PRODUCT INFORMATION

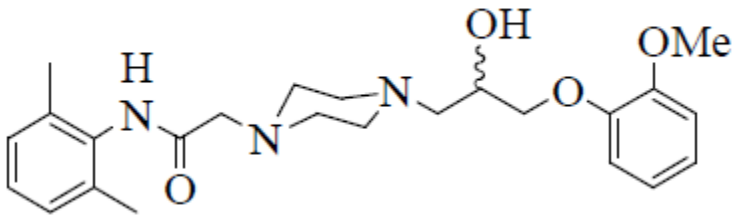
RANEXA® MODIFIED-RELEASE TABLETS

NAME OF THE MEDICINE

Ranolazine

Chemical Structure

Ranolazine is designated chemically as (±)-*N*-(2,6-dimethylphenyl)4-[2-hydroxy-3-(2-methoxyphenoxy)propyl] piperazineacetamide.



The empirical formula for ranolazine is $C_{24}H_{33}N_3O_4$ with a molecular weight of 427.54.

CAS number

95635-55-5

DESCRIPTION

Ranolazine is a white to off-white solid powder. Ranolazine is soluble in dichloromethane and methanol; sparingly soluble in tetrahydrofuran, ethanol, acetonitrile, and acetone; slightly soluble in ethyl acetate, isopropanol, toluene, and ethyl ether; and very slightly soluble in water.

Ranolazine is very slightly soluble at pH above 6.99, slightly soluble at pH from 6.29 to 5.76, sparingly soluble at pH 5.25, soluble at pH from 5.01 to 4.82 and freely soluble below pH 4.40.

The partition coefficient was determined using three different ratios of octanol: water. The log *P* for ranolazine was measured at 2.07 ± 0.06.

RANEXA 375 mg, 500 mg and 750 mg tablets contain the following inactive ingredients: carnauba wax, hypromellose, magnesium stearate, methacrylic acid-ethyl acrylate copolymer (1:1), microcrystalline cellulose, sodium hydroxide and titanium dioxide.

Additional inactive ingredients for the 375 mg tablet include: macrogol, polysorbate 80, indigo carmine aluminium lake.

Additional inactive ingredients for the 500 mg tablet include: macrogol, polyvinyl alcohol, iron oxide yellow, iron oxide red, purified talc.

Additional inactive ingredients for the 750 mg tablet include: glycerol triacetate, lactose, brilliant blue FCF aluminium lake and tartrazine aluminium lake.

PHARMACOLOGY

Pharmacodynamics

The mechanism of action of ranolazine's anti-anginal effects has not been fully determined. Ranolazine has anti-ischaemic and anti-anginal effects that do not depend on reductions in heart

rate or blood pressure. Ranolazine may have some anti-anginal 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 QT_c 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.

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 anti-anginal medicinal products in controlled studies.

Electrocardiographic effects

Dose and plasma concentration-related increases in the QT_c interval (about 6 msec at 1000 mg twice daily), reductions in T wave amplitude, and in some cases, notched T waves, have been observed in patients treated with RANEXA. These effects of ranolazine on the surface electrocardiogram are believed to result from inhibition of the fast-rectifying potassium current, which prolongs the ventricular action potential, and from inhibition of the late sodium current, which shortens the ventricular action potential. A population analysis of combined data from 1,308 patients and healthy volunteers demonstrated a mean increase in QTc from baseline of 2.4 msec per 1000 ng/ml ranolazine plasma concentration. This value is consistent with data from pivotal clinical studies, where mean changes from baseline in QT_cF (Fridericia's correction) after doses of 500 mg and 750 mg twice daily were 1.9 and 4.9 msec, respectively. The slope is higher in patients with clinically significant hepatic impairment.

In a large outcome study (MERLIN-TIMI 36) in 6,560 patients with UA/NSTEMI ACS (Unstable angina /non ST elevated myocardial infarction acute coronary syndrome), there was no difference between RANEXA and placebo 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%).

No pro-arrhythmic effects were observed in 3,162 patients treated with RANEXA based on 7-day Holter monitoring in the MERLIN-TIMI 36 study. There was a significantly lower incidence of arrhythmias in patients treated with RANEXA (80%) versus placebo (87%), including ventricular tachycardia ³ 8 beats (5% versus 8%).

Pharmacokinetics

Absorption

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

The mean absolute bioavailability of ranolazine after oral administration of immediate-release ranolazine tablets ranged from 35−50%, with large inter-individual variability. RANEXA 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, showing slightly more affinity for alpha-1 acid glycoprotein than albumin over the concentration range of 0.25 to 10 µg/mL. The mean steady-state volume of distribution (V_{ss}) is about 180 L.

Metabolism

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). O-demethylation and N-dealkylation have been identified as key metabolic pathways. *In vitro* studies using human liver microsomes indicate that ranolazine is metabolised primarily by CYP3A4, and 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%.

Excretion

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.

Pharmacokinetics in 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.

Congestive Heart Failure (CHF)

CHF NYHA (New York Heart Association) 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 increased 5-fold 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 CKD stage 3). In subjects with severe renal impairment (creatinine clearance 10–30 ml/min CKD stage 4), 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 has 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).

CLINICAL TRIALS

Chronic Stable Angina CARISA trial (study 3033)

CARISA (Combination Assessment of Ranolazine In Stable Angina) was a 12-week, double-blind, randomised, placebo-controlled, parallel group, multiple-dose study in 823 chronic angina patients. Patients were randomised to receive fixed doses of RANEXA 750 mg or 1000 mg twice daily in combination with atenolol 50 mg once daily, or diltiazem 180 mg once daily, or amlodipine 5 mg once daily. The primary efficacy variable was symptom limited exercise duration at trough (12 hours post dose). 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 RANEXA 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 for the 750 mg strength are presented in Table 1 below. Exercise treadmill results showed no increase on effect on exercise at the 1000 mg dose compared to the 750mg dose.

Table 1 Exercise Treadmill Results (CARISA)

	Mean Difference from placebo (sec)	
Study	**CARISA (N = 791)**	
RANEXA Twice-daily Dose	**750 mg**	**1000 mg**
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		
Trough	20	21
Peak	41[b]	35[b]

[a] p-value ≤ 0.05 [b] p-value ≤ 0.005

RANEXA resulted in significant decreases in the number of angina attacks per week and administration of short-acting nitroglycerin compared to placebo (see Table 2 below). Tolerance to RANEXA did not develop during treatment and no rebound increase in angina attacks was observed following abrupt discontinuation.

Table 2 Angina Frequency and Nitroglycerin Use (CARISA)

		Placebo	RANEXA 750 mg[a]
Angina Frequency (attacks/week)	N	258	272
	Mean	3.3	2.5
	p-value vs placebo	-	*0.006*
Nitroglycerin Use (doses/week)	N	252	262
	Mean	3.1	2.1
	p-value vs placebo	-	*0.016*

[a] 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.

Race

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

Elderly and renal impairment

Of the chronic angina patients treated with RANEXA 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.

Study 3036 (MERLIN TIMI)

In a large (n=6560) placebo-controlled trial (MERLIN-TIMI 36 study CVT 3036) in patients with acute coronary syndrome, no benefit was shown for the primary efficacy measure of time to CV death, MI, or severe recurrent ischaemia (ECG changes, hospitalisation, or revascularisation).

Ventricular arrhythmias were less common on RANEXA and there was no statistically significant difference between RANEXA and placebo in the risk of all-cause mortality (relative risk ranolazine: placebo 0.99 with a 95% confidence interval of 0.88 to 1.22).

Diabetes, Class I and II heart failure, and obstructive airway disease were not associated with clinically meaningful increases in the incidence of adverse events.

INDICATIONS

RANEXA is indicated in adults as add-on therapy for the symptomatic treatment of stable angina pectoris in patients taking maximum tolerated doses of a beta-blocker or a calcium channel blocker and have inadequate symptom control.

CONTRAINDICATIONS

- Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, voriconazole, posaconazole, HIV protease inhibitors, clarithromycin).
- Concomitant administration of CYP3A4 inducers (e.g. rifampicin, phenytoin, phenobarbital, carbamazepine, St John's Wort).
- Concomitant administration of Class Ia (e.g. quinidine) or Class III (e.g. sotalol) antiarrhythmics other than amiodarone.
- Severe renal impairment (creatinine clearance < 30 ml/min CKD stage 4) and end stage renal disease (CKD stage 5)

- Moderate or severe hepatic impairment.
- Hypersensitivity to the active substance or to any of the excipients.

PRECAUTIONS

Caution should be exercised when prescribing or up-titrating RANEXA to patients in whom an increased exposure is expected:

- Concomitant administration of moderate CYP3A4 inhibitors (see **Interactions with other medicines)**
- Concomitant administration of P-gp inhibitors (see **Interactions with other medicines)**.
- Mild hepatic impairment.
- Mild to moderate renal impairment (creatinine clearance 30–80 ml/min CKD stages 2-3).
- Elderly patients.
- Patients with low body 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 RANEXA 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 of increased exposure and consequent adverse effects is higher in patients who are CYP2D6 poor metabolisers.

QT 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 **(see Adverse Effects**). 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 RANEXA 500mg to 1000 mg twice daily. Therefore, caution should be observed when treating patients with a history of congenital or a family history of prolonged QT syndrome, in patients with known acquired QT interval prolongation, and in patients treated with drugs affecting the QTc interval (see **Interactions with other Medicines**).

Drug-drug interactions

Co-administration with CYP3A4 inducers is expected to lead to lack of efficacy. RANEXA 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 RANEXA (see **Pharmacokinetics in Special Populations** and **Clinical Trials** section).

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 (CKD stage 2), moderate (CKD stage 3), and severe renal impairment (CKD stage 4) compared with subjects with normal renal function.

Careful dose titration is necessary in mild to moderate renal impairment; CKD stages 2-3 (see **Dosage and Administration).**

RANEXA is contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min CKD stage 4) and end stage renal impairment (CKD stage 5). (See **Contraindications**).

Low weight

The incidence of adverse effects was higher in patients with low body weight (< 60kgs). Dose titration in patients with low body weight should be exercised with caution (see **Clinical Trials** section).

Hepatic impairment

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. RANEXA is contraindicated in patients with moderate or severe hepatic impairment (See **Contraindications**).

Lactose

RANEXA 750 mg tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

Tartrazine Azo colouring agent E102

RANEXA 750 mg tablets contain tartrazine azo colouring agent E102 which may cause allergic reactions.

Effects on Fertility

In a fertility study in male rats, there was evidence of impaired fertility at doses of 300 mg/kg/day ranolazine (1.8-fold the maximum recommended clinical dose based on body surface area comparison). The clinical significance of this finding is not known.

Pregnancy

Pregnancy Category B3

There are no adequate data on the use of ranolazine in pregnant women. Embryofoetal development studies in rats and rabbits found treatment-related effects on development. There was an increased incidence of misshapen sternebrae and reduced ossification of pelvic and cranial bones in foetuses of rats dosed 400 mg/kg/day (1.8–fold the maximum recommended clinical dose based on body surface area comparison). In rabbits, there was reduced ossification of sternebrae in foetuses from dams dosed at 150 mg/kg/day (1.7–fold the maximum recommended clinical dose based on body surface area comparison). These doses were associated with signs of maternotoxicity (including increased maternal mortality).

Lactation

It is unknown whether ranolazine is excreted in human breast milk. The excretion of ranolazine in milk has not been studied in animals. RANEXA should not be used during breastfeeding.

Paediatric population

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

Use in the Elderly

No 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 RANEXA, compared to placebo, had a higher incidence of adverse events, serious adverse events, and drug discontinuations due to adverse events. Dose titration in elderly patients should be exercised with caution (see **Clinical Trials** section).

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.

Genotoxicity

RANEXA has been tested 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, mouse and rat bone marrow micronucleus assays and the Comet assay in rats. The weight of evidence from these studies suggests that ranolazine is not genotoxic.

Carcinogenicity

The weight of evidence from long-term rodent carcinogenicity studies suggests that ranolazine has no primary carcinogenic potential. Doses were tested at up to maximum tolerated doses, which in mice were 50 mg/kg/day (0.15–fold the maximum recommended human dose based on body surface area), while in rats were 150 mg/kg/day (0.9–fold the maximum recommended human dose based on body surface area). A published study reported that ranolazine dose-dependently promoted tumour development when given to transgenic APC (min/+) mice (a transgenic mouse model of spontaneous intestinal tumourigenesis). The clinical significance of this finding is uncertain.

Effects on ability to drive and use machines

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, and hallucination, which may affect the ability to drive and use machines.

Laboratory findings

Small, clinically insignificant, reversible elevations in serum creatinine levels have been observed in healthy subjects and patients treated with RANEXA. 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.

Use in heart failure

Heart failure (NYHA Class I to IV) had no significant effect on ranolazine pharmacokinetics. RANEXA 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 RANEXA is required in patients with heart failure. Dose titration in patients with moderate to severe CHF (NYHA Class III–IV) should be exercised with caution. Vasovagal syncope has been reported as an adverse event with RANEXA and patients with heart failure should be specifically asked about dizziness and syncope during dose titration.

Use in 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 these patients. However patients with diabetes mellitus may have renal impairment and doses should be titrated dependent on their renal function (See **Precautions**; **Renal impairment** section above).

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

INTERACTIONS WITH OTHER MEDICINES

Tables 3 and 4 below show all the potential drug interactions associated with RANEXA.

TABLE 3		
EFFECTS OF OTHER MEDICINES ON RANEXA		
Concomitant medicines	**Potential PK effects**	**Additional information**
CYP3A4 inhibitors		
Ketoconazole [potent inhibitor]	*Contraindicated* Ketoconazole 200 mg twice daily increased the AUC of ranolazine by 3.0 to 3.9- fold	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. Combining ranolazine with potent CYP3A4 inhibitors is contraindicated.
itraconazole voriconazole posaconazole HIV protease inhibitors clarithromycin grapefruit juice [potent inhibitors]	*Contraindicated* *See additional information*	
Diltiazem [moderately potent inhibitor]	Diltiazem (180 to 360 mg once daily), causes dose-dependent increases in average ranolazine steady-state concentrations of 1.5 to 2.4-fold.	Diltiazem is a moderately potent CYP3A4 inhibitor. Careful dose titration of RANEXA is recommended in patients treated with diltiazem and other moderately potent CYP3A4 inhibitors e.g. erythromycin, fluconazole. Down-titration of RANEXA may be required.
Erythromycin Fluconazole [moderately potent inhibitors]	*See additional information*	
Oral contraceptives (OCTs) Hormone Replacement Therapy (HRT) [weak inhibitors]	*See additional information*	The effects of RANEXA with weak CYP3A4 inhibitors such as oral contraceptives (OCTs) and hormone replacement therapy (HRT) are unknown. However, the potential increase in ranolazine exposure is expected to be lower, compared to that with moderate / potent CYP3A4 inhibitors.
P-gp inhibitors		
Verapamil	Verapamil (120 mg three times daily) increases ranolazine steady-state concentrations 2.2-fold.	Ranolazine is a substrate for P-gp. Inhibitors of P-gp increase plasma levels of ranolazine. Careful dose titration of RANEXA is recommended in patients treated with P-gp inhibitors. Down-titration of RANEXA may be required.
Cyclosporin	*See additional information*	
CYP3A4 inducers		
Rifampicin	*Contraindicated* Rifampicin (600 mg once daily) decreases ranolazine steady-state concentrations by approximately 95%.	Initiation of treatment with RANEXA should be avoided during administration of inducers of CYP3A4.
phenytoin phenobarbital carbamazepine St. John's Wort	*Contraindicated* *See additional information*	

CYP2D6 inhibitors		
Paroxetine [potent inhibitor]	Paroxetine 20 mg once daily: - with ranolazine 1000mg twice daily, increased steady-state plasma concentrations of ranolazine by an average of 1.2-fold. - with ranolazine 500 mg twice daily, increased AUC of ranolazine by 62%.	Ranolazine is partially metabolised by CYP2D6; therefore, inhibitors of this enzyme may increase plasma concentrations of ranolazine. No dose adjustment is required.
Others		
Dronedarone	In patients with atrial fibrillation taking combination of ranolazine + dronedarone versus dronedarone alone, the C_{max} of dronedarone was similar in both, whereas the AUC_{0-12} was approximately 1.09-fold higher with the combination.	
Warfarin	There was a statistically significant increase in the maximum prothrombin time (PT) and in the AUC for PT time when ranolazine immediate release tablets, 400 mg three times daily was administered with 5 mg warfarin for 10 days.	Patients who are administered these drugs concurrently should have their prothrombin times closely monitored.

TABLE 4

EFFECTS OF RANEXA ON OTHER MEDICINES

Concomitant medicines	**Potential PK effects**	**Additional information**
Drugs metabolised by CYP3A4 or P-gp		
Simvastatin Lovastatin [sensitive CYP3A4 substrates]	Increased plasma concentrations of CYP3A4 substrates	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 may be required.
Simvastatin	Ranolazine 1000 mg twice daily increased plasma concentrations of simvastatin and its active metabolite by about 2-fold.	Simvastatin metabolism and clearance are highly dependent on CYP3A4. Rhabdomyolysis has been associated with high doses of simvastatin and cases of rhabdomyolysis have been observed in patients receiving RANEXA and simvastatin, in post-marketing experience. Limit the dose of simvastatin to 20 mg once daily in patients taking any dose of RANEXA.
Atorvastatin	Ranolazine 1000 mg twice daily increased C_{max} and AUC of atorvastatin 80mg once daily by 1.4 and 1.3 -fold, respectively, and	Dose limitation of atorvastatin and appropriate clinical monitoring may be considered when taking RANEXA.

TABLE 4		
EFFECTS OF RANEXA ON OTHER MEDICINES		
Concomitant medicines	**Potential PK effects**	**Additional information**
	changed the C_{max} and AUC of atorvastatin metabolites less than 35%.	
Cyclosporin Tacrolimus Sirolimus Everolimus [CYP3A4 substrates with a narrow therapeutic range]	Increased plasma concentrations of CYP3A4 substrates	It is recommended that drug blood levels are monitored when co-administering RANEXA with CYP3A4 substrates and that the dosage is adjusted accordingly.
Tacrolimus	Increased plasma concentrations of tacrolimus	It is recommended that tacrolimus blood levels are monitored when co-administering RANEXA with tacrolimus and that tacrolimus dosage is adjusted accordingly.
Drugs metabolised by CYP2D6		
Metoprolol	Ranolazine 750 mg twice daily increased plasma concentrations of metoprolol by 1.8-fold.	Available data suggest that ranolazine is a mild inhibitor of CYP2D6. Therefore the exposure to metoprolol or other CYP2D6 substrates may be increased during co-administration with RANEXA, and lower doses of these medicinal products may be required.
Propafenone Flecainide Tricyclic antidepressants Antipsychotics	*See additional information*	
Drugs metabolized by CYP2B6		
Bupropion Efavirenz Cyclophosphamide	*See additional information*	The potential for inhibition of CYP2B6 has not been evaluated. Caution is advised during co-administration with CYP2B6 substrates.
OCT2 substrates Organic Cation Transporter-2		
Metformin	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.	It is recommended to monitor blood glucose levels and risks associated with high doses of metformin (and limit the dose as required). Patients treated with RANEXA and other OCT2 substrates, including but not limited to pindolol and varenicline, may be affected to a similar degree. Doses of other OCT2 substrates may require dose adjustments.
Pindolol Varenicline	*See additional information*	
Medicines known to prolong QTc interval		
Certain Antihistamines: Terfenadine Astemizole Mizolastine	*See additional information*	There is a theoretical risk that concomitant treatment of RANEXA with other drugs known to prolong the QTc interval may give rise to a pharmacodynamic interaction and increase the possible risk of ventricular arrhythmias.
Erythromycin	*See additional information*	
certain antiarrhythmics: Disopyramide Procainamide	*See additional information*	

TABLE 4		
EFFECTS OF RANEXA ON OTHER MEDICINES		
Concomitant medicines	**Potential PK effects**	**Additional information**
Quinidine Sotalol	*Contraindicated*	
Tricyclic antidepressants: Imipramine Doxepin Amitriptyline	*See additional information*	
Others		
Digoxin	Increase in plasma digoxin concentrations by an average of 1.5-fold in healthy volunteers receiving Ranolazine 1000 mg twice daily and digoxin 0.125 mg once daily.	Digoxin levels should be monitored following initiation and termination of RANEXA therapy.

ADVERSE EFFECTS

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

Adverse effects in clinical trials

The table below presents the incidence of adverse events from the CARISA study (CVT 3033).

Table 5 Incidence of Adverse Events with a frequency ≥ 2% in any Treatment Group Occurring on or after Visit 2 - CARISA Study 3033

	Treatment		
Body System Preferred Term	**Placebo (n=269)**	**RANEXA 750 mg (n=279)**	**RANEXA 1000 mg (n=275)**
General Disorders and administration site conditions	**28 (10.4)**	**22 (7.9)**	**29 (10.5)**
asthaenia	6 (2.2)	5 (1.8)	13 (4.7)
Cardiac Disorders	**29 (10.8)**	**35 (12.5)**	**28 (10.2)**
angina Pectoris	12 (4.5)	11 (3.9)	8 (2.9)
Gastrointestinal disorders	**18 (6.7)**	**36 (12.9)**	**41 (14.9)**
constipation	2 (0.7)	18 (6.5)	20 (7.3)
dyspepsia	4 (1.5)	7 (2.5)	5 (1.8)
nausea	2 (0.7)	9 (3.2)	14 (5.1)
abdominal Pain	2 (0.7)	2 (0.7)	7 (2.5)
Nervous System Disorders	**9 (3.3)**	**17 (6.1)**	**28 (10.2)**
dizziness	5 (1.9)	10 (3.6)	19 (6.9)
headache	4 (1.5)	7 (2.5)	6 (2.2)

In the placebo group, patients most frequently had an adverse event relating to the cardiovascular body system. For both RANEXA groups, the majority of adverse events were relating to the digestive system. Angina pectoris, an inclusion criterion for the study, was the most common adverse event among patients randomised to placebo and the frequency was higher in that group compared to either dose of RANEXA. Constipation (38 patients, 6.9%) was the most common event amongst patients randomised to RANEXA, irrespective of dose. This event was infrequent in the placebo group. Dizziness (29 patients, 5.2%) and nausea (23 patients, 4.1%) were the next most common events amongst patients randomised to RANEXA. The incidence of constipation, dizziness and nausea was slightly greater at the higher dose of RANEXA.

The adverse events, considered to be at least possibly related to treatment are listed in Table 6. These were reported during the Phase 3 clinical development programme, which included a total of 1,030 chronic angina patients treated with RANEXA. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), and rare (≥ 1/10,000 to < 1/1,000).

Table 6 Tabulated list of adverse reactions from Phase 3 controlled angina studies

	Common	Uncommon	Rare
Metabolism and nutrition disorders		anorexia, decreased appetite, dehydration	hyponatraemia
Psychiatric disorders		anxiety, insomnia, confusional state, hallucination	disorientation
Nervous system disorders	dizziness, headache.	lethargy, syncope, hypoaesthesia, somnolence, tremor, postural dizziness, paraesthesia	amnesia, depressed level of consciousness, loss of consciousness, coordination abnormal, gait disturbance, parosmia
Eye disorders		blurred vision, visual disturbance, diplopia	
Ear and labyrinth disorders		vertigo, tinnitus	impaired hearing
Vascular disorders		hot flush, hypotension	peripheral coldness, orthostatic hypotension
Respiratory, thoracic, and mediastinal disorders		dyspnoea, cough, epistaxis	throat tightness
Gastrointestinal disorders	constipation, vomiting, nausea.	abdominal pain, dry mouth, dyspepsia, flatulence, stomach discomfort	pancreatitis, erosive duodenitis, oral hypoaesthesia
Skin and subcutaneous tissue disorders		pruritus, hyperhydrosis	angioedema, allergic dermatitis, urticaria, cold sweat, rash
Musculoskeletal and connective tissue disorders		pain in extremity, muscle cramp, joint swelling, muscular weakness	
Renal and urinary disorders		dysuria, haematuria, chromaturia	acute renal failure, urinary retention
Reproductive system and breast disorders			erectile dysfunction
General disorders and administration site conditions	asthaenia	fatigue, peripheral oedema	
Investigations		increased blood creatinine, increased blood urea, prolonged QT corrected interval, increased platelet or white blood cell count, decreased weight	elevated levels of hepatic enzyme

Adverse Events in sub-groups (Elderly, renal impairment, low body weight)

In general, adverse events occurred more frequently among elderly patients and patients with renal impairment; however, the types of events in these sub-groups were similar to those observed in the general population. Of the most commonly reported, the following events occurred more often with RANEXA (placebo-corrected frequencies) in elderly (³ 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 ³ 30–80 ml/min CKD stages 2-3) 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 body weight (> 60 kg); however, the placebo-corrected frequencies of the following common adverse events were higher in low body weight than higher body weight patients; nausea (14% versus 2%), vomiting (6% versus 1%), and hypotension (4% versus 2%).

Adverse Events by Ranolazine Dose

Three studies (CVT 3031, CVT 3111, and CVT 3023) evaluated the safety of high doses (up to 3,000 mg orally twice daily) and high plasma concentrations of ranolazine (IV administration with target plasma concentrations up to 15,000 ng/mL). The Phase 2/3 controlled angina studies, showed that dizziness, nausea, and aesthenia were the most clearly dose-dependent adverse events.

The highest recommended dose of RANEXA is 750 mg twice daily.

Discontinuation due to adverse events

At recommended doses, approximately 6% of patients discontinued treatment with RANEXA because of an adverse event in controlled studies in angina patients compared to approximately 3% on placebo. The most common adverse events that led to discontinuation, more frequently on RANEXA than placebo, were; dizziness (1.3% versus 0.1%), nausea (1% versus 0%), asthaenia, constipation, and headache (each 0.5% versus 0%).

Post-Marketing Experience

The following adverse reactions have been identified during post-marketing use of RANEXA. 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 - tremor, paraesthesia, abnormal coordination, and other serious neurologic adverse events have been reported, sometimes concurrently, in patients taking ranolazine. The onset of events was often associated with an increase in ranolazine dose or exposure. Many patients reported symptom resolution following drug discontinuation or dose decrease.

Psychiatric Disorders – hallucination.

Renal and Urinary Disorders – dysuria, urinary retention.

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

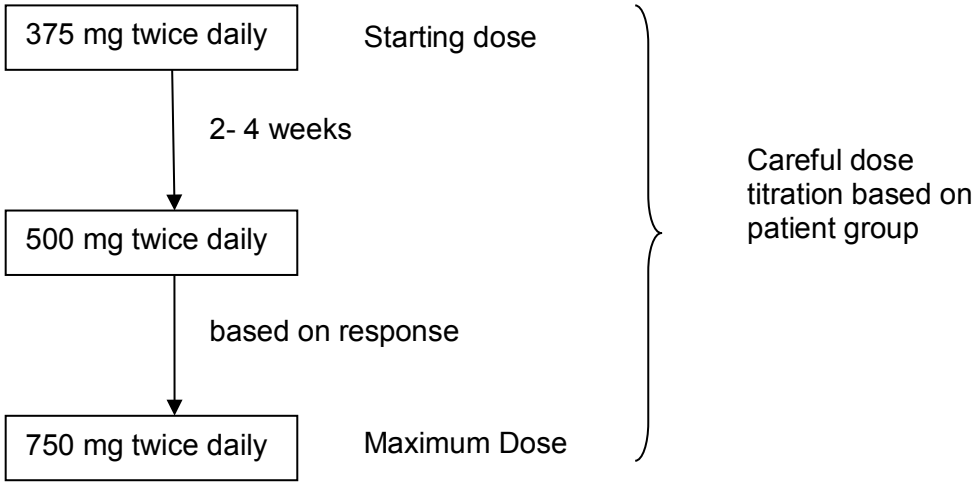
DOSAGE AND ADMINISTRATION

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

Adults

The recommended initial dose of RANEXA is 375 mg twice daily. After 2–4 weeks, the dose should be titrated to 500 mg twice daily and, according to the patient's response, further titrated to a recommended maximum dose of 750 mg twice daily.

If a patient experiences treatment-related adverse events (e.g. dizziness, nausea, or vomiting), down-titration of RANEXA to 500 mg or 375 mg twice daily may be required. If symptoms do not resolve after dose reduction, treatment should be discontinued.



Dose modification

Patients with Renal impairment

Patients with mild to moderate renal impairment (creatinine clearance 30–80 ml/min CKD stages 2-3) require careful dose titration. RANEXA is contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min CKD stage 4) and end stage renal impairment (CKD stage 5). Refer to **Contraindications** section.

Patients with Hepatic impairment

Patients with mild hepatic impairment require careful dose titration (see **Precautions** section). RANEXA is contraindicated in patients with moderate or severe hepatic impairment (see **Contraindications** section).

Concomitant Medicines

Careful dose titration is recommended in patients treated with moderate CYP3A4 inhibitors e.g. diltiazem, fluconazole, erythromycin or P-gp inhibitors e.g. verapamil, cyclosporin. Concomitant administration of potent CYP3A4 inhibitors with RANEXA is contraindicated (see **Contraindications** and **Interactions with other medicines**).

Elderly patients ≥ 75 years of age

Dose titration in elderly patients should be exercised with caution. Elderly patients may have increased ranolazine exposure due to age-related decrease in renal function (see **Pharmacokinetics in Special Populations** and **Precautions**). The incidence of adverse events was higher in the elderly (see **Adverse Effects**).

Low body weight

The incidence of adverse events was higher in patients with low body weight (≤ 60 kg). Dose titration in patients with low body weight should be exercised with caution (see **Pharmacokinetics, Precautions,** and **Adverse Effects).**

Congestive heart failure (CHF)

Dose titration in patients with moderate to severe CHF (NYHA Class III- IV) should be exercised with caution (see **Pharmacokinetics in Special Populations** and **Precautions).**

OVERDOSAGE

In an oral high-dose tolerability study (3000 mg twice daily) 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, immediately contact the Poison Information Centre on 13 11 26. 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.

PRESENTATION AND STORAGE CONDITIONS

RANEXA is supplied as film-coated, modified-release tablets, in PVC/PVDC/Aluminium blister packs of 15 and 60 tablets per carton in the following strengths:

375 mg: Pale blue, oval-shaped tablet engraved with 375 on one side.

500 mg: Light orange, oval-shaped tablet engraved with 500 on one side.

750 mg: Pale green, oval-shaped tablet engraved with 750 on one side.

Not all pack sizes may be marketed. Store below 25ºC. Store in the original package.

NAME AND ADDRESS OF THE SPONSOR

A. Menarini Australia Pty Ltd
Level 8, 67 Albert Ave
Chatswood NSW 2067 Australia

POISON SCHEDULE OF THE MEDICINE

Schedule 4

DATE OF FIRST INCLUSION IN THE ARTG

13 October 2017