ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ranexa 375 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 375 mg of ranolazine.
For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet
Pale blue oval-shaped tablet engraved with 375 on one 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

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 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.

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). 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: 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 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. 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, voriconazol, posaconazol, 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 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: Ranolazine blocks I_{Kr} 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 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 ranolazine (see sections 4.2, 4.3, 4.8, and 5.2).

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 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 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 RANEXA may increase plasma concentrations of these drugs.

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 medicinal products 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 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 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 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 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).

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 RANEXA 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. Ranexa 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. Ranexa 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 Ranexa on the ability to drive 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 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, paresthesia.
Rare: amnesia, depressed level of consciousness, loss of consciousness, coordination abnormal, 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 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 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 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 national reporting system listed in Appendix V.

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

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 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 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 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 arrhythmias (3.0% versus 3.1%).

No proarrhythmic 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 ≥ 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 medicinal products 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, 1000 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 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, 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 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. 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, 1000 mg twice daily, 1500 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 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 Ranexa and placebo when added to standard medical therapy (including beta-blockers, 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 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 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, 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 [^{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 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 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.

In male and female rats, oral administration of ranolazine that produced exposures (AUC) 3.6-fold or 6.6-fold higher than expected in humans, respectively, had no effect on fertility.

Embryofetal toxicity studies were conducted in rats and rabbits: no effect 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

Excipients for all ranolazine prolonged-release tablets:
Carnauba wax
Hypromellose
Magnesium stearate
Methacrylic acid-ethyl acrylate copolymer (1:1)
Microcrystalline cellulose
Sodium hydroxide
Titanium dioxide

Additional excipients for 375 mg tablet:
Macrogol
Polysorbate 80
Blue #2/Indigo Carmine Aluminium Lake (E132)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Blister pack: 5 years
Bottle pack: 4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC/Aluminium blisters of 15 or 20 tablets per blister card. Each carton contains 2, 3, or 5 blister cards (30, 60, or 100 tablets) or one HDPE bottle containing 60 tablets.

Not all pack-sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

Menarini International Operations Luxembourg S.A.

1, Avenue de la Gare, L-1611 Luxembourg
Luxembourg

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/462/001 60 tablets in blister pack
EU/1/08/462/002 60 tablets in bottle
EU/1/08/462/007 30 tablets in blister pack
EU/1/08/462/008 100 tablets in blister pack

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 July 2008
Date of last renewal: 06 March 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Ranexa 500 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg of ranolazine.
For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet
Light orange oval-shaped tablet engraved with 500 on one 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

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 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.

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). 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: 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 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. 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, voriconazol, posaconazol, 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 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: Ranolazine blocks I_{Kr} 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 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 ranolazine (see sections 4.2, 4.3, 4.8, and 5.2).

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 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 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 RANEXA may increase plasma concentrations of these drugs.

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 medicinal products 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 1000 mg twice daily increased plasma concentrations of simvastatin lactone, simvastatin acidby 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 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 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).

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 RANEXA 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. Ranexa 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. Ranexa 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 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 (see section 4.8), which may affect the ability to drive 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, paresthesia.
Rare: amnesia, depressed level of consciousness, loss of consciousness, coordination abnormal, gait disturbance, parosmia.

Eye disorders
Uncommon: blurred vision, visual disturbance, diplpopia.

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 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 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 national reporting system listed in Appendix V.

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

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 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 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 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 arrhythmias (3.0% versus 3.1%).

No proarrhythmic 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 $\geq$ 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 medicinal products 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, 1000 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 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, 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 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. 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, 1000 mg twice daily, 1500 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 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 Ranexa and placebo when added to standard medical therapy (including beta-blockers, 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 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 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, 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 [^{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 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 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.

In male and female rats, oral administration of ranolazine that produced exposures (AUC) 3.6-fold or 6.6-fold higher than expected in humans, respectively, had no effect on fertility.

Embryofetal toxicity studies were conducted in rats and rabbits: no effect 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

Excipients for all ranolazine prolonged-release tablets:
Carnauba wax
Hypromellose
Magnesium stearate
Methacrylic acid-ethyl acrylate copolymer (1:1)
Microcrystalline cellulose
Sodium hydroxide
Titanium dioxide

Additional excipients for 500 mg tablet:
Macrogol

Polyvinyl alcohol-part hydrolyzed
Iron oxide yellow (E172)
Iron oxide red (E172)
Talc

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Blister pack: 5 years
Bottle pack: 4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC/Aluminium blisters of 15 or 20 tablets per blister card. Each carton contains 2, 3, or 5 blister cards (30, 60, or 100 tablets) or one HDPE bottle containing 60 tablets.

Not all pack-sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

Menarini International Operations Luxembourg S.A.
1, Avenue de la Gare, L-1611 Luxembourg
Luxembourg

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/462/003 60 tablets in blister pack
EU/1/08/462/004 60 tablets in bottle
EU/1/08/462/009 30 tablets in blister pack
EU/1/08/462/010 100 tablets in blister pack

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 July 2008
Date of last renewal: 06 March 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Ranexa 750 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 750 mg of ranolazine.
Excipients: Each tablet contains 0.04 mg azo colouring agent E102 and 12.0 mg lactose monohydrate.
For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet
Pale green oval-shaped tablet engraved with 750 on one 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

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 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.

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). 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: 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 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. 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, voriconazol, posaconazol, 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 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: Ranolazine blocks I_{Kr} 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 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 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, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

Azo colouring agent E102: This medicinal product contains the azo colouring agent E102 which may cause allergic reactions.

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 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 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 RANEXA may increase plasma concentrations of these drugs.

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 medicinal products 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 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 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 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 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).

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 RANEXA 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. Ranexa 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. Ranexa 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 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 (see section 4.8), which may affect the ability to drive 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, paresthesia.
Rare: amnesia, depressed level of consciousness, loss of consciousness, coordination abnormal, 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 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 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 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 national reporting system listed in Appendix V.

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

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 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 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 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 arrhythmias (3.0% versus 3.1%).

No proarrhythmic 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 ≥ 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 medicinal products 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, 1000 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 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, 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 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. 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, 1000 mg twice daily, 1500 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 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 Ranexa and placebo when added to standard medical therapy (including beta-blockers, 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 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 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, 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 [^{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 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 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.

In male and female rats, oral administration of ranolazine that produced exposures (AUC) 3.6-fold or 6.6-fold higher than expected in humans, respectively, had no effect on fertility.

Embryofetal toxicity studies were conducted in rats and rabbits: no effect 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

Excipients for all ranolazine prolonged-release tablets:
Carnauba wax
Hypromellose
Magnesium stearate
Methacrylic acid-ethyl acrylate copolymer (1:1)
Microcrystalline cellulose
Sodium hydroxide
Titanium dioxide

Additional excipients for 750 mg tablet:
Glycerol triacetate
Lactose monohydrate
Blue #1/Brilliant Blue FCF Aluminium Lake (E133) and Yellow #5/Tartrazine Aluminium Lake (E102)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Blister pack: 5 years
Bottle pack: 4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC/Aluminium blisters of 15 or 20 tablets per blister card. Each carton contains 2, 3, or 5 blister cards (30, 60, or 100 tablets) or one HDPE bottle containing 60 tablets.

Not all pack-sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

Menarini International Operations Luxembourg S.A.
1, Avenue de la Gare, L-1611 Luxembourg
Luxembourg

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/462/005 60 tablets in blister pack
EU/1/08/462/006 60 tablets in bottle
EU/1/08/462/011 30 tablets in blister pack
EU/1/08/462/012 100 tablets in blister pack

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 July 2008
Date of last renewal: 06 March 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Menarini - Von Heyden GmbH
Leipziger Straβe 7-13
01097 Dresden
Germany

or

Berlin-Chemie AG
Glienicker Weg 125
12489 Berlin
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP shall be submitted every three years.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Carton containing blister strips or carton containing HDPE bottle and bottle label.

1. NAME OF THE MEDICINAL PRODUCT

Ranexa 375 mg prolonged-release tablets
Ranolazine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains 375 mg ranolazine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 prolonged-release tablets
60 prolonged-release tablets
100 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Swallow whole. Do not chew.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Menarini International O. L. S.A.
1, Avenue de la Gare, L-1611 Luxembourg
Luxembourg

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/462/001 60 tablets in blister pack
EU/1/08/462/002 60 tablets in bottle
EU/1/08/462/007 30 tablets in blister pack
EU/1/08/462/008 100 tablets in blister pack

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ranexa 375 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PVC/PVDC/Aluminium blisters

1. NAME OF THE MEDICINAL PRODUCT

Ranexa 375 mg prolonged-release tablets
Ranolazine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Menarini International O.L. S.A.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Carton containing blister strips or carton containing HDPE bottle and bottle label.

1. NAME OF THE MEDICINAL PRODUCT

Ranexa 500 mg prolonged-release tablets
Ranolazine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains 500 mg ranolazine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 prolonged-release tablets
60 prolonged-release tablets
100 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Swallow whole. Do not chew.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Menarini International O. L. S.A.
1, Avenue de la Gare, L-1611 Luxembourg
Luxembourg

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/462/003 60 tablets in blister pack
EU/1/08/462/004 60 tablets in bottle
EU/1/08/462/009 30 tablets in blister pack
EU/1/08/462/010 100 tablets in blister pack

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ranexa 500 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PVC/PVDC/Aluminium blisters

1. NAME OF THE MEDICINAL PRODUCT

Ranexa 500 mg prolonged-release tablets
Ranolazine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Menarini International O.L. S.A.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Carton containing blister strips or carton containing HDPE bottle and bottle label.

1. NAME OF THE MEDICINAL PRODUCT

Ranexa 750 mg prolonged-release tablets
Ranolazine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains 750 mg ranolazine.

3. LIST OF EXCIPIENTS

Contains colouring agent E102 and lactose; see package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 prolonged-release tablets
60 prolonged-release tablets
100 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Swallow whole. Do not chew.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Menarini International O. L. S.A.
1, Avenue de la Gare, L-1611 Luxembourg
Luxembourg

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/462/005 60 tablets in blister pack
EU/1/08/462/006 60 tablets in bottle
EU/1/08/462/011 30 tablets in blister pack
EU/1/08/462/012 100 tablets in blister pack

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ranexa 750 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PVC/PVDC/Aluminium blisters

1. NAME OF THE MEDICINAL PRODUCT

Ranexa 750 mg prolonged-release tablets
Ranolazine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Menarini International O.L. S.A.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Ranexa 375 mg prolonged-release tablets
Ranexa 500 mg prolonged-release tablets
Ranexa 750 mg prolonged-release tablets
Ranolazine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illnes are the same as yours.
- If you get any side effects talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What RANEXA is and what is used for

Ranexa is a medicine used in combination with other medicines to treat angina pectoris, which is a chest pain or discomfort that you feel anywhere along the upper part of your body between your neck and upper abdomen, often brought on by exercise or too much activity.

You must talk to a doctor if you do not feel better or if you feel worse.

2. What you need to know before you take RANEXA

Do not take Ranexa
- if you are allergic to ranolazine or any of the other ingredients of this medicine listed in section 6 of this leaflet.
- if you have severe kidney problems.
- if you have moderate or severe liver problems.
- if you are using certain medicines to treat bacterial infections (clarithromycin, telithromycin), fungal infections (itraconazole, ketoconazole, voriconazol, posaconazol), HIV infection (protease inhibitors), depression (nefazodone) or heart rhythm disorders (e.g. quinidine, dofetilide, or sotalol).

Warning and precautions
Talk to your doctor before taking Ranexa:
- if you have mild or moderate kidney problems.
- if you have mild liver problems.
- if you have ever had an abnormal electrocardiogram (ECG).
- if you are elderly.
- if you have low weight (60 kg or less).
- if you have heart failure.

Your doctor may decide to give you a lower dose or take other precautions if any of these apply to you.

Using other medicines and Ranexa
Do not use the following medicines if you take Ranexa:
- certain medicines to treat bacterial infections (clarithromycin, telithromycin), fungal infections (itraconazole, ketoconazole, voriconazole, posaconazole), HIV infection (protease inhibitors), depression (nefazodone), or heart rhythm disorders (e.g. quinidine, dofetilide, or sotalol).

Tell your doctor or pharmacist before you take Ranexa if you use:
- certain medicines to treat a bacterial infection (erythromycin), or a fungal infection (fluconazole), a medicine used to prevent rejection of a transplanted organ (ciclosporin), or if you are taking some heart tablets such as diltiazem or verapamil. These medicines may cause an increase in the number of side effects, such as dizziness, nausea, or vomiting, which are possible side effects of Ranexa (see section 4). Your doctor may decide to give you a lower dose.
- medicines to treat epilepsy or another neurologic disorder (e.g. phenytoin, carbamazepine, or phenobarbital); are taking rifampicin for an infection (e.g. tuberculosis); or are taking the herbal remedy St. John's Wort, as these medicines may cause Ranexa to be less effective.
- heart medicines containing digoxin or metoprolol, as your doctor may want to change the dose of this medicine whilst you are taking Ranexa.
- certain medicines to treat allergies (e.g. terfenadine, astemizole, mizolastine), heart rhythm disorders (e.g. disopyramide, procainamide), and depression (e.g. imipramine, doxepin, amitriptyline), as these medicines may affect your ECG.
- certain medicines to treat depression (bupropion), psychosis, HIV infection (efavirenz), or cancer (cyclophosphamide).
- certain medicines to treat high levels of cholesterol in the blood (e.g. simvastatin, lovastatin, atorvastatin). These medicines may cause muscle pain and muscle injury. Your doctor may decide to change the dose of this medicine while you are taking Ranexa.
- certain medicines used to prevent transplanted organ rejection (e.g. tacrolimus, ciclosporin, sirolimus, everolimus) as your doctor may decide to change the dose of this medicine while you are taking Ranexa.

Tell your doctor or pharmacist if you are using or have recently used or might use any other medicines.

Ranexa with food and drink
Ranexa can be taken with or without food. While being treated with Ranexa, you should not drink grapefruit juice.

Pregnancy
You should not take Ranexa if you are pregnant unless your doctor has advised you to do so.

Breast-feeding
You should not take Ranexa if you are breast-feeding. Ask your doctor for advice if you are breast-feeding.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Driving and using machines
No studies on the effects of Ranexa on the ability to drive and use machines have been performed. Ask your doctor for advice about driving or using machines.

Ranexa may cause side effects such as dizziness (common), blurred vision (uncommon), confusional state (uncommon), hallucination (uncommon), double vision (uncommon), coordination problems

(rare), that may affect your ability to drive or use machines. If you experience these symptoms, do not drive or operate machinery until they have resolved completely.

Ranexa 750 mg prolonged-release tablets contain the azo colouring agent E102. This colouring agent- may cause allergic reactions.

Ranexa 750 mg prolonged-release tablets contain lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

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

3. How to take RANEXA

Always take this medicine exactly as your doctor has told you to. Check with your doctor or pharmacist if you are not sure.

Always swallow the tablets whole with water. Do not crush, suck, or chew the tablets or break them in half, as this might affect the way the medicine is released from the tablets into your body.

The starting dose for adults is one 375 mg tablet twice a day. After 2−4 weeks, your doctor may increase the dose to get the right effect. The maximum dose of Ranexa is 750 mg twice a day.

It is important that you tell your doctor if you get side effects such as dizziness or feeling or being sick. Your doctor may lower your dose or, if this is not sufficient, stop treatment with Ranexa.

Use in children and adolescents
Children and adolescents under 18 years old should not take Ranexa.

If you take more Ranexa than you should
If you accidentally take too many Ranexa tablets or take a higher dose than recommended by your doctor, it is important that you tell your doctor at once. If you cannot contact your doctor, go to the nearest accident and emergency department. Take along any tablets that are left, including the container and the carton, so that the hospital staff can easily tell what you have taken.

If you forget to take Ranexa
If you forget to take a dose, take it as soon as you remember unless it is nearly time (less than 6 hours) to take your next dose. Do not take a double dose to make up for a forgotten dose.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

You should stop taking Ranexa and see your doctor immediately if you experience the following symptoms of angioedema, which is a rare condition but can be severe:
- swollen face, tongue, or throat
- difficulty swallowing
- hives or difficulty breathing

Tell your doctor if you experience common side effects such as dizziness or feeling sick or vomiting. Your doctor may lower your dose or stop treatment with Ranexa.

Other side effects you may experience include the following:

Common side effects (occur in 1 to 10 users in 100) are:

- Constipation
- Dizziness
- Headache
- Feeling sick, vomiting
- Feeling weak

Uncommon side effects (occur in 1 to 10 users in 1,000) are:

- Altered sensation
- Anxiety, difficulty sleeping, confusional state, hallucination
- Blurred vision, visual disturbance
- Changes in sensation (touch or taste), tremor, feeling tired or sluggish, sleepiness or drowsiness, faint or fainting, dizziness upon standing
- Dark urine, blood in urine, difficulty urinating
- Dehydration
- Difficulty breathing, cough, nose bleed
- Double vision
- Excessive sweating, itching
- Feeling swollen or bloated
- Hot flushes, low blood pressure
- Increases in a substance called creatinine or increases in urea in your blood, increase in blood platelets or white blood cells, changes in ECG heart tracing
- Joint swelling, pain in extremity
- Loss of appetite and/or weight loss
- Muscle cramp
- Ringing in the ears and/or feeling a spinning sensation
- Stomach pain or discomfort, indigestion, dry mouth, or wind

Rare side effects (occur in 1 to 10 users in 10,000) are:

- A lack of ability to urinate
- Abnormal laboratory values for liver
- Acute kidney failure
- Change in sense of smell, numbness in mouth or lips, impaired hearing
- Cold sweat, rash
- Coordination problems
- Decrease in blood pressure upon standing
- Decreased or loss of consciousness
- Disorientation
- Feeling of coldness in hands and legs
- Hives, allergic skin reaction
- Impotence
- Inability to walk due to imbalance
- Inflammation of pancreas or intestine
- Loss of memory
- Throat tightness
- Low level of sodium in the blood (hyponatremia) which can cause tiredness and confusion, muscle twitching, cramps, and coma.

The following has also been reported:

- Muscle weakness.

Reporting of side effects

If you get any any side effects talk to your doctor or pharmacist. This include any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system

listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store RANEXA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on each blister strip of tablets and on the outside of the carton and bottle after EXP.

This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ranexa contains
The active substance in Ranexa is ranolazine. Each tablet contains 375 mg, 500 mg, or 750 mg ranolazine.

The other ingredients are: hypromellose, magnesium stearate, methacrylic acid-ethyl acrylate copolymer, microcrystalline cellulose, sodium hydroxide, titanium dioxide and carnauba wax.

Depending on the tablet strength, the tablet coatings also contain:
375 mg tablet: macrogol, polysorbate 80, Blue #2/Indigo Carmine Aluminium Lake (E132)
500 mg tablet: macrogol, talc, polyvinyl alcohol-part hydrolyzed, iron oxide yellow (E172), iron oxide red (E172)
750 mg tablet: glycerol triacetate, lactose monohydrate, Blue #1/Brilliant Blue FCF Aluminium Lake (E133) and Yellow #5/Tartrazine Aluminium Lake (E102)

What Ranexa looks like and contents of the pack
Ranexa prolonged-release tablets are oval shaped tablets.
The 375 mg tablets are pale blue and are engraved with 375 on one side.
The 500 mg tablets are light orange and are engraved with 500 on one side.
The 750 mg tablets are pale green and are engraved with 750 on one side.

Ranexa is supplied in cartons containing 30, 60, or 100 tablets in blister strips or 60 tablets in plastic bottles. Not all pack-sizes may be marketed.

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Detailed information on this medicine is available on the European Medicines Agency web site http://www.ema.europa.eu.