For the use of a Registered Medical Practitioner only

1. GENERIC NAME AND BRAND NAME

Ranolazine Extended Relaease Tablets 500mg
RANOGARD®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated extended release tablet contains:
Ranolazine.....500 mg
Excipients…….q.s
Colours: Ferric oxide USP NF Yellow & Titanium Dioxide I.P.

3. DOSAGE FORM & STRENGTH

Refer section 1 & 2

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Ranolazine is indicated for the treatment of chronic angina.

4.2 POSOLOGY AND METHOD 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 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 Ranolazine based on clinical response.

4.3 CONTRAINDICATIONS

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, liver cirrhosis
- concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, voriconazole, posaconazole, HIV protease inhibitors, clarithromycin, telithromycin, nefazodone) and inducers of CYP3A
- 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 up-titrating ranolazine to patients in whom an increased exposure is expected:

- Concomitant administration of moderate CYP3A4 inhibitors.

- Concomitant administration of P-gp inhibitors.
- 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).

In patients with a combination of these factors, additional exposure increases are expected. Dose- dependent side effects are likely to occur. If ranolazine 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). 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, ranolazine can be used with caution in these patients when they have a combination of several of the above risk factors.

QT prolongation

Ranolazine blocks IKr and prolongs the QTc interval in a dose-related manner. 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.

Drug-drug interactions

Co-administration with CYP3A4 inducers is expected to lead to lack of efficacy. Ranolazine should not be used in patients treated with CYP3A4 inducers (e.g. rifampicin, phenytoin, phenobarbital, carbamazepine, St. John's Wort).

Renal impairment

Renal function decreases with age and it is therefore important to check renal function at regular intervals during treatment with ranolazine.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Effects of Other Drugs on Ranolazine

Strong CYP3A 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. 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 ranolazine is recommended in patients treated with diltiazem and other moderately potent CYP3A4 inhibitors (e.g. erythromycin, fluconazole). Down-titration of ranolazine may be required.

P-gp Inhibitors
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 ranolazine is recommended in patients treated with P-gp inhibitors. Down-titration of ranolazine may be required.
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 ranolazine may increase plasma concentrations of these drugs.

Available data suggest that ranolazine is a mild inhibitor of CYP2D6. Ranolazine 750 mg twice daily increased plasma concentrations of metoprolol by 1.8-fold. 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 ranolazine, 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, and cyclophosphamide).

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

Simvastatin
Simvastatin metabolism and clearance are highly dependent on CYP3A4. Ranolazine 1000 mg twice daily increased plasma concentrations of simvastatin lactone, simvastatin acid by about 2-fold. Rhabdomyolysis has been associated with high doses of simvastatin and cases of rhabdomyolysis have been observed in patients receiving ranolazine and simvastatin, in postmarketing experience. Limit the dose of simvastatin to 20 mg once daily in patients taking any dose of ranolazine.

Atorvastatin
Ranolazine 1000 mg twice daily increased Cmax and AUC of atorvastatin 80 mg once daily by 1.4- and 1.3 -fold, respectively and changed the Cmax and AUC of atorvastatin metabolites less than 35%. Dose limitation of atorvastatin and appropriate clinical monitoring may be considered when taking ranolazine.
Dose limitation of other statins, metabolised by CYP3A4 (e.g. lovastatin), may be considered when taking ranolazine.

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 ranolazine 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, and everolimus).

Drugs transported by the Organic Cation Transporter-2 (OCT2)
Plasma exposure of metformin (1000 mg twice daily) increased 1.4- and 1.8-fold in subjects with type 2 diabetes mellitus when co-administered with Ranolazine 500 mg and 1000 mg twice daily respectively. The exposure of other OCT2 substrates, including but not limited to pindolol and varenicline, may be affected to a similar degree.
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 USE IN SPECIAL POPULATIONS (SUCH AS PREGNANT WOMEN, LACTATING WOMEN, PAEDIATRIC PATIENTS, GERIATRIC PATIENTS ETC.)

Pregnancy
There are limited amount of data from the use of ranolazine in pregnant women. Studies in animals showed embryo toxicity. The potential risk for humans is unknown. Ranolazine should not be used during pregnancy unless clearly necessary.

Breast-feeding
It is unknown whether ranolazine is excreted in human breast milk. Available pharmacodynamic/ toxicological data in rats have shown excretion of ranolazine in milk. A risk to the suckling child cannot be excluded. Ranolazine should not be used during breast-feeding.

Fertility
In animals, reproduction studies indicated no adverse effects on fertility. 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 Ranolazine on the ability to drive and use machines have been performed. Ranolazine may cause dizziness, blurred vision, diplopia, confusional state, and coordination abnormal, hallucination, which may affect the ability to drive and use machines.

4.8 UNDESIRABLE EFFECTS

Undesirable effects in patients receiving Ranolazine are generally mild to moderate in severity and often develop within the first 2 weeks of treatment.

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

Rare: hyponatremia

Psychiatric disorders

Uncommon: anxiety, insomnia, confusional state, hallucination

Rare: disorientation

Nervous system disorders

Common: dizziness, headache

Uncommon: lethargy, syncope, hypoaesthesia, somnolence, tremor, postural dizziness, paresthesia

Rare: amnesia, depressed level of consciousness, loss of consciousness, coordination abnormal, gait disturbance, parosmia

Not known: myoclonus

Eye disorders

Uncommon: blurred vision, visual disturbance, diplopia

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, muscular weakness.

Renal and urinary disorders

Uncommon: dysuria, haematuria, chromaturia.

Rare: acute renal failure, urinary retention.

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.

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 ranolazine (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 ranolazine. 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.

Reporting of suspected adverse reactions
Health care professionals, patients/consumers are advised to closely monitor the possibility of the above ADRs associated with the use of the above drugs. If such reactions are encountered, please report to the Hetero either by filling of Suspect Adverse Drug Reactions Reporting Form (form.heteroworld.com) or by Hetero Helpline No.1800-120-8689 and for all India safety cases and complaints, please write to drugsafetyindia@heterodrugs.com.

4.9 OVERDOSAGE
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. In postmarketing experience, there have been reports of intentional overdose of Ranolazine alone or in combination with other drugs with a fatal outcome.

5.0 PHARMACOLOGICAL PROPERTIES
5.1 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.

5.2 PHARMACODYNAMIC PROPERTIES

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 3162 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.

5.3 PHARMACOKINETIC PROPERTIES

After oral administration of ranolazine, peak plasma concentrations (Cmax) 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. Ranolazine 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 Cmax was, on average, approximately 1770 (SD 1040) ng/ml, and steady-state AUC0-12 was, on average, 13,700 (SD

8290) ng.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 (Vss) 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 [14C]-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 [14C]-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 increase 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).

6.0 NONCLINICAL PROPERTIES
6.1 ANIMAL TOXICOLOGY OR PHARMACOLOGY
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/m2/day) in mice and 150 mg/kg/day (900 mg/m2/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/m2 basis, and represent the maximum tolerated doses in these species.
In male and female rats, oral administration of ranolazine that produced exposures (AUC) 3.6-fold or 6.6-fold higher than expected in humans, respectively, had no effect on fertility.
Embryofoetal toxicity studies were conducted in rats and rabbits: no effect were noted in rabbit fetuses when mothers were exposed at levels (AUC) of plasma ranolazine similar to expected human levels. In rats, no effects in fetuses was noted when mothers were exposed to 2-fold greater levels (AUC) than expected in humans, whereas decreased fetal weight and reduced ossification were observed when the exposure of mothers was 7.5-fold than those obtained in humans. Post-natal mortality of pups was not recorded when the exposure of nursing mothers was 1.3 fold higher than in expected humans, whereas at 3-fold higher exposure post-natal mortality was recorded, concomitant with evidence of milk excretion of ranolazine in rats. No adverse effects on new-born rats were observed at levels of exposures similar to those observed in humans.

7.0 DESCRIPTION
RANOGARD is supplied for oral administration, as an extended - release tablet of Ranolazine. Each extended - release tablet of RANOGARD contains Ranolazine 500 mg.

8. PHARMACEUTICAL PARTICULARS
8.1 INCOMPATIBILITIES
Not applicable

8.2 SHELF-LIFE
Refer Pack

8.3 PACKING INFORMATION
Refer Pack

8.4 STORAGE AND HANDLING INSTRUCTIONS
Refer Pack

9.0 PATIENT COUNSELLING INFORMATION
Advise the patient to read the approved patient labelling (Patient Information).
Inform patients that Ranolazine will not abate an acute angina episode.
Strong CY3PA Inhibitors, CYP3A Inducers, Liver Cirrhosis
Inform patients that Ranolazine should not be used with drugs that are strong CYP3A inhibitors (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir).
Inform patients that Ranolazine should not be used with drugs that are inducers of CYP3A (e.g., rifampin, rifabutin, rifapentine, barbiturates, carbamazepine, phenytoin, St. John's wort).

Inform patients that Ranolazine should not be used in patients with liver cirrhosis.
Moderate CYP3A Inhibitors, P-gp Inhibitors, Grapefruit Products
Advise patients to inform their physician if they are receiving drugs that are moderate CYP3A inhibitors (e.g., diltiazem, verapamil, and erythromycin).
Advise patients to inform their physician if they are receiving drugs that are P-gp inhibitors (e.g., cyclosporine).
Advise patients to limit grapefruit juice or grapefruit products when taking Ranolazine.

QT Interval Prolongation
Inform patients that Ranolazine may produce changes in the electrocardiogram (QTc interval prolongation).
Advise patients to inform their physician of any personal or family history of QTc prolongation, congenital long QT syndrome, or if they are receiving drugs that prolong the QTc interval such as Class Ia (e.g., quinidine) or Class III (e.g., dofetilide, sotalol, amiodarone) antiarrhythmic agents, erythromycin, and certain antipsychotics (e.g., thioridazine, ziprasidone).

Use in Patients with Renal Impairment
Patients with severe renal impairment may be at risk of renal failure while on Ranolazine.
Advise patients to inform their physician if they have impaired renal function before or while taking ranolazine.
Dizziness, Fainting
Inform patients that ranolazine may cause dizziness and light headedness. Patients should know how they react to ranolazine before they operate an automobile or machinery, or engage in activities requiring mental alertness or coordination.
Advise patients to contact their physician if they experience fainting spells while taking ranolazine.

Administration
Instruct patients to swallow ranolazine tablets whole, with or without meals, and not to crush, break, or chew tablets. Inform patients that if a dose is missed, to take the usual dose at the next scheduled time. The next dose should not be doubled. Inform patients that doses of ranolazine higher than 1000 mg twice daily should not be used.

Advise patients to inform their physician of any other medications taken concurrently with ranolazine, including over-the-counter medications.

10. DETAILS OF MANUFACTURER
Refer Pack for manufacturer details.

Marketed By:
Abbott Healthcare Pvt. Ltd.
Angel Space, Bldg. D-4, Gala No. 1 to 3 &
11 to 13 Ground Floor, 101 to 106 & 111 to 116
First Floor, 201 to 206 & 211 to 216 2nd Floor,
Pimplas, Dist. Thane, Bhiwandi - 421 302,
Maharashtra, India.

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11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE
Refer Pack for Permission/License details

12. DATE OF REVISION
Version 4.0, Dated 22-Oct-25

For Product Complaints/Adverse events or Queries please write to
webmasterindia@abbott.com