140 mm

30 mm

For use in India only

℞

Lurasidone hydrochloride tablets 40 mg, 80 mg

Lurata®

लुराटा ४०

लुराटा ८०

MSN

Label Claim
Each Film coated tablet contains:
Lurasidone Hydrochloride ..... 40 mg
Colours : Titanium dioxide IP
Label Claim
Each film coated tablet contains:
Lurasidone Hydrochloride ..... 80 mg
Colours : Titanium dioxide IP

WARNING

WARNINGS: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; AND SUICIDAL THOUGHTS AND BEHAVIORS
- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.**
- **Lurasidone is not approved for the treatment of patients with dementia-related psychosis**
- **Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants**
- **Monitor for worsening and emergence of suicidal thoughts and behaviors**

TABLE OF CONTENTS

1. INDICATIONS AND USAGE

LURASIDONE is indicated for the treatment of patients with schizophrenia.
The efficacy of LURASIDONE in schizophrenia was established in five 6-week controlled studies of adult patients with schizophrenia.
The effectiveness of LURASIDONE for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LURASIDONE for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

2. DOSAGE AND ADMINISTRATION

The recommended starting dose of LURASIDONE is 40 mg once daily. Initial dose titration is not required. LURASIDONE has been shown to be effective in a dose range of 40 mg per day to 160 mg per day. The maximum recommended dose is 160 mg per day.

Administration Instructions

LURASIDONE should be taken with food (at least 350 calories). Administration with food substantially increases the absorption of LURASIDONE. Administration with food increases the AUC approximately 2-fold and increases the C_{max} approximately 3-fold. In the clinical studies, LURASIDONE was administered with food.

Dose Modifications in Special Populations

Renal Impairment

Dose adjustment is recommended in moderate (creatinine clearance: 30 to <50 mL/min) and severe renal impairment (creatinine clearance <30 mL/min) patients. The recommended starting dose is 40 mg per day. The dose in these patients should not exceed 80 mg per day.

Hepatic Impairment

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

Dose Modifications Due to Drug Interactions

Concomitant Use with CYP3A4 Inhibitors

LURASIDONE should not be used concomitantly with a strong CYP3A4 inhibitor (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, etc.).
If LURASIDONE is being prescribed and a moderate CYP3A4 inhibitor (e.g. diltiazem, atazanavir, erythromycin, fluconazole, verapamil etc.) is added to the therapy, the LURASIDONE dose should be reduced to half of the original dose level. Similarly, if a moderate CYP3A4 inhibitor is being prescribed and LURASIDONE is added to the therapy, the recommended starting dose of LURASIDONE is 40 mg per day, and the maximum recommended dose of LURASIDONE is 80 mg per day.
Grapefruit and grapefruit juice should be avoided in patients taking LURASIDONE, since these may inhibit CYP3A4 and alter LURASIDONE concentrations.

Concomitant Use with CYP3A4 Inducers

LURASIDONE should not be used concomitantly with a strong CYP3A4 inducer (e.g., rifampin, avasimibe, St. John's Wort, phenytoin, carbamazepine, etc.). If LURASIDONE is used concomitantly with a moderate CYP3A4 inducer, it may be necessary to increase the LURASIDONE dose after chronic treatment (7 days or more) with the CYP3A4 inducer.

3. DOSAGE FORMS AND STRENGTHS

LURASIDONE is available in the following dosage forms and strengths
Lurasidone Hydrochloride Tablets 40 mg and Lurasidone Hydrochloride Tablets 80 mg.

4. CONTRAINDICATIONS

- Known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone.
- Strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, etc.)
- Strong CYP3A4 inducers (e.g., rifampin, avasimibe, St. John's Wort, phenytoin, carbamazepine, etc.)

5. WARNINGS AND PRECAUTIONS

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. 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. Lurasidone is not approved for the treatment of patients with Dementia-related psychosis.

Suicidal Thoughts and Behaviors in Adolescents and Young Adults

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.
All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.
The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.
Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.
Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidal thoughts and behaviors, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers.

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

Lurasidone is not approved for the treatment of patients with dementia-related psychosis.

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.
Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.
The diagnostic evaluation of patients with this syndrome is complicated. It is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology. The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. If reintroduced, the patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

Tardive dyskinesia is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.
The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.
There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.
Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.
Given these considerations, Lurasidone 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, drug discontinuation should be considered. However, some patients may require treatment with Lurasidone despite the presence of the syndrome.

Metabolic changes

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

Hyperglycemia and Diabetes Mellitus

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

Hyperprolactinemia

As with other drugs that antagonize dopamine D2 receptors, Lurasidone 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.

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 lurasidone should be discontinued at the first sign of decline in WBC, in the absence of other causative factors.

Orthostatic Hypotension and Syncope

Lurasidone may cause orthostatic hypotension and syncope, perhaps due to its α1-adrenergic receptor antagonism. Associated adverse reactions can include dizziness, lightheadedness, tachycardia, and bradycardia. Generally, these risks are greatest at the beginning of treatment and during dose escalation. Patients at increased risk of these adverse reactions or at increased risk of developing complications from hypotension include those with dehydration, hypovolemia, treatment with antihypertensive medication, history of cardiovascular disease (e.g., heart failure, myocardial infarction, ischemia, or conduction abnormalities), history of cerebrovascular disease, as well as patients who are antipsychotic-naïve. In such patients, consider using a lower starting dose and slower titration, and monitor orthostatic vital signs. Orthostatic hypotension, as assessed by vital sign measurement, was defined by the following vital sign changes: ≥ 20 mm Hg decrease in systolic blood pressure and ≥ 10 bpm increase inpulse from sitting to standing or supine to standing position.

Seizures

As with other antipsychotic drugs, Lurasidone 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.

Potential for Cognitive and Motor Impairment

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

Body Temperature Dysregulation

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

Suicide

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

Activation of Mania/Hypomania

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

510 mm

Dysphagia

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

Neurological Adverse Reactions in Patients with Parkinson's disease or Dementia with Lewy Bodies

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

6. ADVERSE REACTIONS

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

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis.
- Suicidal Thoughts and Behaviors.
- Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-related Psychosis.
- Neuroleptic Malignant Syndrome
- Tardive Dyskinesia.
- Metabolic Changes (Hyperglycemia and Diabetes Mellitus, Dyslipidemia, and Weight Gain), Decreased appetite.
- Hyperprolactinemia
- Leukopenia, Neutropenia, Agranulocytosis, Anemia and Eosinophilia
- Orthostatic Hypotension and Syncope.
- Seizures.
- Potential for Cognitive and Motor Impairment.
- Body Temperature Dysregulation.
- Suicide.
- Activation of Mania/Hypomania, Insomnia, Agitation, Anxiety, Restlessness, Nightmare, Catatonia.
- Dysphagia.
- Neurological Adverse Reactions in Patients with Parkinson's Disease or Dementia with Lewy Bodies.

Other adverse events in clinical trials:

Infections and infestations: Nasopharyngitis

Nervous system disorders: Akathisia, Somnolence, Parkinsonism, Dizziness, Dystonia, Dyskinesia, Lethargy, Dysarthria

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: Hyperhidrosis, Rash, Pruritus, Angioedema

Musculoskeletal and connective tissue disorders: Musculoskeletal stiffness, Blood creatine phosphokinase increase, Joint stiffness, Myalgia, Neck pain, Back pain, Rhabdomyolysis

Renal and urinary disorders: Serum creatinine increased, Dysuria, Renal failure

Pregnancy, puerperium and perinatal conditions: Drug withdrawal syndrome neonatal

Reproductive system and breast disorders: Blood prolactin increased, Breast enlargement, Breast pain, Galactorrhoea, Erectile dysfunction, Amenorrhoea, Dysmenorrhoea

General disorders: Fatigue, Gait disturbance, Sudden death attributable to underlying cardiovascular disease observed during the clinical development programme

7. DRUG INTERACTIONS

Potential for other drugs to affect Lurasidone

Lurasidone is predominantly metabolized by CYP3A4. Lurasidone should not be used concomitantly with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, etc.) or strong CYP3A4 inducers (e.g., rifampin, avasimibe, St. John's wort, phenytoin, carbamazepine, etc.). The Lurasidone dose should be reduced to half of the original level when used concomitantly with moderate inhibitors of CYP3A4 (e.g., diltiazem, atazanavir, erythromycin, fluconazole, verapamil, etc.). If Lurasidone is used concomitantly with a moderate CYP3A4 inducer, it may be necessary to increase the Lurasidone dose.

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

Potential for Lurasidone to Affect Other Drugs

No dose adjustment is needed for lithium, substrates of P-gp (e.g., digoxin), CYP3A4, oral contraceptive combination pill ethinyl estradiol/norgestimate, midazolam or valproate when coadministered with lurasidone.

Drugs prolonging the QTc interval: i.e., antiarrhythmic drugs: [Class IA (quinidine, disopyramide) and Class III (amiodarone, sotalol)], pimozide, thioridazine, methadone, beperidil, cisapride, erythromycin, halofantrine, sparfloxacin: caution is advised when administered concomitantly with lurasidone

8. USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

Risk Summary

There are no adequate and well controlled studies of Lurasidone use in pregnant women. Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

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

Human Data

Safe use of Lurasidone during pregnancy or lactation has not been established; therefore, use of Lurasidone in pregnancy, in nursing mothers, or in women of childbearing potential requires that the benefits of treatment be weighed against the possible risks to mother and child.

Animal Data

No adverse developmental effects were observed in a study in which pregnant rats were given Lurasidone during the period of organogenesis and continuing through weaning at doses up to 10 mg/kg/day, which is approximately half of the maximum recommended human dose (MRHD) of 160 mg/day, based on mg/m^2 body surface area.

No teratogenic effects were seen in studies in which pregnant rats and rabbits were given lurasidone during the period of organogenesis at doses up to 25 and 50 mg/kg/day, respectively. These doses are 1.5- and 6-times, in rats and rabbits, respectively, the MRHD of 160 mg/day based on mg/m^2 body surface area.

Nursing Mothers

Lurasidone was excreted in milk of rats during lactation. It is not known whether lurasidone 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.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies with Lurasidone 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 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 are at an increased risk of death compared to placebo. Lurasidone is not approved for the treatment of patients with dementia-related psychosis.

9. DRUG ABUSE AND DEPENDANCE

LURASIDONE is not a controlled substance. LURASIDONE 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 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 misuse or abuse (e.g., development of tolerance, drug-seeking behavior, increases in dose).

10. OVERDOSAGE

Human Experience

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

Management of Overdosage

Consult a Certified Poison Control Center for up-to-date guidance and advice. There is no specific antidote to LURASIDONE, 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 LURASIDONE. Similarly, the alpha-blocking properties of bretylium might be additive to those of LURASIDONE, 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-induced alpha blockade. In case of severe extrapyramidal symptoms, anticholinergic medication should be administered.

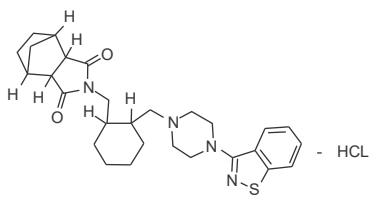
Gastric lavage (after intubation if patient is unconscious) and administration of activated charcoal together with a laxative should be considered.

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

Chemical Name: (3aR,4S,7R,7aS)-2-{(1R,2R)-2-[4-(1,2-benzisothiazol-3-yl)piperazin-1ylmethyl] cyclohexylmethyl}hexahydro-4,7-methano-2H-isoindole-1,3-dione hydrochloride.

Structural formula is:



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

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.

LURASIDONE tablets are intended for oral administration only. Each tablet contains 40 mg, 80 mg of lurasidone hydrochloride.

Inactive ingredients are Lactose Monohydrate, Mannitol, Pregelatinised starch, Croscarmellose Sodium, Povidone K-30,Citric acid anhydrous, Magnesium stearate, Opadry White & Opadry Green

Empirical formula: $C_{28}H_{36}N_4O_2S \cdot HCl$

Molecular weight: 529.14

12. PHARMACOLOGY

Mechanism of Action:

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

Pharmacodynamics:

LURASIDONE is an antagonist with high affinity binding at the dopamine D2 receptors (Ki=1 nM) and the 5-hydroxytryptamine (5-HT, serotonin) receptors 5-HT2A (Ki=0.5 nM) and 5-HT7 (Ki=0.5 nM) receptors. It also binds with moderate affinity to the human α2C adrenergic receptors (Ki=11 nM), is a partial agonist at serotonin 5-HT1A (Ki=6.4 nM) receptors, and is an antagonist at the α2A adrenergic receptors (Ki=41 nM). LURASIDONE exhibits little or no affinity for histamine H1 and muscarinic M1 receptors (IC50 > 1,000 nM).

Pharmacokinetics:

The activity of LURASIDONE is primarily due to the parent drug. The pharmacokinetics of LURASIDONE is dose-proportional within a total daily dose range of 40 mg to 80 mg. Steady-state concentrations of LURASIDONE are reached within 7 days of starting LURASIDONE.

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

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

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

In a food effect study, LURASIDONE mean Cmax and AUC were about 3-times and 2-times, respectively, when administered with food compared to the levels observed under fasting conditions. LURASIDONE exposure was not affected as meal size was increased from 350 to 1000 calories and was independent of meal fat content.

In clinical studies, establishing the safety and efficacy of LURASIDONE, patients were instructed to take their daily dose with food.

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

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 labeled LURASIDONE.

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

13. STORAGE

Store below 30°C.

Keep out of reach of children

Manufactured by:
MSN Laboratories Private Limited
(Formulations Division), Plot No. 42,
Anrich Industrial Estate, Bollaram,
Sangareddy District - 502 325,
Telangana, INDIA.

B32812-01