Professional information for RANEXA

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

RANEXA 375 mg prolonged-release tablets

RANEXA 500 mg prolonged-release tablets

RANEXA 750 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RANEXA 375 mg: Each tablet contains 375 mg ranolazine.

Sugar free.

RANEXA 500 mg: Each tablet contains 500 mg ranolazine.

Sugar free.

RANEXA 750 mg: Each tablet contains 750 mg ranolazine.

Each **RANEXA 750 mg** tablet contains 0,04 mg TARTRAZINE (FD&C Yellow No. 5 lake) and sugar (12 mg lactose monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablets.

RANEXA 375 mg: Pale blue, film coated, biconvex, ovoid shaped tablet debossed with ‘375’ on one side and plain on the other side.

RANEXA 500 mg: Light orange, film coated, biconvex, ovoid shaped tablet debossed with ‘500’ on one side and plain on the other side.

RANEXA 750 mg: Pale green, film coated, biconvex, ovoid shaped tablet debossed with ‘750’ on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Patients should be given the RANEXA patient information leaflet and patient alert card and be instructed to present their patient alert card and list of medicines used to their health care providers at each visit.

Posology

RANEXA is available as 375 mg, 500 mg and 750 mg prolonged-release tablets.

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 (see section 5.1).

If a patient experiences treatment-related side effects, such as 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.

Concomitant treatment with CYP3A4 and P-glycoprotein (P-gp) inhibitors:

Careful dose titration is recommended in patients treated with moderate CYP3A4 inhibitors, such as diltiazem, fluconazole and erythromycin or P-glycoprotein (P-gp) inhibitors, such as verapamil and ciclosporin (see sections 4.4 and 4.5).

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

Renal impairment:

Careful dose titration is recommended in patients with mild to moderate renal impairment (creatinine clearance 30 – 80 mL/min) (see sections 4.4, 4.8 and 5.2).

RANEXA is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min) (see sections 4.3 and 5.2).

Hepatic impairment:

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

Elderly patients:

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

Low weight:

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

Congestive heart failure (CHF):

Dose titration in patients with moderate to severe congestive heart failure (New York Heart Association (NYHA) Class III – IV) should be exercised with caution (see sections 4.4 and 5.2).

Paediatric population:

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

Method of administration

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

4.3 Contraindications

- Hypersensitivity to ranolazine or to any of the excipients listed in section 6.1.
- Severe renal impairment (creatinine clearance < 30 mL/min) (see sections 4.2 and 5.2).
- Moderate or severe hepatic impairment (see sections 4.2 and 5.2).
- Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, voriconazole, posaconazole, HIV protease inhibitors, clarithromycin, telithromycin, nefazodone) (see sections 4.2 and 4.5).
- Concomitant administration of Class Ia (e.g. quinidine) or Class III (e.g. dofetilide, sotalol) antidysrhythmics other than amiodarone.
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

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

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

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

QT prolongation: A population-based analysis of combined data from patients and healthy volunteers demonstrated that the slope of the plasma concentration-QTc relationship was estimated to be 2,4 msec per 1 000 ng/mL, which is approximately equal to a 2- to 7-msec increase over the plasma concentration range for ranolazine 500 to 1 000 mg twice daily. Therefore, caution should be observed when treating patients with a history of congenital or a family history of long QT syndrome, in patients with known acquired QT interval prolongation, and in patients treated with medicines affecting the QTc interval (see section 4.5).

Medicine-medicine 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) (see section 4.5).
Renal impairment: Renal function decreases with age and it is therefore important to check renal function at regular intervals during treatment with Ranexa (see sections 4.2, 4.3, 4.8 and 5.2).

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

Tartrazine: RANEXA 750 mg tablets contains tartrazine (FD&C Yellow No. 5 lake) which may cause allergic reactions.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on RANEXA

CYP3A4 or P-gp inhibitors: Ranolazine is a substrate of cytochrome
CYP3A4. Inhibitors of CYP3A4 increase plasma concentrations of ranolazine. The potential for dose-related adverse events (e.g. nausea, dizziness) may also increase with increased plasma concentrations. Concomitant treatment with ketoconazole 200 mg twice daily increased the AUC of ranolazine by 3,0- to 3,9-fold during RANEXA treatment. Combining ranolazine with potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, voriconazole, posaconazole, HIV protease inhibitors, clarithromycin, telithromycin, nefazodone) is contraindicated (see section 4.3). Grapefruit juice is also a potent CYP3A4 inhibitor.

Diltiazem (180 to 360 mg once daily), a moderately potent CYP3A4 inhibitor, causes dose-dependent increases in average ranolazine steady-state concentrations of 1,5- to 2,4-fold. Careful dose titration of 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 (see sections 4.2 and 4.4).
Ranolazine is a substrate for P-gp. Inhibitors of P-gp (e.g. ciclosporin, verapamil) increase plasma levels of ranolazine. Verapamil (120 mg three times daily) increases ranolazine steady-state concentrations 2,2-fold. Careful dose titration of RANEXA is recommended in patients treated with P gp inhibitors. Down-titration of RANEXA may be required (see sections 4.2 and 4.4).

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

CYP2D6 inhibitors: Ranolazine is partially metabolised by CYP2D6; therefore, inhibitors of this enzyme may increase plasma concentrations of ranolazine. The potent CYP2D6 inhibitor paroxetine,

at a dose of 20 mg once daily, increased steady-state plasma concentrations of ranolazine 1 000 mg twice daily by an average of 1,2-fold. No dose adjustment is required. At the dose level 500 mg twice daily, co-administration of a potent inhibitor of CYP2D6 could result in an increase in ranolazine AUC of about 62 %.

Effects of RANEXA on other medicines

Ranolazine, as in RANEXA, 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 medicine which are transported by P-gp may be increased.

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

Available data suggest that ranolazine is a mild inhibitor of CYP2D6. RANEXA 750 mg twice daily increased plasma concentrations of metoprolol by 1,8-fold. Therefore the exposure to metoprolol or other CYP2D6 substrates (e.g. propafenone and flecainide or, to a lesser extent, tricyclic antidepressants and antipsychotics) may be increased during co administration with RANEXA, and lower doses of these medicines may be required.

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

Digoxin: An increase in plasma digoxin concentrations by an average of 1,5-fold has been reported when RANEXA and digoxin are co-administered. Therefore, digoxin levels should be monitored following initiation and termination of RANEXA therapy.

Simvastatin: Simvastatin metabolism and clearance are highly dependent on CYP3A4. RANEXA 1 000 mg twice daily increased plasma concentrations of simvastatin lactone, simvastatin acid by about 2 fold. Rhabdomyolysis has been associated with high doses of simvastatin and cases of

rhabdomyolysis have been observed in patients receiving RANEXA and simvastatin, in postmarketing experience. Limit the dose of simvastatin to 20 mg once daily in patients taking any dose of RANEXA.

Atorvastatin: Ranexa 1 000 mg twice daily increased C_{max} and AUC of atorvastatin 80 mg once daily by 1,4- and 1,3-fold, respectively and changed the C_{max} and AUC of atorvastatin metabolites less than 35 %. Dose limitation of atorvastatin and appropriate clinical monitoring may be considered when taking RANEXA.
Dose limitation of other statins, metabolised by CYP3A4 (e.g. lovastatin), may be considered when taking RANEXA.

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

Medicines transported by the organic cation transporter-2 (OCT2): Plasma exposure of metformin (1 000 mg twice daily) increased 1,4- and 1,8-fold in subjects with type 2 diabetes mellitus when co-administered with RANEXA 500 mg and 1 000 mg twice daily respectively. The exposure of other OCT2 substrates, including but not limited to pindolol and varenicline, may be affected to a similar degree.

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

4.6 Fertility, pregnancy and lactation

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

Breastfeeding: 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.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

Metabolism and nutrition disorders

Uncommon: anorexia, decreased appetite, dehydration

Rare: hyponatremia

Psychiatric disorders

Uncommon: anxiety, insomnia, confusional state, hallucination

Rare: disorientation

Nervous system disorders

Common: dizziness, headache

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

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

Eye disorders

Uncommon: blurred vision, visual disturbance, diplopia

Ear and labyrinth disorders

Uncommon: vertigo, tinnitus

Rare: impaired hearing

Vascular disorders

Uncommon: hot flush, hypotension

Rare: peripheral coldness, orthostatic hypotension

Respiratory, thoracic and mediastinal disorders

Uncommon: dyspnoea, cough, epistaxis

Rare: throat tightness

Gastrointestinal disorders

Common: constipation, vomiting, nausea

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

Rare: pancreatitis, erosive duodenitis, oral hypaesthesia

Skin and subcutaneous tissue disorders

Uncommon: pruritus, hyperhydrosis

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

Musculoskeletal and connective tissue disorders

Uncommon: pain in extremity, muscle cramps, joint swelling, muscular weakness

Renal and urinary disorders

Uncommon: dysuria, haematuria, chromaturia

Rare: acute renal failure, urinary retention

Reproductive system and breast disorders

Rare: erectile dysfunction

General disorders and administration site conditions

Common: asthenia

Uncommon: fatigue, peripheral oedema

Investigations

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

Rare: elevated levels of hepatic enzyme

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

An increased incidence of adverse events was seen among ranolazine treated patients in the RIVER-PCI trial (see section 5.1) where patients with incomplete revascularisation post-PCI were given ranolazine up to 1 000 mg twice daily or placebo for approximately 70 weeks. In this study, there was a higher reporting rate for congestive heart failure in the ranolazine group (2,2 % vs 1,0 % in placebo). Also, transient ischaemic attack occurred more frequently in patients treated with ranolazine 1 000 mg twice daily compared with placebo (1,0 % vs 0,2 %, respectively); however, the incidence of stroke was similar between treatment groups (ranolazine 1,7 % vs placebo 1,5 %).

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

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

In general, the type and frequency of adverse events reported in patients with low body weight (≤ 60 kg) were similar to those of patients with higher weight (> 60 kg); however, the placebo-corrected frequencies of the following common adverse events were higher in low body

weight than heavier patients: nausea (14 % versus 2 %), vomiting (6 % versus 1 %) and hypotension (4 % versus 2 %).

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of RANEXA is important. It allows continued monitoring of the benefit/risk balance of RANEXA. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRAwebsite.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class:

A 7.1.4 Vasodilators – coronary and other medicines used in angina pectoris

Pharmacotherapeutic group:

Other cardiac preparations, ATC code: C01EB18

Mechanism of action

The mechanism of action of ranolazine is largely unknown. Ranolazine may have some antianginal effects by inhibition of the late sodium current in cardiac cells. This reduces intracellular sodium accumulation and consequently decreases intracellular calcium overload. Ranolazine, via its action to decrease the late sodium current, is considered to reduce these intracellular ionic imbalances during ischaemia. This reduction in cellular calcium overload is expected to improve myocardial relaxation and thereby decrease left ventricular diastolic stiffness. Clinical evidence of inhibition of the late sodium current by ranolazine is provided by a significant shortening of the QTc interval and an improvement in diastolic relaxation in an open-label study of 5 patients with a long QT syndrome (LQT3 having the SCN5A

∆KPQ gene mutation).

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

vasodilation.

Pharmacodynamic effects

Haemodynamic effects:

Minimal decreases in mean heart rate (< 2 beats per minute) and mean

systolic blood pressure (< 3 mm Hg) were observed in patients treated with ranolazine either alone or in combination with other antianginal medicines in

controlled studies.

Electrocardiographic effects:

Dose and plasma concentration-related increases in the QTc interval (about 6 msec at 1 000 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 1 000 ng/mL ranolazine plasma

concentration. This value is consistent with data from pivotal clinical studies, where mean changes from baseline in QTcF (Fridericia's correction) after doses of 500 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, 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 dysrhythmias (3,0 % versus 3,1 %).
No prodysrhythmic 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 dysrhythmias in patients treated with RANEXA (80 %) versus placebo (87 %), including ventricular tachycardia ≥ 8 beats (5 % versus 8 %).

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

In the pivotal study, CARISA, RANEXA was added to treatment with atenolol 50 mg once daily, amlodipine 5 mg once daily, or diltiazem 180 mg once daily. Eight-hundred and twenty-three patients (23 % women) were randomised to receive 12 weeks of treatment with RANEXA 750 mg twice daily, 1 000 mg twice daily or placebo. RANEXA demonstrated greater efficacy than placebo in prolonging exercise time at trough at 12 weeks for both doses studied when used as an add-on therapy. However, there was no difference in exercise duration between the two doses (24 seconds compared to placebo; $p \leq 0,03$).
RANEXA resulted in significant decreases in the number of angina attacks per week and consumption of short-acting nitroglycerin compared to placebo. Tolerance to ranolazine did not develop during treatment and a rebound increase in angina attacks was not observed following abrupt discontinuation. The improvement in exercise duration in women was about 33 % of the improvement in men at the 1 000 mg twice-daily dose level. However, men and women had similar reductions in

frequency of angina attacks and nitroglycerin consumption. Given the dose-dependent side effects and similar efficacy at 750 and 1 000 mg twice daily, a maximum
dose of 750 mg twice daily is recommended.
In a second study, ERICA, RANEXA was added to treatment with amlodipine 10 mg once daily (the maximum labelled dose). Five-hundred and sixty-five patients were randomised to receive an initial dose of RANEXA 500 mg twice daily or placebo for 1 week, followed by 6 weeks of treatment with RANEXA 1 000 mg twice daily or placebo, in addition to concomitant treatment with amlodipine 10 mg once daily. Additionally, 45 % of the study population also received long-acting nitrates. RANEXA resulted in significant decreases in the number of angina attacks per week (p = 0,028) and consumption of short-acting nitroglycerin (p = 0,014) compared to placebo. Both the average number of angina attacks and nitroglycerin tablets consumed decreased by approximately one per week.

In the main dose-finding study, MARISA, ranolazine was used as monotherapy. One-hundred and ninety-one patients were randomised to treatment with RANEXA 500 mg twice daily, 1 000 mg twice daily, 1 500 mg twice daily and matching placebo, each for 1 week in a crossover design. RANEXA was significantly superior to placebo in prolonging exercise time, time to angina and time to 1 mm ST segment depression at all doses studied with an observed dose-response relationship. Improvement of exercise duration was statistically significant compared to placebo for all three doses of ranolazine from 24 seconds at 500 mg twice daily to 46 seconds at 1 500 mg twice daily, showing a dose-related response. In this study, exercise duration was longest in the 1 500 mg group; however, there was a disproportional increase in side effects and the 1 500 mg dose was
not studied further.
In a large outcome study (MERLIN-TIMI 36) in 6 560 patients with UA/NSTEMI ACS, there was no difference in the risk of all-cause mortality (relative risk ranolazine:placebo 0,99), sudden cardiac death (relative risk ranolazine:placebo 0,87) or the frequency of symptomatic documented dysrhythmias (3,0 % versus 3,1 %) between RANEXA and placebo when added to standard medical therapy (including beta-blockers, calcium channel blockers, nitrates, anti-platelet medicines, lipid-lowering medicines and ACE inhibitors). Approximately one-half of the patients in MERLIN-TIMI 36 had a history of angina. The results showed that exercise duration was 31 seconds longer in

ranolazine patients versus placebo patients (p = 0,002). The Seattle angina questionnaire showed significant effects on several dimensions, including angina frequency (p < 0,001), compared to placebo-treated patients.

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

In a phase 3, double-blind, placebo-controlled, event-driven trial (RIVER-PCI) in 2 604 patients aged ≥ 18 years with a history of chronic angina and incomplete revascularisation after percutaneous coronary intervention (PCI) patients were up-titrated to 1 000 mg twice daily (dosage not approved in the current SmPC). No significant difference occurred in the composite primary endpoint (time to first occurrence of ischaemia-driven revascularisation or ischaemia-driven hospitalisation without revascularisation) in the ranolazine group (26,2 %) versus the placebo group (28,3 %), hazard ratio 0,95; 95 % CI 0,82 – 1,10 p = 0,48. The risk of all cause mortality, CV death or major adverse cardiovascular events (MACE) and heart failure hospitalisation was similar between treatment groups in the overall population; however, MACE were reported more frequently in patients ≥ 75 years treated with ranolazine compared with placebo (17,0 % vs 11,3 %, respectively); in addition there was a numerical increase in all cause mortality in patients ≥ 75 years (9,2 % vs. 5,1 %, p = 0,074).

5.2 Pharmacokinetic properties

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

Absorption:

The mean absolute bioavailability of ranolazine after oral administration of immediate-release ranolazine tablets ranged from 35 – 50 %, with large inter-individual variability. 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 1 000 mg twice daily. In a pharmacokinetic study in healthy volunteers, steady-state C_{max} was, on average, approximately 1770 (SD 1040) ng/mL and steady-state

AUC_{0-12} was, on average, 13 700 (SD 8290) ng x h/mL following a dose of 500 mg twice daily. Food does not affect the rate and extent of absorption of

ranolazine.

Distribution:

Approximately 62 % of ranolazine is bound to plasma proteins, mainly alpha 1 acid glycoprotein and weakly to albumin. The mean steady-state volume of distribution (Vss) is about 180 litre.

Elimination:

Ranolazine is eliminated primarily by metabolism. Less than 5 % of the dose is excreted unchanged in the urine and faeces. Following oral administration of a single 500 mg dose of [^{14}C] ranolazine to healthy subjects, 73 % of the radioactivity was recovered in urine and 25 % in faeces.
Clearance of ranolazine is dose dependent, decreasing with increased dose. The elimination half life is about 2 – 3 hours after intravenous administration. The terminal half-life at steady state after oral administration of ranolazine is about 7 hours, due to the absorption rate-limited elimination.

Biotransformation:

Ranolazine undergoes rapid and extensive metabolism. In healthy young adults, ranolazine accounts for approximately 13 % of the radioactivity in plasma following a single oral 500 mg dose of [^{14}C] ranolazine. A large number of metabolites has been identified in human plasma (47 metabolites), urine (> 100 metabolites) and faeces (25 metabolites). Fourteen primary pathways have been identified of which *O*-demethylation and *N*-dealkylation are the most important. *In vitro* studies using human liver microsomes indicate that ranolazine is metabolised primarily by CYP3A4, but also by CYP2D6. At 500 mg twice daily, subjects lacking CYP2D6 activity (poor metabolisers, PM) had 62 % higher AUC than subjects with CYP2D6 metabolising capacity (extensive metabolisers, EM). The corresponding difference at the 1 000 mg twice-daily dose was 25 %.

Special populations

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

and healthy subjects.

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

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

Body weight: Compared to subjects weighing 70 kg, exposure was estimated to be about 1,4-fold higher in subjects weighing 40 kg.

Congestive heart failure (CHF): CHF patients (New York Heart Association (NYHA) Class III and IV) were estimated to have about 1,3-fold higher plasma concentrations.

Renal impairment: In a study evaluating the influence of renal function on ranolazine pharmacokinetics, ranolazine AUC was on average 1,7- to 2-fold higher in subjects with mild, moderate and severe renal impairment compared with subjects with normal renal function. There was a large inter-individual variability in AUC in subjects with renal impairment. The AUC of metabolites increased with decreased renal function. The AUC of one pharmacologically active ranolazine metabolite was 5-fold increased in patients with severe renal impairment.

In the population pharmacokinetic analysis, a 1,2-fold increase in ranolazine exposure was estimated in subjects with moderate impairment (creatinine clearance 40 mL/min). In subjects with severe renal impairment (creatinine

clearance 10 – 30 mL/min), a 1,3- to 1,8-fold increase in ranolazine

exposure was estimated.

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

Hepatic impairment: The pharmacokinetics of ranolazine have been evaluated in patients with mild or moderate hepatic impairment. There are no data in patients with severe hepatic impairment. Ranolazine AUC was unaffected in patients with mild hepatic impairment but increased 1,8-fold in patients with moderate impairment. QT prolongation was more pronounced in these patients.

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

5.3 Preclinical safety data

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

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

In long-term carcinogenicity studies at doses of ranolazine up to 50 mg/kg/day (150 mg/m^2/day) in mice and 150 mg/kg/day (900 mg/m^2/day) in rats, no relevant increases in the incidence of any tumour types were

seen. These doses are equivalent to 0,1 and 0,8 times, respectively, the maximum recommended human dose of 2 grams on a mg/m^2 basis, and represent the maximum tolerated doses in these species.

Signs of embryonal and maternal toxicity, but not teratogenicity, were seen at doses of ranolazine up to 400 mg/kg/day (2 400 mg/m^2/day) in rats and 150 mg/kg/day (1 800 mg/m^2/day) in rabbits. These doses represent 2,7 and 2 times, respectively, the maximum recommended human dose.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients for all RANEXA prolonged-release tablets:

Hypromellose

Magnesium stearate

Methacrylic acid-ethyl acrylate copolymer (1:1)

Microcrystalline cellulose

Sodium hydroxide.

Film coating for RANEXA 375 mg:

Opadry Light Blue containing:

Carnauba wax

FD&C Blue No. 2 lake (E132)

Hypromellose

Polyethylene glycol

Polysorbate

Titanium dioxide.

Film coating for RANEXA 500 mg:

Opadry II Orange containing:

Carnauba wax

Iron oxide red (E172)

Iron oxide yellow (E172)

Polyethylene glycol

Polyvinyl alcohol

Talc

Titanium dioxide.

Film coating for RANEXA 750 mg:

Opadry II Blue containing:

Carnauba wax

FD&C Blue No. 1 lake (E133)

FD&C Yellow No. 5 lake (E102)

Glycerol triacetate

Hypromellose

Lactose monohydrate

Titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the blister strips in the outer carton to protect from light.

6.5 Nature and contents of container

White, PVC/PVDC/Aluminium blister strip. Three (3) blister strips, containing 20 tablets each, packed into an outer carton.

Pack size: 60 tablets.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Menarini South Africa (Pty) Ltd

Waterside Place, Unit 02D, South Gate Office Park

Carl Cronje Drive, Tygervalley

Cape Town, 7530

Tel: +27 21 109 6444

8. REGISTRATION NUMBER(S)

RANEXA 375 mg: 52/7.1.4/0337

RANEXA 500 mg: 52/7.1.4/0338

RANEXA 750 mg: 52/7.1.4/0339

9. DATE OF FIRST AUTHORISATION

06 July 2021

10. DATE OF REVISION OF THE TEXT

07 July 2025