Final Appraisal Report

Ranolazine (Ranexa®) as add-on therapy for symptomatic treatment of stable angina pectoris

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Advice No: 1909 – December 2009

Recommendation of AWMSG

Ranolazine (Ranexa®) is not recommended for use within NHS Wales for the treatment of stable angina pectoris. The case for the cost effectiveness of ranolazine (Ranexa®) has not been proven.

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

This report should be cited as:
1.0 RECOMMENDATION OF AWMSG:

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Wednesday 16th December 2009

The recommendation of AWMSG is:

Ranolazine (Ranexa®) is not recommended for use within NHS Wales for the treatment of stable angina pectoris. The case for the cost effectiveness of ranolazine (Ranexa®) has not been proven.
2.0 PRODUCT DETAILS

2.1 Licensed indication
Ranolazine (Ranexa®) is indicated as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line anti-anginal therapies (such as beta-blockers and/or calcium antagonists).\(^1\)

2.2 Dosing
Ranolazine is available as 375mg, 500mg, and 750mg prolonged-release (PR) tablets. The recommended initial dose of ranolazine 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.\(^1\)

2.3 Market authorisation date
9 July 2008\(^2\)

2.4 UK Launch date
2 March 2009\(^2\)

3.0 DECISION CONTEXT

Stable angina is a clinical syndrome characterised by pain or discomfort in the chest, jaw, shoulder, back or arms, typically following an increase in myocardial oxygen demand precipitated by exertion or emotional stress, that is relieved by rest or glyceryl trinitrate (GTN).\(^3,4\) The most common cause of angina is atherosclerotic coronary heart disease (CHD) resulting in narrowing of the arteries and reduced myocardial perfusion. Angina can be graded by severity of symptoms using the Canadian Cardiovascular Society (CCS) class scale of I - IV (see appendix 1, table 1D).\(^3\)

According to data from the Health Survey for England (2006) (English data only), the prevalence of angina in men and women aged 55 to 64 years is 8.0% and 3.2% respectively, increasing with age to 14.2% and 8.3% respectively, for the age group 65 to 74 years.\(^5\) Combined data suggest that 4.8% of men and 3.3% of women have or have had angina.\(^6\) The Framingham Heart Study found that for men and women with an initial presentation of stable angina the two year incidence rates of non-fatal myocardial infarction (MI) and CHD death were 14.3% and 5.5% in men and 6.2% and 3.8% in women.\(^6\) Refractory angina develops in 5% to 10% of all patients with angina.\(^6\)

Patients with angina due to CHD will receive treatment to prevent cardiovascular events including a lipid lowering agent (statin), an antiplatelet (typically low dose aspirin) and possibly an angiotensin converting enzyme (ACE) inhibitor. To treat the symptoms of angina beta-blockers are usually prescribed first-line. Where beta-blockers are not tolerated, or are ineffective, a calcium channel blocker, long-acting nitrate or nicorandil may be used as monotherapy.\(^3,4\) Alternatively, ivabradine is licensed for use in patients who are intolerant or have a contraindication to receiving a beta-blocker. For patients who fail to respond to maximised monotherapy then a combination of two agents should be tried (commonly a beta-blocker and a calcium channel blocker).\(^3,4\) Scottish Intercollegiate Guidelines Network (SIGN) recommend in their 2007 management of stable angina guidelines (96) that patients who remain symptomatic on two maximised agents should be referred to a cardiologist.\(^3\) Further options include triple therapy and assessment for suitability for revascularisation.\(^4\) Acute attacks are managed with sublingual GTN tablets or spray and may be used before performing activities that are known to bring on angina. National Institute for
Health and Clinical Excellence (NICE) are producing a clinical guideline on the management of stable angina which is due to be published in July 2011.\(^7\)

Ranolazine is a novel agent that does not appear to significantly reduce heart rate or blood pressure and therefore may be used in combination with currently available anti-anginal therapies. Its mechanism of action involves selective inhibition of the late sodium current and is expected to decrease sodium entry into ischaemic myocardial cells, reducing calcium uptake indirectly via the sodium/calcium exchanger to preserve ionic homeostasis and reverse ischaemia-induced contractile dysfunction\(^8\). The company state that the evidence presented in their submission supports the use of ranolazine as add-on therapy for patients with chronic stable angina who are inadequately controlled with, or intolerant to, currently available treatments within Wales; the company indicate a position in therapy for which there is currently no other alternative\(^2\).

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness
The company submission focussed on three randomised placebo-controlled, phase III trials. All trials considered ranolazine as add-on therapy to conventional anti-anginal therapy. Only one of these trials; the Combination Assessment of Ranolazine In Stable Angina [CARISA] study; included patients who received a dose of ranolazine within the licensed therapeutic range. Two trials (Efficacy of Ranolazine In Chronic Angina [ERICA] study and the CARISA study) were conducted specifically in stable angina patients. The third (Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-elevation acute coronary syndromes [MERLIN-TIMI-36]) study was in patients with acute coronary syndromes, half of whom had a history of stable angina. A significant number of patients were on a high dose of 1000mg twice daily. Ranolazine demonstrated statistically significant improvements in exercise duration and angina frequency compared with placebo in patients with stable angina. Clinical improvements were modest compared to placebo. No data on mortality are available. Unlike other anti-anginal medicines, ranolazine does not significantly affect blood pressure or heart rate and therefore may be used in combination with other therapies, particularly where the patient is unable to tolerate further dose increases of their conventional anti-anginal therapies. Ranolazine has a narrow therapeutic window with regard to safety and tolerability. Dose reductions are necessary for the elderly, low weight patients, patients with renal or hepatic impairment or congestive heart failure. Drug-interactions can be significant. These factors may significantly limit the population of patients eligible for treatment.

4.2 Review of the evidence on cost-effectiveness
A cost utility analysis has been conducted of ranolazine add-on therapy compared with no add-on therapy in patients who are inadequately controlled or are intolerant to first-line anti-anginal therapies. The key efficacy data in the model relate to the reduction in angina frequency with ranolazine compared with no add-on therapy, derived from the CARISA study. The incremental cost per quality-adjusted life year (QALY) gained with ranolazine add-on therapy is estimated to be £16,083. However, this should be interpreted in the context of a range of limitations with the model and supporting evidence.

The model would appear to be a very simplistic representation of the treatment pathway for the modelled population. Circumstances in which the no add-on arm of the model could be appropriate would appear limited to those patients in whom no currently available anti-anginal agent can be tolerated at a dose sufficient to control
symptoms and in whom revascularisation is not an option. However, the populations of the trials used to provide efficacy data for the model, and the doses of ranolazine used in those trials, are not the same as the modelled population and treatment.

5.0 LIMITATIONS OF DECISION CONTEXT

- There is limited data on the use of ranolazine in patients on maximised beta-blocker or calcium channel blocker monotherapy (excluding amlodipine).
- There is a lack of data on the efficacy of ranolazine in addition to maximised (but failing) combination anti-anginal therapies.
- No studies have specifically assessed the efficacy of ranolazine in patients who are intolerant to other anti-anginal therapies.
- Only one study provided in the main submission assessed ranolazine within the licensed dosage range however only one third of these patients were receiving individualised maximal tolerated doses of other anti-anginal therapies.
- No information was provided by the company on the comparative efficacy of ranolazine to other anti-anginal agents.
- The majority of patients included within the trials were male Caucasians; the evidence of efficacy of ranolazine in other patient populations is limited.
- The economic model compares ranolazine against no active comparator or intervention. Circumstances where no comparator would be appropriate would appear limited to those patients in whom no currently available anti-anginal agent can be tolerated at a dose sufficient to control symptoms and in whom revascularisation is not an option. No economic evidence is presented in support of ranolazine in patients who can tolerate dose maximised first-line therapies but who do not achieve adequate symptom control.
- There are no trial data from the use of ranolazine specifically in the licensed patient population or in the population that appears to have been modelled for the economic analysis.

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

Four randomised, placebo-controlled trials are included in the company submission; all using the prolonged-release formulation of ranolazine. Study 3031; ‘Monotherapy Assessment of Ranolazine in Stable Angina’ (MARISA), was a four week dose-finding trial evaluating the use of ranolazine as monotherapy. Patients were randomised to ranolazine (500mg, 1000mg or 1500mg twice daily) or placebo for one week with a cross-over design. The primary endpoint of total exercise treadmill test duration was significantly increased for all treatment groups compared to placebo (23.8, 33.9 and 45.9 seconds, respectively; p ≤0.003). As this study is not in line with the current licensed indication for ranolazine it is not discussed further in the clinical efficacy section of this report. Due to increased adverse effects (blurred vision, diplopia, vasovagal syncope, somnolence and lethargy) and withdrawal rates in the 1500mg twice daily group this dose was not used in later trials. CARISA is the pivotal study and the only study to include a dose of ranolazine within the licensed range. ERICA is the only trial designed to assess stable angina patients on maximised anti-anginal therapy (amlodipine) but used a dose of ranolazine above the maximum licensed range. MERLIN-TIMI-36 was not specifically designed to address the use or ranolazine in stable angina and again used doses above the maximum licensed range. Due to concerns raised by the Committee for Medicinal Products for Human Use (CHMP) as a result of the narrow therapeutic window of ranolazine, and as comparable efficacy was demonstrated for the 750mg and 1000mg dose regimens in
the pivotal trial, ranolazine was licensed at a maximum dose of 750mg twice daily\(^9\). Overall the clinical efficacy data presented indicates that ranolazine provides a statistically significant, albeit modest clinical benefit, on exercise duration and reduction in frequency of angina attacks compared to placebo (refer also to appendix 1, tables 1A-C).

6.1 Clinical efficacy

6.1.1 CARISA (Combination Assessment of Ranolazine In Stable Angina)\(^10\)
CARISA was the pivotal study for the license application. Patients (n=823) were randomised to ranolazine 750mg, 1000mg twice daily or placebo twice daily as add-on therapy to a chosen baseline regimen of commonly prescribed anti-anginals: atenolol 50mg once daily, diltiazem prolonged-release 180mg once daily or amlodipine 5mg once daily. The aim of the 12 week study was to determine whether ranolazine improves total exercise duration. The primary endpoint was mean change from baseline in exercise treadmill time 12 hours post ranolazine dose (trough levels) using the last observation carried forward (LOCF) on a modified intention-to-treat (mITT) basis. For the licensed 750mg dose, the mean difference from baseline was 115.4 seconds, which was 23.7 seconds longer than the mean change for placebo (p=0.03; significant). Ranolazine 750mg also reduced the mean number of angina attacks by one per week compared with placebo (2.5 versus 3.3, respectively; p=0.006) and similarly reduced the need for use of GTN. Further results are presented in appendix 1, table 1A. Results were comparable for the 1000mg dose.

6.1.1.1 Points to note
- Due to concern raised by the CHMP, as the base-line treatments were not optimised at maximally tolerated doses, the company submitted a post-hoc subgroup analysis to the European Medicines Evaluation Agency (EMEA) for 249 patients (including 79 on placebo, 88 on ranolazine 750mg) who were considered to be ‘maximally dosed’. Treatment difference for ranolazine 750mg was slightly higher when compared to the whole group (difference from placebo 34.2 seconds; p=0.08 [NS]); results were similar for the 1000mg dose\(^9\).

6.1.2 ERICA (Efficacy of Ranolazine In Chronic Angina)\(^11\)
ERICA compared ranolazine 1000mg twice daily with placebo twice daily in 565 patients with stable angina who despite receiving a maximum dose of amlodipine (10mg once daily) were experiencing three or more angina attacks per week for over three months. Around 46% of patients were also receiving a long acting nitrate (dose was not specified)\(^2\). The primary endpoint of the study was the average weekly rate of angina attacks. Patients receiving ranolazine had a significantly lower rate of angina episodes compared with placebo (trimmed mean 2.88 versus 3.31, respectively; p=0.028). Interestingly, for those patients receiving a long acting nitrate in addition to amlodipine, there was no significant difference between ranolazine and placebo in terms of weekly rate of anginal attacks (3.26 versus 3.70; p=0.15), which could suggest that ranolazine provided little additional benefit in terms of frequency of angina attacks for these sub-set of patients\(^2\). Further results are presented in appendix 1, table 1C.

6.1.2.1 Points to note
- This study was relatively short (six weeks) and the ranolazine dose used in the trial was above the maximum licensed dose; results should therefore be viewed with caution.
- The results may not be applicable to patients taking beta-blockers or calcium channel blockers (other than amlodipine) as patients taking these medicines were prohibited from entering the study.
- Patients were not necessarily receiving optimised treatment for CHD.

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• The mean reduction in attacks with ranolazine compared to placebo was modest (less than two attacks per month).
• The trimmed mean was used (removing the top 2% and bottom 2% of results) to reduce the influence of extreme outliers which could skew the results. This removed the data for patients who reported very frequent attacks, ranging from 47-160 angina attacks per week. No significant difference was found between treatment groups when the conventional mean was used.
• Quality of life was measured using the Seattle Angina Questionnaire (SAQ) (refer to glossary). Change in scores from baseline on the angina frequency dimension were significantly greater in patients receiving ranolazine compared to placebo (22.5 versus 18.5, respectively; p=0.008). None of the other four dimensions were significantly different between treatment groups.
• Patients with more frequent baseline angina episodes (over four per week) seemed to have greater symptom improvement.

6.1.3 MERLIN-TIMI-36 (Metabolic Efficiency with Ranolazine for Less Ischaemia in Non-ST- elevation acute coronary syndromes)\textsuperscript{12-15}
MERLIN-TIMI-36 was designed to evaluate the efficacy and safety of ranolazine for long-term treatment in patients with non-ST elevation acute coronary syndrome (ACS) in combination with standard therapy (refer to appendix 1, table 1B for details). Patients (n=6560) were randomised to receive either placebo or ranolazine intravenous (IV) infusion for up to 96 hours, followed by oral placebo or ranolazine 1000mg twice daily (or reduced dose depending on final infusion rate) for approximately 12 months (mean follow up 348 days). The primary composite endpoint of occurrence of cardiovascular death, MI or recurrent ischaemia did not differ significantly between treatment groups. Though the risk of recurrent ischaemia (defined as worsening angina or ischaemia requiring additional therapy and severe recurrent ischemia, showing electrocardiogram [ECG] changes, leading to hospitalisation or prompting revascularisation) was reduced by ranolazine. Approximately half of the population (n=3565) had a history of stable angina. However, analysis of this sub-group was not mentioned as part of the original study design, results for this sub-group population indicate that ranolazine was associated with reduced need for additional anti-anginal medications, prolonged exercise tolerance and reduced frequency of angina attacks\textsuperscript{14}.

6.1.3.1 Points to note
• The indication and doses used are outside the current license for ranolazine\textsuperscript{1}.
• Worsening angina was the only efficacy outcome that was significantly reduced by ranolazine compared with placebo in the group of patients experiencing recurrent ischemia\textsuperscript{2}.
• In the sub-population of patients with a history of angina ranolazine significantly reduced the primary composite endpoint, recurrent ischemia, severe recurrent ischemia and severe recurrent ischemia prompting revascularisation.
• Health status and Quality of life was assessed using the SAQ, Rose dyspnoea scale, SF-12 and EuroQol-5D. At 12 months follow up in the sub-group of patients with a history of stable angina, the mean effect of ranolazine compared with placebo on SAQ angina frequency scale was 3.43 (95% confidence interval [CI]: 1.81 to 5.05; p<0.001); quality of life scale, treatment satisfaction scale, SF-12, Rose dyspnoea score and EuroQol-5D were also significantly improved with ranolazine (p<0.05). There was no significant difference between treatment groups for the SAQ physical limitation scale\textsuperscript{15}.
6.2 Safety
The most commonly reported adverse events with ranolazine include constipation, nausea, dizziness, vomiting and headache\textsuperscript{1}. Syncope is an infrequent (0.1% -1%) but potentially serious adverse event reported with ranolazine; the majority of cases have been vasovagal or orthostatic in aetiology and not due to ventricular arrhythmias\textsuperscript{1,2,9}.

The QT\textsubscript{c} interval increases by a mean of 2.4 milliseconds with every 1000 nanograms/mL increase in plasma concentration of ranolazine\textsuperscript{9}. Although prolongation of the QT interval was reported with ranolazine in the MERLIN-TIMI-36 trial the incidence of severe ventricular arrhythmias was not increased\textsuperscript{9}. However the Summary of Product Characteristics (SPC) currently advises caution should be observed when treating patients with a history of congenital or a family history of long QT interval, in patients with known acquired QT interval prolongation and in patients treated with drugs affecting the QT\textsubscript{c} interval\textsuperscript{1}.

Ranolazine has a complex pharmacokinetic profile, it is metabolised via CYP3A4 and CYP2D6 to a number of metabolites, one of which may be active\textsuperscript{9}. It displays saturable pharmacokinetics, hence an increase in dose results in more than a proportional increase in plasma concentration. Ranolazine is contraindicated in any patient taking concomitant potent inhibitors of CYP3A4 (e.g. clarithromycin, itraconazole). Careful dose titration and monitoring for adverse effects is required in any patient receiving moderate inhibitors of CYP3A4 (e.g. diltiazem, erythromycin), P-glycoprotein (e.g. verapamil) or who may be poor metabolisers of CYP2D6\textsuperscript{1}. Ranolazine is a potent inhibitor of P-glycoprotein and mild inhibitor of CYP3A4 and CYP2D6\textsuperscript{9}.

Due to the risk of accumulation (and subsequent adverse effects), ranolazine should be avoided in any patient with severe renal impairment or mild to moderate hepatic impairment. Careful dose titration and monitoring for adverse effects is required in patients with mild to moderate renal impairment, mild hepatic impairment, congestive heart failure (NYHA Class III-IV), the elderly and patient’s weighing 60kg or less. In patients with a combination of these factors frequent monitoring is required, dose reduction or drug discontinuation may be necessary\textsuperscript{1}.

All patients should be given the ranolazine package insert leaflet and the Patient Alert Card and instructed to present this to their healthcare professional at each visit. The Patient Alert Card has been introduced as a safety measure to alert patients and healthcare professionals to possible contraindications, dose reduction and precautions and to alert the patient to identify certain specified conditions to their doctor\textsuperscript{9}.

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

7.1 Comparator medications
- Nicorandil
- Ivabradine
- Long-acting nitrates

The company suggest that ranolazine is considered as a treatment option for use in a specific angina population for whom no alternative medicinal therapy is currently available within Wales. For those patients who do not achieve adequate symptom control and have intolerance to further treatment with current standard therapies, there would be no specific comparators. This is in line with guidance on the management of stable angina produced in 2006 by the European Society of Cardiology\textsuperscript{4}. However the
licensed indication for ranolazine is for after failure/intolerance of first line anti-anginal therapies (beta-blockers and/or calcium channel blocker); therefore it is possible that this product may be used earlier and therefore nicorandil, ivabradine and long-acting nitrates could be potential comparators for ranolazine.

7.2 Comparative effectiveness
CARISA is the only study that included a 750mg twice daily dose of ranolazine (maximum recommended dose)\(^\text{10}\). Patients in the MARISA study (ranolazine 500mg twice daily) were on monotherapy and this study is therefore not relevant to the licensed indication. Patients in CARISA received an additional anti-anginal medicine but this did not need to be maximised before starting ranolazine, hence the whole study population did not meet the licensed indication. Post hoc analysis submitted by the company to the EMEA during filing for market authorisation considered a group of patients with angina in whom there would be caution in initiating or increasing the dose of an anti-anginal therapy and may therefore be clinically considered to be on maximised therapy. One-third of patients fell into this category and results were at least comparable to the whole study population\(^9\). This is reassuring but does not consider the population of patients who may be on more than one maximised anti-anginal therapy. ERICA used maximum doses of amlodipine but patients were excluded if they were taking beta-blockers or other calcium channel blockers\(^11\). Long-acting nitrates were allowed in this study but the data for the sub-group of patients taking amlodipine and long-acting nitrates failed to show any additional benefit of ranolazine on anginal frequency compared to placebo.

The current evidence for ranolazine makes it difficult to place its use within existing treatment strategies. The European Society of Cardiology require more data to confirm the place of ranolazine in current therapy but considers its place in therapy is likely to be as add-on therapy or as substitution therapy where conventional medicines are not tolerated\(^4\). There are no clinical trials comparing ranolazine with other second-line anti-anginal therapies. Ranolazine has not been shown to have clinically significant effects on blood pressure or heart rate and may present a clinical advantage to those patients unable to tolerate additional doses of their current anti-anginals or other anti-anginals that do cause these effects. Clinical trial data indicates that ranolazine is not associated with hypoglycaemia and HbA1c levels were reduced in patients receiving ranolazine compared with placebo; the long-term effects of this are unknown and subject to further research\(^2\). In clinical trials with ranolazine around one-fifth of patients had received prior revascularisation procedures\(^9\), however some patients may be suitable or express a preference for revascularisation prior to considering ranolazine.

Ranolazine does not appear to significantly reduce cardiovascular risk but it would appear to have a role in symptomatic treatment. Although ranolazine improves angina frequency and exercise duration the overall difference compared to placebo is clinically modest in the population of patients included within the clinical trials. None of the trials reported the degree of symptom severity according to the Canadian Cardiovascular Angina Classification though patients in the CARISA and ERICA trials reported over three anginal attacks per month\(^10,11\).

Due to its narrow therapeutic window in relation to safety and tolerability, if ranolazine were to be used later in therapy, patients with significant co-morbidities or potentially interacting medicines may be ineligible for treatment.
8.0 REVIEW OF HEALTH ECONOMIC EVIDENCE

8.1 Overview of the key economic issues for AWMSG to consider
The key economic issue to consider is whether the additional benefits offered by ranolazine over the relevant comparator(s) justify the additional costs and if so, whether the total budgetary impact of supporting the use of ranolazine is acceptable (see section 9.0).

8.2 Description and critique of the company’s submission
The company submission describes a cost utility analysis of ranolazine as add-on therapy compared against no add-on therapy in its licensed indication. A Markov model has been developed in which a hypothetical cohort of patients, with characteristics based on the CARISA trial population and who are inadequately controlled or intolerant of first-line anti-anginal therapy, receive ranolazine as add-on therapy or no add-on therapy.

The model would appear to be a very simplistic representation of the treatment pathway for the modelled population. Those who receive no add-on therapy are simply assumed to continue with their first-line treatment until death, even though by definition this is ineffective or intolerable. Those who receive ranolazine in the model may continue on ranolazine until death or may discontinue ranolazine due to adverse effects, in which case they are assumed to continue with their ineffective/intolerable first-line treatment until death. There are viable treatment options available for many patients who are intolerant of, or fail to achieve adequate control on first-line treatments. Circumstances in which no comparator could be appropriate would appear limited to those patients in whom no currently available anti-anginal agent can be tolerated at a dose sufficient to control symptoms and in whom coronary revascularisation is not an option. The model, therefore, appears to relate to a sub-population of the eligible licensed population.

There are several limitations to the economic model. The main efficacy data for the model relates to the frequency of angina attacks based on data from the placebo-controlled CARISA study. This study was conducted in a wider population than the licensed population, used higher initial doses of ranolazine than are recommended in the SPC, and the first-line therapies to which ranolazine or placebo were added were not optimised. The ERICA and MERLIN TIMI-36 trials are used as support for assumptions of efficacy in patients taking optimised first-line therapies and for sustained efficacy; however, these trials were also conducted using unlicensed ranolazine doses in patients that are unrepresentative of the modelled patient cohort. It should be noted that none of the clinical trials of ranolazine have been conducted in the modelled population, and there is no evidence presented that the addition of ranolazine leads to reduced doses of first-line anti-anginal therapies to a level where adequate control is achieved and therapy is appreciably more tolerated. The model outputs need careful interpretation in the context of these limitations.

8.3 Population
The modelled population is intended to reflect the licensed indication for ranolazine. The baseline characteristics of the hypothetical cohort are based on those of patients in the CARISA study (see Table 1A, Appendix 1), which the CHMP considered to be sufficiently representative of a broad European population with stable angina. The company submission includes data from a survey of 405 patients with angina at Cardiff and Vale NHS Trust, which indicates that this population was on average older by almost 10 years (73.6 years versus 64.0 years), and there were twice as many females (47.9% versus 23.5%), than the CARISA population (Data on File).
8.4 Perspective and time horizon
The analysis is conducted from the perspective of NHS Wales.

The company submission states that a lifetime horizon has been adopted, which is assumed to be 20 years\(^2\). The Markov cycle is one year, which the company considers to be appropriate to accommodate annual death rates, etc\(^2\). However, it is worth noting that the CARISA study, from which efficacy data have been derived, randomised patients to receive ranolazine or placebo for 12 weeks of treatment\(^9\).

8.5 Comparator
Ranolazine as add-on therapy to first-line therapy is effectively compared against no add-on treatment in the model\(^2\). The 2007 SIGN clinical guideline on stable angina\(^3\) recommends beta-blockers as the first-line therapy for symptoms. When adequate symptom control is not achieved with beta-blockers, an appropriate calcium channel blocker should be added. In those patients who are intolerant of beta-blockers, it recommends treatment with either rate-limiting calcium channel blockers, long-acting nitrates, or nicorandil\(^5\). Another available option is ivabradine\(^3,16\), although the SIGN guideline notes that, while symptomatic benefit has been demonstrated for this drug, long-term protection against cardiovascular events has yet to be determined\(^3\) (which can also be said of ranolazine). The British National Formulary (BNF) also indicates that long-acting nitrates can be added in to calcium channel blocker therapy\(^16\), and both the BNF and SIGN guidelines indicate that patients should be referred to a specialist if a combination of two drugs at maximum therapeutic doses is ineffective at controlling symptoms\(^5,16\). Revascularisation may be appropriate in such patients\(^16\).

There are, therefore, a range of potential options available to many patients who do not achieve adequate symptom control with first-line anti-anginal therapies\(^4,6\). Circumstances in which no comparator would be appropriate would appear limited to those patients in whom no currently available anti-anginal agent can be tolerated at a dose sufficient to control symptoms and in whom revascularisation is not an option. It should be noted that none of the clinical trials of ranolazine have been conducted in such a patient population, and there is no evidence presented that the addition of ranolazine leads to reduced doses of first-line anti-anginal therapies to a level where adequate control is achieved and therapy is appreciably more tolerable.

The company submission comments that revascularisation is not considered a comparator to ranolazine in the model due to a lack of clinical studies to allow such a comparison to be made\(^2\). This in itself is not a sufficient reason to disregard viable comparators from the model, and the omission of all viable comparators limits the modelled population to being a sub-group of the licensed population.

8.6 Clinical inputs
8.6.1 Efficacy data
8.6.1.1 Frequency of angina attacks
The main efficacy data used in the model relate to the frequency of angina attacks, which are derived from patients in the CARISA study who received ranolazine at a dose of 750mg twice daily\(^10\). This study was conducted in a wider population than the licensed population (e.g. over a fifth of patients had unstable angina), and used higher initial doses of ranolazine (750mg and 1000mg twice daily\(^10\)) than are recommended in the SPC\(^1\) (see sections 2.2 and 6.1). In addition, the first-line therapies to which ranolazine or placebo were added were not optimised\(^9\).
The first-line monotherapies taken by patients in the CARISA study were atenolol 50mg, amlodipine 5mg or diltiazem 180mg\(^\text{10}\), none of which can be considered maximum therapeutic doses\(^\text{16}\). In response to concerns raised by CHMP that this study used sub-optimal first-line therapies, the company conducted a sub group analysis in those patients (around a third of the trial population) in whom these doses were considered by the company to be “maximal” doses (i.e. those patients in whom the company considered extreme caution would be needed before increasing the dose of, or initiating, anti-anginal therapies that have significant haemodynamic effects or have an effect on AV node conduction). This post hoc analysis indicated that the addition of ranolazine had similar effects in these patients as in the whole study population in terms of exercise parameters measured on the treadmill and in terms of ECG parameters\(^\text{9}\). Nonetheless, there are no data presented in relation to angina attack frequency for this subgroup of patients, and angina frequencies used in the model are based on the entire placebo and the entire ranolazine 750mg groups\(^\text{2}\). The company submission notes that data from the ERICA study, in which first-line therapy was with amlodipine at the maximum recommended dose of 10mg and 45% of patients also received long acting nitrates\(^\text{11}\), supports the reduction in angina attack frequency observed in the CARISA study. However, the ERICA study compared placebo against addition of ranolazine at a dose of 1000mg twice daily, which is higher than the maximum dose recommended in the SPC\(^\text{1}\) (see section 6.1).

The reduction in frequency of angina attacks observed at 12 weeks against placebo in the CARISA trial is assumed to remain constant throughout ranolazine treatment\(^\text{2}\). The basis of this assumption is the MERLIN-TIMI 36 trial. This was conducted in a different patient population to the CARISA study\(^\text{10}\), who were using a wider range of cardiovascular therapies and received a higher dose of ranolazine than is recommended\(^\text{1}\). Patients in MERLIN-TIMI 36 had non-ST segment elevation myocardial infarction/unstable angina and ranolazine was initiated IV followed by 1,000mg orally twice-daily within 48 hours of an ischaemic event. In this study, the addition of ranolazine treatment failed to reduce the incidence of the primary composite endpoint of cardiovascular death, myocardial infarction and recurrent ischaemia in all patients, but did reduce the overall incidence of recurrent ischaemia alone compared with placebo over a median of 348 days of treatment\(^\text{12}\). Specifically in patients with a history of angina, the frequency of angina attacks was reduced as measured by one domain of a disease specific-health related quality of life instrument\(^\text{15}\).

There would appear to be a degree of uncertainty in the extent to which these data reflect the proposed use of ranolazine in patients with stable angina in clinical practice.

8.6.1.2 Revascularisation and hospitalisation
Although the model does not compare the addition of ranolazine against revascularisation, the model does permit patients to experience revascularisation. Data on revascularisations are reportedly derived from the MERLIN-TIMI 36 trial\(^\text{14}\). The incidence of revascularisations in patients with a prior history of angina in this trial is reported in the company submission to be reduced with ranolazine compared with placebo\(^\text{2}\), although these are not verified as the cited reference appears to provide data on revascularisations only as part of a composite of improved severe recurrent ischaemia, defined as ischemia associated with new electrocardiographic changes or leading to hospital stay or revascularisation\(^\text{14}\).

The model does not appear to account for hospitalisations that do not lead to revascularisation.
8.6.1.3 Mortality
It is assumed in the model that there is no difference in survival between treatment arms. However, Welsh Government statistical data are used to determine death due to any cause in the model\(^2\). The QALYs that are estimated by the model are driven by the frequency of angina attacks and the assumed impact of these upon health-related quality of life (see 8.6.3).

8.6.2 Adverse events
Adverse event and treatment discontinuation data are reportedly derived from the CARISA study\(^{10}\). The incidence of drop-outs from the study due to adverse effects is provided in the cited reference, but the incidence of any treatment-related adverse event, that is used to establish the incidence of adverse events that do not lead to discontinuation, are not verifiable from the data provided. These are used to determine the additional discontinuations due to adverse effects with ranolazine treatment. In the model, the probabilities of modelled outcomes in patients who discontinue treatment with ranolazine are assumed to revert to the same as those patients who receive no add-on treatment.

8.6.3 Utility weights
The frequency of angina attacks drives health-related quality of life (HRQoL) in the model. Although the MERLIN-TIMI 36 trial assessed HRQoL, the company notes that this trial used a composite endpoint from which it is not possible to discern the impact of angina frequency alone\(^2\). In the absence of trial-derived data, a study was conducted to establish the impact of angina attack frequency upon HRQoL, using data from a survey conducted among patients in Cardiff and Vale NHS Trust in 2008. Based on data from 405 responders to the survey, who completed the EQ-5D and the SAQ, a regression model was constructed that indicated that the number of weekly angina attacks was the most predictive variable of health utility in this patient group. The correlation between the number of angina episodes per week and utility score has been used to determine the utility difference between ranolazine and no-add on treatment, based on the reduction in the number of angina attacks observed with ranolazine treatment in the CARISA study\(^2\).

Disutility due to adverse events has simply been assumed to be represented by a 0.01 decrement in utility for the duration of the cycle in which it occurs, which the company considers favours the comparator due to the cycle length employed (one year) and the fact that adverse events could be transient. This decrement has been tested in sensitivity analysis\(^2\).

Revascularisation is assumed to result in an improvement in utility of 0.18 over the pre-vascularisation utility value that persists for the remainder of the patient’s lifetime\(^2\). This increment is referenced to a study that compared outcomes and the cost effectiveness of coronary artery by-pass surgery and stenting in patients with multivessel disease\(^{17}\).

8.7 Healthcare resource utilisation and cost
8.7.1 Drug costs
The costs of first-line anti-anginal therapies in the model is based on the average weighted use of beta-blocker (atenolol 50mg; 43.9%) and calcium channel blockers (diltiazem 180mg and amlodipine 5mg once daily; 56.1% assumed to be split evenly) used in the CARISA study. However, the costs for atenolol seem to be based on those for 100mg daily and amlodipine 5-10mg daily\(^2\) rather than 5mg daily as in the CARISA study\(^{10}\). The doses of first-line therapies in the CARISA were criticised as being sub-optimal by the CHMP\(^9\), and so the use of the costs of these higher doses may be more
appropriate to those used in practice. However, this does not negate the uncertainty that exists in the outcomes with the use of sub-optimal doses.

The costs of ranolazine are as per the current list price\(^2\).

8.7.2 Adverse event costs
The CHMP notes that the adverse events seen with the use of ranolazine are dose-related and usually of moderate intensity\(^9\). At targeted therapeutic concentrations, adverse events were relatively benign and the frequency of serious adverse events was low. The most common are dizziness, nausea, vomiting and angina pectoris\(^9\). The model does not consider these adverse events individually. Resource use and costs due to adverse effects are simply assumed to be composed only of a GP visit\(^2\). There are no other costs considered for those who discontinue treatment due to adverse events, or those who continue after experiencing adverse events.

8.7.3 Other resource use and costs
The costs and resource use associated with discontinuation of ranolazine are simply assumed to be those associated with one GP visit. The costs of revascularisation are reportedly based on those estimated in a study of the costs of angina in the UK in 2000\(^18\), that have been inflated to 2007/8 prices. The costs actually used appear to relate to the costs of repeat coronary artery bypass graft (CABG) procedure (£5,900 in year 2000 prices\(^18\)). In the CARISA study, 13.4% of placebo recipients had previous history of CABG, and 19.7% percutaneous coronary intervention, compared with 19% and 16.5% of ranolazine recipients, respectively\(^10\).

8.8 Discounting
Costs and outcomes have been discounted at 3.5% per annum, which is the preferred discount rate. Rates of 0% and 6% have been explored in sensitivity analyses\(^2\).

8.9 Results
8.9.1 Base-case analysis
Compared with no-add on therapy, the incremental cost per QALY gained for the addition of ranolazine to first-line anti-anginal therapy is estimated to be £16,083. This is based on a gain of 0.33 QALYs (5.56 versus 5.23) and additional costs of £5,309.74 (£7,981.17 versus £2,671.44)\(^2\).

8.9.2 Sensitivity analysis
8.9.2.1 Deterministic sensitivity analyses
All parameter values were varied within the range +/- 10%. This demonstrated that the frequency of angina attacks and the utility decrement associated with each angina attack were the most influential parameters on the model outputs.

The discount rate (range 0% to 6%) and modelled time horizon (1 to 20 years) had little impact on the base case estimated incremental cost per QALY gained\(^2\).

8.9.2.2 Probabilistic sensitivity analysis
Multiple sampling from distributions fitted to parameters were performed. The mean incremental cost per QALY gained is estimated to be £22,925 (95% CI: £15,167 to £30,638), and the median £16,121/QALY gained. The probabilities of the addition of ranolazine to first-line therapies being cost effective at willingness to pay thresholds of £20,000/QALY and £30,000/QALY are 63.29% and 81.52%, respectively\(^2\).

8.10 Review of published evidence on cost-effectiveness
Standard literature searches did not identify any published evidence on the cost-effectiveness of ranolazine.
9.0 REVIEW OF EVIDENCE ON BUDGET IMPACT

9.1 Description and critique of the company’s submission
The scenario of use in the budget impact analysis appears to relate to patients who are assumed not to be achieving adequate symptom control with their first-line therapies and who would not be able to undergo dose increases of their first-line therapies due to intolerance of adverse effects such as bradycardia and/or hypotension. Estimation of the number of patients who are intolerant to first-line therapies is based on rates of drop-out due to the specific adverse effects of bradycardia and/or hypotension from selected trials of beta-blockers, calcium channel blockers, nicorandil and ivabradine. Based on these, and estimates of the prevalence and incidence of stable angina, the company has produced estimates of the minimum and maximum numbers of eligible patients, and a weighted average of these. However, the approach that has been adopted to estimate overall eligible patient numbers, and hence the estimated budget impact, would appear to be subject to considerable uncertainty. All estimates should be interpreted with caution.

9.2 Perspective and time horizon
The budget impact analysis is conducted from the perspective of NHS Wales and considers a time horizon of five years.

9.3 Data sources
9.3.1 Incident and prevalent cases
The prevalence of stable angina is estimated to be 3.03% in the company submission, based on the range of estimates 2% to 4.05% from NHS Direct Wales and the Health Survey for England. Reportedly based on Office for National Statistics (ONS) population projections for adults in Wales in 2009, this equates to 71,768 patients with angina. These figures are assumed to relate to stable angina.

A study that estimated the costs of angina in the UK in 2000 suggested that 60% of patients with angina take beta-blockers, 50% take calcium channel blockers and 18% take potassium channel activators. It is assumed that these data from almost 10 years ago are still valid. In the CARISA study, used to provide efficacy data for the cost utility analysis, 43.9% of patients were reported to be taking beta-blockers and 56.1% calcium channel blockers. Based on company-obtained market research, it is estimated that 0.51% of patients currently receive ivabradine.

The proportion of these patients who are intolerant to each of these classes of therapies has been estimated by extracting data from trials and other studies of beta-blockers (atenolol and bisoprolol), calcium channel blockers (verapamil, nifedipine, amlodipine), nicorandil and ivabradine in relation to withdrawals/discontinuations due to the adverse effects of low heart rate and/or blood pressure. It is acknowledged within the submission that withdrawals may occur due to other adverse effects, and other adverse effects have been used as a proxy where low heart rate/blood pressure data are not available. However, there would seem to be several sources of uncertainty with this approach.

There are no details presented of the search strategy used to identify appropriate trials to provide these data, and there seems to be no account taken of the extent to which each of these agents are actually used in practice. For example, a trial of verapamil is used to provide an estimate of the proportion of patients who would discontinue verapamil out of the 71,768 patients estimated to have stable angina in Wales in 2009; however, no consideration is given to the extent to which verapamil would be used in practice as a first-line therapy in this patient population. Diltiazem appears not to be considered as a calcium channel blocker for the estimation of the proportion of this
patient group who experience intolerable adverse effects, despite the fact that this was used as one of the first-line therapies in the CARISA trial\textsuperscript{10}, and there are potentially other agents that could be used that are also not considered (e.g. felodipine, metoprolol\textsuperscript{16}). It should also be noted that these data relate only to the estimation of the number of patients who are intolerant of first-line therapies, and not to those patients who are inadequately controlled on first-line therapies.

The company submission then goes on to estimate the maximum and minimum total number of patients from each of the classes of agents considered\textsuperscript{2}, based on the number of patients estimated to be intolerant via the adverse event rate data extracted from the trials of the individual agents above. A weighted average of the maximum and minimum numbers is then presented, such that the number of patients with stable angina in Wales in 2009 who are intolerant of first-line therapies is 1,124\textsuperscript{2}. This figure should be interpreted with caution.

The incidence of angina is estimated to be 0.25\%, reportedly based on British Heart Foundation figures. An annual death rate of 2.64\% over the next five years has been assumed, based on the average of male and female death rates for people aged 18 years and older obtained from ONS data. These data have been combined with the prevalence estimates for stable angina, the estimated proportion of patients receiving beta-blockers, calcium channel blockers, nicorandil and ivabradine, and the estimated proportions of patients intolerant to these drugs as described above. The weighted average number of patients (i.e. weighted average of the minimum and maximum numbers of patients estimated to be intolerant based on the selected trials of first-line therapies) with stable angina who are intolerant of first-line therapies is estimated to be 1,189 in 2010, rising to 1,437 in 2014\textsuperscript{2}. These figures should be interpreted with caution.

9.3.2 Projected rate of adoption and market share
The company submission considers that all patients with stable angina who are intolerant of first-line therapies would be eligible for add-on treatment with ranolazine, and 100\% uptake is considered in the base case analysis\textsuperscript{2}. However, the analysis also considers a range of uptake levels of 10\% to 100\% in 2010\textsuperscript{2}.

9.3.3 Costs and resource use
Although nicorandil and ivabradine are considered in the calculation of the net number of patients eligible for treatment with ranolazine, the costs of first-line therapies considered in the analysis relate only to beta-blockers and calcium channel blockers. The stated reason for this is that these are the agents considered in the CARISA study upon which the economic model is based\textsuperscript{2}. The annual costs of beta-blockers, calcium channel blockers and ranolazine are calculated as in the economic model (see section 8.7.1). The proportion of patients using beta-blockers and calcium channel blockers (described as “usual care”) is assumed to be the same as in the CARISA study (43.9\% and 56.1\%, respectively). The resultant annual weighted average drug costs per patient of usual care plus ranolazine is estimated to be £622.59, and £26.66 for usual care without ranolazine add-on therapy\textsuperscript{2}.

The costs associated with revascularisation, as in the economic model, have also been incorporated into the budget impact analysis. However, the budget impact analysis assumes there are no drop-outs from ranolazine treatment due to adverse events. It is reported that the economic model has been adapted with these assumptions and has been run over the 20-year time horizon, as in the cost utility analysis. From this, an average annual cost per patient has been estimated. This results in an average annual cost per patient for ranolazine plus usual care of £575, compared with £173 for usual care alone. This incorporates savings associated with a modelled reduction in
revascularisation procedures with ranolazine treatment. It should be noted that the modelled 20 year costs, from which the average annual costs have been derived, were discounted at 3.5%.

9.4 Results

Table 1. Company-estimated budget impact scenarios of the addition of ranolazine to usual care with beta-blockers or calcium channel blockers

<table>
<thead>
<tr>
<th>Scenario based on minimum net number of patients</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>£406,023</td>
<td>£413,508</td>
<td>£419,681</td>
<td>£424,630</td>
<td>£428,443</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Scenario based on maximum net number of patients</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>£2,552,854</td>
<td>£2,599,911</td>
<td>£2,638,723</td>
<td>£2,669,835</td>
<td>£2,693,813</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Scenario based on weighted average net number of patients</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>£477,030</td>
<td>£485,568</td>
<td>£492,586</td>
<td>£498,186</td>
<td>£502,472</td>
<td></td>
</tr>
</tbody>
</table>

These scenarios of budget impact should be interpreted with caution due to the range of assumptions employed. They relate to 100% uptake of ranolazine in all eligible patients. In addition, these are reported to be average annual costs based on a 20-year time horizon of analysis. These figures are discounted at 3.5% per annum.

9.5 Sensitivity analysis

The company has provided a further analysis of the budget impact in 2010 based on uptake in the range of 10% to 100%. As would be expected, the weighted average budget impact in 2010 ranges from £47,703 at 10% uptake, to £477,030 at 100% uptake in 2010. Without some indication of the likely extent of uptake, this analysis would appear to be of limited value.

9.6 Table of comparative unit costs

There is a range of potential options available to patients who do not achieve adequate symptom control with first-line anti-anginal therapies, as described in section 8.5. Table 2 provides example costs of individual agents that may be used in the management of patients before referral to a specialist is warranted. However, it should be noted that these may be used in combination in some patients.
Table 2. Example annual costs of selected anti-anginal therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Example dose</th>
<th>Annual cost £</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta-blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atenolol (non-proprietary)</td>
<td>100mg once daily</td>
<td>11.18</td>
</tr>
<tr>
<td>Bisoprolol (non-proprietary)</td>
<td>10mg once daily</td>
<td>21.06</td>
</tr>
<tr>
<td><strong>Calcium channel blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amlodipine (non-proprietary)</td>
<td>5 – 10mg once daily</td>
<td>14.56 - 16.77</td>
</tr>
<tr>
<td>Felodipine</td>
<td>5 – 10mg once daily</td>
<td>116.09 - 156.13</td>
</tr>
<tr>
<td>Diltiazem (Adizem SR®)</td>
<td>90mg – 180mg twice daily</td>
<td>116.74 - 194.35</td>
</tr>
<tr>
<td><strong>Nitrates (long-acting)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isosorbide mononitrate</td>
<td>60 - 120mg once daily</td>
<td>58.50 - 117</td>
</tr>
<tr>
<td>(Monomil XL®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other anti-anginal agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicorandil (Ikorel®)</td>
<td>10 - 20mg twice daily</td>
<td>99.52 - 189.07</td>
</tr>
<tr>
<td>Ivabradine (Procoralan®)</td>
<td>5 - 7.5mg twice daily</td>
<td>507</td>
</tr>
<tr>
<td>Ranolazine (Ranexa®)</td>
<td>500mg – 750mg twice daily</td>
<td>595.92</td>
</tr>
</tbody>
</table>

This table does not imply therapeutic equivalence of the drugs or doses. Some of these agents may be used in combination (Ranolazine is licensed only for use in combination with first-line anti-anginal agents). See the individual Summaries of Product Characteristics and BNF for recommendations. All costs calculated from BNF list prices.

10.0 ADDITIONAL INFORMATION

10.1 Guidance and audit requirements
- In addition to receiving the patient information leaflet for ranolazine, patients must also be given the ‘Patient Alert Card’ which highlights prescribing issues and safety considerations.
- Although patients with angina would routinely be managed in the primary care setting, ranolazine should be initiated by a cardiologist.

10.2 Related advice
- The Cardiac Disease National Service Framework for Wales. June 2009

10.3 Ongoing studies
Three ongoing trials were included in the company submission (all commercial in confidence), none appear to significantly alter the clinical evidence provided for use in stable angina.

10.4 Patient Organisation Information
A patient organisation submission by HEART UK was provided to members.

10.5 Medical expert/Clinical expert summary
The views of medical / clinical experts were provided to members.
GLOSSARY

Incidence:
The rate at which new cases occur in a population during a specified period\textsuperscript{21}.

Prevalence:
The proportion of a population that are cases at a point in time\textsuperscript{21}.

Seattle Angina Questionnaire (SAQ-UK):
SAQ-UK is a UK-validated measure of health outcome for angina patients. It comprises five dimensions (anginal frequency, physical limitation, anginal stability, disease perception and treatment satisfaction) scored by patients on a scale of 0 to 100. Zero indicates worst and 100 best possible level of health or satisfaction\textsuperscript{22}.
REFERENCES

8. Belardinelli, Shryock, Fraser H. The mechanism of ranolazine action to reduce ischemia-induced diastolic dysfunction. Eur Heart J (supplements) 2006; 8: A10-13
### Table 1A. Prospective study of ranolazine versus placebo as add-on therapy in stable angina pectoris (CARISA) – pivotal trial

<table>
<thead>
<tr>
<th>Ref</th>
<th>Study type</th>
<th>No. patients</th>
<th>Inclusion/exclusion criteria</th>
<th>Baseline characteristics</th>
<th>Treatment regimens</th>
<th>Outcomes (ranolazine 750mg bd versus placebo bd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARISA CVT3033 2,9,10</td>
<td>Phase III, multicentre, double-blind, placebo-controlled parallel group, RCT 12 week trial 118 centres in 15 countries</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Randomised: n=823</td>
<td>Placebo; n=269</td>
<td>Ranolazine 750mg; n=279</td>
<td>Ranolazine 1000mg; n=275</td>
<td>mITT: n=791</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo; n=258</td>
<td>Ranolazine 750mg; n=272</td>
<td>Ranolazine 1000mg; n=261</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Inclusion criteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ≥ 21 years of age</td>
<td>• Mean age 64 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ≥ 3 month history effort angina</td>
<td>• 50% ≥ 65 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• CHD</td>
<td>• 78% male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>• 98% Caucasian</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• NYHA III-IV CHF</td>
<td>• 64% hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• MI/unstable angina/PCI/CABG in last 2 months</td>
<td>• 22% unstable angina</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Condition known to interfere with ECG</td>
<td>• 58% prior MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Medication known to prolong QTc interval</td>
<td>• 29% CHF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Medication known to inhibit/induce CYP3A4</td>
<td>• 18% prior PCI/CABG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Digoxin</td>
<td>• 23% DM</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>• Significant renal/hepatic impairment</td>
<td>• 4.5 average angina attacks/week</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• No additional anti-anginal medicines (except GTN)</td>
<td>• 4 GTN tablets average use/week</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Background:</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>amiodipine 5mg od (n=256) or diltiazem 180mg od (n=213) or atenolol 50mg od (n=354)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and placebo bd versus ranolazine 750mg bd or 1000mg bd*</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Trough ranolazine levels (12 hours post dose)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>418.3 (6.3)</td>
<td>416.4 (6.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranolazine 750mg bd</td>
<td>416.4 (6.2)</td>
<td>416.4 (6.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline:</td>
<td>91.7 (8.3)</td>
<td>115.4 (8.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference from placebo:</td>
<td>-23.7 (10.9); p=0.03 (S)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary endpoint: Time to onset of angina (seconds), mean (SE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>326.7 (6.4)</td>
<td>324.7 (6.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranolazine 750mg bd</td>
<td>324.7 (6.5)</td>
<td>324.7 (6.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline:</td>
<td>114.3 (9.2)</td>
<td>144.0 (8.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference from placebo:</td>
<td>-29.7 (12.1); p=0.01 (S)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary endpoint: Time to ECG ischemia (seconds), mean (SE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>296.9 (8.9)</td>
<td>310.0 (9.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranolazine 750mg bd</td>
<td>310.0 (9.1)</td>
<td>310.0 (9.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline:</td>
<td>125.1 (9.2)</td>
<td>145.1 (9.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference from placebo:</td>
<td>-19.9 (12.2); p=0.10</td>
<td></td>
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<tr>
<td>Peak ranolazine levels (4 hours post dose)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Placebo</td>
<td>296.9 (8.9)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranolazine 750mg bd</td>
<td>310.0 (9.1)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline:</td>
<td>125.1 (9.2)</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Difference from placebo:</td>
<td>-19.9 (12.2); p=0.10</td>
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</table>
## Table 1B. Prospective study of ranolazine versus placebo in non-ST-elevation acute coronary syndromes (NSTE-ACS) (MERLIN-TIMI-36)

<table>
<thead>
<tr>
<th>Ref</th>
<th>Study type</th>
<th>No. patients</th>
<th>Inclusion/exclusion criteria</th>
<th>Baseline characteristics</th>
<th>Treatment regimens</th>
<th>Outcomes (ranolazine versus placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MERLIN-TIMI-36 CVT3036 2,12-15</td>
<td>Phase III multicentre, double-blind, placebo-controlled, parallel group, RCT</td>
<td>N=6,560</td>
<td><strong>Inclusion criteria</strong>&lt;br&gt;• ≥ 18 years of age&lt;br&gt;• Hospitalised with NSTE-ACS defined as chest discomfort occurring at rest, lasting ≥ 10 minutes and consistent with myocardial ischemia&lt;br&gt;• Presence of ischemic symptoms (≥ 5 minute) at rest within 48 hours of enrolment&lt;br&gt;• At least one of following indicators of moderate to high risk: elevated cardiac troponin (above local MI limit) or CK-MB (&gt;ULN), ST depression (horizontal or down-sloping) ≥0.1mV, DM (requiring medication) or TIMI Risk Score for UA/NSTEMI ≥3.</td>
<td><strong>Baseline characteristics</strong>&lt;br&gt;• Median age 64 years&lt;br&gt;• 18% age ≥ 75 years&lt;br&gt;• 65% male&lt;br&gt;• 95% Caucasian&lt;br&gt;• 74% hypertension&lt;br&gt;• 34% prior MI&lt;br&gt;• 17% CHF&lt;br&gt;• 27% prior PCI/CABG&lt;br&gt;• 34% DM</td>
<td>IV infusion of placebo versus ranolazine 200mg IV over 1 hour then 80mg/hour (titrated to tolerability) IV infusion for 12-96 hours. Then 375mg to 1000mg bd oral ranolazine based initially on final infusion rate.</td>
<td><strong>All patients</strong>&lt;br&gt;Placebo (n=3281) Ranolazine (n=3279)&lt;br&gt;&lt;br&gt;<strong>Primary endpoint</strong>&lt;br&gt;Composite of CV death, MI or recurrent ischemia (%)&lt;br&gt;Hazard ratio (95% CI): 0.92 (0.83-1.02); p=0.11 (NS)&lt;br&gt;&lt;br&gt;<strong>Main secondary endpoint</strong>&lt;br&gt;Composite of CV death, MI or severe recurrent ischemia (%)&lt;br&gt;Hazard ratio (95% CI): 0.96 (0.86-1.08); p=0.50 (NS)&lt;br&gt;&lt;br&gt;<strong>Other secondary endpoints</strong>&lt;br&gt;Recurrent ischemia (%)&lt;br&gt;Hazard ratio (95% CI): 0.87 (0.76-0.99); p=0.03 (S)&lt;br&gt;&lt;br&gt;Worsening angina (%)&lt;br&gt;Hazard ratio (95% CI): 0.77 (0.62-0.97); p=0.02 (S)&lt;br&gt;&lt;br&gt;Increase/addition of anti-anginal therapy (%)&lt;br&gt;Hazard ratio (95% CI): 0.77 (0.62-0.97); p=0.02 (S)&lt;br&gt;&lt;br&gt;<strong>Chronic angina sub-group (n=3565 [54%])</strong>&lt;br&gt;<strong>Primary endpoint</strong>&lt;br&gt;(as above [%])&lt;br&gt;Hazard ratio (95% CI): 0.86 (0.75-0.97); p=0.017 (S)&lt;br&gt;&lt;br&gt;<strong>Main secondary endpoint</strong>&lt;br&gt;(as above [%])&lt;br&gt;Hazard ratio (95% CI): 0.89 (0.78-1.03); p=0.12 (NS)&lt;br&gt;&lt;br&gt;<strong>Other secondary endpoints</strong>&lt;br&gt;Recurrent ischemia (%)&lt;br&gt;Hazard ratio (95% CI): 0.78 (0.67-0.91); p=0.002 (S)&lt;br&gt;&lt;br&gt;Worsening angina (%)&lt;br&gt;Hazard ratio (95% CI): 0.77 (0.59-1.00); p=0.048 (S)&lt;br&gt;&lt;br&gt;Increase/addition of anti-anginal therapy (%)&lt;br&gt;Hazard ratio (95% CI): 0.77 (0.64-0.92); p=0.005 (S)</td>
</tr>
</tbody>
</table>

* effect driven by impact of ranolazine on recurrent ischemia

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**Study details**

- **Inclusion criteria**
  - Persistent acute ST-segment elevation ≥0.1mV
  - Successful revascularisation of culprit stenosis
  - Acute pulmonary oedema, sustained systolic BP <90mmHg, cardiogenic shock
  - Abnormalities of ECG known to interfere with monitoring of ischemia
  - Medication known to prolong QTc interval or inhibit CYP3A4
  - Digoxin
  - Significant renal/hepatic impairment

- **Exclusion criteria**
  - Persistent acute ST-segment elevation ≥0.1mV
  - Successful revascularisation of culprit stenosis
  - Acute pulmonary oedema, sustained systolic BP <90mmHg, cardiogenic shock
  - Abnormalities of ECG known to interfere with monitoring of ischemia
  - Medication known to prolong QTc interval or inhibit CYP3A4
  - Digoxin
  - Significant renal/hepatic impairment

- **Medication**
  - Median age 64 years
  - 18% age ≥ 75 years
  - 65% male
  - 95% Caucasian
  - 74% hypertension
  - 34% prior MI
  - 17% CHF
  - 27% prior PCI/CABG
  - 34% DM

- **Follow-up**
  - Median follow-up: 348 days.

- **Treatment regimen**
  - IV infusion of placebo versus ranolazine 200mg IV over 1 hour then 80mg/hour (titrated to tolerability) IV infusion for 12-96 hours. Then 375mg to 1000mg bd oral ranolazine based initially on final infusion rate.

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**Notes**

- **Phase III multicentre, double-blind, placebo-controlled, parallel group, RCT**
- **Patients were followed for up to 24 months**
- **442 sites in 17 countries**
- **Index event:**
  - 47% UA
  - 51% NSTEMI
  - 2% other

---

**Outcomes**

- **Composite of CV death, MI or recurrent ischemia (%)**
  - 753 (23.5) vs 696 (21.8) for placebo vs ranolazine
  - Hazard ratio (95% CI): 0.92 (0.83-1.02); p=0.11 (NS)
- **Composite of CV death, MI or severe recurrent ischemia (%)**
  - 625 (19.2) vs 602 (18.7) for placebo vs ranolazine
  - Hazard ratio (95% CI): 0.96 (0.86-1.08); p=0.50 (NS)
- **Recurrent ischemia (%)**
  - 494 (16.1) vs 430 (13.9) for placebo vs ranolazine
  - Hazard ratio (95% CI): 0.87 (0.76-0.99); p=0.003 (S)
- **Worsening angina (%)**
  - 175 (5.9) vs 135 (4.2) for placebo vs ranolazine
  - Hazard ratio (95% CI): 0.77 (0.62-0.97); p=0.02 (S)
- **Increase/addition of anti-anginal therapy (%)**
  - 391 (13.0%) vs 316 (10.6) for placebo vs ranolazine

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* effect driven by impact of ranolazine on recurrent ischemia
Table 1C. Prospective study of ranolazine versus placebo as add-on therapy to amlodipine (max dose) in stable angina pectoris (ERICA)

<table>
<thead>
<tr>
<th>Ref</th>
<th>Study type</th>
<th>No. patients</th>
<th>Inclusion/exclusion criteria</th>
<th>Baseline characteristics</th>
<th>Treatment regimens</th>
<th>Outcomes (ranolazine 1000mg bd* versus placebo bd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERICA</td>
<td>Phase III, multicentre, double-blind, placebo-controlled, parallel group, RCT</td>
<td>Randomised: n=565</td>
<td>Inclusion criteria • ≥ 18 years of age • ≥ 3 month history effort angina • CHD • ≥ 3 episodes of angina/week</td>
<td>Mean age 62 years • 73% male • 99% Caucasian • 90% hypertension • 36% unstable angina • 80% prior MI • 52% CHF • 11% prior PCI/CABG • 19% DM • 5.6 average angina attacks/week • 4-5 GTN tablets average use/week</td>
<td>Background: Amlodipine 10mg od and placebo bd versus ranolazine 1000mg bd (titrated from 500mg bd)</td>
<td>Primary endpoint: Weekly rate of angina episodes, trimmed mean (SE) Placebo (n=281): 3.31 (0.22) Ranolazine 1000mg bd (n=277): 2.88 (0.19); p=0.028 (S) Secondary endpoint: Weekly rate of GTN consumption, trimmed mean (SE) Placebo (n=281): 2.68 (0.22) Ranolazine 1000mg bd (n=277): 2.03 (0.20); p=0.014 (S)</td>
</tr>
<tr>
<td>CVT3037</td>
<td>Placebo: n=284</td>
<td>Ranolazine: n=281</td>
<td>Exclusion criteria • NYHA IV CHF • MI/ unstable angina in last 2 months • QTc &gt;500ms at study entry • Condition known to interfere with ECG • Medication known to prolong QTc interval • Medication known to inhibit/induce CYP3A4 • Digoxin • Beta-blockers • Calcium channel blockers (other than amlodipine) • Significant renal/hepatic impairment</td>
<td>Back</td>
<td>Background</td>
<td>*Only 1000mg twice daily dose used in this trial, however this is above the maximum licensed dose and therefore results should be viewed with caution.</td>
</tr>
</tbody>
</table>

ACE I= angiotensin converting enzyme inhibitor; bd= twice daily; BP= blood pressure; CABG= coronary artery bypass graft; CHD= coronary heart disease; CHF= congestive heart failure; CI= confidence interval; CK-MB= creatinine kinase muscle/brain; CV= cardiovascular; DM= diabetes mellitus; ECG= electrocardiogram; GLY IIb-IIIa= glycoprotein IIb-IIIa receptor inhibitor; GTN= glyceryl trinitrate; IV= intravenous; MI= myocardial infarction; NS = non-significant; NSTEMI= non-ST elevation myocardial infarction; NSTE-ACS= non-ST elevation acute coronary syndrome; od= once daily; OLE = open label extension; PCI= percutaneous coronary intervention; RCT= randomised controlled trial; S= significant; SE= standard error; TIMI= thrombolysis in myocardial infarction ; UA = unstable angina; ULN= upper limit normal.
### Appendix 1

**Table 1D. Canadian Cardiovascular Society Angina Classification**

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Ordinary activity such as walking or climbing stairs does not precipitate</td>
</tr>
<tr>
<td></td>
<td>angina</td>
</tr>
<tr>
<td>Class II</td>
<td>Angina precipitated by emotion, cold weather or meals and by walking up</td>
</tr>
<tr>
<td></td>
<td>stairs</td>
</tr>
<tr>
<td>Class III</td>
<td>Marked limitations of ordinary physical activity</td>
</tr>
<tr>
<td>Class IV</td>
<td>Inability to carry out any physical activity without discomfort – anginal</td>
</tr>
<tr>
<td></td>
<td>symptoms may be present at rest</td>
</tr>
</tbody>
</table>

Ranolazine (Ranexa®) is not recommended for use within NHS Wales for the treatment of stable angina pectoris.