GRANADA 40 mg film-coated tablet

GRANADA 80 mg film-coated tablet

1. Name of the medicinal product

GRANADA 40 mg film-coated tablet

GRANADA 80 mg film-coated tablet

2. Qualitative and quantitative composition

GRANADA 40 mg film-coated tablet

Each film coated tablet contains lurasidone HCl 40 mg

GRANADA 80 mg film-coated tablet

Each film coated tablet contains lurasidone HCl 80 mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

GRANADA 40 mg film-coated tablet

White, round, biconvex film coated tabletwith engraved LU and 40 on one side and plain on the other.

GRANADA 80 mg film-coated tablet

Pale green, oval, biconvex film coated tablet with engraved LU and 80 on one side and plain on the other.

4. Clinical particulars

4.1 Therapeutic indication

Lurasidone is indicated for the treatment of schizophrenia.

4.2 Posology and method of administration

Adults

The recommended starting dose is 40 mg once daily. Initial dose titration is not required. Lurasidone is effective in a dose range of 40 to 160 mg once daily. Lurasidone should be taken with food (at least 350 calories).

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

Adolescents

The recommended starting dose of lurasidone is 40 mg/day. Lurasidone was studied in adolescent patients 13 to 17 years of age with schizophrenia at daily doses of 40 mg and 80 mg. Lurasidone should be taken with food.

Renal Impairment

After administration of a single dose of 40 mg to patients with mild, moderate and severe renal impairment, mean C_{max} increased by 40%, 92%, and 54%, respectively and mean $AUC_{(0-\infty)}$ increased by 53%, 91% and 2-times, respectively compared to healthy matched subjects.

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

Hepatic Impairment

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

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

Concomitant use with CYP3A4 inhibitors

Lurasidone is contraindicated in combination 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) 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 therapy, the maximum recommended dose of lurasidone is 80 mg/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 is contraindicated in combination with a strong CYP3A4 inducer (e.g., rifampin, avasimibe, St. John's wort, phenytoin, carbamazepine, etc.). If lurasidone is used in combination 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.

Switching between antipsychotic medicinal products

Data were collected in an open-label study to evaluate switching stable but symptomatic patients with schizophrenia from other antipsychotics to lurasidone. The recommended starting dose of lurasidone is 40 mg/day. Initial dose titration is not required.

Pediatric Population

The safety and effectiveness of lurasidone in pediatric patients aged less than 13 years have not been established.

Elderly Population

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

4.3 Contraindication

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

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

4.4 Special warning and precautions for use

Increased mortality in elderly patients with dementia-related psychosis

Elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death. Most deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Use with caution in patients with Lewy body dementia or Parkinson disease dementia due to greater risk of adverse effects, increased sensitivity to extrapyramidal effects, and association with irreversible cognitive decompensation or death. Lurasidone is not approved for the treatment of dementia-related psychosis.

Neuroleptic Malignant Syndrome

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

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, including lurasidone. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Given these considerations, lurasidone should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear in a patient on lurasidone, drug discontinuation should be considered.

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. Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < $1000/mm^3$) should discontinue lurasidone and have their WBC followed until recovery.

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.

Metabolic Changes

Hyperglycemia and diabetes mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control.

Dyslipidemia

Increases in total cholesterol and triglyceride concentrations have been observed with atypical antipsychotic use, incidence varies with product. Compared to other antipsychotics, the risk of metabolic side effects like dyslipidemia with lurasidone is minimal to low.

Weight gain

Weight gain has been observed with atypical antipsychotic use. Compared to other antipsychotics, the risk of weight gain with lurasidone is minimal to low. Clinical monitoring of weight is recommended.

Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, lurasidone elevates prolactin levels.

Orthostatic hypotension and syncope

Lurasidone may cause orthostatic hypotension, perhaps due to its α_1 -adrenergic receptor antagonism. Lurasidone should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction, ischemia, or conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

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.

4.5 Interaction with other medicinal products and other forms of interactions

Effects on lurasidone

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

Lurasidone is predominantly metabolized by CYP3A4; interaction of lurasidone with strong and moderate inhibitors or inducers of this enzyme has been observed (Table 1). Lurasidone is contraindicated in combination 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.).

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

Table 1: Summary of effect of coadministered medicines on exposure to lurasidone in healthy subjects or patients with schizophrenia

Coadministered medicine	**Dose schedule**		**Effect on lurasidone pharmacokinetics**		**Recommendation**
	Coadministered medicine	**Lurasidone**	**C_{max}**	**AUC**	
Ketoconazole (strong CYP3A4 inhibitor)	400 mg/day for 7 days	10 mg single dose	6.8-fold increase	9.3-fold increase	Coadministration of lurasidone is contraindicated
Diltiazem (moderate CYP3A4 inhibitor)	240 mg/day for 5 days	20 mg single dose	2.1-fold increase	2.2-fold increase	Lurasidone dose should not exceed 80 mg/day if coadministered
Rifampicin (strong CYP3A4 inducer)	600 mg/day for 8 days	40 mg single dose	85% decrease	82-83% decrease	Coadministration of lurasidone is contraindicated
Lithium	600 mg BID for 8 days	120 mg/day for 8 days	92%[a]	107%[a]	No lurasidone dose adjustment required

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

Effects on coadministered drug

Digoxin (P-gp substrate)

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

Lithium

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

Midazolam (CYP3A4 substrate)

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

Oral contraceptive (estrogen/progesterone)

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

4.6 Pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with lurasidone. Lurasidone should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

Lactation

Lurasidone was excreted in milk of rats during lactation. It is not known whether lurasidone or its metabolites are excreted in human milk. Breast feeding in women receiving lurasidone should be considered only if the potential benefit justifies the potential risk to the child.

4.7 Effects on ability to drive and use machine

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

4.8 Undesirable effects

Lurasidone has been evaluated for safety at doses of 20 mg, 40 mg, 80 mg, 120 mg and 160 mg in clinical studies in patients with schizophrenia treated for up to 52 weeks.

Adults

Short-term studies

The following findings are based on the short-term, placebo-controlled studies for schizophrenia in which lurasidone was administered at daily doses ranging from 20 to 160 mg (n=1508).

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) in patients treated with lurasidone were somnolence, akathisia, nausea and parkinsonism.

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

Table 2: Adverse reactions in 2% or more of lurasidone-treated patients and that occurred at greater incidence than in the placebo-treated patients in short-term schizophrenia studies

Body system or organ class **Dictionary-derived term**	**Percentage of patients reporting reaction**	
	Placebo **(N=708)**	**All lurasidone** **(N=1508)**
Gastrointestinal disorders		
Nausea	5	10
Vomiting	6	8
Dyspepsia	5	6
Salivary hypersecretion	<1	2
Musculoskeletal and connective tissue disorders		
Back pain	2	3
Nervous system disorders		
Somnolence*	7	17
Akathisia	3	13
Parkinsonism**	5	10
Dizziness	2	4

Dystonia***	<1	5
Psychiatric disorders		
Insomnia	8	10
Agitation	4	5
Anxiety	4	5
Restlessness	1	2
Note: Figures rounded to the nearest integer * Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence ** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor *** Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus		

Long-term studies

In the long-term studies (≥28 weeks) with lurasidone in adults with schizophrenia (N=768), the most common adverse reactions (≥10%) in patients treated with lurasidone were somnolence, insomnia, akathisia, and nausea.

Other adverse reactions observed during the premarketing evaluation of lurasidone

Following is a list of adverse reactions reported by patients treated with lurasidone 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 2 or those that appear elsewhere in the lurasidone label are not included. Although the reactions reported occurred during treatment with lurasidone, they were not necessarily caused by it.

Reactions are further categorized by organ class and listed in order of decreasing frequency according to the following definitions: those occurring in at least 1/100 patients (frequent) (only those not already listed in the tabulated results from placebo-controlled studies appear in this listing); those occurring in 1/100 to 1/1000 patients (infrequent); and those occurring in fewer than 1/1000 patients (rare).

- Blood and lymphatic system disorders: Infrequent: anemia
- Cardiac disorders: Frequent: tachycardia; Infrequent: AV block 1st degree, angina pectoris, bradycardia
- Ear and labyrinth disorders: Infrequent: vertigo
- Eye disorders: Frequent: blurred vision
- Gastrointestinal disorders: Frequent: abdominal pain, diarrhea; Infrequent: dysphagia, gastritis

- General disorders and administrative site conditions: Rare: sudden death
- Investigations: Frequent: CPK increased
- Metabolism and nutritional system disorders: Frequent: decreased appetite
- Musculoskeletal and connective tissue disorders: Rare: rhabdomyolysis
- Nervous system disorders: Infrequent: cerebrovascular accident, dysarthria
- Psychiatric disorders: Infrequent: abnormal dreams, panic attack, sleep disorder
- Renal and urinary disorders: Infrequent: dysuria; Rare: renal failure
- Reproductive system and breast disorders: Infrequent: amenorrhea, dysmenorrhea; Rare: breast enlargement, breast pain, galactorrhea, erectile dysfunction
- Skin and subcutaneous tissue disorders: Frequent: rash, pruritus; Rare: angioedema
- Vascular disorders: Frequent: hypertension

Adolescents

Short-term Studies

The following findings are based on the short-term, placebo-controlled premarketing study for schizophrenia in which lurasidone was administered at daily doses ranging from 40 to 120 ng in adolescents ages 13-17 years (n=326).

The most common adverse events reported (incidence 25% and at least twice the rate of placebo) in patients treated with Lurasidone were somnolence, nausea, akathisia, and vomiting.

Adverse events reported with the use of Lurasidone (incidence of 2% or greater, rounded to the nearest percent and Lurasidone incidence greater than placebo) that occurred during acute therapy (up to 6-weeks in adolescent patients with schizophrenia) are shown in Table 3.

Table 3: Adverse events in 2% or more of lurasidone-treated adolescent patients that occurred at greater incidence than in the placebo-treated adolescent patients in the short-term schizophrenia study

Body system or organ class **Dictionary-derived term**	**Percentage of patients reporting reaction**	
	Placebo (N=112)	**All lurasidone (N=214)**
Gastrointestinal disorders		
Nausea	3	14
Vomiting	2	8
Diarrhea	<1	4

Dry mouth	0	2
Infections and infestations		
Viral infection	<1	2
Nervous system disorders		
Somnolence*	7	15
Akathisia	2	9
Dizziness	<1	5
Note: Figures rounded to the nearest integer * Somnolence includes adverse event terms: hypersomnia, sedation, and somnolence		

Postmarketing experiences

Hypersensitivity (occurring in at least 1/100 patients) and hyponatremia (occurring in 1/100 to 1/1000 patients) have been identified during the post approval use of lurasidone.

Hypersensitivity may include symptoms such as throat swelling, tongue swelling, urticarial, or symptoms of angioedema. Hypersensitivity may also include symptoms of severe cutaneous reactions such as dermatitis bullous, rash maculopapular, skin eruption, and skin exfoliation.

4.9 Overdose

Overdose data are limited. A specific toxic dose has not been established.

Similar to other atypical antipsychotic agents in that it has a propensity to produce extrapyramidal effects. Lurasidone does have alpha-1-adrenergic antagonist activity which may produce hypotension and other hemodynamic effects.

There are limited experience on mild to moderate poisoning. Drowsiness/lethargy, vomiting, tachycardia, hypertension, hypotension, conduction disturbance, dystonia, and ataxia have been reported.

There is no information on severe toxicity with lurasidone. Severe overdose might cause hypotension and altered mental status.

<u>Management of overdose</u>

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.

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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

It has been suggested that the efficacy of lurasidone in schizophrenia is mediated through a combination of central dopamine Type 2 (D_2) and serotonin Type 2 ($5\text{-}HT_{2A}$) receptor antagonism.

In vitro receptor binding studies revealed that lurasidone is an antagonist with high affinity at dopamine D_2 receptors (K_i = 0.994 nM) and the 5-hydroxytryptamine (5-HT, serotonin) receptors $5\text{-}HT_{2A}$ (K_i = 0.470 nM) and $5\text{-}HT_7$ (K_i= 0.495 nM), is an antagonist with moderate affinity for α_{2C} adrenergic receptors (K_i = 10.8 nM), is a partial agonist at serotonin $5\text{-}HT_{1A}$ (K_i = 6.38 nM) receptors, an antagonist at α_{2C} (K_i = 40.7 nM) and α_1 (K_i = 47.9 nM) adrenergic receptors. Lurasidone exhibits little or no affinity for histamine H_1 and muscarinic M_1 receptors (IC_{50} >1,000 nM).

The addition of serotonin antagonism to dopamine antagonism (classic neuroleptic mechanism) is thought to improve negative symptoms of psychoses and reduce the incidence of extrapyramidal side effects as compared to typical antipsychotics.

Schizophrenia

Adults

Short-term studies

The efficacy of lurasidone in the treatment of schizophrenia was established in five short-term (6-week), placebo-controlled, studies in adult patients who met DSM-IV criteria for schizophrenia. An active control arm (olanzapine or quetiapine XR) was included in two studies to assess assay sensitivity.

Several instruments were used for assessing psychiatric signs and symptoms in these studies:

1. Positive and Negative Syndrome Scale (PANSS), is a multi-item inventory of general psychopathology used to evaluate the effects of drug treatment in schizophrenia. PANSS total scores may range from 30 to 210.
2. Brief Psychiatric Rating Scale derived (BPRSd), derived from the PANSS, is a multi-item inventory primarily focusing on positive symptoms of schizophrenia, whereas the PANSS includes a wider range of positive, negative and other symptoms of schizophrenia. BPRSd scores may range from 18 to 126.

3. The Clinical Global Impression severity scale (CGI-S) is a validated 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 (Table 4):

1. In a 6-week, placebo-controlled trial (N=145) involving two fixed doses of lurasidone (40 or 120 mg/day), both doses of lurasidone at Endpoint were superior to placebo on the BPRSd total score, and the CGI-S.
2. In a 6-week, placebo-controlled trial (N=180) involving a fixed dose of lurasidone (80 mg/day), lurasidone at Endpoint was superior to placebo on the BPRSd total score, and the CGI-S.
3. In a 6-week, placebo and active-controlled trial (N=473) involving two fixed doses of lurasidone (40 or 120 mg/day) and an active control (olanzapine), both lurasidone doses and the active control at Endpoint were superior to placebo on the PANSS total score, and the CGI-S.
4. In a 6-week, placebo-controlled trial (N=489) involving three fixed doses of lurasidone (40, 80 or 120 mg/day), only the 80 mg/day dose of lurasidone at Endpoint was superior to placebo on the PANSS total score, and the CGI-S.
5. In a 6-week, placebo and active-controlled trial (N=482) involving two fixed doses of lurasidone (80 or 160 mg/day) and an active control (quetiapine XR), both lurasidone doses and the active control at Endpoint were superior to placebo on the PANSS total score, and the CGI-S.

Table 4: Summary of results for primary efficacy endpoints

Study number	**Primary endpoint**	**LS mean (SE)$^{\alpha}$ difference from placebo in change from baseline**					
		Lurasidone				**Olanzapine**	**Quetiapine XR**
		40 mg/day	**80 mg/day**	**120 mg/day**	**160 mg/day**	**15 mg/day**	**600 mg/day**
1	BPRSd	-5.6* (2.1)	-	-6.7* (2.2)	-	-	-
2	BPRSd	-	-4.7* (1.8)	-	-	-	-
3	PANSS	-9.7* (2.9)	-	-7.5* (3.0)	-	-12.6$^{\#}$ (2.8)	-
4	PANSS	-2.1 (2.5)	-6.4* (2.5)	-3.5 (2.5)	-	-	-

5	PANSS	-	-11.9[*] (2.6)	-	-16.2[*] (2.5)	-	-17.5[#] (2.6)

[*]adjusted p-value $\leq$0.05

[#]non-adjusted p-value $\leq$0.05

[α]Least Squares Mean (Standard Error)

BPRSd: Brief Psychiatric Rating Scale derived; PANSS: Positive and Negative Syndrome Scale

Long-term Studies

The efficacy of lurasidone for the long-term treatment of schizophrenia was established in two studies in adult patients. One study was a double-blind, placebo-controlled, randomized withdrawal study in patients aged 18 to 75 years, inclusive, experiencing an acute episode of schizophrenia. A total of 676 patients entered the open-label lurasidone stabilization phase (minimum of 12 weeks and maximum of 24 weeks). A total of 285 patients completed the open-label phase, met the criteria for clinical stability, and were randomized into the double-blind phase (maximum of 28 weeks) where they received either lurasidone 40 or 80 mg/day or placebo. Patients treated with lurasidone experienced a statistically significant longer time to relapse than patients who received placebo.

One study was a 12-month, double-blind, parallel-group, active-controlled (quetiapine XR) study in patients with schizophrenia, aged 18 to 75 years, inclusive. A total of 218 patients who received flexible doses of either lurasidone (40, 80, 120, or 160 mg/day) or quetiapine XR (200, 400, 600, or 800 mg/day) were included in the non-inferiority analysis. Lurasidone was demonstrated to be non-inferior to quetiapine XR in time to relapse.

Adolescents

The efficacy of lurasidone in the treatment of schizophrenia in adolescent patients (13 to 17 years of age) was evaluated in one 6-week, placebo-controlled study of patients (N=327) who met DSM-IV criteria for schizophrenia. Both the 80 mg and 40 mg doses of lurasidone demonstrated superiority over placebo on the PANSS total score after 6 weeks of double-blind treatment (Table 5).

Table 5: Summary of results for primary efficacy endpoints

Primary endpoint	**LS mean (SE)[α] difference from placebo in change from baseline**	
	Lurasidone	
	40 mg/day	**80 mg/day**
PANSS	-8.0 (2.21)*	-7.7 (2.22)*

[*]adjusted p-value $\leq$0.001

[α]Least Squares Mean (Standard Error)

PANSS: Positive and Negative Syndrome Scale

ECG Changes

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

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

5.2 Pharmacokinetic properties

Adults

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 20 mg to 160 mg. Steady-state concentrations of lurasidone are reached within 7 days of starting lurasidone. Following administration of 40 mg, the mean elimination half-life was 18 hours (7% coefficient of variation).

Children and adolescents

The pharmacokinetics of lurasidone, in pediatric patients 6-17 years of age, was similar to those in adults. There were no clinically relevant differences between genders in the pharmacokinetics of lurasidone in patients with schizophrenia.

Absorption

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.

In a food effect study, lurasidone 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 exposure was not affected as meal size was increased from 350 to 1000 calories and was independent of meal fat content.

Distribution

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

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 non-major active metabolites (ID-14283 and ID-14326) and two major non-active metabolites (ID-20219 and ID-20220).

Total excretion of radioactivity in urine and feces combined was approximately 89%, with about 80% recovered in feces and 9% recovered in urine, after a single dose of [14C]-labeled lurasidone.

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

5.3 Preclinical safety data

Reproductive toxicity

Lurasidone was not teratogenic in rats and rabbits. There are no adequate and well-controlled studies of lurasidone in pregnant women. 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 maximum recommended human dose (MRHD) of 160 mg/day based on body surface area. No adverse developmental effects were seen 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; this dose is approximately half of the MRHD based on body surface area.

Lurasidone was administered orally to female rats at doses of 0.1, 1.5, 15, or 150 mg/kg/day for 15 consecutive days prior to mating, during the mating period, and through day 7 of gestation. Estrus cycle irregularities were seen at 1.5 mg/kg and above; the no-effect dose of 0.1 mg/kg is approximately 0.006 times the MRHD of 160 mg/day based on body surface area. Fertility was reduced only at the highest dose and this was shown to be reversible after a 14 day drug-free period. The no-effect dose for reduced fertility was 15 mg/kg, which is 0.9 times the MRHD based on body surface area.

Fertility was not affected in male rats treated orally with lurasidone for 64 consecutive days prior to mating and during the mating period at doses up to 150 mg/kg/day (9 times the MRHD based on body surface area).

Mutagenicity

Lurasidone was not genotoxic in the Ames test, the in vitro chromosomal aberration test in Chinese Hamster Lung (CHL) cells, or the in vivo mouse bone marrow micronucleus test.

Carcinogenicity

Lifetime carcinogenicity studies were conducted in ICR mice and Sprague-Dawley rats. Lurasidone was administered orally at doses of 30, 100, 300, or 650 (the high dose was reduced from 1200 in males) mg/kg/day to ICR mice and 3, 12, or 36 (high dose reduced from 50) mg/kg/day to Sprague-Dawley rats. In the mouse study, there were increased incidences of malignant mammary gland tumors and pituitary gland adenomas in females at all doses; the lowest dose tested 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.

In rats, an increased incidence of mammary gland carcinomas was seen in females at the two higher doses; the no-effect dose of 3 mg/kg produced plasma levels (AUC) 0.4 times those in humans receiving the MRHD. No increases in tumors were seen in male rats up to highest dose tested, which produced plasma levels (AUC) 6 times those in human receiving the MRHD. Proliferative and/or neoplastic changes in the mammary and pituitary glands of rodents have been observed following chronic administration of antipsychotic drugs and are considered to be prolactin mediated. The relevance of this increased incidence of prolactin-mediated pituitary or mammary gland tumors in rodents in terms of human risk is unknown.

6. Pharmaceutical particulars

6.1 List of excipients

Mannitol, Pregelatinized Corn Starch, Croscarmellose Sodium, Povidone, Colloidal Silicon Dioxide, Magnesium Stearate, Hypromellose, Triethyl Citrate, Simethicone, Talc, Titanium Dioxide

6.2 Incompatibilities

- Not applicable

6.3 Shelf life

- 2 years

6.4 Special precautions for storage

- Store below 30 °C

6.5 Nature and contents of container

Aluminium - Aluminium blister (Al foil-Al/PVC) contains 10 tablets. Supply with paper box contain 1, 3, 10 blisters.

7. Marketing authorization holder

Manufacturer

Unison Laboratories Co., Ltd.

Chachoengsao, Thailand

8. Marketing authorization numbers

- GRANADA 40 Reg. No. 1A 49/67 (NG)
- GRANADA 80 Reg. No. 1A 50/67 (NG)

9. Date of first authorization/renewal of the authorization

6 September 2024

10. Date of revision of the text

November 2024