

2nd Re-Submission

ranolazine, 375mg, 500mg and 750mg prolonged-release tablets
(Ranexa®) SMC No. (565/09)

A. Menarini Pharma UK SRL

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a second resubmission

ranolazine (Ranexa®) is not recommended for use within NHS Scotland.

Indication under review: 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).

When added to standard doses of antianginal drugs, ranolazine increased exercise duration at trough drug levels compared with placebo after 12 weeks treatment. Although significant the effect size was modest.

The submitting company did not present a sufficiently robust clinical and economic case to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

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).

Dosing Information

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

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

Product availability date

2 March 2009

Summary of evidence on comparative efficacy

Ranolazine has a novel mechanism of action, involving selective inhibition of the late sodium current into cardiac cells which results in a decrease in intracellular sodium ions and prevents intracellular calcium overload, thereby enhancing the performance of the heart muscle. The antianginal effect is achieved without clinically significant effects on heart rate or blood pressure.

The submitting company has requested that the Scottish Medicines Consortium (SMC) considers this product when positioned for use in patients who have persistent angina symptoms despite maximally tolerated medical treatment in whom the up-titration or addition of other agents is contraindicated or not tolerated, due to their effect on heart rate and/or blood pressure, and are ineligible for revascularisation.

The key phase III study, CARISA,¹ involved an "add-on" design where two doses of ranolazine were added to one other commonly prescribed antianginal therapy. It was a randomised, three-arm, double-blind, placebo controlled study with three phases: a single-blind placebo qualifying phase during which patients had to exhibit symptom-limited exercise duration, a double-blind treatment phase lasting 12 weeks and a two-day rebound assessment phase. Patients included had chronic stable angina for at least three months, a diagnosis of coronary artery disease and were treated for a minimum of five days with background antianginal therapy which included either atenolol 50mg once daily, amlodipine 5mg once daily or a once daily preparation of diltiazem 180mg. Doses were fixed throughout the study and all other antianginal therapies except sublingual glyceryl trinitrate 'as required' were prohibited. The study parameters were measured with exercise tolerance tests (ETTs) and were recorded at trough drug levels (12 hours after dosing) 2, 6 and 12 weeks after dosing. At 2 and 12 weeks after randomisation, measurements were also made at peak levels (four hours after dosing). The primary end-point was the change from baseline in exercise duration at trough drug levels after 12 weeks, in the intention-to-treat population, with stratification according to background drug therapy. The last

observation carried forward method of imputation of missing data was used. Secondary endpoints included the frequency of angina attacks as reported daily by the patients.

Eight hundred and twenty-three patients were randomised to ranolazine 750mg twice daily (n=279), ranolazine 1,000mg twice daily (n=275) or placebo twice daily (n=269). The primary outcome demonstrated a statistically significant mean increase in exercise duration for patients treated with ranolazine compared with placebo. Exercise duration increased by 92 seconds from baseline (around 420 seconds) in the placebo group and by 115 and 116 seconds in the ranolazine 750 and 1,000mg groups, respectively, giving a treatment difference of 23.7 ± 10.9 seconds for ranolazine 750mg and 24.0 ± 11.0 seconds for 1,000mg.

For the secondary endpoint of frequency of anginal attacks per week at 12 weeks, there was a significant reduction for both doses of ranolazine compared with placebo: a baseline mean of around 4.5 angina attacks per week, was reduced in the placebo group to 3.3 ± 0.3 attacks per week, in the ranolazine 750mg group to 2.5 ± 0.2 and in the ranolazine 1,000mg group to 2.1 ± 0.2 attacks per week. Glyceryl trinitrate consumption at 12 weeks was significantly reduced for both ranolazine doses when compared with placebo.

The European Medicines Agency (EMA) noted in the European Public Assessment Report (EPAR) that a post hoc subgroup analysis of 249 patients who, prior to randomisation, were deemed, due to their haemodynamic status, to be maximally dosed with other antianginal drugs showed similar results to the whole study population. Only 88 of these patients received a licensed dose of ranolazine.²

A supportive study, ERICA³, used different background therapy: amlodipine 10mg once daily taken for at least two weeks before entering the study, and allowed the use of long-acting nitrates (used by 46% of the study population). Following a placebo qualifying phase, patients entered a double-blind initial phase for one week when patients were randomised to placebo or ranolazine 500mg twice daily, then a double-blind treatment phase lasting six weeks when ranolazine treated patients had their dose increased to 1,000mg twice daily. Enrolled patients had similar inclusion criteria to the pivotal study, but were required to have experienced at least three angina attacks per week in the qualification period rather than have symptom-limited ETT. The primary efficacy end-point was the weekly frequency of self-reported angina attacks during the full-dose treatment phase, 'trimmed' to average all observations except extreme outliers at the top and bottom 2%. Five hundred and sixty five patients were randomised to receive ranolazine (n=281) or placebo (n=284). Ranolazine significantly reduced the number of attacks per week: the trimmed mean of weekly attacks fell from 5.59 ± 0.21 to 2.88 ± 0.19 for the ranolazine group, compared with 5.68 ± 0.26 falling to 3.31 ± 0.22 in the placebo group. Glyceryl trinitrate consumption decreased similarly.

Summary of evidence on comparative safety

Adverse events were generally mild to moderate in severity with the most commonly treatment related events being constipation (6.3% in ranolazine patients, 1.1% in the placebo groups); dizziness (4.9% and 1.1% respectively); nausea (3.8% and 0.3%); headache (1.8% and 0.7%) and asthenia (1.4% and 0%).

Among the least frequent but medically important serious adverse events reported was syncope, however this was mainly attributable to orthostatic or vasovagal aetiology, with no evidence of association with arrhythmias.

There is evidence that ranolazine can prolong the QT interval in a dose-dependent manner and the Summary of Product Characteristics advises that caution should be exerted in those patients with a history that might suggest QT prolongation.

Summary of clinical effectiveness issues

Ranolazine has been shown to increase exercise tolerance and reduce the frequency of angina attacks in patients with stable angina pectoris. However the EMA concluded that the benefits of ranolazine could be regarded as modest.²

The submitting company has requested that SMC considers the use of ranolazine only in patients who have persistent angina symptoms, despite maximally tolerated medical treatment, and in whom the up-titration or addition of other agents is contraindicated or not tolerated, due to their effect on heart rate and/or blood pressure, and are ineligible for revascularisation. The company acknowledged in its submission, however, that relatively few patients in the pivotal study would be likely to fall into this category. Ranolazine does offer antianginal efficacy with minimal haemodynamic effects and thus may have benefits in patients who cannot tolerate the initiation or upward titration of currently available antianginal drugs because of their depressive effects on blood pressure and heart rate. A post hoc subgroup analysis in patients with depressed cardiac function and considered to be maximally dosed showed similar results to the whole study population.²

The studies had several limitations. Baseline therapies were not optimised prior to adding ranolazine. The maximum recommended dose of ranolazine is 750mg twice daily. Around a third of the patients in the pivotal study and all patients in the supportive study were treated with an unlicensed dose of 1,000mg twice daily. The pivotal study explicitly excluded those with overt heart failure (NYHA class III or IV) or systolic blood pressure of <100mmHg. Although patients were receiving monotherapy with either a beta-blocker or calcium channel blocker, it is unclear whether they were intolerant of alternative first-line antianginal therapy.¹ The supportive study was very short, (six weeks), and only used ranolazine as add-on to one specific calcium channel blocker and not to the broader range of therapy stated in the marketing authorisation. Its primary end-point included an element of subjectivity by using patient diaries to record and monitor angina episodes.³

Ranolazine should be used with caution in several significant patient groups, for example, the elderly, those with renal impairment (contraindicated in severe renal impairment), those who weigh < 60kg, those with congestive heart failure and those deemed susceptible to QT prolongation. Interaction with other drugs is an issue, especially as many of them are likely to be co-prescribed, for example diltiazem, digoxin and simvastatin. Patients are requested to carry a "Patient Alert Card" while taking ranolazine.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing ranolazine as “third-line” therapy to ‘no additional treatment’ in a sub-population of the licensed indication where patients were treated with beta-blockers or a calcium channel blocker (CCB), required additional medical treatment but were unsuitable for other antianginals.

The evaluation was structured as a Markov model with a one-month cycle and a 5-year time horizon. While the effects may be felt over the patient’s lifetime, the 5-year horizon was selected because the company was concerned that clinical evidence could not be extrapolated over an entire lifetime. A 20-year time horizon was used in a sensitivity analysis.

Costs considered were the medicines prescribed. The only other costs were a GP consultation for an adverse event and an additional GP consultation when treatment was discontinued.

The efficacy analysis concentrated on reduction in angina attacks from the baseline with the effectiveness of each medicine being expressed as a percentage reduction from the assumed baseline rate of 4.5 attacks per week. Data for ranolazine in terms of efficacy, adverse events and withdrawals from treatment were taken from the relevant arm of the main clinical study. In response to SMC concerns about the relevance of the clinical evidence to the proposed sub-population, the company provided data on a sub-group of the CARISA study who had maximum cardiodepression and therefore may have been unsuitable for alternative treatments. While the company acknowledged this did not precisely match the niche they said that it provided evidence the clinical benefits were at least as great as for the overall trial results.

Utility values were taken from two sources. The baseline utility of 0.6 was based on the assumed similarity of patients in the licensed indication with UK patients in a published economic evaluation carried out alongside a clinical study of angina treatment, so this was assumed to correspond to 4.5 angina attacks per week (the baseline rate from the CARISA study). The increased utility resulting from reductions in attacks was based on a commissioned survey carried out in a secondary care population where the attack frequency and utility values were plotted to produce an equation that linked the two values. This suggested that a reduction in angina attacks of 1 per week was associated with a utility gain of about 3.5%.

On this basis the company estimated a cost per quality adjusted life year (QALY) for ranolazine compared to ‘no additional active treatment’ of £17,729, based on an added cost over 5 years of £1,881 and a QALY gain of 0.107.

Sensitivity analysis provided by the company suggested that the main factors of importance are the impact of ranolazine on angina attack frequency and the conversion of any benefits into utility. Threshold analysis showed that if the relative reduction in weekly angina attack rate was varied from a base case value of 0.61 to 0.64, the cost per QALY ratio increased to above £20,000. Similarly, at a utility gain of 3% rather than the base case value of 3.5%, the cost per QALY ratio exceeded £20,000. The submitting company also provided some additional sensitivity analysis showing the impact of varying these two parameters simultaneously. The results indicated that the cost per QALY had the potential to rise steeply when more pessimistic values were assumed for both attack frequency and utilities simultaneously. For example, if the

utility gain was reduced to 2.5% and the relative reduction in attack rate to 0.74, the cost per QALY rose to £72, 346.

The main concerns were as follows:

(i) The clinical evidence does not match the sub-population role proposed – the submitting company provided some additional evidence from a sub-group within their trial of maximum cardio-depression but it was unclear how much weight to attach to this. SMC clinical experts were asked to comment on how the use of these data and responses were mixed in terms of how useful the information was in support of the proposed sub-population.

(ii) As quality of life was not measured in the trial, the submitting company used information from a survey to assess likely changes in utility from reductions in angina attacks. Sensitivity analysis indicated that the results were sensitive to the utility values used and there were some limitations in the way the quality of life scores were derived. For example, it has been assumed cross-sectional utility data reflect what happens to an individual over time.

Given these limitations, the economic case has not been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

In July 2011 the National Institute for Health and Clinical Excellence (NICE) published Clinical Guideline 126, Stable angina, which includes ranolazine as an option in patients with uncontrolled symptoms who cannot tolerate beta blockers and/or calcium channel blockers or where these drugs are contraindicated.

In February 2007 the Scottish Intercollegiate Guidelines Network (SIGN) Guideline 96: Management of stable angina was published. The guideline recommends that beta-blockers should be used first line to treat the symptoms of stable chronic angina and that calcium channel blockers, long-acting nitrates or nicorandil should be used to treat patients who are intolerant of beta-blockers. In terms of combination therapy, it is recommended that if a beta-blocker alone is not adequately controlling anginal symptoms then a calcium channel blocker should be added. Other suggested additions to monotherapy are isosorbide mononitrate and nicorandil. No three drug combinations are recommended and if patients are not controlled with maximal therapy of two drugs they should be considered for referral to a cardiologist.

Additional information: comparators

Drugs which are likely to be added to either a beta-blocker or calcium channel blocker have been included. This corresponds to the licensed indication.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Ranolazine	375mg to 750mg twice daily, orally	594*
Ivabradine	5mg to 7.5mg twice daily, orally	522*
Nicorandil	10mg to 30mg twice daily, orally	89 to 276

Calcium channel blockers

Diltiazem (longer acting formulations)	90mg twice daily to 360mg once daily, orally	69 to 180
Verapamil MR	240mg once or twice daily, orally	81 to 162
Nifedipine MR	10mg twice daily to 90 mg once daily, orally	26 to 159
Nicardipine	20mg three times daily to 30mg four times daily, orally	85 to 136
Diltiazem (standard formulations)	60mg to 120mg three times daily, orally	39 to 107
Felodipine	5mg to 10mg once daily, orally	50 to 63
Verapamil	80mg to 120mg three times daily, orally	25 to 62
Amlodipine	5mg to 10mg once daily, orally	14 to 16

Nitrates

Isosorbide dinitrate	30mg to 120mg daily, in divided doses, orally	238 to 524
Isosorbide dinitrate MR	20mg to 40mg twice daily, orally	34 to 83
Isosorbide mononitrate MR	25mg to 120mg once daily, orally	77 to 103
Isosorbide mononitrate	20mg to 120mg in divided doses, daily, orally	15 to 29

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 21.09.11 *Costs same across dose range

Additional information: budget impact

The submitting company estimated the population eligible for treatment in line with the positioning proposed to be around 2,700 patients. Based on an estimated uptake of 10% in year 1 and 50% in year 5, the impact on the medicines budget was estimated at £119k in year 1 and £619k in year 5. As no medicines would be displaced this also represents the net impact.

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

1.) Chaitman BR, Pepine CJ, Parker JO et al. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. JAMA 2004;291:309-316.

2.) The European Medicines Agency (EMA) European Public Assessment Report. Ranolazine (Latixa®). EMEA H-C-805. <http://www.ema.europa.eu>

3.) Stone PH, Gratsiansky NA, Blokhin A et al. Antianginal efficacy of ranolazine when added to treatment with amlodipine: the ERICA (Efficacy of Ranolazine in Chronic Angina) trial. J Am Coll Cardiol 2006;48: 566-575.

This assessment is based on data submitted by the applicant company up to and including 14 November 2011.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.