Lurasidone Hydrochloride Tablets
084-2025-02
2104100

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

LURASIDONE HYDROCHLORIDE tablets, for oral use

Initial U.S. Approval: 2010

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Lurasidone hydrochloride is not approved for the treatment of patients with dementia-related psychosis (5.1).**
- **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. (5.2).**

RECENT MAJOR CHANGES

Warnings and Precautions (5.7) 1/2025

INDICATIONS AND USAGE

Lurasidone hydrochloride tablets are an atypical antipsychotic indicated for the treatment of:

- Schizophrenia in adults and adolescents (13 to 17 years) (1, 14.1)
- Depressive episode associated with Bipolar I Disorder (bipolar depression) in adults and pediatric patients (10 to 17 years) as monotherapy (1, 14.2)
- Depressive episode associated with Bipolar I Disorder (bipolar depression) in adults as adjunctive therapy with lithium or valproate (1, 14.2)

DOSAGE AND ADMINISTRATION

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

Indication	Starting Dose	Recommended Dose
Schizophrenia - adults (2.1)	40 mg per day	40 mg to 160 mg per day
Schizophrenia - adolescents (13 to 17 years) (2.1)	40 mg per day	40 mg to 80 mg per day
Bipolar Depression - adults (2.2)	20 mg per day	20 mg to 120 mg per day
Bipolar Depression - pediatric patients (10 to 17 years) (2.2)	20 mg per day	20 mg to 80 mg per day

- Moderate and Severe Renal Impairment: Recommended starting dose is 20 mg per day, and the maximum recommended dose is 80 mg per day (2.4, 8.6).
- Moderate and Severe Hepatic Impairment: Recommended starting dose is 20 mg per day. The maximum recommended dose is 80 mg per day in moderate hepatic impairment and 40 mg per day in severe hepatic impairment (2.5, 8.7).
- Concomitant Use of a Moderate CYP3A4 inhibitor (e.g., diltiazem): Lurasidone hydrochloride tablets dose should be reduced to half of the original dose level. Recommended starting dose is 20 mg per day. Maximum recommended dose is 80 mg per day (2.6, 7.1).
- Concomitant Use of a Moderate CYP3A4 Inducer: It may be necessary to increase the dose of lurasidone hydrochloride tablets (2.6, 7.1).

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

- Known hypersensitivity to lurasidone hydrochloride tablets or any components in the formulation (4).
- Concomitant use with a strong CYP3A4 inhibitor (e.g., ketoconazole) (2.6, 4, 7.1).
- Concomitant use with a strong CYP3A4 inducer (e.g., rifampin) (2.6, 4, 7.1).

WARNINGS AND PRECAUTIONS

- Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis: Increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) (5.3).
- Neuroleptic Malignant Syndrome: Manage with immediate discontinuation and close monitoring (5.4).
- Tardive Dyskinesia: Discontinue if clinically appropriate (5.5).
- Metabolic Changes: Monitor for hyperglycemia/diabetes mellitus, dyslipidemia and weight gain (5.6).
- Hyperprolactinemia: Prolactin elevations may occur (5.7).
- Leukopenia, Neutropenia, and Agranulocytosis: Perform complete blood counts (CBC) in patients with a pre-existing low white blood cell count (WBC) or a history of leukopenia or neutropenia. Consider discontinuing lurasidone hydrochloride if a clinically significant decline in WBC occurs in the absence of other causative factors (5.8).
- Orthostatic Hypotension and Syncope: Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope (5.9).

ADVERSE REACTIONS

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

- Adult patients with schizophrenia: somnolence, akathisia, extrapyramidal symptoms, and nausea
- Adolescent patients (13 to 17 years) with schizophrenia: somnolence, nausea, akathisia, EPS (non-akathisia), rhinitis (80 mg only), and vomiting
- Adult patients with bipolar depression: akathisia, extrapyramidal symptoms, and somnolence
- Pediatric patients (10 to 17 years) with bipolar depression: nausea, weight increase, and insomnia.

To report SUSPECTED ADVERSE REACTIONS, contact Annora Pharma Private Limited at 1-866-495- 1995 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause extrapyramidal and or/withdrawal symptoms in neonates with third trimester exposure (8.1).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 02/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS

*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; and SUICIDAL THOUGHTS AND BEHAVIORS

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. Lurasidone hydrochloride is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1)]*.

Suicidal Thoughts and Behaviors

Antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adults in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

Lurasidone hydrochloride tablets are indicated for:

- Treatment of adult and adolescent patients (13 to 17 years) with schizophrenia *[see Clinical Studies (14.1)]*.
- Monotherapy treatment of adult and pediatric patients (10 to 17 years) with major depressive episode associated with bipolar I disorder (bipolar depression) *[see Clinical Studies (14.2)]*.
- Adjunctive treatment with lithium or valproate in adult patients with major depressive episode associated with bipolar I disorder (bipolar depression) *[see Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Schizophrenia

Adults

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

[illegible]

Age Range	Drug-Placebo Difference in Number of Patients of Suicidal Thoughts or Behaviors per 1000 Patients Treated
	Increases Compared to Placebo
< 18	14 additional patients
18 to 24	5 additional patients
	Decreases Compared to Placebo
25 to 64	1 fewer patient
≥ 65	6 fewer patients

It is unknown whether the risk of suicidal thoughts and behaviors in pediatric and young adult patients extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with MDD that antidepressants delay the recurrence of depression.

Monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing lurasidone hydrochloride, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

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

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

5.4 Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including lurasidone hydrochloride. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

If NMS is suspected, immediately discontinue lurasidone hydrochloride and provide intensive symptomatic treatment and monitoring.

5.5 Tardive Dyskinesia

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

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

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, lurasidone hydrochloride 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 lurasidone hydrochloride, drug discontinuation should be considered. However, some patients may require treatment with lurasidone hydrochloride despite the presence of the syndrome.

5.6 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of hyperglycemia-related adverse events in patients treated with the atypical antipsychotics.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Schizophrenia

Adults

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 3.

Table 3: Change in Fasting Glucose in Adult Schizophrenia Studies

	Placebo	Lurasidone Hydrochloride 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 schizophrenia studies (primarily open-label extension studies), lurasidone hydrochloride 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).

Adolescents

In studies of adolescents and adults with schizophrenia, changes in fasting glucose were similar. In the short-term, placebo-controlled study of adolescents, fasting serum glucose mean values were -1.3 mg/dL for placebo (n=95), +0.1 mg/dL for 40 mg/day (n=90), and +1.8 mg/dL for 80 mg/day (n=92).

Bipolar Depression

Adults

Monotherapy

Data from the adult short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study are presented in Table 4.

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

[illegible]

MEDICATION GUIDE

Lurasidone Hydrochloride [illegible]

What is the most important information I should know about lurasidone hydrochloride tablets?

Lurasidone hydrochloride tablets may cause serious side effects, including:

- **Increased risk of death in elderly people with dementia-related psychosis.** [illegible] lost touch with reality (psychosis) due to confusion and memory loss (dementia). [illegible] psychosis.
- **Increased risk of suicidal thoughts or actions in children and young adults.** [illegible] adults within the first few months of treatment and when the dose is changed.
  - **Depression and other serious mental illnesses are the most important** [illegible] **having suicidal thoughts or actions.** These include people who have (or have a [illegible] suicidal thoughts or actions.

How can I watch for and try to prevent suicidal thoughts and actions in myself [illegible]

- Pay close attention to any changes, especially sudden changes in mood, behavio[illegible] when the dose is changed.
- Call the healthcare provider right away to report new or sudden changes in mood, [illegible]
- Keep all follow-up visits with the healthcare provider as scheduled. Call the healthc[illegible]

Call a healthcare provider right away if you or your family member has any [illegible]

- thoughts about suicide or dying
- new or worse depression
- feeling very agitated or restless
- trouble sleeping (insomnia)
- acting aggressive, being angry, or violent
- an extreme increase in activity and talking (mania)
- attempts [illegible]
- new or w[illegible]
- panic att[illegible]
- new or w[illegible]
- acting o[illegible]
- other un[illegible]

What are Lurasidone hydrochloride tablets?

Lurasidone hydrochloride tablets are a prescription medicine used: [illegible]

Artwork information			
Customer	Annora	Market	USA
Dimensions (mm)	460 x 900 mm	Non Printing Colors	Die cut
Pharma Code No.	Front-1098 & Back-1099		
Printing Colours	Black		

Others: Pharma code position and Orientation are tentative, will be changed based on folding size.

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

Extrapyramidal Symptoms
Schizophrenia
Adults
In the short-term, placebo-controlled schizophrenia studies, for lurasidone hydrochloride-treated patients, the incidence of reported events related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness, was 13.5% and 5.8% for placebo-treated patients. The incidence of akathisia for lurasidone hydrochloride-treated patients was 12.9% and 3.0% for placebo-treated patients. Incidence of EPS by dose is provided in Table 24.

Table 24: Incidence of EPS Compared to Placebo in Adult Schizophrenia Studies

Adverse Event Term	Placebo (N=708) (%)	Lurasidone Hydrochloride 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

Adolescents
In the short-term, placebo-controlled, study of schizophrenia in adolescents, the incidence of EPS, excluding events related to akathisia, for lurasidone hydrochloride-treated patients was higher in the 40 mg (10%) and the 80 mg (7.7%) treatment groups vs. placebo (3.6%); and the incidence of akathisia-related events for lurasidone hydrochloride-treated patients was 8.9% vs. 1.8% for placebo-treated patients. Incidence of EPS by dose is provided in Table 25.

Table 25: Incidence of EPS Compared to Placebo in the Adolescent Schizophrenia Study

Adverse Event Term	Placebo (N=112) (%)	Lurasidone Hydrochloride 40 mg/day (N=110) (%)	80 mg/day (N=104) (%)
All EPS events	5	14	14
All EPS events, excluding Akathisia/Restlessness	4	7	7
Akathisia	2	9	9
Parkinsonism**	<1	4	0
Dyskinesia	<1	<1	1
Dystonia*	0	<1	1

Note: Figures rounded to the nearest integer
* Dystonia includes adverse event terms: dystonia, trismus, oculogyric crisis, oromandibular dystonia, tongue spasm, and torticollis
** Parkinsonism includes adverse event terms: bradykinesia, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, parkinsonism, and psychomotor retardation

Bipolar Depression
Adults
Monotherapy
In the adult short-term, placebo-controlled monotherapy bipolar depression study, for lurasidone hydrochloride-treated patients, the incidence of reported events related to EPS, excluding akathisia and restlessness was 6.9% and 2.4% for placebo-treated patients. The incidence of akathisia for lurasidone hydrochloride-treated patients was 9.4% and 2.4% for placebo-treated patients. Incidence of EPS by dose groups is provided in Table 26.

Table 26: Incidence of EPS Compared to Placebo in the Adult Monotherapy Bipolar Depression Study

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

Note: Figures rounded to the nearest integer
* Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus
** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

Adjunctive Therapy with Lithium or Valproate
In the adult short-term, placebo-controlled adjunctive therapy bipolar depression studies, for lurasidone hydrochloride-treated patients, the incidence of EPS, excluding akathisia and restlessness, was 13.9% and 8.7% for placebo. The incidence of akathisia for lurasidone hydrochloride-treated patients was 10.8% and 4.8% for placebo-treated patients. Incidence of EPS is provided in Table 27.

Table 27: Incidence of EPS Compared to Placebo in the Adult Adjunctive Therapy Bipolar Depression Studies

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

Note: Figures rounded to the nearest integer
* Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus
** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

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

Pediatric Patients (10 to 17 years)
In the 6-week, placebo-controlled study of bipolar depression in pediatric patients 10 to 17 years, the incidence of EPS, excluding events related to akathisia, for lurasidone hydrochloride-treated patients was similar in the lurasidone hydrochloride 20 to 80 mg/day (3.4%) treatment group vs. placebo (3.5%); and the incidence of akathisia-related events for lurasidone hydrochloride-treated patients was 2.9% vs. 3.5% for placebo-treated patients. Incidence of EPS by dose is provided in Table 28.

Table 28: Incidence of EPS Compared to Placebo in the Bipolar Depression Study in Pediatric Patients (10 to 17 years)

Adverse Event Term	Placebo (N=172) (%)	Lurasidone Hydrochloride 20 to 80 mg/day (N=175) (%)
All EPS events*	5	6
All EPS events, excluding Akathisia/Restlessness	4	3
Akathisia	4	3
Parkinsonism**	<1	<1
Dystonia***	1	<1
Salivary hypersecretion	<1	<1
Psychomotor hyperactivity	0	<1
Tardive Dyskinesia	<1	0

Note: Figures rounded to the nearest integer
* EPS include adverse event terms: akathisia, cogwheel rigidity, dyskinesia, dystonia, hyperkinesia, joint stiffness, muscle rigidity, muscle spasms, musculoskeletal stiffness, oculogyric crisis, parkinsonism, tardive dyskinesia, and tremor
** Parkinsonism includes adverse event terms: bradykinesia, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, parkinsonism, and psychomotor retardation
*** Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus

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

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

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

Adjunctive Therapy with Lithium or Valproate
The mean change from baseline for lurasidone hydrochloride-treated adult patients for the SAS, BAS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in lurasidone hydrochloride-treated patients and placebo for the BAS (lurasidone hydrochloride, 8.7%; placebo, 2.1%), the SAS (lurasidone hydrochloride, 2.8%; placebo, 2.1%) and the AIMS (lurasidone hydrochloride, 2.8%; placebo, 0.6%).

Pediatric Patients (10 to 17 years)
The mean change from baseline for lurasidone hydrochloride-treated pediatric patients 10 to 17 years with bipolar depression for the SAS, BAS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in lurasidone hydrochloride-treated patients and placebo for the BAS (lurasidone hydrochloride, 4.6%; placebo, 2.4%), the SAS (lurasidone hydrochloride, 0.6%; placebo, 0%) and was the same for the AIMS (lurasidone hydrochloride, 0%; placebo, 0%).

Dystonia
Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first-generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Schizophrenia
Adults
In the short-term, placebo-controlled schizophrenia clinical studies, dystonia occurred in 4.2% of lurasidone hydrochloride-treated subjects (0.0% lurasidone hydrochloride tablets 20 mg, 3.5% lurasidone hydrochloride tablets 40 mg, 4.5% lurasidone hydrochloride tablets 80 mg, 6.5% lurasidone hydrochloride tablets 120 mg and 2.5% lurasidone hydrochloride tablets 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 lurasidone hydrochloride tablets 80 mg/day and three were receiving lurasidone hydrochloride tablets 120 mg/day.

Adolescents
In the short-term, placebo-controlled, adolescent schizophrenia study, dystonia occurred in 1% of lurasidone hydrochloride-treated patients (1% lurasidone hydrochloride tablets 40 mg and 1% lurasidone hydrochloride tablets 80 mg) compared to 0% of patients receiving placebo. No patients discontinued the clinical study due to dystonic events.

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

Adjunctive Therapy with Lithium or Valproate
In the adult short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression studies, dystonia occurred in 1.1% of lurasidone hydrochloride tablets-treated subjects (20 to 120 mg) compared to 0.6% of subjects receiving placebo. No subject discontinued the clinical study due to dystonic events.

Pediatric Patients (10 to 17 years)
In the 6-week, placebo-controlled bipolar depression study in pediatric patients 10 to 17 years, dystonia occurred in 0.6% of lurasidone hydrochloride-treated patients compared to 1.2% of patients receiving placebo. No patients discontinued the clinical study due to dystonic events.

Other Adverse Reactions Observed During the Premarketing Evaluation of Lurasidone Hydrochloride
Following is a list of adverse reactions reported by adult patients treated with lurasidone hydrochloride tablets at multiple doses of ≥ 20 mg once daily within the premarketing database of 2905 patients with schizophrenia. The reactions listed are those that could be of clinical importance, as well as reactions that are plausibly drug-related on pharmacologic or other grounds. Reactions listed in Table 19 or those that appear elsewhere in the lurasidone hydrochloride label are not included.

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

Clinical Laboratory Changes
Schizophrenia
Adults
Serum Creatinine: In short-term, placebo-controlled trials, the mean change from Baseline in serum creatinine was +0.05 mg/dL for lurasidone hydrochloride-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 lurasidone hydrochloride-treated patients and 1.6% (11/681) on placebo. The threshold for high creatinine value varied from > 0.79 to > 1.3 mg/dL based on the centralized laboratory definition for each study (Table 29).

Table 29: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in Adult Schizophrenia Studies

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

Adolescents
Serum Creatinine: In the short-term, placebo-controlled, adolescent schizophrenia study, the mean change from Baseline in serum creatinine was -0.009 mg/dL for lurasidone hydrochloride-treated patients compared to +0.017 mg/dL for placebo-treated patients. A creatinine shift from normal to high (based on the centralized laboratory definition) occurred in 7.2% (14/194) of lurasidone hydrochloride-treated patients and 2.9% (3/103) on placebo (Table 30).

Table 30: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in the Adolescent Schizophrenia Study

Laboratory Parameter	Placebo (N=103)	Lurasidone Hydrochloride 40 mg/day (N=97)	Lurasidone Hydrochloride 80 mg/day (N=97)
Serum Creatinine Elevated	2.9%	7.2%	7.2%

Bipolar Depression
Adults
Monotherapy
Serum Creatinine: In the adult short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, the mean change from Baseline in serum creatinine was +0.01 mg/dL for lurasidone hydrochloride-treated patients compared to -0.02 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 2.8% (9/322) of lurasidone hydrochloride-treated patients and 0.6% (1/162) on placebo (Table 31).

Table 31: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in the Adult Monotherapy Bipolar Depression Study

Laboratory Parameter	Placebo (N=168)	Lurasidone Hydrochloride 20 to 60 mg/day (N=164)	Lurasidone Hydrochloride 80 to 120 mg/day (N=167)
Serum Creatinine Elevated	<1%	2%	4%

Adjunctive Therapy with Lithium or Valproate
Serum Creatinine: In adult short-term, placebo-controlled premarketing adjunctive studies for bipolar depression, the mean change from Baseline in serum creatinine was +0.04 mg/dL for lurasidone hydrochloride-treated patients compared to -0.01 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 4.3% (15/360) of lurasidone hydrochloride-treated patients and 1.6% (5/334) on placebo (Table 32).

Table 32: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in the Adult Adjunctive Therapy Bipolar Depression Studies

Laboratory Parameter	Placebo (N=334)	Lurasidone Hydrochloride 20 to 120 mg/day (N=360)
Serum Creatinine Elevated	2%	4%

Pediatric Patients (10 to 17 years)
Serum Creatinine: In the 6-week, placebo-controlled bipolar depression study in pediatric patients 10 to 17 years, the mean change from Baseline in serum creatinine was +0.021 mg/dL for lurasidone hydrochloride-treated patients compared to +0.009 mg/dL for placebo-treated patients. A creatinine shift from normal to high (based on the centralized laboratory definition) occurred in 6.7% (11/163) of lurasidone hydrochloride-treated patients and 4.5% (7/155) on placebo (Table 33).

Table 33: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in the Bipolar Depression Study in Pediatric Patients (10 to 17 years)

Laboratory Parameter	Placebo (N=155)	Lurasidone Hydrochloride 20 to 80 mg/day (N=163)
Serum Creatinine Elevated	4.5%	6.7%

Pediatric Patients (6 to 17 years)
In a 104-week, open-label study in pediatric patients with schizophrenia, bipolar depression, or autistic disorder, the mean change from baseline to Week 104 in serum creatinine was +0.07 mg/dL. In patients with a normal serum creatinine at baseline, 6% experienced a shift to high at endpoint.

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

7 DRUG INTERACTIONS
7.1 Drugs Having Clinically Important Interactions with Lurasidone Hydrochloride

Table 34: Clinically Important Drug Interactions with Lurasidone Hydrochloride

Strong CYP3A4 Inhibitors	
Clinical Impact:	Concomitant use of lurasidone hydrochloride with strong CYP3A4 inhibitors increased the exposure of lurasidone compared to the use of lurasidone hydrochloride alone *[see Clinical Pharmacology (12.3)]*.
Intervention:	Lurasidone hydrochloride should not be used concomitantly with strong CYP3A4 inhibitors *[see Contraindications (4)]*.
Examples:	Ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil
Moderate CYP3A4 Inhibitors	
Clinical Impact:	Concomitant use of lurasidone hydrochloride with moderate CYP3A4 inhibitors increased the exposure of lurasidone compared to the use of lurasidone hydrochloride alone *[see Clinical Pharmacology (12.3)]*.
Intervention:	Lurasidone hydrochloride dose should be reduced to half of the original level when used concomitantly with moderate inhibitors of CYP3A4 *[see Dosage and Administration (2.6)]*.
Examples:	Diltiazem, atazanavir, erythromycin, fluconazole, verapamil
Strong CYP3A4 Inducers	
Clinical Impact:	Concomitant use of lurasidone hydrochloride with strong CYP3A4 inducers decreased the exposure of lurasidone compared to the use of lurasidone hydrochloride alone *[see Clinical Pharmacology (12.3)]*.
Intervention:	Lurasidone hydrochloride should not be used concomitantly with strong CYP3A4 inducers *[see Contraindications (4)]*.
Examples:	Rifampin, avasimibe, St. John's wort, phenytoin, carbamazepine
Moderate CYP3A4 Inducers	
Clinical Impact:	Concomitant use of lurasidone hydrochloride with moderate CYP3A4 inducers decreased the exposure of lurasidone compared to the use of lurasidone hydrochloride alone *[see Clinical Pharmacology (12.3)]*.
Intervention:	Lurasidone hydrochloride dose should be increased when used concomitantly with moderate inducers of CYP3A4 *[see Dosage and Administration (2.6)]*.
Examples:	Bosentan, efavirenz, etravirine, modafinil, nafcillin

7.2 Drugs Having No Clinically Important Interactions with Lurasidone Hydrochloride
Based on pharmacokinetic studies, no dosage adjustment of lurasidone hydrochloride is required when administered concomitantly with lithium, valproate, or substrates of P-gp or CYP3A4 *[see Clinical Pharmacology (12.3)]*.

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

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

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

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

Pregnant rabbits were treated with oral lurasidone at doses of 2, 10, and 50 mg/kg/day during the period of organogenesis. These doses are 0.2, 1.2 and 6 times the MRHD of 160 mg/day based on mg/m². No teratogenic or embryo-fetal effects were observed up to 6 times the MRHD of 160 mg/day based on mg/m².

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

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

8.4 Pediatric Use
Schizophrenia
The safety and effectiveness of lurasidone hydrochloride 40 mg/day and 80 mg/day for the treatment of schizophrenia in adolescents (13 to 17 years) was established in a 6-week, placebo-controlled clinical study in 326 adolescent patients *[see Dosage and Administration (2.1), Adverse Reactions (6.1), and Clinical Studies (14.1)]*.

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

Bipolar Depression
The safety and effectiveness of lurasidone hydrochloride 20 to 80 mg/day for the treatment of bipolar depression in pediatric patients (10 to 17 years) was established in a 6-week, placebo-controlled clinical study in 347 pediatric patients *[see Dosage and Administration (2.2), Adverse Reactions (6.1), and Clinical Studies (14.2)]*.

The safety and effectiveness of lurasidone hydrochloride has not been established in pediatric patients less than 10 years of age with bipolar depression.

Irritability Associated with Autistic Disorder
The effectiveness of lurasidone hydrochloride 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 lurasidone hydrochloride tablets 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 lurasidone hydrochloride or placebo. Vomiting occurred at a higher rate than reported in other lurasidone hydrochloride studies (4/49 or 8% for 20 mg, 14/51 or 27% for 60 mg, and 2/49 or 4% for placebo), particularly in children ages 6 to 12 (13 out of 18 patients on lurasidone hydrochloride 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.

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

8.5 Geriatric Use
Clinical studies with lurasidone hydrochloride 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), lurasidone hydrochloride tablets concentrations (20 mg/day) were similar to those in young subjects. It is unknown whether dose adjustment is necessary on the basis of age alone.

Elderly patients with dementia-related psychosis treated with lurasidone hydrochloride are at an increased risk of death compared to placebo. Lurasidone hydrochloride is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.1, 5.3)]*.

8.6 Renal Impairment
Reduce the maximum recommended dosage in patients with moderate or severe renal impairment (CLcr < 50 mL/minute). Patients with impaired renal function (CLcr < 50 mL/minute) had higher exposure to lurasidone than patients with normal renal function *[see Clinical Pharmacology (12.3)]*. Greater exposure may increase the risk of lurasidone hydrochloride-associated adverse reactions *[see Dosage and Administration (2.4)]*.

8.7 Hepatic Impairment
Reduce the maximum recommended dosage in patients with moderate to severe hepatic impairment (Child-Pugh score ≥ 7). Patients with moderate to severe hepatic impairment (Child-Pugh score ≥ 7) generally had higher exposure to lurasidone than patients with normal hepatic function *[see Clinical Pharmacology (12.3)]*. Greater exposure may increase the risk of lurasidone hydrochloride-associated adverse reactions *[see Dosage and Administration (2.5)]*.

8.8 Other Specific Populations
No dosage adjustment for lurasidone hydrochloride is required on the basis of a patient's sex, race, or smoking status *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
Lurasidone hydrochloride is not a controlled substance.

9.2 Abuse
Lurasidone hydrochloride 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 lurasidone hydrochloride 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 lurasidone hydrochloride misuse or abuse (e.g., development of tolerance, drug-seeking behavior, increases in dose).

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

10.2 Management of Overdosage
No specific antidotes for lurasidone hydrochloride are known. In managing overdose, provide supportive care, including close medical supervision and monitoring, and consider the possibility of multiple drug involvement. If an overdose occurs, consult a Certified Poison Control Center (1-800-222-1222 or www.poison.org).

Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with an acute overdose of lurasidone hydrochloride.

Similarly, the alpha-blocking properties of bretylium might be additive to those of lurasidone hydrochloride, 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 lurasidone hydrochloride-induced alpha blockade. In case of severe extrapyramidal symptoms, anticholinergic medication should be administered.

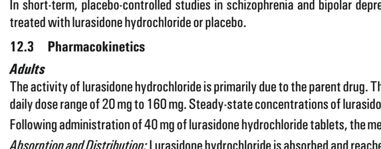
Gastric lavage (after intubation if patient is unconscious) and administration of activated charcoal together with a laxative should be considered.

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
Lurasidone hydrochloride 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 methanol.
Lurasidone hydrochloride tablets are intended for oral administration only. Each tablet contains 20 mg, 40 mg, 60 mg, 80 mg, or 120 mg of lurasidone hydrochloride.
Inactive ingredients are croscarmellose sodium, hypromellose, magnesium stearate, mannitol, polyethylene glycol, pregelatinized starch (maize), and titanium dioxide.

12 CLINICAL PHARMACOLOGY
12.1 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 D_2 and serotonin Type 2 ($5HT_{2A}$) receptor antagonism.

12.2 Pharmacodynamics
Lurasidone is an antagonist with high affinity binding at the dopamine D_2 receptors (Ki of 1 nM) and the serotonin $5\text{-}HT_{2A}$ (Ki of 0.5 nM) and $5\text{-}HT_7$ (Ki of 0.5 nM) receptors. It also binds with moderate affinity to the human α_{2C} adrenergic receptors (Ki of 11 nM), is a partial agonist at serotonin $5\text{-}HT_{1A}$ (Ki of 6.4 nM) receptors, and is an antagonist at the α_{2A} adrenergic receptors (Ki of 41 nM). Lurasidone exhibits little or no affinity for histamine H_1 and muscarinic M_1 receptors (IC_{50} > 1,000 nM).

ECG Changes
The effects of lurasidone hydrochloride 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 lurasidone hydrochloride doses of 120 mg daily, 600 mg daily and completed the study. The maximum mean (upper 1-sided, 95% CI) increase in baseline-adjusted QTc intervals based on individual correction method (QTcI) was 7.5 (11.7) ms and 4.6 (9.5) ms, for the 120 mg and 600 mg dose groups respectively, observed at 2 to 4 hours after dosing. In this study, there was no apparent dose (exposure)-response relationship.

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

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

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

Absorption and Distribution: Lurasidone hydrochloride is absorbed and reaches peak serum concentrations in approximately 1 to 3 hours. It is estimated that 9 to 19% of an administered dose is absorbed. Following administration of 40 mg of lurasidone hydrochloride tablets, the mean (%CV) apparent volume of distribution was 6173 (17.2) L. Lurasidone hydrochloride is highly bound (~99%) to serum proteins.

In a food effect study, lurasidone hydrochloride 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. Lurasidone hydrochloride exposure was not affected as meal size was increased from 350 to 1000 calories and was independent of meal fat content *[see Dosage and Administration (2.3)]*.

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

Metabolism and Elimination: Lurasidone hydrochloride is metabolized mainly via CYP3A4. The major biotransformation pathways are oxidative *N*-dealkylation, hydroxylation of norbornane ring, and *S*-oxidation. Lurasidone hydrochloride 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, lurasidone hydrochloride is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP4A11, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 enzymes. Because lurasidone hydrochloride is not a substrate for CYP1A2, smoking is not expected to have an effect on the pharmacokinetics of lurasidone hydrochloride.

Transporter proteins: In vitro studies suggest lurasidone hydrochloride is not a substrate of OATP1B1 or OATP1B3, however, is probably a substrate of P-gp and BCRP. *In vitro* studies indicate that lurasidone hydrochloride is not expected to inhibit transporters OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2-K and BSEP at clinically relevant concentrations. Lurasidone hydrochloride is not a clinically significant inhibitor of P-gp. However, it may inhibit BCRP.

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 [¹⁴C]-labeled lurasidone hydrochloride.

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

Drug Interaction Studies
Effects of other drugs on the exposure of lurasidone are summarized in Figure 1. A population PK analyses concluded that coadministration of lithium 300 to 2,400 mg/day or valproate 300 to 2,000 mg/day with lurasidone for up to 6 weeks has minimal effect on lurasidone exposure.

And the effects of lurasidone hydrochloride on the exposures of other drugs are summarized in Figure 2. A population PK analyses concluded that coadministration of lurasidone has minimal effect on lithium and valproate exposure when it is coadministered with lithium 300 to 2,400 mg/day or valproate 300 to 2,000 mg/day.

Figure 1: Impact of Other Drugs on Lurasidone Hydrochloride Pharmacokinetics

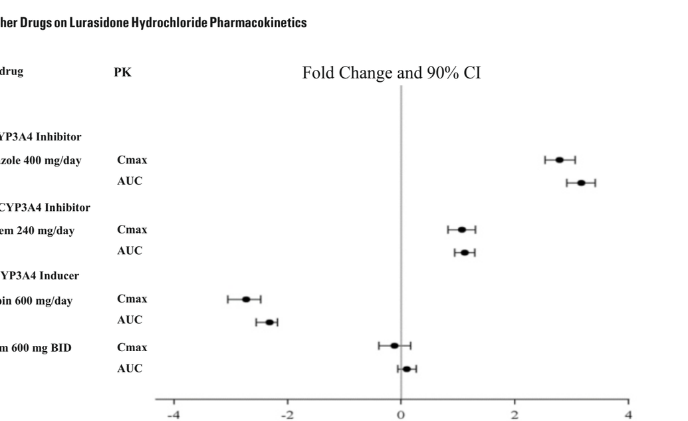
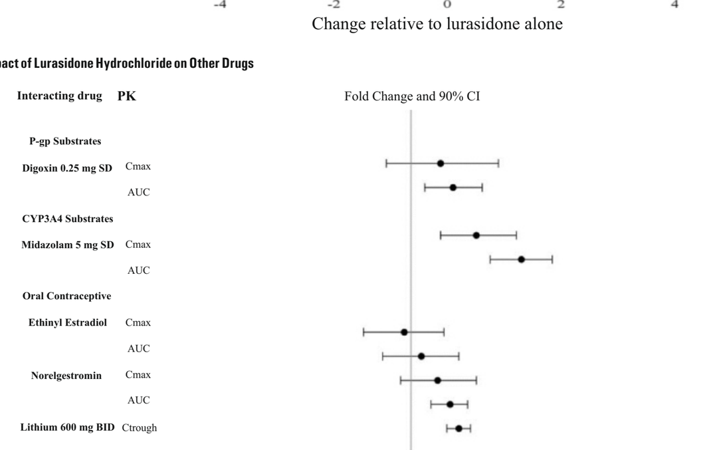


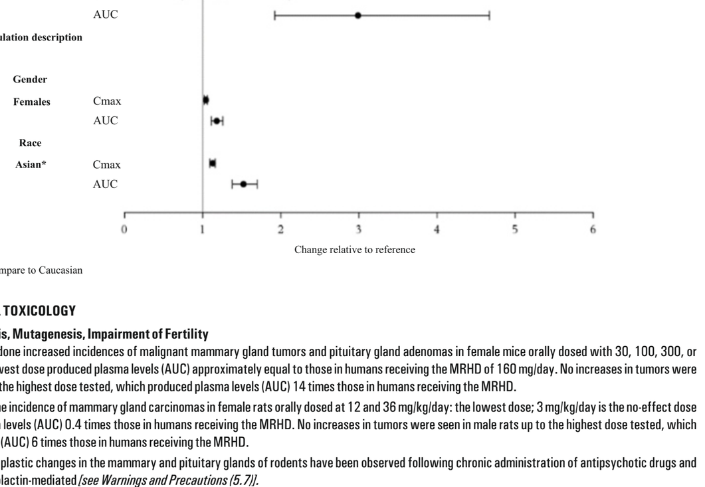
Figure 2: Impact of Lurasidone Hydrochloride on Other Drugs



Studies in Specific Populations
The effect of intrinsic patient factors on the pharmacokinetics of lurasidone hydrochloride is presented in Figure 3.

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

Figure 3: Impact of Other Patient Factors on Lurasidone Hydrochloride Pharmacokinetics



*Compare to Caucasian

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: Lurasidone 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.

Lurasidone 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 *[see Warnings and Precautions (5.7)]*.

Mutagenesis: Lurasidone did not cause mutation or chromosomal aberration when tested *in vitro* and *in vivo test battery*. Lurasidone 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 2,000 mg/kg which is 61 times the MRHD of 160 mg/day based on mg/m² body surface area.

Impairment of Fertility: Estrus cycle irregularities were seen in rats orally administered lurasidone 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/m². 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/m².

Lurasidone 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/m².

14 CLINICAL STUDIES
14.1 Schizophrenia
Adults
The efficacy of lurasidone hydrochloride 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 lurasidone hydrochloride tablets (40 or 120 mg/day), both doses of lurasidone hydrochloride 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 lurasidone hydrochloride tablets (80 mg/day), lurasidone hydrochloride 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 lurasidone hydrochloride tablets (40 or 120 mg/day) and an active control (olanzapine), both lurasidone hydrochloride 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 lurasidone hydrochloride tablets (40, 80 or 120 mg/day), only the 80 mg/day dose of lurasidone hydrochloride tablets 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 lurasidone hydrochloride tablets (80 or 160 mg/day) and an active control (quetiapine extended-release), both lurasidone hydrochloride doses and the active control at Endpoint were superior to placebo on the PANSS total score, and the CGI-S.

Thus, the efficacy of lurasidone hydrochloride tablets at doses of 40, 80, 120 and 160 mg/day has been established (Table 35).

Table 35: Primary Efficacy Results for Studies in Adult Patients with Schizophrenia (BPRSd or PANSS Scores)

Study	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
		Primary Efficacy Measure: BPRSd		
1	Lurasidone Hydrochloride (40 mg/day)*	54.2 (8.8)	-9.4 (1.6)	-5.6 (-9.8, -1.4)
	Lurasidone Hydrochloride (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	Lurasidone Hydrochloride (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	Lurasidone Hydrochloride (40 mg/day)*	96.6 (10.7)	-25.7 (2.0)	-9.7 (-15.3, -4.1)
	Lurasidone Hydrochloride (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	Lurasidone Hydrochloride (40 mg/day)	96.5 (11.5)	-19.2 (1.7)	-2.1 (-7.0, 2.8)
	Lurasidone Hydrochloride (80 mg/day)*	96.0 (10.8)	-23.4 (1.8)	-6.4 (-11.3, -1.5)
	Lurasidone Hydrochloride (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	Lurasidone Hydrochloride (80 mg/day)*	97.7 (9.7)	-22.2 (1.8)	-11.9 (-16.9, -6.9)
	Lurasidone Hydrochloride (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.

Adolescents (13 to 17 years)
The efficacy of lurasidone hydrochloride, was established in a 6-week, multicenter, randomized, double-blind, placebo-controlled study of adolescents (13 to 17 years) who met DSM-IV-TR criteria for schizophrenia (N=326). Patients were randomized to one of two fixed-doses of lurasidone hydrochloride (40 or 80 mg/day) or placebo.

The primary rating instrument used to assess psychiatric signs and symptoms was the PANSS. The key secondary instrument was the CGI-S.

For both dose groups, lurasidone hydrochloride was superior to placebo in reduction of PANSS and CGI-S scores at Week 6. On average, the 80 mg/day dose did not provide additional benefit compared to the 40 mg/day dose.

The primary efficacy results are provided in Table 36.

Table 36: Primary Efficacy Results (PANSS Total Score) for the Adolescent Schizophrenia Study

Treatment Group	Primary Efficacy Measure: PANSS Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Lurasidone hydrochloride (40 mg/day)*	94.5 (10.97)	-18.6 (1.59)	-8.0 (-12.4, -3.7)
Lurasidone hydrochloride (80 mg/day)*	94.0 (11.12)	-18.3 (1.60)	-7.7 (-12.1, -3.4)
Placebo	92.8 (11.08)	-10.5 (1.59)	--

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.
* Doses statistically significantly superior to placebo.

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

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

For both dose groups, lurasidone hydrochloride was superior to placebo in reduction of MADRS and CGI-BP-S scores at Week 6. The primary efficacy results are provided in Table 37. The high dose range (80 to 120 mg per day) did not provide additional efficacy on average, compared to the low dose range (20 to 60 mg per day).

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

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

Lurasidone hydrochloride was superior to placebo in reduction of MADRS and CGI-BP-S scores at Week 6, as an adjunctive therapy with lithium or valproate (Table 37).

Table 37: Primary Efficacy Results for Adult Studies in Depressive Episodes Associated with Bipolar I Disorder (MADRS Scores)

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

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

Pediatric Patients (10 to 17 years)
The efficacy of lurasidone hydrochloride was established in a 6-week, multicenter, randomized, double-blind, placebo-controlled study of pediatric patients (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 lurasidone hydrochloride tablets 20 to 80 mg/day or placebo. At the end of the clinical study, most patients (67%) received 20 mg/day or 40 mg/day.

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 CDRS-R is a 17-item clinician-rated scale with total scores ranging from 17 to 113. 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 CGIBP-S depression score.

Lurasidone hydrochloride 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 38.

Table 38: Primary Efficacy Results for the Study in Depressive Episodes 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)
Lurasidone hydrochloride (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.

16 HOW SUPPLIED/STORAGE AND HANDLING
Lurasidone Hydrochloride Tablets 20 mg: White to off white, round, biconvex tablets, debossed with "L" on one side and "1" on the other side.
Lurasidone Hydrochloride Tablets 40 mg: White to off white, round, biconvex tablets, debossed with "L" on one side and "2" on the other side.
Lurasidone Hydrochloride Tablets 60 mg: White to off white, oblong, biconvex tablets, debossed with "L" on one side and "3" on the other side.
Lurasidone Hydrochloride Tablets 80 mg: White to off white, oval, biconvex tablets, debossed with "L" on one side and "4" on the other side.
Lurasidone Hydrochloride Tablets 120 mg: White to off white, oval, biconvex tablets, debossed with "L" on one side and "5" on the other side.
Tablets are supplied in the following strengths and package configurations (Table 39).

Table 39: Package Configuration for Lurasidone Hydrochloride Tablets

Tablet Strength	Package Configuration	NDC Code
20 mg	Bottles of 30	31722-080-30
	Bottles of 90	31722-080-90
	Bottles of 500	31722-080-05
40 mg	Bottles of 30	31722-081-30
	Bottles of 90	31722-081-90
	Bottles of 500	31722-081-05
60 mg	Bottles of 30	31722-082-30
	Bottles of 90	31722-082-90
	Bottles of 500	31722-082-05
80 mg	Bottles of 30	31722-083-30
	Bottles of 90	31722-083-90
	Bottles of 500	31722-083-05
120 mg	Bottles of 30	31722-084-30
	Bottles of 90	31722-084-90
	Bottles of 500	31722-084-05

Storage
Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) *[See USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Suicidal Thoughts and Behavior
Advise patients and caregivers to look for the emergence of suicidality, especially early during treatment and when the dosage is adjusted up or down and instruct them to report such symptoms to the healthcare provider *[see Boxed Warning, Warnings and Precautions (5.2)]*.

Neuroleptic Malignant Syndrome
Counsel patients about a potentially fatal adverse reaction referred to as Neuroleptic Malignant Syndrome (NMS). Advise patients, family members, or caregivers to contact the healthcare provider or to report to the emergency room if they experience signs and symptoms of NMS *[see Warnings and Precautions (5.4)]*.

Tardive Dyskinesia
Counsel patients on the signs and symptoms of tardive dyskinesia and to contact their healthcare provider if these abnormal movements occur *[see Warnings and Precautions (5.5)]*.

Metabolic Changes
Educate patients about the risk of metabolic changes, how to recognize symptoms of hyperglycemia and diabetes mellitus, and the need for specific monitoring, including blood glucose, lipids, and weight *[see Warnings and Precautions (5.6)]*.

Hyperprolactinemia
Counsel patients on signs and symptoms of hyperprolactinemia that may be associated with chronic use of lurasidone hydrochloride. Advise them to seek medical attention if they experience any of the following: amenorrhea or galactorrhea in females, erectile dysfunction or gynecomastia in males *[see Warnings and Precautions (5.7)]*.

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 lurasidone hydrochloride *[see Warnings and Precautions (5.8)]*.

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

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 lurasidone hydrochloride therapy does not affect them adversely *[see Warnings and Precautions (5.12)]*.

Heat Exposure and Dehydration
Educate patients regarding appropriate care in avoiding overheating and dehydration *[see Warnings and Precautions (5.13)]*.

Activation of Mania or Hypomania
Advise patients and their caregivers to observe for signs of activation of mania/hypomania *[see Warnings and Precautions (5.14)]*.

Concomitant Medication
Advise 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 *[see Drug Interactions (7)]*.

Pregnancy
Advise patients that lurasidone hydrochloride may cause extrapyramidal and/or withdrawal symptoms in a neonate. Advise patients to notify their healthcare provider with a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Manufactured for:
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- ○ **increased fat levels (cholesterol and triglycerides) in your blood.**
- ○ **weight gain.** You and your healthcare provider should check your weight regularly during treatment with lurasidone hydrochloride tablets.
- **Increased prolactin levels in your blood (hyperprolactinemia).** Your healthcare provider may do blood tests to check your prolactin levels during treatment with lurasidone hydrochloride tablets. Tell your healthcare provider if you have any of the following signs and symptoms of hyperprolactinemia:

Females:
- ○ absence of your menstrual cycle
- ○ secretion of breast milk when you are not breastfeeding

Males:
- ○ problems getting or maintaining an erection (erectile dysfunction)
- ○ enlargement of breasts (gynecomastia)

Low white blood cell count. Your healthcare provider may do blood tests during the first few months of treatment with lurasidone hydrochloride tablets.

Decreased blood pressure (orthostatic hypotension). You may feel lightheaded or faint when you rise too quickly from a sitting or lying position.

Falls. Lurasidone hydrochloride tablets may make you sleepy or dizzy, may cause a decrease in your blood pressure when changing position (orthostatic hypotension), and can slow your thinking and motor skills which may lead to falls that can cause fractures or other injuries.

Seizures (convulsions)
- **Problems controlling your body temperature so that you feel too warm.** See "What should I avoid while taking lurasidone hydrochloride tablets?"
- **Mania or hypomania** (manic episodes) in people with a history of bipolar disorder. Symptoms may include:
  - ○ greatly increased energy
  - ○ racing thoughts
  - ○ unusually grand ideas
  - ○ talking more or faster than usual
  - ○ severe problems sleeping
  - ○ reckless behavior
  - ○ excessive happiness or irritability

Difficulty swallowing

The most common side effects of lurasidone hydrochloride tablets include:
- **Adults with schizophrenia:**
  - ○ sleepiness or drowsiness
  - ○ restlessness and feeling like you need to move around (akathisia)
  - ○ difficulty moving, slow movements, muscle stiffness, or tremor
  - ○ nausea
- **Children 13 to 17 years of age with schizophrenia:**
  - ○ sleepiness or drowsiness
  - ○ nausea
  - ○ restlessness and feeling like you need to move around (akathisia)
  - ○ difficulty moving, slow movements, muscle stiffness, or tremor
  - ○ runny nose
  - ○ vomiting
- **Adults with bipolar depression:**
  - ○ restlessness and feeling like you need to move around (akathisia)
  - ○ difficulty moving, slow movements, muscle stiffness, or tremor
  - ○ sleepiness or drowsiness
- **Children 10 to 17 years of age with bipolar depression:**
  - ○ nausea
  - ○ weight gain
  - ○ problems sleeping (insomnia)

These are not all of the possible side effects of lurasidone hydrochloride tablets.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store lurasidone hydrochloride tablets?
- Store lurasidone hydrochloride tablets at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep lurasidone hydrochloride tablets and all medicines out of the reach of children.

General information about the safe and effective use of lurasidone hydrochloride tablets.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use lurasidone hydrochloride tablets for a condition for which it was not prescribed. Do not give lurasidone hydrochloride tablets to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about lurasidone hydrochloride tablets that is written for health professionals.

What are the ingredients in lurasidone hydrochloride tablets?
Active ingredient: lurasidone hydrochloride
Inactive ingredients: croscarmellose sodium, hypromellose, magnesium stearate, mannitol, polyethylene glycol, pregelatinized starch (maize), and titanium dioxide.

Medication Guide available at http://camberpharma.com/medication-guides

Manufactured for:
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Piscataway, NJ 08854

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For more information, call 1-866-495- 1995.

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

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