PATIENT INFORMATION LEAFLET (PIL)

Laroza® 20 mg, 40 mg, 80 mg and 120 mg Film-coated Tablets

Lurasidone Hydrochloride

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See "Possible side effects".

The product is known by the name above but will be referred to as Laroza throughout the rest of this leaflet.

In this leaflet:

1. Serious side effects
2. What Laroza is and what it is used for
3. What you need to know before you take Laroza
4. How to take Laroza
5. Possible side effects
6. How to store Laroza
7. Contents of the pack and other information

1. Serious side effects
- **Increased risk of death in elderly people with dementia-related psychosis**. Medicines like Laroza can raise the risk of death in elderly people who have lost touch with reality (psychosis) due to confusion and memory loss (dementia). Lurasidone is not approved for the treatment of people with dementia-related psychosis.
- **Increased risk of suicidal thoughts or actions in children and young adults**. Antidepressant medicines may increase suicidal thoughts or actions in some children and young adults within the first few months of treatment and when the dose is changed. Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions. These include people who have (or have a family history of) depression, bipolar illness (also called manic-depressive illness), or a history of suicidal thoughts or actions.

How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?
- Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
- Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
- Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:
- Thoughts about suicide or dying - Attempts to commit suicide - New or worse depression - New or worse anxiety - Feeling very agitated or restless - Panic attacks - Trouble sleeping (insomnia) - New or worse irritability - Acting aggressive, being angry, or violent - Acting on dangerous impulses - An extreme increase in activity and talking (mania) - Other unusual changes in behavior or mood

2. What Laroza is and what it is used for

Laroza is a prescription medicine used:
- To treat people 13 years of age or older with schizophrenia
- Alone to treat people 10 years of age and older with depressive episodes that happen with Bipolar I Disorder (bipolar depression).
- With the medicine lithium or valproate to treat adults with depressive episodes that happen with Bipolar I Disorder (bipolar depression).

It is not known if lurasidone is safe and effective in children: - Less than 13 years of age with schizophrenia - Less than 10 years of age with bipolar depression - For the treatment of irritability associated with autistic disorder.

3. What you need to know before you take Laroza

Do not take Laroza if you are
- Allergic to lurasidone hydrochloride or any of the ingredients in Laroza. See the end of this package leaflet for a complete list of ingredients in Laroza.
- Taking certain other medicines called CYP3A4 inhibitors or inducers including ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, rifampin, avasimibe, St. John's wort, phenytoin, or carbamazepine. Ask your healthcare provider if you are not sure if you are taking any of these medicines.

Warnings and Precautions

Before taking Laroza, tell your healthcare provider about all of your medical conditions, including if you:
• Have or have had heart problems or stroke • Have or have had low or high blood pressure • Have or have had diabetes or high blood sugar or have a family history of diabetes or high blood sugar. • Have or have had high levels of total cholesterol or triglycerides • Have or have had high prolactin levels • Have or have had low white blood cell count • Have or have had seizures • Have or have had kidney or liver problems • Are pregnant or plan to become pregnant. It is not known if lurasidone will harm your unborn baby. Talk to your healthcare provider about the risk to your unborn baby if you take lurasidone during pregnancy.
- Tell your healthcare provider if you become pregnant or think you are pregnant during treatment with Laroza
• Are breastfeeding or plan to breastfeed. It is not known if lurasidone passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during the treatment with lurasidone.

Other medicines and Laroza

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Laroza and other medicines may affect each other causing possible serious side effects. Laroza may affect the way other medicines work, and other medicines may affect how Laroza works. Your healthcare provider can tell you if it is safe to take Laroza with your other medicines. Do not start or stop any other medicines during treatment with Laroza without talking to your healthcare provider first. Know the medicines you take. Keep a list of your medicines to show your healthcare provider and pharmacist when you get a new medicine.

Laroza with food, drink and alcohol

Avoid eating grapefruit or drinking grapefruit juice during treatment with Laroza. Grapefruit and grapefruit juice may affect the amount of Laroza in your blood.

Driving and using machines

Do not drive, operate heavy machinery, or do other dangerous activities until you know how Laroza affects you. Laroza may make you drowsy.

Pregnancy and breast-feeding

Before taking Laroza, tell your healthcare provider if you:
• Are pregnant or plan to become pregnant. It is not known if lurasidone will harm your unborn baby. Talk to your healthcare provider about the risk to your unborn baby if you take lurasidone during pregnancy.
- Tell your healthcare provider if you become pregnant or think you are pregnant during treatment with Laroza
• Are breastfeeding or plan to breastfeed. It is not known if lurasidone passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with lurasidone.

Laroza contains lactose

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

4. How to take Laroza
- Take Laroza exactly as your healthcare provider tells you to take it. Do not change the dose or stop taking Laroza without first talking to your healthcare provider.
- Take Laroza by mouth, with food (at least 350 calories).
- If you take too much Laroza, call your healthcare provider or poison control center or go to the nearest hospital emergency room right away.

What should I avoid while taking Laroza
- Do not drive, operate heavy machinery, or do other dangerous activities until you know how Laroza affects you. Laroza may make you drowsy
- Avoid eating grapefruit or drinking grapefruit juice during treatment with Laroza. Grapefruit and grapefruit juice may affect the amount of Laroza in your blood.
- Do not become too hot or dehydrated during treatment with Laroza
  - Do not exercise too much. - In hot weather, stay inside in a cool place if possible. - Stay out of the sun. - Do not wear too much clothing or heavy clothing. - Drink plenty of water.

5. Possible side effects

Lurasidone may cause serious side effects, including:
- See "Serious side effects"
- Stroke (cerebrovascular problems) in elderly people with dementia-related psychosis that can lead to death.
- Neuroleptic malignant syndrome (NMS) a serious condition that can lead to death. Call your healthcare provider or go to the nearest hospital emergency room right away if you have some or all of the following signs and symptoms of NMS: - High fever - Stiff muscles - Confusion - Increased sweating - Changes in your breathing, heart rate, and blood pressure
- Uncontrolled body movements (tardive dyskinesia). Laroza may cause movements that you cannot control in your face, tongue, or other body parts. Tardive dyskinesia may not go away, even if you stop taking Laroza. Tardive dyskinesia may also start after you stop taking Laroza.
- Problems with your metabolism such as:
  - High blood sugar (hyperglycemia) and diabetes. Increase in blood sugar can happen in some people who take Laroza. Extremely high blood sugar can lead to coma or death. if you have diabetes or risk factors for diabetes (such as being overweight or a family history of diabetes), your healthcare provider should check your blood sugar before you start and during treatment with Laroza

  Call your healthcare provider if you have any of these symptoms of high blood sugar during treatment with Laroza:
  - Feel very thirsty - Need to urinate more than usual - Feel very hungry - Feel weak or tired - Feel sick to your stomach - Feel confused, or your breath smells fruity - Increased fat levels (cholesterol and triglycerides) in your blood.
  - Weight gain. You and your healthcare provider should check your weight regularly during treatment with Laroza.
- Increased prolactin levels in your blood (hyperprolactinemia). Your healthcare provider may do blood tests to check your prolactin levels during treatment with Laroza. Tell your healthcare provider if you have any of the following signs 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 Laroza
- Decreased blood pressure (orthostatic hypotension). You may feel lightheaded or faint when you rise too quickly from a sitting or lying position.
- Falls. Laroza 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 Laroza".
- Mania or hypomania (manic episodes) in people with a history of bipolar disorder. Symptoms may include:
  - Greatly increased energy - Severe problems sleeping - Racing thoughts - Reckless behavior - Unusually grand ideas - Excessive happiness or irritability - Talking more or faster than usual
- Difficulty swallowing

The most common side effects of lurasidone in adults 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.

Call your doctor for medical advice about side effects.

6. How to store Laroza

Keep this medicine out of the sight and reach of children. Do not store above 30°C. Store in the original package. Do not use this medicine after the expiry date which is stated on the carton after "EXP". The expiry date refers to the last day of that month. Do not use this medicine if you notice any visible signs of deterioration. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

7. Contents of the pack and other information

What Laroza contains

The active substance is lurasidone hydrochloride. Each film-coated tablet contains 20 mg, 40 mg, 80 mg or 120 mg lurasidone hydrochloride. The other ingredients are Mannitol D, lactose monohydrate, pregelatinized starch, croscarmellose sodium, Povidone K-30, citric acid anhydrous powder, magnesium stearate vegetable grade and Opadry white 03B28796.

What Laroza looks like and contents of the pack

Laroza 20 mg Film-coated tablets are white to off-white round film-coated tablets, plain on both sides in aluminum/aluminum blisters. Laroza 40 mg Film-coated Tablets are white to off-white round film-coated tablets, plain on both sides in aluminum/aluminum blisters. Laroza 80 mg Film-coated Tablets are white to off white oval shaped film-coated tablets plain on both sides in aluminum/aluminum blisters. Laroza 120 mg Film-coated Tablets are white to off white capsule shaped film-coated tablet plain on both sides in aluminum/aluminum blisters.

Pack size: 30 film-coated tablets.

Marketing Authorization Holder, Batch releaser and Bulk manufacturer

Hikma Pharmaceuticals, Bayader Wadi El Seer, Industrial Area, P.O. Box 182400, Amman 11118, Jordan
Tel: + (962-6) 5802900; Fax: + (962-6) 5817102, Website: www.hikma.com

For any information about this medicine, please contact the local representative of the Marketing Authorization Holder.

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Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly (see details below). By reporting side effects, you can also help provide more information on the safety of this medicine.
• Jordan: Jordan Food and Drug Administration- Rational Drug Use and Pharmacovigilance department
Tel: + (962-6) 5632000, e-mail: jpc@jfda.jo, Website: www.jfda.jo, Smart phones application: JFDA, Paper reporting form: Yellow card

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***The following information is intended for healthcare professionals only*:**

Indications:

Laroza is indicated for: • Treatment of adult and adolescent patients (13 to 17 years) with schizophrenia. • Monotherapy treatment of adult and pediatric patients (10 to 17 years) with major depressive episodes associated with bipolar I disorder (bipolar depression). • Adjunctive treatment with lithium or valproate in adult patients with major depressive episodes associated with bipolar I disorder (bipolar depression).

Posology and method of administration

Schizophrenia

• *Adults:* 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.

• *Adolescents (13-17 years)*: 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 80 mg per day. The maximum recommended dose is 80 mg per day.

Depressive Episodes Associated with Bipolar I Disorder

• *Adults:* The recommended starting dose of lurasidone is 20 mg given once daily as monotherapy or as adjunctive therapy with lithium or valproate. Initial dose titration is not required. Lurasidone has been shown to be effective in a dose range of 20 mg per day to 120 mg per day as monotherapy or as adjunctive therapy with lithium or valproate. The maximum recommended dose, as monotherapy or as adjunctive therapy with lithium or valproate, is 120 mg per day. In the monotherapy study, the higher dose range (80 mg to 120 mg per day) did not provide additional efficacy, on average, compared to the lower dose range (20 to 60 mg per day).

• *Pediatric Patients (10 – 17 years)*: The recommended starting dose of lurasidone is 20 mg given once daily as monotherapy. Initial dose titration is not required. The dose may be increased after one week based on clinical response. Lurasidone has been shown to be effective in a dose range of 20 mg per day to 80 mg per day as monotherapy. At the end of the clinical study, most of the patients (67%) received 20 mg or 40 mg once daily. The maximum recommended dose is 80 mg per day.

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

Administration Information

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.

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.

Dose Modifications for Renal Impairment

Dose adjustment is recommended in moderate (creatinine clearance: 30 to <50 mL/min) and severe renal impairment (creatinine clearance <30 mL/min) patients. The recommended starting dose is 20 mg per day. The dose in these patients should not exceed 80 mg per day.

Dose Modifications for Hepatic Impairment

Dose adjustment is recommended in moderate (Child-Pugh Score = 7 to 9) and severe hepatic impairment (Child-Pugh Score = 10 to 15) patients. The recommended starting dose is 20 mg 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 of CYP3A4 Inhibitors and CYP3A4 Inducers

Concomitant Use with CYP3A4 Inhibitors

Laroza should not be used concomitantly with a strong CYP3A4 inhibitor (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, etc.). If Laroza is being prescribed and a moderate CYP3A4 inhibitor (e.g. diltiazem, atazanavir, erythromycin, fluconazole, verapamil etc.) is added to the therapy, the Laroza dose should be reduced to half of the original dose level. Similarly, if a moderate CYP3A4 inhibitor is being prescribed and Laroza is added to the therapy, the recommended starting dose of Laroza is 20 mg per day, and the maximum recommended dose of Laroza is 80 mg per day. Grapefruit and grapefruit juice should be avoided in patients taking Laroza, since these may inhibit CYP3A4 and alter Laroza concentrations.

Concomitant Use with CYP3A4 Inducers

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

Pediatric Use

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

• *Bipolar Depression:* The safety and effectiveness of lurasidone 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.

The safety and effectiveness of lurasidone 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 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 20 mg/day and 40 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 or placebo. Vomiting occurred at a higher rate than reported in other lurasidone 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 with vomiting).

• *Juvenile animal studies:* Adverse effects were seen on growth, physical and neurobehavioral development at doses as low as 0.2 times the MRHD based on mg/m^2. 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/m^2. The adverse effects included dose-dependent decreases in femoral length, bone mineral content, body and brain weights at 2 times the MRHD in both sexes, and motor hyperactivity at 0.2 and 2 times the MRHD in both sexes based on mg/m^2. In females, there was a delay in attainment of sexual maturity at 2 times the MRHD, associated with decreased serum estradiol. Mortality occurred in both sexes during early post-weaning period and some of the male weanlings died after only 4 treatments at doses as low as 2 times the MRHD based on mg/m^2. Histopathological findings included increased colloid in the thyroids and inflammation of the prostate in males at 10 times MRHD based on mg/m^2, and mammary gland hyperplasia, increased vaginal mucification, and increased ovarian atretic follicles at doses as low as 0.2 times the MRHD based on mg/m^2. Some of these findings were attributed to transiently elevated serum prolactin which was seen in both sexes at all doses. However, there were no changes at any dose level in reproductive parameters (fertility, conception indices, spermatogenesis, estrous cycle, gestation length, parturition, number of pups born). The no effect dose for neurobehavioral changes in males is 0.2 times the MHRD based on mg/m^2 and could not be determined in females. The no effect dose for growth and physical development in both sexes is 0.2 times the MRHD based on mg/m^2.

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.

Other Specific Populations

No dosage adjustment for Laroza is required on the basis of a patient's sex, race, or smoking status.

Council of Arab Health Ministers, Union of Arab Pharmacists

THIS IS A MEDICAMENT
- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of reach of children.

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