SUMMARY OF PRODUCT CHARACTERISTICS

1.3 Product Information

1.3.1 Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

NIZACARD 1000 (Ranolazine Extended-Release Tablets 1000 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Extended-release tablet contains 1000 mg of Ranolazine.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Extended-Release Tablets

Ranolazine Extended-Release Tablets 1000 mg:

Blue colored, oblong shaped film coated tablets debossed with 'R19' on one side and 'H' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ranolazine Tablets is indicated for the treatment of chronic angina.

Ranolazine Tablets may be used with beta-blockers, nitrates, calcium channel blockers, anti-platelet therapy, lipid-lowering therapy, ACE inhibitors, and angiotensin receptor blockers.

4.2 Posology and method of administration

Dosing Information

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

The maximum recommended daily dose of Ranolazine Tablets is 1000 mg twice daily.

If a dose of Ranolazine Tablets 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 Tablets is taken in combination with certain other drugs. Limit the maximum dose of Ranolazine Tablets to 500 mg twice daily in patients on moderate

CYP3A inhibitors such as diltiazem, verapamil, and erythromycin. Use of Ranolazine Tablets with strong CYP3A inhibitors is contraindicated Use of P-gp inhibitors, such as cyclosporine, may increase exposure to Ranolazine Tablets. Titrate Ranolazine Tablets based on clinical response.

4.3 Contraindications

Ranolazine Tablets is contraindicated in patients:

•Taking strong inhibitors of CYP3A

•Taking inducers of CYP3A

•With liver cirrhosis

4.4 Special warnings and special precautions for use

QT Interval Prolongation

Ranolazine Tablets 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 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 Ranolazine Tablets. If acute renal failure develops (e.g., marked increase in serum creatinine associated with an increase in blood urea nitrogen [BUN]), discontinue Ranolazine Tablets 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.

Patient Counseling Information

Advise the patient to read the FDA-approved patient labeling.

Inform patients that Ranolazine Tablets will not abate an acute angina episode.

Strong CY3PA Inhibitors, CYP3A Inducers, Liver Cirrhosis

Inform patients that Ranolazine Tablets should not be used with drugs that are strong CYP3A inhibitors (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir).

Inform patients that Ranolazine Tablets 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 Tablets 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, 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 Tablets.

QT Interval Prolongation

Inform patients that Ranolazine Tablets 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 Tablets. Advise patients to inform their physician if they have impaired renal function before or while taking Ranolazine Tablets.

Dizziness, Fainting

Inform patients that Ranolazine Tablets may cause dizziness and lightheadedness. Patients should know how they react to Ranolazine Tablets 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 Tablets.

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 Tablets higher than 1000 mg twice daily should not be used.

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

Nonclinical Toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility.

Ranolazine Tablets 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/m2/day) and 50 mg/kg/day for 24 months in mice (150 mg/m2/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 Tablets 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 Tablets that produced exposures (AUC) approximately 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 Ranolazine Tablets 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.

Animal Data

Embryofetal toxicity studies were conducted in rats and rabbits orally administered Ranolazine Tablets 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 Tablets at exposures (AUC) equal to the MRHD.

Lactation

Risk Summary

There are no data on the presence of Ranolazine Tablets in human milk, the effects on the breastfed infant, or the effects on milk production. However, Ranolazine Tablets is present in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Ranolazine Tablets and any potential adverse effects on the breastfed infant from Ranolazine Tablets or from the underlying maternal condition.

Adult female rats were administered Ranolazine Tablets 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 Tablets 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 Ranolazine Tablets 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 Tablets, 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 Tablets is contraindicated in patients with liver cirrhosis. In a study of cirrhotic patients, the Cmax of Ranolazine Tablets 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 Ranolazine Tablets in subjects with severe renal impairment (CrCL <30 mL/min) was stopped when 2 of 4 subjects developed acute renal failure after receiving Ranolazine Tablets 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 Ranolazine Tablets if acute renal failure develops.

In a separate study, Cmax 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 Tablets 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 Tablets pharmacokinetics. Ranolazine Tablets 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 Tablets 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 Tablets pharmacokinetics. No dose adjustment is required in patients with diabetes.

Ranolazine Tablets produces small reductions in HbA1c in patients with diabetes, the clinical significance of which is unknown. Ranolazine Tablets should not be considered a treatment for diabetes.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of Other Drugs on Ranolazine Tablets

Strong CYP3A Inhibitors

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

Moderate CYP3A Inhibitors

Limit the dose of Ranolazine Tablets 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 Tablets and P-gp inhibitors, such as cyclosporine, may result in increases in Ranolazine Tablets concentrations. Titrate Ranolazine Tablets based on clinical response in patients concomitantly treated with predominant P-gp inhibitors such as cyclosporine.

Effects of Ranolazine Tablets on Other Drugs

Drugs Metabolized by CYP3A

Limit the dose of simvastatin in patients on any dose of Ranolazine Tablets to 20 mg once daily, when Ranolazine Tablets 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 Tablets may increase plasma concentrations of these drugs.

Drugs Transported by P-Gp

Concomitant use of Ranolazine Tablets 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 Tablets, and lower doses of these drugs may be required.

Drugs Transported by OCT2

In subjects with type 2 diabetes mellitus, concomitant use of Ranolazine Tablets 1000 mg twice daily and metformin results in increased plasma levels of metformin. When Ranolazine Tablets 1000 mg twice daily is co-administered with metformin, metformin dose should not exceed 1700 mg/day. Monitor blood glucose levels and risks associated with high exposures of metformin.

Metformin exposure was not significantly increased when given with Ranolazine Tablets 500 mg twice daily.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk Summary

There are no available data on Ranolazine Tablets 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.

Animal Data

Embryofetal toxicity studies were conducted in rats and rabbits orally administered Ranolazine Tablets 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 Tablets at exposures (AUC) equal to the MRHD.

Lactation

Risk Summary

There are no data on the presence of Ranolazine Tablets in human milk, the effects on the breastfed infant, or the effects on milk production. However, Ranolazine Tablets is present in rat milk]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Ranolazine Tablets and any potential adverse effects on the breastfed infant from Ranolazine Tablets or from the underlying maternal condition.

Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

Geriatric Use

Of the chronic angina patients treated with Ranolazine Tablets 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 Tablets, 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.

4.7 Undesirable effects

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 2018 patients with chronic angina were treated with Ranolazine Tablets in controlled clinical trials. Of the patients treated with Ranolazine Tablets, 1026 were enrolled in three double-blind, placebo-controlled, randomized studies (CARISA, ERICA, MARISA) of up to 12 weeks' duration. In addition, upon study completion, 1251 patients received treatment with Ranolazine Tablets, in open-label, long-term studies; 1227 patients were exposed to Ranolazine Tablets, for more than 1 year, 613 patients for more than 2 years, 531 patients for more than 3 years, and 326 patients for more than 4 years.

At recommended doses, about 6% of patients discontinued treatment with Ranolazine Tablets because of an adverse event in controlled studies in angina patients compared to about 3% on placebo. The most common adverse events that led to discontinuation more frequently on Ranolazine Tablets than placebo were dizziness (1.3% versus 0.1%), nausea (1% versus 0%), asthenia, constipation, and headache (each about 0.5% versus 0%). Doses above 1000 mg twice daily are poorly tolerated.

In controlled clinical trials of angina patients, the most frequently reported treatment-emergent adverse reactions (>4% and more common on Ranolazine Tablets than on placebo) were dizziness (6.2%), headache (5.5%), constipation (4.5%), and nausea (4.4%). Dizziness may be dose-related. In open-label, long-term treatment studies, a similar adverse reaction profile was observed.

The following additional adverse reactions occurred at an incidence of 0.5 to 4.0% in patients treated with Ranolazine Tablets and were more frequent than the incidence observed in placebo-treated patients:

Cardiac Disorders – bradycardia, palpitations

Ear and Labyrinth Disorders – tinnitus, vertigo

Eye Disorders – blurred vision

Gastrointestinal Disorders – abdominal pain, dry mouth, vomiting, dyspepsia

General Disorders and Administrative Site Adverse Events – asthenia, peripheral edema

Metabolism and Nutrition Disorders – anorexia

Nervous System Disorders – syncope (vasovagal)

Psychiatric Disorders – confusional state

Renal and Urinary Disorders – hematuria

Respiratory, Thoracic, and Mediastinal Disorders – dyspnea

Skin and Subcutaneous Tissue Disorders – hyperhidrosis

Vascular Disorders – hypotension, orthostatic hypotension

Other (<0.5%) but potentially medically important adverse reactions observed more frequently with Ranolazine Tablets than placebo treatment in all controlled studies included: angioedema, renal failure, eosinophilia, chromaturia, blood urea increased, hypoesthesia, paresthesia, tremor, pulmonary fibrosis, thrombocytopenia, leukopenia, and pancytopenia.

A large clinical trial in acute coronary syndrome patients was unsuccessful in demonstrating a benefit for Ranolazine Tablets, but there was no apparent proarrhythmic effect in these high-risk patients.

Laboratory Abnormalities

Ranolazine Tablets produces elevations of serum creatinine by 0.1 mg/dL, regardless of previous renal function, likely because of inhibition of creatinine's tubular secretion. In general, the elevation has a rapid onset, shows no signs of progression during long-term therapy, is reversible after discontinuation of Ranolazine Tablets, and is not accompanied by changes in BUN. In healthy volunteers, Ranolazine Tablets 1000 mg twice daily had no effect upon the glomerular filtration rate. More marked and progressive increases in serum creatinine, associated with increases in BUN or potassium, indicating acute renal failure, have been reported after initiation of Ranolazine Tablets in patients with severe renal impairment.

Post marketing Experience

The following adverse reactions have been identified during post approval use of Ranolazine Tablets .Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Nervous System Disorders – Abnormal coordination, myoclonus, paresthesia, tremor, and other serious neurologic adverse events have been reported to occur, sometimes concurrently, in patients taking Ranolazine Tablets. The onset of events was often associated with an increase in Ranolazine Tablets dose or exposure. Many patients reported symptom resolution following drug discontinuation or dose decrease.

Metabolism and Nutrition Disorders – Cases of hypoglycemia have been reported in diabetic patients on anti diabetic medication.

Psychiatric Disorders – hallucination

Renal and Urinary Disorders – dysuria, urinary retention

Skin and Subcutaneous Tissue Disorders – angioedema, pruritus, rash.

4.8 Overdose

High oral doses of Ranolazine Tablets 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 Ranolazine Tablets.

Since Ranolazine Tablets is about 62% bound to plasma proteins, hemodialysis is unlikely to be effective in clearing Ranolazine Tablets.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-Anginal (Beta Blockers) ATC code: CO1EB18.

Mechanism of action

The mechanism of action of Ranolazine Tablet's antianginal effects has not been determined. Ranolazine Tablets 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 Tablets 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 Tablets on the surface electrocardiogram is the result of inhibition of I_{Kr}, which prolongs the ventricular action potential.

Pharmacodynamic effects

Hemodynamic Effects

Patients with chronic angina treated with Ranolazine Tablets 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 Tablets. These effects are believed to be caused by Ranolazine Tablets and not by its metabolites. The relationship between the change in QTc and Ranolazine Tablets plasma concentrations is linear, with a slope of about 2.6 m sec/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 Tablets 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 m sec, 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 Tablets 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 Tablets.

No proarrhythmic effects were observed on 7-day Holter recordings in 3162 acute coronary syndrome patients treated with Ranolazine Tablets. There was a significantly lower incidence of arrhythmias (ventricular tachycardia, bradycardia, supraventricular tachycardia, and new atrial fibrillation) in patients treated with Ranolazine Tablets (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.

5.2 Pharmacokinetic properties

Absorption and Distribution

After oral administration of Ranolazine Tablets, peak plasma concentrations of Ranolazine Tablets are

reached between 2 and 5 hours. After oral administration of ^{14}C-Ranolazine Tablets as a solution, 73% of the dose is systemically available as Ranolazine Tablets or metabolites. The bioavailability of Ranolazine Tablets from Ranolazine Tablets relative to that from a solution of Ranolazine Tablets is 76%. Because Ranolazine Tablets is a substrate of P-gp, inhibitors of P-gp may increase the absorption of Ranolazine Tablets.

Food (high-fat breakfast) has no important effect on the Cmax and AUC of Ranolazine Tablets. Therefore, Ranolazine Tablets may be taken without regard to meals. Over the concentration range of 0.25 to 10 μg/mL, Ranolazine Tablets is approximately 62% bound to human plasma proteins.

Metabolism and Excretion

Ranolazine Tablets is metabolized mainly by CYP3A and, to a lesser extent, by CYP2D6. Following a single oral dose of Ranolazine Tablets solution, approximately 75% of the dose is excreted in urine and 25% in feces. Ranolazine Tablets 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 Tablets, and display apparent half-lives ranging from 6 to 22 hours.

Drug Interactions

EFFECT OF OTHER DRUGS ON RANOLAZINE TABLETS

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

Strong CYP3A Inhibitors

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

Moderate CYP3A Inhibitors

Plasma levels of Ranolazine Tablets with Ranolazine Tablets 1000 mg twice daily are increased by 50 to 130% by diltiazem 180 to 360 mg, respectively. Plasma levels of Ranolazine Tablets with Ranolazine Tablets 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 Tablets in healthy volunteers.

CYP3A Inducers

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

CYP2D6 Inhibitors

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

Digoxin

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

Effect of Ranolazine Tablets on Other Drugs

In vitro Ranolazine Tablets and its O-demethylated metabolite are weak inhibitors of CYP3A and moderate inhibitors of CYP2D6 and P-gp. *In vitro* Ranolazine Tablets 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 Ranolazine Tablets 1000 mg twice daily. Mean exposure to atorvastatin (80 mg daily) is increased by 40% following co-administration with Ranolazine Tablets (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 Ranolazine Tablets.

Diltiazem

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

P-gp Substrates

Ranolazine Tablets increases digoxin concentrations by 50% in healthy volunteers receiving Ranolazine Tablets1000 mg twice daily and digoxin 0.125 mg once daily

CYP2D6 Substrates

Ranolazine Tablets 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 Tablets 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 Tablets 500 mg twice daily and 1000 mg twice daily, respectively. If co-administered with Ranolazine Tablets 1000 mg twice daily, do not exceed metformin doses of 1700 mg/day.

5.3 Preclinical safety data

Chronic Stable Angina

CARISA (Combination Assessment of Ranolazine Tablets In Stable Angina) was a study in 823 chronic angina patients randomized to receive 12 weeks of treatment with twice-daily Ranolazine Tablets 750 mg, 1000 mg, or placebo, who also continued on daily doses of atenolol 50 mg, amlodipine 5 mg, or diltiazem CD 180 mg. Sublingual nitrates were used in this study as needed.

In this trial, statistically significant ($p < 0.05$) increases in modified Bruce treadmill exercise duration and time to angina were observed for each Ranolazine Tablets dose versus placebo, at both trough (12 hours after dosing) and peak (4 hours after dosing) plasma levels, with minimal effects on blood pressure and heart rate. The changes versus placebo in exercise parameters are presented in Table 1. Exercise treadmill results showed no increase in effect on exercise at the 1000 mg dose compared to the 750 mg dose.

Table 1 Exercise Treadmill Results (CARISA)

	Mean Difference from Placebo (sec)	
Study	CARISA (N=791)	
Ranolazine Tablets Twice-daily Dose	750 mg	1000mg
Exercise Duration		

Trough	24[a]	24[a]
Peak	34[b]	26[a]
Time to Angina		
Trough	30[a]	26[a]
Peak	38[b]	38[b]
Time to 1 mm ST-Segment		
Depression	20	21
Trough Peak	41[b]	35[b]
Peak		
[a] p-value ≤0.05		
[b] p-value ≤0.005		

Table 2 Angina Frequency and Nitroglycerin Use (CARISA)

		Placebo	Ranolazine Tablets 750 Mg[a]	Ranolazine Tablets 1000 Mg[a]
Angina Frequency(attacks/week)	N	258	272	261
	Mean	3.3	2.5	2.1
	P-Value vs placebo	-	0.006	<0.001
Nitroglycerin Use(doses/week)	N	252	262	244
	Mean	3.1	2.1	1.8
	P-Value vs placebo	-	0.016	<0.001

Tolerance to Ranolazine Tablets did not develop after 12 weeks of therapy. Rebound increases in angina, as measured by exercise duration, have not been observed following abrupt discontinuation of Ranolazine Tablets.

Ranolazine Tablets has been evaluated in patients with chronic angina who remained symptomatic despite treatment with the maximum dose of an antianginal agent. In the ERICA (Efficacy of

Ranolazine Tablets in Chronic Angina) trial, 565 patients were randomized to receive an initial dose of Ranolazine Tablets 500 mg twice daily or placebo for 1 week, followed by 6 weeks of treatment with Ranolazine Tablets 1000 mg twice daily or placebo, in addition to concomitant treatment with amlodipine 10 mg once daily. In addition, 45% of the study population also received long-acting nitrates. Sublingual nitrates were used as needed to treat angina episodes. Results are shown in Table 3. Statistically significant decreases in angina attack frequency (p=0.028) and nitroglycerin use (p=0.014) were observed with Ranolazine Tablets compared to placebo. These treatment effects appeared consistent across age and use of long-acting nitrates.

Table.3 Angina Frequency and Nitroglycerin Use (ERICA)

		Placebo	Ranolazine Tablets[a]
Angina Frequency(attacks/week)	N	281	277
	Mean	4.3	3.3
	Median	2.4	2.2
Nitroglycerin Use(doses/week)	N	281	277
	Mean	3.6	2.7
	Median	1.7	1.3
[a] 1000 mg twice daily			

Gender

Effects on angina frequency and exercise tolerance were considerably smaller in women than in men. In CARISA, the improvement in Exercise Tolerance Test (ETT) in females was about 33% of that in males at the 1000 mg twice-daily dose level. In ERICA, where the primary endpoint was angina attack frequency, the mean reduction in weekly angina attacks was 0.3 for females and 1.3 for males.

Race

There were insufficient numbers of non-Caucasian patients to allow for analyses of efficacy or safety by racial subgroup.

Lack of Benefit in Acute Coronary Syndrome

In a large (n=6560) placebo-controlled trial (MERLIN-TIMI 36) in patients with acute coronary syndrome, there was no benefit shown on outcome measures. However, the study is somewhat reassuring regarding pro arrhythmic risks, as ventricular arrhythmias were less common on Ranolazine Tablets, and there was no difference between Ranolazine Tablets and placebo in the risk of all-cause mortality (relative risk Ranolazine Tablets: placebo 0.99 with an upper 95% confidence limit of 1.22).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methacrylic Acid copolymer USP/NF (Eudragit L10055), Microcrystalline cellulose USP/NF(Avicel PH 200), Hypromellose USP 2910 5CPS, (Methocel E5LV Premium),Sodium Hydrochloride, USP/NF, Purified water, HIS/USP/Ph.Eur@, Magnesium stearate, USP/NF (Ligamed MF-2-V- VEG), Opadry II Blue 85F505115, IH((Polyvinyl Alcohol-Part Hydrolyzed, Macrogol/Peg,Titanium Dioxide, Talc, Fd&C Blue #2/Indigo Carmine Aluminum Lake, Fd&C Blue #1/Brilliant Blue Fcf Aluminum Lake)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Blister pack

3 x 10’s Clear PVC/PVdC Blister Pack.

6.6 Instructions for use and handling and disposal

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

7. Marketing Authorisation Holder

Hetero Labs Limited

7-2-A2, Hetero Corporate

Industrial Estates

Sanath Nagar, Hyderabad-500 018

Telangana, India

Manufacturer

Hetero Labs Limited, Unit III,

22-110, IDA,

Jeedimetla, Hyderabad,

Telangana, INDIA.

Telephone No.: +91-40-23096171/172/173/174

Fax No.: +91-40-23095105.

8. Marketing Authorisation Number(s)

NA

9. CATEGORY FOR DISTRIBUTION

Prescription Preparations (PP)

10. DATE OF PUBLICATION OF THIS PACKAGE INSERT

NA