SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ranolazine Aspire 750 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 750 mg of ranolazine
Excipient with known effect
Each coated tablet contains 19.22 mg of lactose (as monohydrate).
For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet
Light blue approx. 19.00 mm x 9.20 mm oblong shaped tablets debossed with RAN750 on one side and plain on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ranolazine Aspire 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

Posology

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

Adults:

The recommended initial dose of Ranolazine Aspire 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 adverse events (e.g. dizziness, nausea, or vomiting), downtitration of Ranolazine Aspire 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 (e.g. diltiazem, fluconazole, erythromycin) or P-gp inhibitors (e.g. verapamil, ciclosporin) (see sections 4.4 and 4.5).

Concomitant administration of 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). Ranolazine 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). Ranolazine is contraindicated in patients with moderate or severe hepatic impairment (see sections 4.3 and 5.2).

Elderly

Dose titration in elderly patients should be exercised with caution (see section 4.4). 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 CHF (NYHA Class III–IV) should be exercised with caution (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of ranolazine in children below the age of 18 years have not been established.

No data are available.

Method of administration

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

4.3 Contraindications

Hypersensitivity to the active substance 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) antiarrhythmics other than amiodarone.

4.4 Special warnings and precautions for use

Caution should be exercised when prescribing or uptitrating ranolazine 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 ranolazine is used in patients with a combination of several of these factors, monitoring of adverse events should be frequent, the dose reduced, and treatment discontinued, if needed.

The risk for increased exposure leading to adverse events in these different subgroups is higher in patients lacking CYP2D6 activity (poor metabolisers, PM) than subjects with CYP2D6 metabolising capacity (extensive metabolisers, EM) (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, ranolazine can be used with caution in these patients when they have a combination of several of the above risk factors.

QT prolongation:

Ranolazine blocks IKr and prolongs the QTc interval in a dose-related manner. A population-based analysis of combined data from patients and healthy volunteers demonstrated that the slope of the plasma concentration-QTc relationship was estimated to be 2.4 msec per 1000 ng/ml, which is approximately equal to a 2- to 7- msec increase over the plasma concentration range for ranolazine 500 to 1000 mg twice daily. Therefore, caution should be observed when treating patients with a history of congenital or a family history of long QT syndrome, in patients with known acquired QT interval prolongation, and in patients treated with drugs affecting the QTc interval (see section 4.5 also).

Drug-drug interaction:

Co-administration with CYP3A4 inducers is expected to lead to lack of efficacy. Ranolazine should not be used in patients treated with CYP3A4 inducers (e.g. rifampicin, phenytoin, phenobarbital, carbamazepine, St.John's Wort) (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 ranolazine (see sections 4.2, 4.3, 4.8, and 5.2).

Lactose:

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

Sodium:

This medicine contains less than 1 mmol sodium (23 mg) per prolonged-release tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on ranolazine

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 ranolazine 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 ranolazine is recommended in patients treated with diltiazem and other moderately potent CYP3A4 inhibitors (e.g. erythromycin, fluconazole). Down titration of ranolazine may be required (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 2.2fold. Careful dose titration of ranolazine is recommended in patients treated with P-gp inhibitors. Down titration of ranolazine 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 ranolazine 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 1000 mg twice daily by an average of 1.2-fold. No dose adjustment is required. At the dose level 500 mg twice

daily, co-administration of a potent inhibitor of CYP2D6 could result in an increase in ranolazine AUC of about 62%.

Effects of ranolazine on other medicinal products

Ranolazine is a moderate to potent inhibitor of P-gp and a mild inhibitor of CYP3A4, and may increase plasma concentrations of P-gp or CYP3A4 substrates. Tissue distribution of drugs which are transported by P-gp may be increased.

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

Available data suggest that ranolazine is a mild inhibitor of CYP2D6. Ranolazine 750 mg twice daily increased plasma concentrations of metoprolol by 1.8-fold. Therefore the exposure to metoprolol or other CYP2D6 substrates (e.g. propafenone and flecainide or, to a lesser extent, tricyclic antidepressants and antipsychotics) may be increased during co-administration with ranolazine, and lower doses of these medicinal products may be required.

The potential for inhibition of CYP2B6 has not been evaluated. Caution is advised during coadministration 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 ranolazine and digoxin are co-administered. Therefore, digoxin levels should be monitored following initiation and termination of ranolazine therapy.

Simvastatin:

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

Atorvastatin:

Ranolazine 1000 mg twice daily increased Cmax and AUC of atorvastatin 80 mg once daily by 1.4- and 1.3 - fold, respectively and changed the Cmax and AUC of atorvastatin metabolites less than 35%. Dose limitation of atorvastatin and appropriate clinical monitoring may be considered when taking

ranolazine. Dose limitation of other statins, metabolised by CYP3A4 (e.g. lovastatin), may be considered when taking ranolazine.

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

Drugs transported by the Organic Cation Transporter-2 (OCT2):

Plasma exposure of metformin (1000 mg twice daily) increased 1.4- and 1.8-fold in subjects with type 2 diabetes mellitus when co-administered with ranolazine 500 mg and 1000 mg twice daily respectively. The exposure of other OCT2 substrates, including but not limited to pindolol and varenicline, may be affected to a similar degree.
There is a theoretical risk that concomitant treatment of ranolazine with other drugs known to prolong the QTc interval may give rise to a pharmacodynamic interaction and increase the possible risk of ventricular arrhythmias. Examples of such drugs include certain antihistamines (e.g. terfenadine, astemizole, mizolastine), certain antiarrhythmics (e.g. quinidine, disopyramide, procainamide), erythromycin, and tricyclic antidepressants (e.g. imipramine, doxepin, amitriptyline).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data from the use of ranolazine in pregnant women. Studies in animals showed embryo toxicity (see Section 5.3). The potential risk for humans is unknown. Ranolazine should not be used during pregnancy unless clearly necessary

Breast-feeding

It is unknown whether ranolazine is excreted in human breast milk. Available pharmacodynamic/toxicological data in rats have shown excretion of ranolazine in milk (for details see Section 5.3). A risk to the suckling child cannot be excluded. Ranolazine should not be used during breast feeding.

Fertility

In animals, reproduction studies indicated no adverse effects on fertility (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 ranolazine on the ability to drive and use machines have been performed. Ranolazine may cause dizziness, blurred vision, diplopia, confusional state, coordination abnormal, and hallucination (see section 4.8), which may affect the ability to drive and use machines.

4.8 Undesirable effects

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

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), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Metabolism and nutrition disorders

Uncommon: anorexia decreased appetite, dehydration.

Rare: hyponatremia

Psychiatric disorders

Uncommon: anxiety, insomnia, confusional state, hallucination.

Rare: disorientation

Nervous system disorders

Common: dizziness, headache.

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

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

Not known: myoclonus.

Eye disorders

Uncommon: blurred vision, visual disturbance, diplopia.

Ear and labyrinth disorders

Uncommon: vertigo, tinnitus.

Rare: impaired hearing.

Vascular disorders

Uncommon: hot flush, hypotension.

Rare: peripheral coldness, orthostatic hypotension.

Respiratory, thoracic, and mediastinal disorders

Uncommon: dyspnoea, cough, epistaxis.

Rare: throat tightness.

Gastrointestinal disorders

Common: constipation, vomiting, nausea.

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

Rare: pancreatitis, erosive duodenitis, oral hypoaesthesia.

Skin and subcutaneous tissue disorders

Uncommon: pruritus, hyperhydrosis.

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

Musculoskeletal and connective tissue disorders

Uncommon: pain in extremity, muscle cramp, joint swelling, muscular weakness.

Renal and urinary disorders

Uncommon: dysuria, haematuria, chromaturia.

Rare: acute renal failure, urinary retention.

Reproductive system and breast disorders

Rare: erectile dysfunction.

General disorders and administration site conditions

Common: asthenia.

Uncommon: fatigue, peripheral oedema.

Investigations

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

Rare:
Elevated levels of hepatic enzyme.

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 medicinal products, 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 revascularization post-PCI were given ranolazine up to 1000 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 ischemic attack occurred more frequently in patients treated with ranolazine 1000 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 ranolazine (placebo-corrected frequencies) in elderly (≥ 75 years of age) than younger patients (< 75 years of age): constipation (8% versus 5%), nausea (6% versus 3%), hypotension (5% versus 1%), and vomiting (4% versus 1%).

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

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

nausea (14% versus 2%), vomiting (6% versus 1%), and hypotension (4% versus 2%).

Laboratory findings:
Small, clinically insignificant, reversible elevations in serum creatinine levels have been observed in healthy subjects and patients treated with ranolazine. There was no renal toxicity related to these findings. A renal function study in healthy volunteers demonstrated a reduction in creatinine clearance with no change in glomerular filtration rate consistent with inhibition of renal tubular secretion of creatinine.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiac therapy, 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 ΔKPQ 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 medicinal products in controlled studies.

Electrocardiographic effects:

Dose and plasma concentration-related increases in the QTc 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 ranolazine. 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 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 ranolazine 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 proarrhythmic effects were observed in 3,162 patients treated with ranolazine based on 7-day Holter monitoring in the MERLIN-TIMI 36 study. There was a significantly lower incidence of arrhythmias in patients treated with ranolazine (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 ranolazine in the treatment of patients with chronic angina, either alone or when the benefit from other antianginal medicinal products was suboptimal.

In the pivotal study, CARISA, ranolazine 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 ranolazine 750 mg twice daily, 1000 mg twice daily, or placebo. Ranolazine 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; $p \leq 0.03$).

Ranolazine 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 1000 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 1000 mg twice daily, a maximum dose of 750 mg twice daily is recommended.

In a second study, ERICA, ranolazine 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 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. Additionally, 45% of the study population also received long acting nitrates. Ranolazine resulted in significant decreases in the number of angina attacks per week ($p = 0.028$) and consumption of shortacting 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 ninetyone patients were randomised to treatment with ranolazine 500 mg twice daily, 1000 mg twice daily, 1500 mg twice daily, and matching placebo, each for 1 week in a crossover design. Ranolazine 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 1500 mg twice daily, showing a dose-related response. In this study, exercise duration was longest in the 1500 mg group; however, there was a disproportional increase in side effects, and the 1500 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 arrhythmias (3.0% versus 3.1%) between ranolazine and placebo when added to standard medical therapy (including betablockers, calcium channel blockers, nitrates, anti-platelet agents, lipid-lowering medicinal products, 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 2604 patients aged ≥18 years with a history of chronic angina and incomplete revascularisation after percutaneous coronary intervention (PCI) patients were up-titrated to 1000 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 ranolazine, peak plasma concentrations (Cmax) are typically observed between 2 and 6 hours. Steady state is generally achieved within 3 days of twice-daily dosing.

<u>Absorption</u>

The mean absolute bioavailability of ranolazine after oral administration of immediate-release ranolazine tablets ranged from 35−50%, with large inter-individual variability. Ranolazine exposure increases more than in proportion to dose. There was a 2.5- to 3-fold increase in steady-state AUC as the dose was increased from 500 mg to 1000 mg twice daily. In a pharmacokinetic study in healthy volunteers, steadystate Cmax was, on average, approximately 1770 (SD 1040) ng/ml, and steady-state AUC0-12 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 (V_{ss}) is about 180 l.

Elimination

Ranolazine is eliminated primarily by metabolism. Less than 5% of the dose is excreted unchanged in the urine and faeces. Following oral administration of a single 500 mg dose of [^{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 [14C]ranolazine. A large number of metabolites has been identified in human plasma (47 metabolites), urine (> 100 metabolites), and faeces (25 metabolites). Fourteen primary pathways have been identified of which O-demethylation and N-dealkylation are the most important. *In vitro* studies using human liver microsomes indicate that ranolazine is metabolised primarily by CYP3A4, but also by CYP2D6. At 500 mg twice daily, subjects lacking CYP2D6 activity (poor metabolisers, PM) had 62% higher AUC than subjects with CYP2D6 metabolising capacity (extensive metabolisers, EM). The corresponding difference at the 1000 mg twice-daily dose was 25%.

Special populations

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

Gender effects:

Gender had no clinically relevant effect on pharmacokinetic parameters.

Elderly patients:

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

Body weight:

Compared to subjects weighing 70 kg, exposure was estimated to be about 1.4-fold higher in subjects weighing 40 kg.

CHF:
CHF NYHA Class III and IV were estimated to have about 1.3-fold higher plasma concentrations.

Renal impairment

In a study evaluating the influence of renal function on ranolazine pharmacokinetics, ranolazine AUC was on average 1.7- to 2-fold higher in subjects with mild, moderate, and severe renal impairment compared with subjects with normal renal function. There was a large inter-individual variability in AUC in subjects with renal impairment. The AUC of metabolites increased with decreased renal function. The AUC of one pharmacologically active ranolazine metabolite was 5-fold 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 adrenocortical axis was noted in humans.

In long-term carcinogenicity studies at doses of ranolazine up to 50 mg/kg/day (150 mg/m2/day) in mice and 150 mg/kg/day (900 mg/m2/day) in rats, no relevant increases in the incidence of any tumour types were seen. These doses are equivalent to 0.1 and 0.8 times, respectively, the maximum recommended human dose of 2 grams on a mg/m2 basis, and represent the maximum tolerated doses in these species. In male and female rats, oral administration of ranolazine that produced exposures (AUC) 3.6-fold or 6.6fold higher than expected in humans, respectively, had no effect on fertility.

Embryofetal toxicity studies were conducted in rats and rabbits: no effects were noted in rabbit fetuses when mothers were exposed at levels (AUC) of plasma ranolazine similar to expected human levels. In rats, no effects in fetuses was noted when mothers were exposed to 2-fold greater levels (AUC) than expected in humans, whereas decreased fetal weight and reduced ossification were observed when the exposure of mothers was 7.5-fold than those obtained in humans. Post-natal mortality of pups was not recorded when the exposure of nursing mothers was 1.3 fold higher than in expected humans, whereas at 3-fold higher exposure post-natal mortality was recorded, concomitant with evidence of milk excretion of ranolazine in rats. No adverse effects on newborn rats were observed at levels of exposures similar to those observed in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline cellulose
Lactose monohydrate
Methacrylic acid-ethyl acrylate copolymer
Sodium hydroxide
Hypromellose

Magnesium stearate

Film-coating:

Titanium dioxide
Macrogol
Triacetin,

Additional excipient for 750 mg tablet:

Brilliant Blue FCF Aluminium Lake (E133)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25

6.5 Nature and contents of container

PVC/ PE/PVDC White Opaque /Aluminium Lidding foil blister packs in the pack size of 28, 30, 56, 60 or 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Aspire Pharma Limited
4 Rotherbrook Court,
Bedford Road,
Petersfield,
Hampshire,

GU32 3QG

8 MARKETING AUTHORISATION NUMBER(S)

PL 35533/0267

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/01/2025

10 DATE OF REVISION OF THE TEXT

04/03/2025