## 1.3 PRODUCT INFORMATION

### 1.3.1 Summary of product Characterstics (SmPC)

The Summary of Product Characteristics has been enclosed in the following pages.

# SUMMARY OF PRODUCT CHARACTERSTICS

**SUMMARY OF PRODUCT CHARACTERISTICS**

**RANCV 500/1000**

**(Ranolazine Extended Release Tablets 500 mg/1000 mg)**

## 1. NAME OF THE MEDICINAL PRODUCT

RANCV 500 [Ranolazine Extended Release Tablets 500 mg]

RANCV 1000 [Ranolazine Extended Release Tablets 1000 mg]

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated extended tablet contains 500 mg of ranolazine.

Each film coated extended tablet contains 1000 mg of ranolazine.

For excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Extended release tablet.

RANCV 500:

Caplet shaped Yellow coloured smooth film coated tablets.

RANCV 1000:

Caplet shaped Yellow coloured smooth film coated tablets.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

RANCV is indicated in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapies (such as beta-blockers and/or calcium antagonists).

### 4.2 Posology and method of administration

Posology

RANCV is available as 500 mg and 1000 mg extended-release tablets.

Initiate RANCV dosing at 500 mg twice daily and increase to 1000 mg twice daily, as needed, based on clinical symptoms. Take RANCV with or without meals. Swallow RANCV tablets whole; do not crush, break, or chew.

The maximum recommended daily dose of RANCV is 1000 mg twice daily.

If a dose of RANCV is missed, take the prescribed dose at the next scheduled time; do not double the next dose.

Concomitant treatment with CYP3A4 and P-glycoprotein (P-gp) inhibitors: Careful dose titration is recommended in patients treated with moderate CYP3A4 inhibitors (e.g. diltiazem, fluconazole,

erythromycin) or P-gp inhibitors (e.g. verapamil, ciclosporin) (see sections 4.4 and 4.5).

Concomitant administration of potent CYP3A4 inhibitors is contraindicated (see sections 4.3 and 4.5).

Renal impairment: Careful dose titration is recommended in patients with mild to moderate renal impairment (creatinine clearance 30–80 ml/min) (see sections 4.4, 4.8, and 5.2). RANCV is contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min) (see sections 4.3 and 5.2).

Hepatic impairment: Careful dose titration is recommended in patients with mild hepatic impairment (see sections 4.4 and 5.2). RANCV is contraindicated in patients with moderate or severe hepatic impairment (see sections 4.3 and 5.2).

Elderly: Dose titration in elderly patients should be exercised with caution (see section 4.4). Elderly may have increased ranolazine exposure due to age-related decrease in renal function (see section 5.2). The incidence of adverse events was higher in the elderly (see section 4.8).

Low weight: The incidence of adverse events was higher in patients with low weight (≤ 60 kg). Dose titration in patients with low weight should be exercised with caution (see sections 4.4, 4.8, and 5.2).

Congestive heart failure (CHF): Dose titration in patients with moderate to severe CHF (NYHA Class III–IV) should be exercised with caution (see sections 4.4 and 5.2).

*Paediatric population*

The safety and efficacy of RANCV in children below the age of 18 years have not been established. No data are available

Method of administration

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

**4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

Severe renal impairment (creatinine clearance < 30 ml/min) (see sections 4.2 and 5.2).

Moderate or severe hepatic impairment (see sections 4.2 and 5.2).

Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, voriconazol, posaconazol, HIV protease inhibitors, clarithromycin, telithromycin, nefazodone) (see sections 4.2 and 4.5).

Concomitant administration of Class Ia (e.g. quinidine) or Class III (e.g. dofetilide, sotalol) antiarrhythmics other than amiodarone.

**4.4 Special warnings and precautions for use**

Caution should be exercised when prescribing or uptitrating ranolazine to patients in whom an increased exposure is expected:

• Concomitant administration of moderate CYP3A4 inhibitors (see sections 4.2 and 4.5).
• Concomitant administration of P-gp inhibitors (see sections 4.2 and 4.5).
• Mild hepatic impairment (see sections 4.2 and 5.2).
• Mild to moderate renal impairment (creatinine clearance 30–80 ml/min) (see sections 4.2, 4.8, and 5.2).
• Elderly (see sections 4.2, 4.8, and 5.2).
• Patients with low weight (≤ 60 kg) (see sections 4.2, 4.8, and 5.2).
• Patients with moderate to severe CHF (NYHA Class III–IV) (see sections 4.2 and 5.2).

In patients with a combination of these factors, additional exposure increases are expected. Dose-dependent side effects are likely to occur. If RANCV is used in patients with a combination of several of these factors, monitoring of adverse events should be frequent, the dose reduced, and treatment discontinued, if needed.

The risk for increased exposure leading to adverse events in these different subgroups is higher in patients lacking CYP2D6 activity (poor metabolisers, PM) than subjects with CYP2D6 metabolising capacity (extensive metabolisers, EM) (see section 5.2). The above precautions are based on the risk in a CYP2D6 PM patient, and are needed when the CYP2D6 status is unknown. There is a lower need for precautions in patients with CYP2D6 EM status. If the CYP2D6 status of the patient has been determined (e.g. by genotyping) or is previously known to be EM, RANCV can be used with caution in these patients when they have a combination of several of the above risk factors.

QT prolongation: A population-based analysis of combined data from patients and healthy volunteers demonstrated that the slope of the plasma concentration-QTc relationship was estimated to be 2.4 msec per 1000 ng/ml, which is approximately equal to a 2- to 7-msec increase over the plasma concentration range for ranolazine 500 to 1000 mg twice daily. Therefore, caution should be observed when treating patients with a history of congenital or a family history of long QT syndrome, in patients with known acquired QT interval prolongation, and in patients treated with drugs affecting the QTc interval (see section 4.5 also).

Drug-drug interactions: Co-administration with CYP3A4 inducers is expected to lead to lack of efficacy. RANCV should not be used in patients treated with CYP3A4 inducers (e.g. rifampicin, phenytoin, phenobarbital, carbamazepine, St. John's Wort) (see section 4.5).

Renal impairment: Renal function decreases with age and it is therefore important to check renal function at regular intervals during treatment with ranolazine (see sections 4.2, 4.3, 4.8, and 5.2).
Azo colouring agent E102: This medicinal product contains the azo colouring agent E102 which may cause allergic reactions.

**4.5 Interaction with other medicinal products and other forms of interaction**

Effects of other medicinal products on ranolazine

CYP3A4 or P-gp inhibitors: Ranolazine is a substrate of cytochrome CYP3A4. Inhibitors of CYP3A4 increase plasma concentrations of ranolazine. The potential for dose-related adverse events (e.g. nausea, dizziness) may also increase with increased plasma concentrations. Concomitant treatment with ketoconazole 200 mg twice daily increased the AUC of ranolazine by 3.0- to 3.9-fold during ranolazine treatment. Combining ranolazine with potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, voriconazole, posaconazole, HIV protease inhibitors, clarithromycin, telithromycin, nefazodone) is contraindicated (see section 4.3). Grapefruit juice is also a potent CYP3A4 inhibitor.

Diltiazem (180 to 360 mg once daily), a moderately potent CYP3A4 inhibitor, causes dose-dependent increases in average ranolazine steady-state concentrations of 1.5- to 2.4-fold. Careful dose titration of RANCV is recommended in patients treated with diltiazem and other moderately potent CYP3A4 inhibitors (e.g. erythromycin, fluconazole). Down-titration of RANCV may be required (see sections 4.2 and 4.4).

Ranolazine is a substrate for P-gp. Inhibitors of P-gp (e.g. ciclosporin, verapamil) increase plasma levels of ranolazine. Verapamil (120 mg three times daily) increases ranolazine steady-state concentrations 2.2-fold. Careful dose titration of RANCV is recommended in patients treated with P-gp inhibitors. Down-titration of RANCV may be required (see sections 4.2 and 4.4).

CYP3A4 inducers: Rifampicin (600 mg once daily) decreases ranolazine steady-state concentrations by approximately 95%. Initiation of treatment with RANCV should be avoided during administration of inducers of CYP3A4 (e.g. rifampicin, phenytoin, phenobarbital, carbamazepine, St. John's Wort) (see section 4.4).

CYP2D6 inhibitors: Ranolazine is partially metabolised by CYP2D6; therefore, inhibitors of this enzyme may increase plasma concentrations of ranolazine. The potent CYP2D6 inhibitor paroxetine, at a dose of 20 mg once daily, increased steady-state plasma concentrations of ranolazine 1000 mg twice daily by an average of 1.2-fold. No dose adjustment is required. At the dose level 500 mg twice daily, co-administration of a potent inhibitor of CYP2D6 could result in an increase in ranolazine AUC of about 62%.

Effects of ranolazine on other medicinal products

Ranolazine is a moderate to potent inhibitor of P-gp and a mild inhibitor of CYP3A4, and may increase plasma concentrations of P-gp or CYP3A4 substrates. Tissue distribution of drugs which are transported by P-gp may be increased.

Dose adjustment of sensitive CYP3A4 substrates (e.g., simvastatin, lovastatin) and CYP3A4 substrates with a narrow therapeutic range (e.g., ciclosporin, tacrolimus, sirolimus, everolimus) may be required as RANCV may increase plasma concentrations of these drugs.

Available data suggest that ranolazine is a mild inhibitor of CYP2D6. Therefore the exposure to metoprolol or other CYP2D6 substrates (e.g. propafenone and flecainide or, to a lesser extent, tricyclic antidepressants and antipsychotics) may be increased during co-administration with RANCV, and lower doses of these medicinal products may be required.

The potential for inhibition of CYP2B6 has not been evaluated. Caution is advised during co-administration with CYP2B6 substrates (e.g. bupropion, efavirenz, cyclophosphamide).

Digoxin: An increase in plasma digoxin concentrations by an average of 1.5-fold has been reported when RANCV and digoxin are co-administered. Therefore, digoxin levels should be monitored following initiation and termination of RANCV therapy.

Simvastatin: Simvastatin metabolism and clearance are highly dependent on CYP3A4. RANCV 1000 mg twice daily increased plasma concentrations of simvastatin lactone, simvastatin acid, and the HMG-CoA reductase inhibitor activity by 1.4- to 1.6-fold. Rhabdomyolysis has been associated with high doses of simvastatin and cases of rhabdomyolysis have been observed in patients receiving RANCV and simvastatin, in postmarketing experience. Limit the dose of simvastatin to 20 mg once daily in patients taking any dose of RANCV. Dose limitation of other statins, metabolised by CYP3A4 (lovastatin), may be considered in patients taking RANCV.

Tacrolimus, ciclosporin, sirolimus, everolimus: Increased plasma concentrations of tacrolimus, a CYP3A4 substrate, have been observed in patients after ranolazine administration. It is recommended that tacrolimus blood levels are monitored when co-administering RANCV and tacrolimus and that tacrolimus dosage is adjusted accordingly. This is also recommended for other CYP3A4 substrates with a narrow therapeutic range (e.g., ciclosporin, sirolimus, everolimus).

There is a theoretical risk that concomitant treatment of ranolazine with other drugs known to prolong the QTc interval may give rise to a pharmacodynamic interaction and increase the possible risk of ventricular arrhythmias. Examples of such drugs include certain antihistamines (e.g. terfenadine, astemizole, mizolastine), certain antiarrhythmics (e.g. quinidine, disopyramide, procainamide), erythromycin, and tricyclic antidepressants (e.g. imipramine, doxepin, amitriptyline).

**4.6 Pregnancy and lactation**

Pregnancy: There are no adequate data from the use of ranolazine in pregnant women. Animal studies are insufficient with respect to effects on pregnancy and embryofoetal development (see section 5.3). The potential risk for humans is unknown. RANCV should not be used during pregnancy unless clearly necessary.

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

Fertility: In animals, reproduction studies indicated no adverse effects on fertility (see section 5.3). The effect of ranolazine on human fertility is unknown.

**4.7 Effects on ability to drive and use machines**

No studies on the effects of RANCV on the ability to drive and use machines have been performed. RANCV may cause dizziness, blurred vision, confusional state and hallucination (see section 4.8), which may affect the ability to drive and use machines.

**4.8 Undesirable effects**

Undesirable effects in patients receiving RANCV are generally mild to moderate in severity and often develop within the first 2 weeks of treatment. These were reported during the Phase 3 clinical development programme, which included a total of 1,030 chronic angina patients treated with RANCV.

The adverse events, considered to be at least possibly related to treatment, are listed below by body system, organ class, and absolute frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), and very rare (< 1/10,000).

Metabolism and nutrition disorders

*Uncommon:* anorexia, decreased appetite, dehydration.

Psychiatric disorders

*Uncommon:* anxiety, insomnia, confusional state, hallucination.

*Rare:* disorientation.

Nervous system disorders

*Common:* dizziness, headache.

*Uncommon:* lethargy, syncope, hypoaesthesia, somnolence, tremor, postural dizziness.

*Rare:* amnesia, depressed level of consciousness, loss of consciousness, parosmia.

Eye disorders

*Uncommon:* blurred vision, visual disturbance.

Ear and labyrinth disorders

*Uncommon:* vertigo, tinnitus.

*Rare:* impaired hearing.

Vascular disorders

*Uncommon:* hot flush, hypotension.

*Rare:* peripheral coldness, orthostatic hypotension.

Respiratory, thoracic, and mediastinal disorders

*Uncommon:* dyspnoea, cough, epistaxis.

*Rare:* throat tightness.

Gastrointestinal disorders

*Common:* constipation, vomiting, nausea.

*Uncommon:* abdominal pain, dry mouth, dyspepsia, flatulence, stomach discomfort.

*Rare:* pancreatitis, erosive duodenitis, oral hypoaesthesia.

Skin and subcutaneous tissue disorders

*Uncommon:* pruritus, hyperhydrosis.

*Rare:* angioedema, allergic dermatitis, urticaria, cold sweat, rash.

Musculoskeletal and connective tissue disorders

*Uncommon:* pain in extremity, muscle cramp, joint swelling.

Renal and urinary disorders

*Uncommon:* dysuria, haematuria, chromaturia.

*Rare:* acute renal failure

Reproductive system and breast disorders

*Rare:* erectile dysfunction.

General disorders and administration site conditions

*Common:* asthenia.

*Uncommon:* fatigue, peripheral oedema.

Investigations

*Uncommon:* increased blood creatinine, increased blood urea, prolonged QT corrected interval, increased platelet or white blood cell count, decreased weight.

*Rare:* elevated levels of hepatic enzyme.

The adverse event profile was generally similar in the MERLIN-TIMI 36 study. In this long term study, acute renal failure was also reported with an incidence less than 1% in placebo and ranolazine patients. Evaluations in patients who may be considered at higher risk of adverse events when treated with other antianginal medicinal products, e.g. patients with diabetes, Class I and II heart failure, or obstructive airway disease, confirmed that these conditions were not associated with clinically meaningful increases in the incidence of adverse events.

Elderly, renal impairment, and low weight: In general, adverse events occurred more frequently among elderly patients and patients with renal impairment; however, the types of events in these subgroups were similar to those observed in the general population. Of the most commonly reported, the following events occurred more often with RANCV (placebo-corrected frequencies) in elderly (≥ 75 years of age) than younger patients (< 75 years of age): constipation (8% versus 5%), nausea (6% versus 3%), hypotension (5% versus 1%), and vomiting (4% versus 1%).

In patients with mild or moderate renal impairment (creatinine clearance ≥ 30–80 ml/min) compared to those with normal renal function (creatinine clearance > 80 ml/min), the most commonly reported events and their placebo-corrected frequencies included: constipation (8% versus 4%), dizziness (7% versus 5%), and nausea (4% versus 2%).

In general, the type and frequency of adverse events reported in patients with low body weight (≤ 60 kg) were similar to those of patients with higher weight (> 60 kg); however, the placebo-corrected frequencies of the following common adverse events were higher in low body weight than heavier patients: nausea (14% versus 2%), vomiting (6% versus 1%), and hypotension (4% versus 2%).

Laboratory findings: Small, clinically insignificant, reversible elevations in serum creatinine levels have been observed in healthy subjects and patients treated with RANCV. There was no renal toxicity related to these findings. A renal function study in healthy volunteers demonstrated a reduction in creatinine clearance with no change in glomerular filtration rate consistent with

inhibition of renal tubular secretion of creatinine.

**4.9 Overdose**

In an oral high-dose tolerability study in angina patients, the incidence of dizziness, nausea, and vomiting increased in a dose-dependent manner. In addition to these adverse events, diplopia, lethargy, and syncope were observed in an intravenous overdose study in healthy volunteers. In the event of overdose, the patient should be closely monitored and the treatment should be symptomatic and supportive.

Approximately 62% of ranolazine is bound to plasma proteins, and therefore, complete clearance by haemodialysis is unlikely.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Other cardiac preparations, ATC code: C01EB18

Mechanism of action: The mechanism of action of ranolazine is largely unknown. Ranolazine may have some antianginal effects by inhibition of the late sodium current in cardiac cells. 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. Clinical evidence of inhibition of the late sodium current by ranolazine is provided by a significant shortening of the QTc interval and an improvement in diastolic relaxation in an open-label study of 5 patients with a long QT syndrome (LQT3 having the SCN5A ΔKPQ gene mutation).

These effects do not depend upon changes in heart rate, blood pressure, or vasodilation.

Pharmacodynamic effects

Haemodynamic effects: Minimal decreases in mean heart rate (< 2 beats per minute) and mean systolic blood pressure (< 3 mm Hg) were observed in patients treated with ranolazine either alone or in combination with other antianginal medicinal products in controlled studies.

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 Ranexa. 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 cirrhotic 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 Ranexa. There was a significantly lower incidence of arrhythmias (ventricular tachycardia, bradycardia, supraventricular tachycardia, and new atrial fibrillation) in patients treated with Ranexa (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.

Clinical efficacy and safety: Clinical studies have demonstrated the efficacy and safety of RANCV in the treatment of patients with chronic angina, either alone or when the benefit from other antianginal medicinal products was sub-optimal.

In the pivotal study, CARISA, RANCV was added to treatment with atenolol 50 mg once daily, amlodipine 5 mg once daily, or diltiazem 180 mg once daily. Eight-hundred and twenty-three patients (23% women) were randomised to receive 12 weeks of treatment with 750 mg twice daily, 1000 mg twice daily, or placebo. RANCV demonstrated greater efficacy than placebo in prolonging exercise time at trough at 12 weeks for both doses studied when used as an add-on therapy. However, there was no difference in exercise duration between the two doses (24 seconds compared to placebo; $p \leq 0.03$).

RANCV resulted in significant decreases in the number of angina attacks per week and consumption of short-acting nitroglycerin compared to placebo. Tolerance to ranolazine did not develop during treatment and a rebound increase in angina attacks was not observed following abrupt discontinuation.

The improvement in exercise duration in women was about 33% of the improvement in men at the 1000 mg twice-daily dose level. However, men and women had similar reductions in frequency of angina attacks and nitroglycerin consumption.

In a second study, ERICA, RANCV was added to treatment with amlodipine 10 mg once daily (the maximum labelled dose). Five-hundred and sixty-five patients were randomised to receive an initial

dose of RANCV 500 mg twice daily or placebo for 1 week, followed by 6 weeks of treatment with RANCV 1000 mg twice daily or placebo, in addition to concomitant treatment with amlodipine 10 mg once daily. Additionally, 45% of the study population also received long-acting nitrates. RANCV resulted in significant decreases in the number of angina attacks per week ($p = 0.028$) and consumption of short-acting nitroglycerin ($p = 0.014$) compared to placebo. Both the average number of angina attacks and nitroglycerin tablets consumed decreased by approximately one per week.

In the main dose-finding study, MARISA, ranolazine was used as monotherapy. One-hundred and ninety-one patients were randomised to treatment with RANCV 500 mg twice daily, 1000 mg twice daily, 1500 mg twice daily, and matching placebo, each for 1 week in a crossover design. RANCV was significantly superior to placebo in prolonging exercise time, time to angina, and time to 1 mm ST segment depression at all doses studied with an observed dose-response relationship. Improvement of exercise duration was statistically significant compared to placebo for all three doses of ranolazine from 24 seconds at 500 mg twice daily to 46 seconds at 1500 mg twice daily, showing a dose-related response. In this study, exercise duration was longest in the 1500 mg group; however, there was a disproportional increase in side effects, and the 1500 mg dose was not studied further.

In a large outcome study (MERLIN-TIMI 36) in 6,560 patients with UA/NSTEMI ACS, there was no difference in the risk of all-cause mortality (relative risk ranolazine:placebo 0.99), sudden cardiac death (relative risk ranolazine:placebo 0.87), or the frequency of symptomatic documented arrhythmias (3.0% versus 3.1%) between RANCV and placebo when added to standard medical therapy (including beta-blockers, calcium channel blockers, nitrates, anti-platelet agents, lipid-lowering medicinal products, and ACE inhibitors). Approximately one-half of the patients in MERLIN-TIMI 36 had a history of angina. The results showed that exercise duration was 31 seconds longer in ranolazine patients versus placebo patients ($p = 0.002$). The Seattle Angina Questionnaire showed significant effects on several dimensions, including angina frequency ($p < 0.001$), compared to placebo-treated patients.

A small proportion of non-Caucasians was included in the controlled clinical studies; therefore, no conclusions can be drawn regarding the effect and safety in non-Caucasians.

**5.2 Pharmacokinetic properties**

After oral administration of RANCV, peak plasma concentrations ($C_{max}$) are typically observed between 2 and 6 hours. Steady state is generally achieved within 3 days of twice-daily dosing.

Absorption: The mean absolute bioavailability of ranolazine after oral administration of immediate-

release ranolazine tablets ranged from 35−50%, with large inter-individual variability. RANCV exposure increases more than in proportion to dose. There was a 2.5- to 3-fold increase in steady-state AUC as the dose was increased from 500 mg to 1000 mg twice daily. In a pharmacokinetic study in healthy volunteers, steady-state $C_{max}$ was, on average, approximately 1770 (SD 1040) ng/ml, and steady-state $AUC_{0-12}$ was, on average, 13,700 (SD 8290) ng x h/ml following a dose of 500 mg twice daily. Food does not affect the rate and extent of absorption of ranolazine.

Distribution: Approximately 62% of ranolazine is bound to plasma proteins, mainly alpha-1 acid glycoprotein and weakly to albumin. The mean steady-state volume of distribution ($V_{ss}$) is about 180 l.

Elimination: Ranolazine is eliminated primarily by metabolism. Less than 5% of the dose is excreted unchanged in the urine and faeces. Following oral administration of a single 500 mg dose of [$^{14}$C]-ranolazine to healthy subjects, 73% of the radioactivity was recovered in urine and 25% in faeces.

Clearance of ranolazine is dose-dependent, decreasing with increased dose. The elimination half-life is about 2−3 hours after intravenous administration. The terminal half-life at steady state after oral administration of ranolazine is about 7 hours, due to the absorption rate-limited elimination.

Biotransformation: Ranolazine undergoes rapid and extensive metabolism. In healthy young adults, ranolazine accounts for approximately 13% of the radioactivity in plasma following a single oral 500 mg dose of [$^{14}$C]-ranolazine. A large number of metabolites has been identified in human plasma (47 metabolites), urine (> 100 metabolites), and faeces (25 metabolites). Fourteen primary pathways have been identified of which O-demethylation and N-dealkylation are the most important. *In vitro* studies using human liver microsomes indicate that ranolazine is metabolised primarily by CYP3A4, but also by CYP2D6. At 500 mg twice daily, subjects lacking CYP2D6 activity (poor metabolisers, PM) had 62% higher AUC than subjects with CYP2D6 metabolising capacity (extensive metabolisers, EM). The corresponding difference at the 1000 mg twice-daily dose was 25%.

Special populations

The influence of various factors on the pharmacokinetics of ranolazine was assessed in a population pharmacokinetic evaluation in 928 angina patients and healthy subjects.

Gender effects: Gender had no clinically relevant effect on pharmacokinetic parameters.

Elderly patients: Age alone had no clinically relevant effect on pharmacokinetic parameters. However, the elderly may have increased ranolazine exposure due to age-related decrease in renal

function.

Body weight: Compared to subjects weighing 70 kg, exposure was estimated to be about 1.4-fold higher in subjects weighing 40 kg.

CHF: CHF NYHA Class III and IV were estimated to have about 1.3-fold higher plasma concentrations.

Renal impairment: In a study evaluating the influence of renal function on ranolazine pharmacokinetics, ranolazine AUC was on average 1.7- to 2-fold higher in subjects with mild, moderate, and severe renal impairment compared with subjects with normal renal function. There was a large inter-individual variability in AUC in subjects with renal impairment. The AUC of metabolites increased with decreased renal function. The AUC of one pharmacologically active ranolazine metabolite was 5-fold increased in patients with severe renal impairment.

In the population pharmacokinetic analysis, a 1.2-fold increase in ranolazine exposure was estimated in subjects with moderate impairment (creatinine clearance 40 ml/min). In subjects with severe renal impairment (creatinine clearance 10–30 ml/min), a 1.3- to 1.8-fold increase in ranolazine exposure was estimated.

The influence of dialysis on the pharmacokinetics of ranolazine has not been evaluated.

Hepatic impairment: The pharmacokinetics of ranolazine have been evaluated in patients with mild or moderate hepatic impairment. There are no data in patients with severe hepatic impairment. Ranolazine AUC was unaffected in patients with mild hepatic impairment but increased 1.8-fold in patients with moderate impairment. QT prolongation was more pronounced in these patients.

Paediatric population: The pharmacokinetic parameters of ranolazine have not been studied in the paediatric population (< 18 years).

**5.3 Preclinical safety data**

Adverse reactions not observed in clinical studies, but seen in animals at levels similar to clinical exposure, were as follows: Ranolazine was associated with convulsions and increased mortality in rats and dogs at plasma concentrations approximately 3-fold higher than at the proposed maximum clinical dose.

Chronic toxicity studies in rats indicated that treatment was associated with adrenal changes at exposures slightly greater than those seen in clinical patients. This effect is associated with increased plasma cholesterol concentrations. No similar changes have been identified in humans. No effect on the adreno-cortical axis was noted in humans.

In long-term carcinogenicity studies at doses of ranolazine up to 50 mg/kg/day (150 mg/m$^2$/day) in

mice and 150 mg/kg/day (900 mg/m$^2$/day) in rats, no relevant increases in the incidence of any tumour types were seen. These doses are equivalent to 0.1 and 0.8 times, respectively, the maximum recommended human dose of 2 grams on a mg/m$^2$ basis, and represent the maximum tolerated doses in these species.

Signs of embryonal and maternal toxicity, but not teratogenicity, were seen at doses of ranolazine up to 400 mg/kg/day (2400 mg/m$^2$/day) in rats and 150 mg/kg/day (1800 mg/m$^2$/day) in rabbits. These doses represent 2.7 and 2 times, respectively, the maximum recommended human dose.

Animal studies do not indicate direct or indirect harmful effects of ranolazine with respect to male or female fertility.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS:

Tablet core:

Microcrystalline cellulose, methacrylic acid co-polymer, hydroxy propyl methyle cellulose, sodium hydroxide, magnesium stearate.

Film coat:

Lactose monohydrate, hypromellose, titanium dioxide, macrogol, iron oxide yellow and carnauba wax.

### 6.2 INCOMPATIBILITIES:

Not applicable

### 6.3 SHELF LIFE:

24 months.

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE:

Do not Store above 30°C. Store in the original package in order to protect from moisture.

### 6.5 NATURE AND CONTENTS OF CONTAINER:

10 tablets are packed in plain Aluminium blister foil (lid foil) one side and printed aluminium foil on another side in the form of blister pack (10's). Three blister packs are further packed into printed carton along with instruction for use.

### 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL:

Any unused product or waste material should be disposed off in accordance with local requirements.

**7. MARKETING AUTHORISATION HOLDER:**

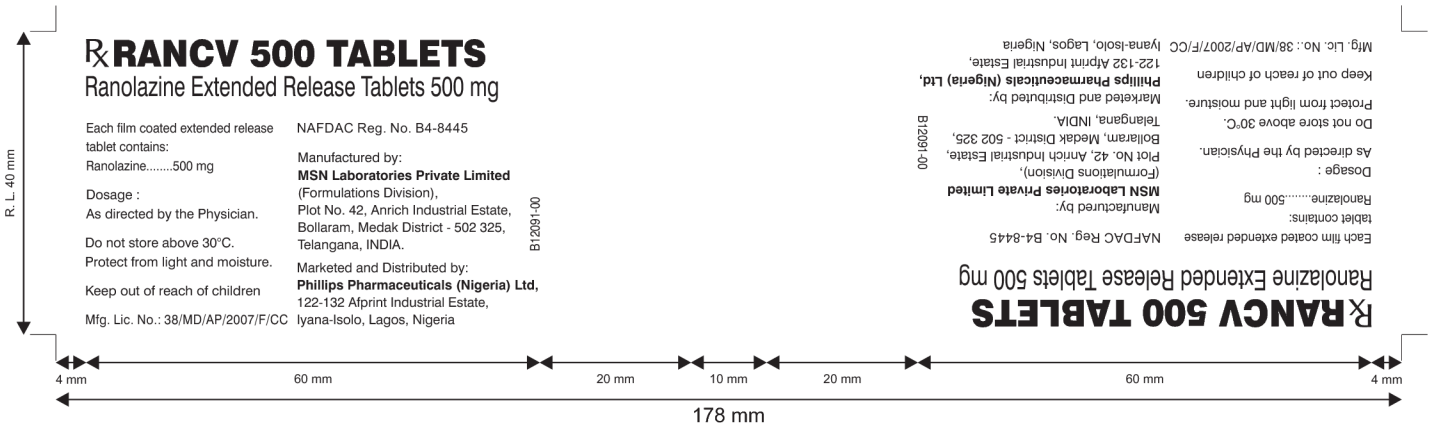
MSN LABORATORIES PRIVATE LIMITED,
MSN House, Plot No. : C-24, Industrial Estate,
Sanath Nagar, Hyderabad – 500 018
Andhra Pradesh, India.

**8. DATE OF REVISION OF THE TEXT:** Sep, 2014.

LEGAL CATEGORY: POM

### 1.3.2 Labelling (outer & inner labels)

The artworks of container label, carton & Pack Insert for RANCV 500 (Ranolazine Extended Release Tablets 500 mg) are enclosed in the following pages.




℞ RANCV 500 TABLETS
Ranolazine Extended Release Tablets 500 mg
Each film coated extended release tablet contains:
Ranolazine.....500 mg
Dosage :
As directed by the Physician.
Do not store above 30°C.
Protect from light and moisture.
Keep out of reach of children
Mfg. Lic. No.: 38/MD/AP/2007/F/CC
NAFDAC Reg. No. B4-8445
Manufactured by:
MSN Laboratories Private Limited
(Formulations Division),
Plot No. 42, Anrich Industrial Estate,
Bollaram, Medak District - 502 325,
Telangana, INDIA.
Marketed and Distributed by:
Phillips Pharmaceuticals (Nigeria) Ltd,
122-132 Afprint Industrial Estate,
Iyana-Isolo, Lagos, Nigeria
B12091-00

Black

## Foil Width 178 mm
## Blister Size 85 x 60mm (Repeat 1.33)
## Size : 4+ 60 + 20 +10 +20 + 60 + 4

MSN LABORATORIES PRIVATE LIMITED — PACKAGING DEVELOPMENT

| Artwork Information | | Specification for Printed Foil | |
|---|---|---|---|
| | | Test | Specification |
| Brand Name | RANCV 500 TABLET | Description | Printed hard tampered aluminium foil with VMCH coating on the sealing side. |
| Generic Name | Ranolazine Extended Release Tablets 500 mg | | |
| Pack Style | 10's | Thickness of Aluminium | 0.018 to 0.022 mm |
| Foil Width | 178 mm | Width | 178 ± 1.0 mm (177 – 179 mm) |
| Item Code | B12091-00 | Aluminium foil GSM | 49.86 to 58.54 GSM |
| Supersede Code | 00 | VMCH Coating GSM | 4 to 6 GSM |
| Change Part No: | – | NC Coating | NA |
| Version | 00 | Pin Holes | Nil |
| Date & Time | | Ink Adhesion Test | No Ink Lifting |
| Country | NIGERIA | Inner Core Diameter | 76 ± 1 mm |
| Customer | NA | PRC/Non-PRC | NA |
| Font Type | NA | Eye Mark Size | NA |
| Font Size (min.) | NA | Perforation/Non-Perforation | Non-Perforation |
| Developed by | Brahmam | Colours | BLACK |
| Reviewed by | Srilakshmi | | |


DIMENSION : 90 X 30 X 65mm

Cyber XL Board 300 gsm, UV Varnish except over printing area.

**MSN LABORATORIES PRIVATE LIMITED** — **PACKAGING DEVELOPMENT**

| Artwork Information | | Specification for Printed Carton | |
|---|---|---|---|
| | | Parameter | Specification |
| Brand Name | RANCV 500 TABLETS | Substrate | Cyber XL board with reverse tuck in type |
| Generic Name | Ranolazine Extended Release Tablets 500 mg | GSM | 300 ± 5% |
| Pack Style | 3 x 10's Pack | Varnish/Lamination | UV Varnish except over printing area |
| Dimensions | 90 x 30 x 65 mm (LxWxH) | Mode of supply | Bundles 25's, 50's & 100's |
| Item Code | B22091-00 | Pharmacode | 1305 |
| Supersede Code | NA | Font Type | Arial & Swis721 Hv BT |
| Version | 00 | Font Size (min.) | 6 pt |
| Date & Time | | Reviewed by | Srilakshmi |
| Country | NIGERIA | Colours | PANTONE 485 C, PANTONE 273 C, Black |
| Customer | NA | | |
| Developed by | Brahmam | | |

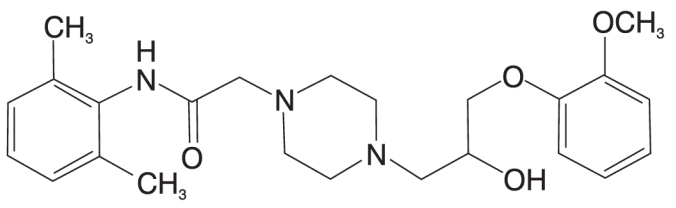
Prescription only medication

# RANCV 500/1000 TABLETS

Ranolazine Extended Release Tablets 500 mg/1000 mg

**RANCV 500/1000 TABLETS**

(Ranolazine Extended Release Tablets 500/1000 mg)
Each film coated extended release tablet contains:
Ranolazine..... 500/1000 mg
Ranolazine is a racemic mixture, chemically described as 1-Piperarazineacetamide, N-(2,6-dimethylphenyl)-4- [2-hydroxy -3- (2-methoxyphenoxy) propyl]-, (±)-. It has empirical formula of $C_{24}H_{33}N_3O_4$. A molecular weight of 427.54 g/mole, and the following structural formula:




**CLINICAL PHARMACOLOGY**

**Mechanism of Action**

The mechanism of action of ranolazine's antianginal effects has not been determined. Ranolazine has anti-ischemic and antianginal effects that do not depend upon reductions in heart rate or blood pressure. It does not affect the rate-pressure product, a measure of myocardial work, at maximal exercise. Ranolazine at therapeutic levels can inhibit the cardiac late sodium current (INa). However, the relationship of this inhibition to angina symptoms is uncertain.
The QT prolongation effect of ranolazine on the surface electrocardiogram is the result of inhibition of IKr, which prolongs the ventricular action potential.

**Pharmacodynamics**

**Hemodynamic Effects**

Patients with chronic angina treated with RANCV 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 RANCV. 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 cirrhotic 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 3162 acute coronary syndrome patients treated with RANCV. There was a significantly lower incidence of arrhythmias (ventricular tachycardia, bradycardia, supraventricular tachycardia, and new atrial fibrillation) in patients treated with RANCV (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**

Ranolazine is extensively metabolized in the gut and liver and its absorption is highly variable. For example, at a dose of 1000 mg twice daily, the mean steady-state $C_{max}$ was 2600 ng/mL with 95% confidence limits of 400 and 6100 ng/mL. The pharmacokinetics of the (+) R-and (-) S-enantiomers of ranolazine are similar in healthy volunteers. The apparent terminal half-life of ranolazine is 7 hours. Steady state is generally achieved within 3 days of twice-daily dosing with RANCV. At steady state over the dose range of 500 to 1000 mg twice daily, $C_{max}$ and AUC0-τ increase slightly more than proportionally to dose, 2.2-and 2.4-fold, respectively. With twice-daily dosing, the trough:peak ratio of the ranolazine plasma concentration is 0.3 to 0.6. The pharmacokinetics of ranolazine is unaffected by age, gender, or food.

**Absorption and Distribution**

After oral administration of RANCV, 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 RANCV 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 $C_{max}$ and AUC of ranolazine. Therefore, RANCV 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.

**Drug Interactions**

**Effects of Other Drugs on Ranolazine**

In vitro data indicate that ranolazine is a substrate of CYP3A and, to a lesser degree, of CYP2D6. Ranolazine is also a substrate of P-glycoprotein.

Strong CYP3A Inhibitors

Plasma levels of ranolazine with RANCV 1000 mg twice daily are increased by 220% when co-administered with ketoconazole 200 mg twice daily

Moderate CYP3A Inhibitors

Plasma levels of ranolazine with RANCV 1000 mg twice daily are increased by 50 to 130% by diltiazem 180 to 360 mg, respectively. Plasma levels of ranolazine with RANCV 750 mg twice daily are increased by 100% by verapamil 120 mg three times daily.

Weak CYP3A Inhibitors

The weak CYP3A inhibitors simvastatin (20 mg once daily) and cimetidine (400 mg three times daily) do not increase the exposure to ranolazine in healthy volunteers.

CYP3A Inducers

Rifampin 600 mg once daily decreases the plasma concentrations of ranolazine (1000 mg twice daily) by approximately 95%.

CYP2D6 Inhibitors

Paroxetine 20 mg once daily increased ranolazine concentrations by 20% in healthy volunteers receiving RANCV 1000 mg twice daily. No dose adjustment of RANCV is required in patients treated with CYP2D6 inhibitors.

Digoxin

Plasma concentrations of ranolazine are not significantly altered by concomitant digoxin at 0.125 mg once daily.

Effect of Ranolazine on Other Drugs

In vitro ranolazine and its O-demethylated metabolite are weak inhibitors of CYP3A and moderate inhibitors of CYP2D6 and P-gp. In vitro ranolazine is an inhibitor of OCT2.

CYP3A Substrates

The plasma levels of simvastatin, a CYP3A substrate, and its active metabolite are increased by 100% in healthy volunteers receiving 80 mg once daily and RANCV 1000 mg twice daily. Mean exposure to atorvastatin (80 mg daily) is increased by 40% following co-administration with RANCV (1000 mg twice daily) in healthy volunteers. However, in one subject the exposure to atorvastatin and metabolites was increased by ~400% in the presence of RANCV.

Diltiazem

The pharmacokinetics of diltiazem is not affected by ranolazine in healthy volunteers receiving diltiazem 60 mg three times daily and RANCV 1000 mg twice daily.

P-gp Substrates

Ranolazine increases digoxin concentrations by 50% in healthy volunteers receiving RANCV 1000 mg twice daily and digoxin 0.125 mg once daily.

CYP2D6 Substrates

RANCV 750 mg twice daily increases the plasma concentrations of a single dose of immediate release metoprolol (100 mg), a CYP2D6 substrate, by 80% in extensive CYP2D6 metabolizers with no need for dose adjustment of metoprolol. In extensive metabolizers of dextromethorphan, a substrate of CYP2D6, ranolazine inhibits partially the formation of the main metabolite dextrorphan.

OCT2 Substrates

In subjects with type 2 diabetes mellitus, the exposure to metformin is increased by 40% and 80% following administration of ranolazine 500 mg twice daily and 1000 mg twice daily, respectively. If co-administered with RANCV 1000 mg twice daily, do not exceed metformin doses of 1700 mg/day.

**INDICATIONS AND USAGE**

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

**WARNINGS AND PRECAUTIONS**

**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 proarrhythmia or sudden death. However, there is little experience with high doses (>1000 mg twice daily) or exposure, other QT-prolonging drugs, potassium channel variants resulting in a long QT interval, in patients with a family history of (or congenital) long

MSN LABORATORIES PRIVATE LIMITED — PACKAGING DEVELOPMENT

| Artwork Information | | Specification for Printed Leaflet | |
|---|---|---|---|
| | | Parameter | Specification |
| Brand Name | RANCV 500/1000 TABLET | Substrate | Bible Paper |
| Generic Name | Ranolazine Extended Release Tablets 500/1000 mg | GSM | 40 ± 10% |
| Pack Style | NA | Mode of supply | Tray Pack |
| Dimensions | 160 x 450mm | Pharmacode | 1306 |
| Folding Size | 160 x 28mm | Font Type | Arial |
| Item Code | B32091-01 | Font Size (min.) | 5.5 pt |
| Supersede Code | B32091-00 | Developed by | Swaroop |
| Version | 00 | Reviewed by | Srilakshmi |
| Date & Time | - | Colours | Black |
| Country | NIGERIA | | |
| Customer | NA | | |

*Pharma code position is not fixed, so it may vary based on the printer's requirement.

QT syndrome, or in patients with known acquired QT interval prolongation.

**Renal Failure**

Acute renal failure has been observed in some patients with severe renal impairment (creatinine clearance [CrCL] <30 mL/min) while taking RANCV. If acute renal failure develops (e.g., marked increase in serum creatinine associated with an increase in blood urea nitrogen [BUN]), discontinue RANCV 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.

**NONCLINICAL TOXICOLOGY**

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Ranolazine tested negative for genotoxic potential in the following assays: Ames bacterial mutation assay, Saccharomyces assay for mitotic gene conversion, chromosomal aberrations assay in Chinese hamster ovary (CHO) cells, mammalian CHO/HGPRT gene mutation assay, and mouse and rat bone marrow micronucleus assays.
There was no evidence of carcinogenic potential in mice or rats. The highest oral doses used in the carcinogenicity studies were 150 mg/kg/day for 21 months in rats (900 mg/m$^2$/day) and 50 mg/kg/day for 24 months in mice (150 mg/m$^2$/day). These maximally tolerated doses are 0.8 and 0.1 times, respectively, the daily maximum recommended human dose (MRHD) of 2000 mg on a surface area basis. A published study reported that ranolazine promoted tumor formation and progression to malignancy when given to transgenic APC (min/+) mice at a dose of 30 mg/kg twice daily. The clinical significance of this finding is unclear.
In male and female rats, oral administration of ranolazine that produced exposures (AUC) approximatelty 3-fold or 5-fold higher, respectively, than the MRHD had no effect on fertility.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

There are no available data on RANCV use in pregnant women to inform any drug-associated risks. Studies in rats and rabbits showed no evidence of fetal harm at exposures 4 times the maximum recommended human dose (MRHD)
In the U.S. general population, the estimated background risk of major birth defects and of miscarriage of clinically recognized pregnancies is 2-4% and 15-20%, respectively.

**Data**

**Animal Data**

Embryofetal toxicity studies were conducted in rats and rabbits orally administered ranolazine during organogenesis. In rats, decreased fetal weight and reduced ossification were observed at doses (corresponding to 4-fold the AUC for the MRHD) that caused maternal weight loss. No adverse fetal effects were observed in either species exposed (AUC) to ranolazine at exposures (AUC) equal to the MRHD.

**Lactation**

**Risk Summary**

There are no data on the presence of ranolazine in human milk, the effects on the breastfed infant, or the effects on milk production. However, ranolazine is present in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RANCV and any potential adverse effects on the breastfed infant from RANCV or from the underlying maternal condition.
Adult female rats were administered ranolazine orally from gestation day 6 through postnatal day 20. No adverse effects on pup development, behavior, or reproduction parameters were observed at a maternal dosage level of 60 mg/kg/day (equal to the MHRD based on AUC). At maternally toxic doses, male and female pups exhibited
increased mortality and decreased body weight, and female pups showed increased motor activity. The pups were potentially exposed to low amounts of ranolazine via the maternal milk.

**Pediatric Use**

Safety and effectiveness have not been established in pediatric patients.

**Geriatric Use**

Of the chronic angina patients treated with RANCV in controlled studies, 496 (48%) were ≥65 years of age, and 114 (11%) were ≥75 years of age. 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 RANCV, compared to placebo, had a higher incidence of adverse events, serious adverse events, and drug discontinuations due to adverse events. 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**

RANCV is contraindicated in patients with liver cirrhosis. In a study of cirrhotic patients, the $C_{max}$ of ranolazine was increased 30% in cirrhotic patients with mild (Child-Pugh Class A) hepatic impairment, but increased 80% in cirrhotic patients with moderate (Child-Pugh Class B) hepatic impairment compared to patients without hepatic impairment. This increase was not enough to account for the 3-fold increase in QT prolongation seen in cirrhotic patients with mild to moderate hepatic impairment

**Use in Patients with Renal Impairment**

A pharmacokinetic study of RANCV in subjects with severe renal impairment (CrCL <30 mL/min) was stopped when 2 of 4 subjects developed acute renal failure after receiving RANCV 500 mg twice daily for 5 days (lead-in phase) followed by 1000 mg twice a day (1 dose in one subject and 11 doses in the other). Increases in creatinine, BUN, and potassium were observed in 3 subjects during the 500 mg lead-in phase. One subject required hemodialysis, while the other 2 subjects improved upon drug discontinuation. Monitor renal function periodically in patients with moderate to severe renal impairment. Discontinue RANCV if acute renal failure develops.
In a separate study, $C_{max}$ was increased between 40% and 50% in patients with mild, moderate, or severe renal impairment compared to patients with no renal impairment, suggesting a similar increase in exposure in patients with renal failure independent of the degree of impairment. The pharmacokinetics of ranolazine has not been assessed in patients on dialysis.

**Use in Patients with Heart Failure**

Heart failure (NYHA Class I to IV) had no significant effect on ranolazine pharmacokinetics. RANCV had minimal effects on heart rate and blood pressure in patients with angina and heart failure NYHA Class I to IV. No dose adjustment of RANCV is required in patients with heart failure.

**Use in Patients with Diabetes Mellitus**

A population pharmacokinetic evaluation of data from angina patients and healthy subjects showed no effect of diabetes on ranolazine pharmacokinetics. No dose adjustment is required in patients with diabetes.
RANCV produces small reductions in HbA1c in patients with diabetes, the clinical significance of which is unknown. RANCV should not be considered a treatment for diabetes.

**DOSAGE AND ADMINISTRATION**

**Dosing Information**

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

**OVERDOSAGE**

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. Severe tremor, unsteady gait/incoordination, dysphasia, and hallucinations have been reported in cases of overdose with RANCV.
Since ranolazine is about 62% bound to plasma proteins, hemodialysis is unlikely to be effective in clearing ranolazine.

**CONTRAINDICATIONS**

RANCV is contraindicated in patients:
- Taking strong inhibitors of CYP3A
- Taking inducers of CYP3A
- With liver cirrhosis

**STORAGE**

Do not store above 30°C. Protect from light and moisture.
Keep out of reach of children.

**PACKING INFORMATION:**

Rancv 500 Tablets: Blister pack of 10 Tablets
Rancv 1000 Tablets: Blister pack of 10 Tablets

B32091-01

**Date of Revision of text:** October 2016

NAFDAC Reg. No. B4-8445

NAFDAC Reg. No. B4-8446

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

Marketed and Distributed by:
**Phillips Pharmaceuticals (Nigeria) Ltd,**
122-132 Afprint Industrial Estate,
Iyana-Isolo, Lagos, Nigeria

### 1.3.3 Package Insert (also known as patient information PIL)

Patient Information leaflet for RANCV 500 (Ranolazine Extended Release Tablets 500 mg) has been enclosed inthe following pages.

**DRUG INTERACTIONS**:

**Effects of Other Drugs on Ranolazine**

**Strong CYP3A Inhibitors**

Do not use Ranolazine with strong CYP3A inhibitors, including ketoconazole, itraconazole, clarithromycin, nefazodone, nelfinavir, ritonavir, indinavir, and saquinavir.

**Moderate CYP3A Inhibitors**

Limit the dose of Ranolazine to 500 mg twice daily in patients on moderate CYP3A inhibitors, including diltiazem, verapamil, erythromycin, fluconazole, and grapefruit juice or grapefruit-containing products.

**P-gp Inhibitors**

Concomitant use of Ranolazine and P-gp inhibitors, such as cyclosporine, may result in increases in ranolazine concentrations. Titrate Ranolazine based on clinical response in patients concomitantly treated with predominant P-gp inhibitors such as cyclosporine.

**CYP3A Inducers**

Do not use Ranolazine with CYP3 A inducers such as rifampin, rifabutin, rifapentin, phenobarbital, phenytoin, carbamazepine, and St. John's wort.

**Effects of Ranolazine on Other Drugs**

**Drugs Metabolized by CYP3A**

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.

**Drugs Transported by P-gp**

Concomitant use of ranolazine and digoxin results in increased exposure to digoxin. The dose of digoxin may have to be adjusted.

**Drugs Metabolized by CYP2D6**

The exposure to CYP2D6 substrates, such as tricyclic antidepressants and antipsychotics, may be increased during co-administration with Ranolazine, and lower doses of these drugs may be required.

**DOSAGE AND ADMINISTRATION**

**Dosing Information**

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 moderate CYP3 A 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 Ranolazine based on clinical response .

**OVER DOSE**

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.

**CONTRAINDICATIONS**

Ranolazine is contraindicated in patients:

- Taking strong inhibitors of CYP3 A
- Taking inducers of CYP3 A
- With liver cirrhosis.

**STORAGE**

Store below 25°C.

**PACKING INFORMATION**:

Blister/PVC/PVDC pack of 10 Tablets

**Manufactured by**

**MSN Laboratories Private Limited**

Plot No 42,Anrich Industrial Estate,

Bollaram, Medak Dist. 502 325, A.P ,INDIA

## Ranolazine Extended Release tablets

**RANCV 500**

Ranolazine Extended Release tablets 500 mg

Each film coated extended release tablet contains

Ranolazine----------500 mg

**Colors:** Iron oxide Yellow & Titanium dioxide USP/BP

**RANCV 1000**

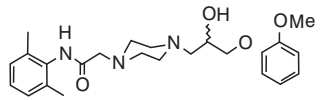
Ranolazine Extended Release tablets 1000 mg

Each film coated extended release tablet contains

Ranolazine----------1000 mg

**Colors:** Iron oxide Yellow & Titanium dioxide USP/BP

Ranolazine is a racemic mixture, chemically described as 1-piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (±)-. It has an empirical formula of C24H33N3O4, a molecular weight of 427.54 g/mole, and the following structural formula:




**PHARMACOLOGY**

**Mechanism of Action**

The mechanism of action of ranolazine's antianginal effects has not been determined. Ranolazine has anti-ischemic and antianginal effects that do not depend upon reductions in heart rate or blood pressure. It does not affect the rate-pressure product, a measure of myocardial work, at maximal exercise. Ranolazine at therapeutic levels can inhibit the cardiac late sodium current ($I_{Na}$)- However, the relationship of this inhibition to angina symptoms is uncertain.

The QT prolongation effect of ranolazine on the surface electrocardiogram is the result of inhibition of $I_{Kr}$, which prolongs the ventricular action potential.

**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 cirrhotic 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**

Ranolazine is extensively metabolized in the gut and liver and its absorption is highly variable. For example, at a dose of 1000 mg twice daily, the mean steady-state Cmax was 2600 ng/mL with 95% confidence limits of 400 and 6100 ng/mL. The pharmacokinetics of the (+) R- and (-) S-enantiomers of ranolazine are similar in healthy volunteers. The apparent terminal half-life of ranolazine is 7 hours. Steady state is generally achieved within 3 days of twice-daily dosing with Ranolazine. At steady state over the dose range of 500 to 1000 mg twice daily, Cmax and $AUC_{0-t}$ increase slightly more than proportionally to dose, 2.2- and 2.4-fold, respectively. With twice-daily dosing, the trough: peak ratio of the ranolazine plasma concentration is 0.3 to 0.6. The pharmacokinetics of ranolazine is unaffected by age, gender, or food.

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**Absorption and Distribution**

After oral administration of Ranolazine, peak plasma concentrations of ranolazine are reached between 2 and 5 hours. After oral administration of $^{14}$C-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 $\mu$g/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.

**DRUG INTERACTIONS**

**Effect of other drugs on ranolazine**

In vitro data indicate that ranolazine is a substrate of CYP3A and, to a lesser degree, of CYP2D6. Ranolazine is also a substrate of P-glycoprotein.

**Strong CYP3A Inhibitors**

Plasma levels of ranolazine with Ranolazine 1000 mg twice daily are 3.2-fold higher if coadministered with ketoconazole 200 mg twice daily.

**Moderate CYP3A Inhibitors**

Plasma levels of ranolazine with Ranolazine 1000 mg twice daily are increased about 50 to 130% by diltiazem 180 to 360 mg, respectively. Plasma levels of ranolazine by Ranolazine 750 mg twice daily are increased about 100% by verapamil 120 mg three times daily.

**Weak CYP3A Inhibitors**

The weak CYP3A inhibitors simvastatin (20 mg once daily) and cimetidine (400 mg three times daily) do not increase the exposure to ranolazine in healthy volunteers.

**CYP3A Inducers**

Rifampin 600 mg once daily decreases the plasma concentrations of ranolazine (1000 mg twice daily) by approximately 95%.

**CYP2D6 Inhibitors**

Paroxetine 20 mg once daily increased ranolazine concentrations 20% in healthy volunteers receiving Ranolazine 1000 mg twice daily. No dose adjustment of Ranolazine is required in patients treated with CYP2D6 inhibitors.

**Digoxin**

Plasma concentrations of ranolazine are not significantly altered by concomitant digoxin at 0.125 mg once daily.

**Effect of ranolazine on other drugs**

In vitro ranolazine and its O-demethylated metabolite are weak inhibitors of CYP3A and moderate inhibitors of CYP2D6 and P-gp. In vitro ranolazine is an inhibitor of OCT2.

**CYP3A Substrates**

The plasma levels of simvastatin, a CYP3 A substrate, and its active metabolite are each doubled in healthy subjects receiving 80 mg once daily and Ranolazine 1000 mg twice daily.

**Diltiazem**

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.

**P-gp Substrates**

Ranolazine increases digoxin concentrations 50% in healthy volunteers receiving Ranolazine 1000 mg twice daily and digoxin 0.125 mg once daily.

**CYP2D6 Substrates**

Ranolazine 750 mg twice daily increases the plasma concentrations of a single dose of immediate release metoprolol (100 mg), a CYP2D6 substrate, by 80% in extensive CYP2D6 metabolizers with no need for dose adjustment of metoprolol. In extensive metabolizers of dextromethorphan, a substrate of CYP2D6, ranolazine inhibits partially the formation of the main metabolite dextrorphan.

**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.

**PRECAUTIONS**

**QT Interval Prolongation**

Ranolazine blocks $I_{Kr}$ 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 proarrhythmia or sudden death. However, there is little experience with high doses ( > 1000 mg twice daily) or exposure, other QT-prolonging drugs, potassium channel variants resulting in a long QT interval, in patients with a family history of (or congenital) long QT syndrome, or in patients with known acquired QT interval prolongation.

**NONCLINICAL TOXICOLOGY**

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Ranolazine tested negative for genotoxic potential in the following assays: Ames bacterial mutation assay, Saccharomyces assay for mitotic gene conversion, chromosomal aberrations assay in Chinese hamster ovary (CHO) cells, mammalian CHO/HGPRT gene mutation assay, and mouse and rat bone marrow micronucleus assays.

There was no evidence of carcinogenic potential in mice or rats. The highest oral doses used in the carcinogenicity studies were 150 mg/kg/day for 21 months in rats (900 mg/m$^2$/day) and 50 mg/kg/day for 24 months in mice (150 mg/m$^2$/day). These maximally tolerated doses are 0.8 and 0.1 times, respectively, the maximum recommended human dose (MRHD) of 2 grams on a surface area basis. A published study reported that ranolazine promoted tumor formation and progression to malignancy when given to transgenic APC (min/+) mice at a dose of 30 mg/kg twice daily . The clinical significance of this finding is unclear.

**Reproductive Toxicology Studies**

Animal reproduction studies with ranolazine were conducted in rats and rabbits.

There was an increased incidence of misshapen sternebrae and reduced ossification of pelvic and cranial bones in fetuses of pregnant rats dosed at 400 mg/kg/day (2 times the MRHD on a surface area basis). Reduced ossification of sternebrae was observed in fetuses of pregnant rabbits dosed at 150 mg/kg/day (1.5 times the MRHD on a surface area basis). These doses in rats and rabbits were associated with an increased maternal mortality rate.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Pregnancy Category C**

In animal studies, ranolazine at exposures 1.5 (rabbit) to 2 (rat) times the usual human exposure caused maternal toxicity and misshapen sternebrae and reduced ossification in offspring. These doses in rats and rabbits were associated with an increased maternal mortality rate . 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.

**Nursing Mothers**

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.

**Pediatric Use**

Safety and effectiveness have not been established in pediatric patients.

**Geriatric Use**

Of the chronic angina patients treated with Ranolazine in controlled studies, 496 (48%) were ? 65 years of age, and 114 (11%) were ? 75 years of age. 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, compared to placebo, had a higher incidence of adverse events, serious adverse events, and drug discontinuations due to adverse events. 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**

Ranolazine is contraindicated in patients with liver cirrhosis. In a study of cirrhotic patients, the Cmax of ranolazine was increased 30% in cirrhotic patients with mild (Child-Pugh Class A) hepatic impairment, but increased 80% in cirrhotic patients with moderate (Child-Pugh Class B) hepatic impairment compared to patients without hepatic impairment. This increase was not enough to account for the 3-fold increase in QT prolongation seen in cirrhotic patients with mild to moderate hepatic impairment.

**Use in Patients with Renal Impairment**

Compared to patients with no renal impairment, Cmax was increased between 40% and 50% in patients with mild, moderate or severe renal impairment suggesting a similar increase in exposure in patients with renal failure independent of the degree of impairment. The pharmacokinetics of ranolazine has not been assessed in patients on dialysis.

**Use in Patients with Heart Failure**

Heart failure (NYHA Class I to IV) had no significant effect on ranolazine pharmacokinetics. Ranolazine had minimal effects on heart rate and blood pressure in patients with angina and heart failure NYHA Class I to IV. No dose adjustment of Ranolazine is required in patients with heart failure.

**Use in Patients with Diabetes Mellitus**

A population pharmacokinetic evaluation of data from angina patients and healthy subjects showed no effect of diabetes on ranolazine pharmacokinetics. No dose adjustment is required in patients with diabetes.

Ranolazine produces small reductions in HbAlc in patients with diabetes, the clinical significance of which is unknown. Ranolazine should not be considered a treatment for diabetes.