Front Side

210 mm

240 mm

RANOLAZINE

CARTINEX

500 mg Extended-Release Tablet

ANTI-ANGINA

PRODUCT NAME:
CARTINEX

DOSAGE FORM AND STRENGTH:
Tablets 500 mg

PHARMACOLOGIC CATEGORY: Other cardiac preparations

PRODUCT DESCRIPTION:
Orange coloured, oval shaped film-coated tablets with plain on both surfaces.

FORMULATION/COMPOSITION:
Each film-coated extended-release tablet contains:
Ranolazine ..... 500 mg

PHARMACODYNAMICS/PHARMACOKINETICS:
Pharmacodynamics:
Hemodynamic Effects
Patients with chronic angina treated with Ranolazine in controlled clinical studies had minimal changes in mean heart rate (< 2 bpm) and systolic blood pressure (< 3 mm Hg). Similar results were observed in subgroups of patients with CHF NYHA Class I or II, diabetes, or reactive airway disease, and in elderly patients.
Electrocardiographic Effects
Dose and plasma concentration-related increases in the QTc interval, reductions in T wave amplitude, and, in some cases, notched T waves have been observed in patients treated with Ranolazine. These effects are believed to be caused by Ranolazine and not by its metabolites. The relationship between the change in QTc and Ranolazine plasma concentrations is linear, with a slope of about
2.6 msec/1000 ng/mL, through exposures corresponding to doses several-fold higher than the maximum recommended dose of 1000 mg twice daily. The variable blood levels attained after a given dose of Ranolazine give a wide range of effects on QTc. At Tmax following repeat dosing at 1000 mg twice daily, the mean change in QTc is about 6 msec, but in the 5% of the population with the highest plasma concentrations, the prolongation of QTc is at least 15 msec. In subjects with mild or moderate hepatic impairment, the relationship between plasma level of Ranolazine and QTc is much steeper.
Age, weight, gender, race, heart rate, congestive heart failure, diabetes, and renal impairment did not alter the slope of the QTc-concentration relationship of Ranolazine.
No proarrhythmic effects were observed on 7-day Holter recordings in 3,162 acute coronary syndrome patients treated with Ranolazine. There was a significantly lower incidence of arrhythmias (ventricular tachycardia, bradycardia, supraventricular tachycardia, and new atrial fibrillation) in patients treated with Ranolazine (80%) versus placebo (87%), including ventricular tachycardia ≥ 3 beats (52% versus 61%). However, this difference in arrhythmias did not lead to a reduction in mortality, a reduction in arrhythmia hospitalization, or a reduction in arrhythmia symptoms.

Pharmacokinetics:
Absorption and Distribution
After oral administration of Ranolazine, peak plasma concentrations of ranolazine are reached between 2 and 5 hours. After oral administration of 14C-ranolazine as a solution, 73% of the dose is systemically available as ranolazine or metabolites. The bioavailability of ranolazine from Ranolazine tablets relative to that from a solution of ranolazine is 76%. Because ranolazine is a substrate of P-gp, inhibitors of P-gp may increase the absorption of ranolazine.
Food (high-fat breakfast) has no important effect on the Cmax and AUC of ranolazine. Therefore, Ranolazine may be taken without regard to meals. Over the concentration range of 0.25 to 10 µg/mL, ranolazine is approximately 62% bound to human plasma proteins.
Metabolism and Excretion
Ranolazine is metabolized mainly by CYP3A and, to a lesser extent, by CYP2D6. Following a single oral dose of ranolazine solution, approximately 75% of the dose is excreted in urine and 25% in feces. Ranolazine is metabolized rapidly and extensively in the liver and intestine; less than 5% is excreted unchanged in urine and feces. The pharmacologic activity of the metabolites has not been well characterized. After dosing to steady state with 500 mg to 1500 mg twice daily, the four most abundant metabolites in plasma have AUC values ranging from about 5 to 33% that of ranolazine, and display apparent half-lives ranging from 6 to 22 hours.

INDICATIONS:
Ranolazine is indicated for the treatment of chronic angina.
Ranolazine may be used with beta-blockers, nitrates, calcium channel blockers, anti-platelet therapy, lipid-lowering therapy, ACE inhibitors, and angiotensin receptor blockers.

DOSAGE AND MODEL ROUTE OF ADMINISTRATION:
Initiate Ranolazine dosing at 500 mg twice daily and increase to 1000 mg twice daily, as needed, based on clinical symptoms. Take Ranolazine with or without meals. Swallow Ranolazine tablets whole; do not crush, break, or chew.
The maximum recommended daily dose of Ranolazine is 1000 mg twice daily.
If a dose of Ranolazine is missed, take the prescribed dose at the next scheduled time; do not double the next dose.

Dose Modification
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 diltiazem, verapamil, and other moderate CYP3A inhibitors. Down-titrate Ranolazine based on clinical response in patients concomitantly treated with P-gp inhibitors, such as cyclosporine.

CONTRAINDICATIONS &PRECAUTION(S), WARNING(S)
Ranolazine is contraindicated in patients:
Taking strong inhibitors of CYP3A
Taking inducers of CYP3A
With clinically significant hepatic impairment

PRECAUTIONS & WARNINGS:
QT Interval Prolongation
Ranolazine blocks IKr and prolongs the QTc interval in a dose-related manner.
Clinical experience in an acute coronary syndrome population did not show an increased risk of proarrhythmic or sudden death. However, there is little experience with high doses (> 1000 mg twice daily) or exposure, other QT-prolonging drugs, or potassium channel variants resulting in a long QT interval.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

PREGNANCY AND LACTATION:
Pregnancy
There are no adequate well-controlled studies in pregnant women. Ranolazine should be used during pregnancy only when the potential benefit to the patient justifies the potential risk to the fetus.
Lactation
It is not known whether ranolazine is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from ranolazine in nursing infants, decide whether to discontinue nursing or to discontinue Ranolazine, taking into account the importance of the drug to the mother.

INTERACTIONS:
Effects of Other Drugs on Ranolazine
Ranolazine is primarily metabolized by CYP3A and is a substrate of P-glycoprotein (P-gp).
CYP3A Inhibitors
Do not use Ranolazine with strong CYP3A inhibitors, including ketoconazole, itraconazole, clarithromycin, nefazodone, nelfinavir, ritonavir, indinavir, and saquinavir. Ketoconazole (200 mg twice daily) increases average steady-state plasma concentrations of ranolazine 3.2-fold.
Limit the dose of Ranolazine to 500 mg twice daily in patients on moderate CYP3A inhibitors, including diltiazem, verapamil, aprepitant, erythromycin, fluconazole, and grapefruit juice or grapefruit-containing products. Diltiazem (180–360 mg daily) and verapamil (120 mg three times daily) increase ranolazine steady-state plasma concentrations about 2-fold.
Weak CYP3A inhibitors such as simvastatin (20 mg once daily) and cimetidine (400 mg three times daily) do not increase the exposure to ranolazine in healthy volunteers.
P-gp Inhibitors
Down-titrate Ranolazine based on clinical response in patients concomitantly treated with P-gp inhibitors, such as cyclosporine.
CYP3A and P-gp Inducers
Avoid co-administration of Ranolazine and CYP3A inducers such as rifampin, rifabutin, Rifapentine, phenobarbital, phenytoin, carbamazepine, and St. John's wort. Rifampin (600 mg once daily) decreases the plasma concentration of ranolazine (1000 mg twice daily) by approximately 95% by induction of CYP3A and, probably, P-gp.
CYP2D6 Inhibitors
The potent CYP2D6 inhibitor, paroxetine (20 mg once daily), increases ranolazine concentrations 1.2-fold. No dose adjustment of Ranolazine is required in patients treated with CYP2D6 inhibitors.
Digoxin
Digoxin (0.125 mg) does not significantly alter ranolazine levels.
Effects of Ranolazine on Other Drugs
In vitro studies indicate that ranolazine and its O-demethylated metabolite are weak inhibitors of CYP3A, moderate inhibitors of CYP2D6 and moderate P-gp inhibitors. Ranolazine and its most abundant metabolites are not known to inhibit the metabolism of substrates for CYP 1A2, 2C8, 2C9, 2C19, or 2E1 in human liver microsomes, suggesting that ranolazine is unlikely to alter the pharmacokinetics of drugs metabolized by these enzymes.
Drugs Metabolized by CYP3A
The plasma levels of simvastatin, a CYP3A substrate, and its active metabolite are each increased about 2-fold in healthy subjects receiving simvastatin (80 mg once daily) and Ranolazine (1000 mg twice daily). Dose adjustments of simvastatin are not required when Ranolazine is co-administered with simvastatin.
The pharmacokinetics of diltiazem is not affected by ranolazine in healthy volunteers receiving diltiazem 60 mg three times daily and Ranolazine 1000 mg twice daily.
Drugs Transported by P-gp
Ranolazine (1000 mg twice daily) causes a 1.5-fold elevation of digoxin plasma concentrations. The dose of digoxin may have to be adjusted.
Drugs Metabolized by CYP2D6
Ranolazine or its metabolites partially inhibit CYP2D6. There are no studies of concomitant use of Ranolazine with other drugs metabolized by CYP2D6, such as tricyclic antidepressants and antipsychotics, but lower doses of CYP2D6 substrates may be required.

ADVERSE EFFECTS:
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
A total of 2,018 patients with chronic angina were treated with ranolazine in controlled clinical trials. Of the patients treated with Ranolazine, 1,026 were enrolled in three double-blind, placebo-controlled, randomized studies (CARISA, ERICA, MARISA) of up to 12 weeks duration. In addition, upon study completion, 1,251 patients received treatment with Ranolazine in open-label, long-term studies; 1,227 patients were exposed to Ranolazine for more than 1 year, 613 patients for more than 2 years, 531 patients for more than 3 years, and 326 patients for more than 4 years.
At recommended doses, about 6% of patients discontinued treatment with Ranolazine because of an adverse event in controlled studies in angina patients compared to about 3% on placebo. The most common adverse events that led to discontinuation more frequently on Ranolazine than placebo were dizziness (1.3% versus 0.1%), nausea (1% versus 0%), asthenia, constipation, and headache (each about 0.5% versus 0%). Doses above 1000 mg twice daily are poorly tolerated.
In controlled clinical trials of angina patients, the most frequently reported treatment-emergent adverse reactions (> 4% and more common on Ranolazine than on placebo) were dizziness (6.2%), headache (5.5%), constipation (4.5%), and nausea (4.4%). Dizziness may be dose-related. In open-label, long-term treatment studies, a similar adverse reaction profile was observed.
The following additional adverse reactions occurred at an incidence of 0.5 to 2.0% in patients treated with Ranolazine and were more frequent than the incidence observed in placebo-treated patients:
Cardiac Disorders – bradycardia, palpitations
Ear and Labyrinth Disorders – tinnitus, vertigo
Gastrointestinal Disorders – abdominal pain, dry mouth, vomiting
General Disorders and Administrative Site Adverse Events – peripheral edema
Respiratory, Thoracic, and Mediastinal Disorders – dyspnea
Vascular Disorders – hypotension, orthostatic hypotension
Other (< 0.5%) but potentially medically important adverse reactions observed more frequently with Ranolazine than placebo treatment in all controlled studies included: angioedema, renal failure, eosinophilia, blurred vision, confusional state, hematuria, hypoesthesia, paresthesia, tremor, pulmonary fibrosis, thrombocytopenia, leukopenia, and pancytopenia.
A large clinical trial in acute coronary syndrome patients was unsuccessful in demonstrating a benefit for Ranolazine, but there was no apparent proarrhythmic effect in these high-risk patients.

OVERDOSAGE AND TREATMENT:
High oral doses of ranolazine produce dose-related increases in dizziness, nausea, and vomiting. 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, hemodialysis is unlikely to be effective in clearing ranolazine.

STORAGE CONDITION:
Store at temperatures not exceeding 30°C.

DOSAGE FORMS AND PACKAGING AVAILABLE:
Tablets
Alu/amber-colored PVC/PVDC Blister pack of 10's (Box of 30's)

INSTRUCTIONS AND SPECIAL PRECAUTIONS FOR HANDLING AND DISPOSAL (IF APPLICABLE):
Not Applicable

NAME AND ADDRESS OF MARKETING AUTHORIZATION HOLDER:
Marketing Authorization Holder
Brown & Burk Philippines Inc
U-501, 5/F., SEDCCO 1 Bldg., 120 Rada cor.,
Legaspi Sts., Legaspi Village, Makati City, Philippines

NAME AND ADDRESS OF MANUFACTURER:
MICRO LABS LIMITED
92, Sipcot Industrial Complex,
Hosur – 635 126 (T.N), INDIA.

CAUTION STATEMENT:
FOODS, DRUGS, DEVICES, AND COSMETICS ACT PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

ADR REPORTING STATEMENT:
FOR SUSPECTED ADVERSE DRUG REACTION, REPORT TO THE FDA:
www.fda.gov.ph
Seek medical attention immediately at the first sigh of Adverse Drug Reaction.

REGISTRATION NUMBER:
DR-XY43998

DATE OF FIRST AUTHORIZATION:
16 December 2014

DATE OF REVISION OF PACKAGE INSERT:
Oct. 2019

EXG-ML01I-1805

Back Side

210 mm

240 mm

35 mm | 35 mm | 35 mm | 35 mm | 35 mm | 35 mm

PHARMACODE READING DIRECTION

14 (L) x 8 (H) mm

PHARMACODE READING DIRECTION

247

35 mm | 35 mm | 35 mm | 35 mm | 35 mm | 35 mm

Paper 35 to 60 gsm

Size : 210 (L) x 240 (H) mm
Drg. No.: W0990005916Z-000
Folding size: 35 x 120 mm
Carton size: 65 x 30 x 97 mm

MICRO LABS LIMITED, BANGALORE, INDIA			
1	Product Name	Cartinex	Colours Used
2	Strength	500 mg	■ BLACK
3	Component	Leaflet	
4	Category	Export - Philippines	
5	Dimension	210 (L) x 240 (H) mm	
6	Artwork Code	EXG-ML01I-1805	
7	Pharma Code	247	
8	Reason for Change	Size and New Regulation	

	Prepared by (DTP)	Checked by (PD)	Approved by			
			Head CQA	Head Production/ Packing (Site)	Head QC (Site)	Head QA (Site)
Sign	Kantharaju L.					
Date	19-09-2022					