	0	3	1
Nervous System Disorders				
Somnolence*	7	15	13	15
Akathisia	2	9	9	9
Dizziness	1	5	5	5

Note: Figures rounded to the nearest integer
* Somnolence includes adverse event terms: hypersomnia, sedation, and somnolence
** Viral Infection includes adverse event terms: nasopharyngitis, influenza, viral infection, upper respiratory tract infection
*** Rhinitis incudes adverse event terms: rhinitis, allergic rhinitis, rhinorrhea, and nasal congestion

In the long-term clinical studies, the most common ADRs (incidence ≥ 5%) in patients treated with LATUDA were headache, nausea somnolence, akathisia, and weight increased.

Irritability Associated with Autistic Disorder in Pediatric Patients

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

Short-term Studies

The following findings are based on a short-term, placebo-controlled premarketing studies for irritability associated with autistic disorder in which LATUDA was administered at daily doses ranging from 20 to 80 mg in pediatric patients ages 6-17 years (n=149).

The most common adverse events reported (incidence ≥ 5% and at least twice the rate of placebo) in patients treated with LATUDA were vomiting, somnolence, nasopharyngitis, akathisia, nausea, fatigue, and weight increased.

Adverse events reported 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 agitation associated with autism) are shown in Table 11.

Table 11: Adverse Events in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in the Short-term Autism Study

	Percentage of Patients Reporting Reaction	
Body System or Organ Class Dictionary-derived Term	**Placebo (N=49)**	**All LATUDA (N=100)**
Cardiac Disorders		
Tachycardia	0	2
Gastrointestinal Disorders		
Vomiting	4	18
Nausea	0	5
Gastritis	0	4
Constipation	2	3
Abdominal Discomfort	0	2
General Disorders And Administration Site Conditions		
Fatigue	2	5
Pyrexia	0	3

Body System or Organ Class Dictionary-derived Term	Percentage of Patients Reporting Reaction Placebo (N=49)	 All LATUDA (N=100)
Infections and Infestations		
Nasopharyngitis	0	8
Upper Respiratory Tract Infection	2	3
Rhinitis	0	2
Injury, Poisoning And Procedural Complications		
Laceration	2	3
Torus Fracture	0	2
Investigations		
Weight Increased	2	5
Weight Decreased	0	2
Nervous System Disorders		
Somnolence*	6	16
Akathisia	0	6
Psychomotor Hyperactivity	2	4
Lethargy	0	2
Psychiatric Disorders		
Aggression	0	3
Emotional Disorder	0	2
Initial Insomnia	0	2
Respiratory, Thoracic And Mediastinal Disorders		
Cough	4	5
Oropharyngeal Pain	0	2
Skin And Subcutaneous Tissue Disorders		
Urticaria	0	2

Note: Figures rounded to the nearest integer

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

Tabulated summary of adverse reactions from Schizophrenia and Autistic Disorder Clinical Studies in Pediatric and Adolescent Subjects

Table 12 includes a list of MedDRA terms that reflect adverse reactions and abnormal laboratory investigations reported by patients in clinical studies of schizophrenia and autism disorder within the database of 314 pediatric and adolescent subjects treated with

LATUDA at doses of ≥20 mg once daily. The reactions listed are considered plausibly drug-related on pharmacologic or other grounds, and are of clinical relevance in this patient population.

Within each frequency grouping, adverse reactions are presented in the alphabetic order. The frequency terms listed are categorized using CIOMS guidelines as follows: Very common (≥10%), common (≥ 1% and < 10%), uncommon (≥ 0.1% and < 1%), and rare (≥ 0.01% and < 0.1%). Based on the incidence rates from pediatric studies, the ADRs were categorized into "common" and "very common" as shown in Table 12.

Table 12: Tabulated Summary of Adverse Reactions from Schizophrenia and Autistic Disorder Clinical Studies in Pediatric and Adolescent Subjects

System Organ Class	Adverse Drug Reactions	
	Frequency	
	Very Common	Common
Cardiac Disorders		
		Tachycardia
Gastrointestinal Disorders		
	Nausea, Vomiting	*Dry mouth*
General Disorders and Administrative Site Conditions		
		Fatigue
Nervous System Disorders		
	Somnolence	*Akathisia, Dizziness,*

Bipolar Depression

Adults

Short-term Studies

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).

The most common adverse events reported (incidence ≥ 5% and at least twice the rate of placebo) in patients treated with LATUDA were akathisia and parkinsonism.

Adverse events reported 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-monotherapy) are shown in Table 13.

Table 13: (Treatment Emergent) Adverse Events in 2% or More of LATUDA-Treated Adult Patients (Monotherapy) That Occurred at Greater Incidence than in the Placebo-Treated Adult Patients in a Short-term Bipolar Depression Study

	Percentage of Patients Reporting Reaction	
Body System or Organ Class Dictionary-derived Term	**Placebo (N=168)**	**All LATUDA (N=331)**
Gastrointestinal Disorders		
Nausea	8	14
Dry Mouth	4	5
Vomiting	2	4
Diarrhea	2	4
Infections and infestations		
Nasopharyngitis	1	4
Nervous System Disorders		
Somnolence*	7	11
Akathisia	2	9
Parkinsonism**	2	6
Psychiatric Disorders		
Anxiety	1	4

Note: Figures rounded to the nearest integer

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

** Parkinsonism includes adverse event terms: drooling, muscle rigidity, parkinsonism, and tremor

Dose-Related Adverse Reactions in the Monotherapy Study:

In the adult short-term, placebo-controlled study (involving lower and higher LATUDA dose ranges) [see Clinical Studies (5.2)] 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.

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).

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

Adverse events reported 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-adjunctive therapy) are shown in Table 14.

Table 14: (Treatment Emergent) Adverse Events in 2% or More of LATUDA-Treated (Adjunctive Therapy) Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in a Short-term Bipolar Depression Study

	Percentage of Patients Reporting Reaction	
Body System or Organ Class Dictionary-derived Term	**Placebo+Li/VPA (N=334)**	**All LATUDA+Li/VPA (N=360)**
Gastrointestinal Disorders		
Nausea	10	14
Vomiting	1	4
General Disorders		
Fatigue	2	3
Infections and Infestations		
Nasopharyngitis	2	4
Investigations		
Weight Increased	1	3
Metabolism and Nutrition Disorders		
Increased Appetite	2	3
Nervous System Disorders		
Parkinsonism**	8	13
Somnolence*	5	11
Akathisia	5	11
Psychiatric Disorders		
Restlessness	1	4

Note: Figures rounded to the nearest integer

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

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

Pediatric Patients

The following findings are based on the pediatric patients short-term, placebo-controlled study for bipolar depression in which LATUDA was administered at daily doses ranging from 20 to 80 mg in pediatric patients 10-17 years (N=175).

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence ≥5%, and at least twice the rate of placebo) in pediatric patients (10 to 17 years) treated with LATUDA were nausea, weight increase, and insomnia.

Adverse Reactions Associated with Discontinuation of Treatment: The incidence of discontinuation due to adverse reactions between LATUDA- and placebo-treated pediatric patients 10 to 17 years was 2% and 2%, respectively.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-*Treated Patients:* Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in patients with bipolar depression) 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 the Short-term Bipolar Depression Study in Pediatric Patients (10 to 17 years)

	Percentage of Patients Reporting Reaction	
Body System or Organ Class **Dictionary-derived Term**	**Placebo** **(N=172)**	**LATUDA** **20 to 80 mg/day** **(N=175)**
Gastrointestinal Disorders		
Nausea	6	16
Vomiting	4	6
Abdominal Pain Upper	2	3
Diarrhea	2	3
Abdominal Pain	1	3
General Disorders And Administration Site Conditions		
Fatigue	2	3
Investigations		
Weight Increased	2	7
Metabolism and Nutrition Disorders		
Decreased Appetite	2	4
Nervous System Disorders		
Somnolence*	6	11
Extrapyramidal symptoms**	5	6
Dizziness	5	6
Psychiatric Disorders		

Insomnia	2	5
Abnormal Dreams	2	2
Respiratory, Thoracic and Mediastinal Disorders		
Oropharyngeal Pain	2	2

Note: Figures rounded to the nearest integer
*Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence
**EPS includes adverse event terms: akathisia, cogwheel rigidity, dyskinesia, dystonia, hyperkinesia, joint stiffness, muscle rigidity, muscle spasms, musculoskeletal stiffness, oculogyric crisis, parkinsonism, tardive dyskinesia, and tremor

Description of selected adverse reactions

Post marketing reports of clinically serious cases of skin and other hypersensitivity reactions have been reported in association with LATUDA treatment, including some reports of Stevens-Johnson syndrome.

Hypersensitivity may also include symptoms such as throat swelling, tongue swelling, urticaria, or symptoms of angioedema, rash or pruritus.

Hyponatremia: hyponatremia has been identified during the post-approval use of LATUDA.

Events of interest to the class
Extrapyramidal symptoms (EPS): In the short-term placebo controlled studies, the incidence of reported events related to EPS, excluding akathisia and restlessness, was 13.5% for LATUDA-treated subjects versus 5.8% for placebo-treated subjects. The incidence of akathisia for LATUDA-treated subjects was 12.9% versus 3.0% for placebo-treated subjects.

Dystonia: 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, difficulty swallowing, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity, higher potency and at higher doses of first generation antipsychotic medicinal products. An elevated risk of acute dystonia is observed in males and younger age groups.

Venous thromboembolism: Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs -Frequency unknown.

Somnambulism (sleep walking) and sleep-related eating disorder: Risk of somnambulism (sleep walking) and sleep-related eating disorder have been associated with the use of atypical antipsychotics.

12 DRUG ABUSE AND DEPENDENCE

12.1 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).

13 OVERDOSAGE

13.1 Management of Overdose

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.

14 DOSAGE AND ADMINISTRATION

14.1 Schizophrenia

Adults

The efficacy of LATUDA has been established at doses of 40, 80, 120 and 160 mg/day. The recommended starting dose of LATUDA is 40 mg once daily. Initial dose titration is not required. Patients should be treated with the lowest effective dose that provides optimal clinical response and tolerability, which is expected to be 40 mg or 80 mg once daily for most patients. Dose increase should be based on physician judgement and observed clinical response. In the six week controlled trials, there was no suggestion of added benefit with the 120 mg/day dose compared to 40 and 80 mg/day. In the pooled analyses, added benefit occurred at 160 mg/day compared to lower doses. Doses above 80 mg may be considered for certain patients based on individual clinical judgement. The maximum recommended dose is 160 mg/day. LATUDA should be taken with food (at least 350 calories).

Patients who have been receiving LATUDA for the treatment of schizophrenia, may continue maintenance therapy at the same dose.

Adolescents

The recommended starting dose of LATUDA is 40 mg/day. In a placebo-controlled clinical trial, LATUDA has been shown to be effective at doses of 40mg/day and 80mg/day. The maximum recommended dose is 80mg/day. Patients should be treated with the lowest effective dose that provides optimal clinical response and tolerability. In the placebo-controlled clinical trial, no additional benefit was demonstrated for 80mg over 40mg. LATUDA should be taken with food.

Switching Antipsychotics

There are no systematically collected data to specifically address switching patients from other antipsychotics to LATUDA or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized.

14.2 Depressive Episodes Associated with Bipolar I Disorder

Adults

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 (5.2)]. 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 (5.2)]. As the incidence of certain adverse events increase with dose [see Adverse Reactions (11)] patients should be treated with the lowest effective dose of LATUDA.

Pediatric Patients (13 – 17 years)

The recommended starting dose of LATUDA is 20 mg given once daily as monotherapy. Initial dose titration is not required. The dose may be increased after one week based on clinical response. LATUDA has been shown to be effective in a dose range of 20 mg per day to 80 mg per day as monotherapy. At the end of the clinical study, most of the patients (67%) received 20 mg or 40 mg once daily [see Clinical Studies (5.2)]. The maximum recommended dose is 80 mg per day.

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

14.3 Administration Instructions

Administration with food substantially increases the absorption of LATUDA. Administration with food increases the AUC approximately 2-fold and increases the Cmax approximately 3-fold. In the clinical studies, LATUDA was administered with food.

14.4 Dose Modifications in Special Populations

Renal Impairment

After administration of a single dose of 40 mg to patients with mild, moderate and severe renal impairment, mean Cmax increased by 40%, 92%, and 54%, respectively and mean AUC(0-∞) increased by 53%, 91% and 2-times, respectively compared to healthy matched subjects.

Caution should be exercised when starting LATUDA in patients with renal impairment. As the 20 mg tablet is not available in Singapore, it is not recommended that LATUDA be used in patients with moderate (creatinine clearance: 30 to <50 mL/min) or severe renal impairment (creatinine clearance <30 mL/min).

Hepatic Impairment

In a single-dose study of 20 mg, LATUDA mean AUC (0-last) was 1.5-times higher in subjects with mild hepatic impairment (Child-Pugh Class A), 1.7-times higher in subjects with moderate hepatic impairment (Child-Pugh class B) and 3-times higher in subjects with severe hepatic impairment (Child-Pugh Class C) compared to the values for healthy matched subjects. Mean Cmax was 1.3, 1.2, and 1.3-times higher for mild, moderate and severe hepatic impaired patients, respectively, compared to the values for healthy matched subjects.

Caution should be exercised when starting LATUDA in patients with hepatic impairment. As the 20 mg tablet is not available in Singapore, it is not recommended that LATUDA be used in patients with moderate (Child-Pugh Score = 7 to 9) or severe hepatic impairment (Child-Pugh Score = 10 to 15).

14.5 Dose Modifications Due to Drug Interactions

Concomitant Use with CYP3A4 Inhibitors

LATUDA should not be used in combination with a strong CYP3A4 inhibitor (e.g. ketoconazole) *[see Contraindications]*.

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 therapy, the recommended starting dose of LATUDA is 20 mg per day, the maximum recommended dose of LATUDA is 80 mg/day.

Grapefruit and grapefruit juice should be avoided in patients taking LATUDA, since these may inhibit CYP3A4 and alter LATUDA concentrations.

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]*. 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.

15 DOSAGE FORMS AND STRENGTHS

LATUDA tablets are available in the following shape and color (Table 16) with respective one-sided debossing:

Table 16: 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

16 HOW SUPPLIED/STORAGE AND HANDLING

LATUDA tablets are white to off-white, round (20 mg or 40 mg) and pale green, oval (80 mg) and identified with strength-specific one-sided debossing, “L20” (20 mg). “L40” (40 mg) or “L80” (80 mg). Tablets are supplied in the following strengths and package configurations (Table 17):

Table 17: Package Configuration for LATUDA Tablets

Tablet Strength	Package Configuration
20 mg	10 tablets in aluminium/ aluminium blister, 3 blisters are placed in a paper carton.
40 mg	10 tablets in aluminium/ aluminium blister, 3 blisters are placed in a paper carton.
80 mg	10 tablets in aluminium/ aluminium blister, 3 blisters are placed in a paper carton.

Storage

Store LATUDA tablets below 30°C (86°F).

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Repacked By:

OLIC (Thailand) Limited, Ayutthaya, Thailand

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