120x200mm

Ranola®
(Ranolazine)

Highnoon

COMPOSITION
Ranola 500mg Tablet:
Each extended-release tablet contains:
Ranolazine 500mg

Ranola 1000mg Tablet:
Each extended-release tablet contains:
Ranolazine 1000mg

DESCRIPTION
Ranolazine is a racemic mixture chemically described as 1- piperazineacetamide, N-(2,6 dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy) propyl].

MECHANISM OF ACTION
Ranolazine is an antianginal drug. Its mechanism of action is unclear but may involve inhibition of the late sodium current in cardiac myocytes; this reduces intracellular sodium accumulation and consequently decreases intracellular calcium overload. Ranolazine, via its action to decrease the late sodium current, is considered to reduce these intracellular ionic imbalances during ischaemia. This reduction in cellular calcium overload is expected to improve myocardial relaxation and thereby decrease left ventricular diastolic stiffness. It also inhibits fatty acid oxidation, but this does not appear to occur at therapeutic plasma concentration. It is given orally, as extended release dosage form, for the treatment of stable angina pectoris.

PHARMACOKINETICS
Absorption of Ranolazine is highly variable and peak plasma concentrations occur about 2 to 5 hours after an oral dose of the modified-release preparation. Ranolazine is extensively metabolized in the gastrointestinal tract and liver. Four main metabolites have been identified. Protein binding of Ranolazine is about 62%. About 75% of a dose is excreted in the urine with the remainder in the faeces, with less than 5% as unchanged drug. The apparent terminal half life for the modified-release preparation of the Ranolazine is 7 hours, and steady state occurs within 3 days.

INDICATIONS
It is indicated for the treatment of stable angina. It may be used with beta-blockers, nitrates, calcium channel blockers, antiplatelet therapy, lipid lowering therapy, ACE inhibitors and angiotensin receptor blockers.

DOSAGE AND ADMINISTRATION
It may be used alone or as an adjunct to other antianginal drugs. The initial dose is 500 mg twice daily, increasing to a maximum of 1 gm twice daily, if necessary. The dose should be limited to 500 mg twice daily in patients taking some interacting drugs. The maximum recommended dose is 1000 mg twice daily.

It should be swallowed whole and not crushed, broken, or chewed. They may be taken with or without food.

Dose adjustments may be needed when ranolazine is taken in combination with certain other drugs. Limit the maximum dose of ranolazine to 500 mg twice daily in patients on moderate CYP3A inhibitors such as diltiazem, verapamil and erythromycin. Use of ranolazine with strong CYP3A inhibitors is contraindicated. Use of P-gp inhibitors, such as cyclosporine, may increase exposure to ranolazine. Titrate it, based on clinical response.

CONTRAINDICATIONS
It is contraindicated in patients with;
- Hypersensitivity to the active substance or to any of the excipients
- Severe renal impairment (creatinine clearance < 30 ml/min)
- Moderate or severe hepatic impairment. With severe liver cirrhosis
- Concomitant administration of strong inhibitors of CYP3A4
- Taking inducers of CYP3A4

ADVERSE REACTIONS
The reported adverse events are; nausea, vomiting, headache, dry mouth, abdominal pain, dyspepsia, dyspnea, constipation, dizziness, vertigo, tinnitus, asthenia, peripheral oedema and palpitations. Rarely reported effects include bradycardia, hematuria, paresthesia, hypotension, orthostatic hypotension, anorexia, decreased appetite, dehydration, syncope, confusional state, hyperhidrosis, blurred vision, hallucination, hypoglycemia, anxiety, insomnia, disorientation, lethargy, hypoesthesia, somnolence, tremor, myoclonus, abnormal coordination, amnesia, loss of consciousness, gait disturbance, parosmia diplopia, hot flush, cough, epistaxis, pancreatitis, erosive duodenitis, urinary retention, muscle cramps, joint swelling, pain in extremity, muscular weakness, allergic dermatitis, cold sweat, angioedema, rash, pruritus, acute renal failure, dysuria, urinary retention, eosinophilia, chromaturia, blood urea increased, pulmonary fibrosis, thrombocytopenia, leukopenia, and pancytopenia.

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DRUG INTERACTIONS
- Ranolazine is mainly metabolized by the P450 isoenzyme CYP3A4 and may interact with other drugs that affect or are affected by this enzyme.
- Ranolazine is contraindicated with potent inhibitors of CYP3A4 such as ketoconazole, itraconazole, ritonavir and related antifungals, clarithromycin and telithromycin, HIV protease inhibitors and nefazodone.
- It may be used with caution in patients taking moderate CYP3A4 inhibitors or P- glycoprotein inhibitors such as diltiazem, verapamil, fluconazole, erythromycin, ciclosporin and grapefruit juice or grapefruit products.
- Ranolazine may itself act as inhibitors of some enzymes.
- Limit the dose of simvastatin in patients on any dose of ranolazine to 20 mg once daily, when ranolazine is co-administered. Dose adjustment of other sensitive CYP3A substrates (e.g., lovastatin) and CYP3A substrates with a narrow therapeutic range (e.g., cyclosporine, tacrolimus, sirolimus) may be required as ranolazine may increase plasma concentrations of these drugs.
- Plasma concentrations of digoxin, a glycoprotein substrate may also be increased and dose adjustment may be required; dose reduction may also be needed for drugs metabolized by CYP2D6, such as tricyclic antidepressants and some antipsychotics.
- Do not use Ranolazine with CYP3A4 inducers such as rifampin, rifabutin, Phenobarbital, phenytoin, carbamazepine and St. John's wort.
- Ranolazine may theoretically interact with other drugs that increase the QT interval.
- In subjects with type 2 diabetes mellitus, concomitant use of ranolazine 1000 mg twice daily and metformin results in increased plasma levels of metformin. When ranolazine 1000 mg twice daily is co-administered with metformin, metformin dose should not exceed 1700 mg/day. Monitor blood glucose levels and risks associated with high exposures of metformin.

WARNING AND PRECAUTIONS
Caution should be exercised when prescribing or up titrating ranolazine to patients in whom an increased exposure is expected:
- Concomitant administration of moderate CYP3A4 inhibitors
- Concomitant administration of P-gp inhibitors
- With severe liver cirrhosis
- Mild hepatic impairment
- Mild to moderate renal impairment (creatinine clearance 30–80 ml/min)
- Elderly
- Patients with low weight (≤ 60 kg)
- Patients with moderate to severe CHF (NYHA Class III–IV)
- Dose related prolongation of the QT interval may occur; Ranolazine should be used with caution in patients with pre-existing QT prolongation, and in those at increased risk of QT prolongation.
- Acute renal failure has been observed in some patients with severe renal impairment (creatinine clearance [CrCL] <30 mL/min) while taking Ranolazine. If acute renal failure develops (e.g., marked increase in serum creatinine associated with an increase in blood urea nitrogen, discontinue Ranolazine and treat appropriately. Monitor renal function after initiation and periodically in patients with moderate to severe renal impairment (CrCL <60 mL/min) for increases in serum creatinine accompanied by an increase in BUN.

PREGNANCY AND LACTATION
Pregnancy
There are no adequate data from the use of ranolazine in pregnant women. The potential risk for humans is unknown. Ranolazine should not be used during pregnancy unless clearly necessary.

Lactating Mothers
It is unknown whether ranolazine is excreted in human breast milk. The excretion of ranolazine in milk has not been studied in animals. Ranolazine should not be used during breast-feeding.

Pediatric Use
Safety and effectiveness have not been established in pediatric patients.

Geriatric Use
No overall differences in efficacy were observed between older and younger patients. There were no differences in safety for patients ≥ 65 years compared to younger patients, but patients ≥ 75 years of age on Ranolazine.

In general, dose selection for an elderly patient should usually start at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease, or other drug therapy.

Use in Patients with Hepatic Impairment
It is contraindicated in patients with liver cirrhosis.

Use in Patients with Renal Impairment
Monitor renal function periodically in patients with moderate to severe renal impairment. Discontinue Ranolazine if acute renal failure develops.

Use in Patients with Heart Failure
No dose adjustment of Ranolazine is required in patients with heart failure.

Use in Patients with Diabetes Mellitus
No dose adjustment is required in patients with diabetes.

OVER DOSAGE
High oral doses of Ranolazine produce dose related increase in QT prolongation, bradycardia, myoclonic activity, severe tremor, unsteady gait/incoordination, dizziness, hypotension, nausea, vomiting, dysphasia, and hallucinations High intravenous exposure also produces diplopia, paresthesia, confusion and syncope. In addition to general supportive measures continuous ECG monitoring may be warranted in the event of overdose. Since Ranolazine is about 62% bound to plasma proteins, therefore, complete clearance by hemodialysis is unlikely.

DOSAGE AND INSTRUCTIONS
To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in a dry place. Protect from light.

PRESENTATION
Ranola 500mg Tablets:
Alu. Alu. Blister Pack of 2 x 7's.
Alu. Alu. Blister Pack of 2 x 10's.
Ranola 1000mg Tablets:
Alu. Alu. Blister Pack of 2 x 7's.
Alu. Alu. Blister Pack of 2 x 10's.

رنولا®
(رنولازین)

خوراک و ہدایات:
صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

Manufactured by
HIGHNOON LABORATORIES LTD
17.5 KM, Multan Road, Lahore, Pakistan.
www.highnoon-labs.com

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