RANCARD XR
(Ranolazine)

500 mg & 1000 mg

COMPOSITION

Rancard XR 500 mg:

Each extended-release tablet contains:

Ranolazine…….. 500 mg

Rancard XR 1000 mg:

Each extended-release tablet contains:

Ranolazine ……..1000 mg

THERAPEUTIC INDICATIONS

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

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 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.

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
A pharmacokinetic study of RANOLAZINE in subjects with severe renal impairment (CrCL <30 mL/min) was stopped when 2 of 4 subjects developed acute renal failure after receiving Ranolazine 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 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 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 HbA1c in patients with diabetes, the clinical significance of which is unknown. Ranolazine should not be considered a treatment for diabetes.

Method of administration

Oral

CONTRAINDICATIONS

Ranolazine is contraindicated in patients:

• Taking strong inhibitors of CYP3A

• Taking inducers of CYP3A

• With liver cirrhosis

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 QTprolonging 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. If acute renal failure develops (e.g., marked increase in serum creatinine associated with an increase in blood urea nitrogen [BUN]), discontinue RANOLAZINE and treat appropriately. Monitor renal function after initiation and periodically in patients with moderate to severe renal impairment (CrCL <60 mL/min) for increases in serum creatinine accompanied by an increase in BUN.

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 CYP3A inducers such as rifampin, rifabutin, rifapentine, 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.

Drugs Transported by OCT2: In subjects with type 2 diabetes mellitus, concomitant use of RANOLAZINE 1000 mg twice daily and metformin results in increased plasma levels of metformin. When RANOLAZINE 1000 mg twice daily is co-administered with metformin, metformin dose should not exceed 1700 mg/day. Monitor blood glucose levels and risks associated with high exposures of metformin. Metformin exposure was not significantly increased when given with Ranolazine 500 mg twice daily.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Risk Summary

There are no available data on Ranolazine 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 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 Ranolazine and any potential adverse effects on the breastfed infant from Ranolazine 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.

EFFECTS ON ABILITY TO DRIVE

No studies on the effects of Ranexa on the ability to drive and use machines have been performed. Ranexa may cause dizziness, blurred vision, diplopia, confusional state, coordination abnormal, hallucination, which may affect the ability to drive and use machines.

ADVERSE DRUG REACTIONS

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at pv@searlecompany.com

OVERDOSE

Hypotension, QT prolongation, bradycardia, myoclonic activity, severe tremor, unsteady gait/incoordination, dizziness, nausea, vomiting, dysphasia, and hallucinations have been seen in cases of oral overdose of Ranolazine. In cases of extreme overdose of Ranolazine fatal outcomes have been reported. In clinical studies, high intravenous exposure resulted in 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

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 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.

Pharmacokinetic properties

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 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 RANOLAZINE, peak plasma concentrations of ranolazine are reached between 2 and 5 hours. After oral administration of 14C-ranolazine as a solution, 73% of the dose is systemically available as ranolazine or metabolites. The bioavailability of ranolazine from Ranolazine

tablets relative to that from a solution of ranolazine is 76%. Because ranolazine is a substrate of P-gp, inhibitors of P-gp may increase the absorption of ranolazine.

Food (high-fat breakfast) has no important effect on the Cmax and AUC of ranolazine. Therefore, RANOLAZINE may be taken without regard to meals. Over the concentration range of 0.25 to 10 □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.

Summary of Clinical Studies

Chronic Stable Angina

CARISA (Combination Assessment of Ranolazine In Stable Angina) was a study in 823 chronic angina patients randomized to receive 12 weeks of treatment with twice-daily Ranolazine 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 dose versus placebo, at both trough (12 hours after 0dosing) 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 below. Exercise treadmill results showed no increase in effect on exercise at the 1000 mg dose compared to the 750 mg dose.

Table: Angina Frequency and Nitroglycerin Use (ERICA)			
		Placebo	**Ranolazine 1000mg twice daily**
Angina Frequency (attacks/week)	N	281	277
	Mean	4.3	3.3
	P-value vs placebo	2.4	2.2
Nitroglycerin Use (doses/week)	N	281	277
	Mean	3.6	2.7
	P-value vs placebo	1.7	1.3

Table: Exercise Treadmill Results (CARISA) Mean Difference from Placebo (sec)		
Study CARISA (N=791)		
Ranolazine Twice-daily Dose	**750 mg**	**1000 mg**
Exercise Duration Trough Peak	24[a] 34[b]	24[a] 26[a]
Time to Angina Trough Peak	30[a] 38[b]	26[a] 38[b]
Time to 1 mm ST-Segment Depression Trough Peak	20	21
	41[b]	35[b]

a p-value less than equal to 0.05

b p-value less than equal to p-value 0.005

The effects of Ranolazine on angina frequency and nitroglycerin use are shown in Table below.

Table: Angina Frequency and Nitroglycerin Use (CARISA)				
		Placebo	**Ranolazine 750mg[a]**	**Ranolazine 1000mg[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 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.

Ranolazine 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 In Chronic Angina) trial, 565 patients were randomized to receive an initial dose of Ranolazine 500 mg twice daily or placebo for 1 week, followed by 6 weeks of treatment with Ranolazine 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 below. Statistically significant decreases in angina attack frequency (p=0.028) and nitroglycerin use (p=0.014) were observed with Ranolazine compared to placebo. These treatment effects appeared consistent across age and use of long-acting nitrates.

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 proarrhythmic risks, as ventricular arrhythmias were less common on ranolazine, and there was no difference between Ranolazine and placebo in the risk of all-cause mortality (relative risk ranolazine: placebo 0.99 with an upper 95% confidence limit of 1.22).

PRECLINICAL SAFETY DATA

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) approximately 3-fold or 5-fold higher, respectively, than the MRHD had no effect on fertility.

PRESENTATION

Rancard XR 500 mg tablets are available in alu-alu blister pack of 2 x 7 Tablets.
Rancard XR 1000 mg tablets are available in alu-alu blister pack of 2 x 7 Tablets.

INSTRUCTIONS

To be sold on prescription of a registered medical practitioner only

Protect from moisture, freezing, excessive heat and sunlight.

Keep out of the reach children

REGISTRATION NUMBER

Rancard XR 500 mg: 076285

Rancard XR1000 mg: 076286

M.L. 000016

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Manufactured by:

The Searle Company Limited

F-319, S.I.T.E., Karachi-Pakistan

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