# AWMSG Secretariat Assessment Report – Advice no. 1710
# Ranolazine (Ranexa®▼) for the treatment of stable angina pectoris

## 1.0 PRODUCT DETAILS

| | |
|---|---|
| **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]. |
| **Dosing** | Ranolazine is available as 375 mg, 500 mg and 750 mg prolonged release tablets. The recommended initial dose of ranolazine is 375 mg twice daily. After two to four weeks, the dose should be titrated to 500 mg twice daily and, according to the patient's response, further titrated to a recommended maximum dose of 750 mg twice daily[1]. |
| **Marketing authorisation date** | 9 July 2008[2]. |
| **UK launch date** | 2 March 2009[2]. |

## 2.0 DECISION CONTEXT

### 2.1 Background

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[3,4]. According to data from the 2006 Health Survey for England, the prevalence of angina in men and women aged 55 to 64 years is 8.0% and 3.2% respectively, increasing to 14.2% and 8.3% respectively for the age group 65 to 74 years[5]. The same survey data estimates that across all age groups 4.8% of men and 3.3% of women have or have had angina[5].

Treatment of stable angina is primarily aimed at symptom control. Beta-blockers are usually prescribed first line; where these 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 combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose or when beta-blockers are contraindicated or not tolerated. For patients who fail to respond to maximised monotherapy, a combination of two agents should be tried (commonly a beta-blocker and a calcium channel blocker)[3,4].

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 ischemic myocardial cells, reducing calcium uptake indirectly via the sodium/calcium exchanger to preserve ionic homeostasis and reverse ischemia-induced contractile dysfunction[6].

### 2.2 Comparators

Ranolazine is indicated as an add-on therapy for stable angina patients not adequately controlled on first line therapy. Therefore any treatment used after or in combination with first line treatment could be considered a potential comparator for ranolazine. This includes:

- Nicorandil
- Ivabradine
- Long-acting nitrates

However, the company suggest that since ranolazine has a different mechanism of action from existing anti-anginal therapies, it may also offer an additional treatment option for patients in whom standard treatments are ineffective or contra-indicated[2].

### 2.3 Guidance and related advice

- European Society of Cardiology. Guidelines on the management of stable angina pectoris (2006)[3].
- Scottish Intercollegiate Guidelines Network. Management of stable angina (clinical guideline 96). February 2007[4].
- The Cardiac Disease National Service Framework for Wales. June 2009[7].
- The National Institute for Health and Clinical Excellence are producing a clinical guideline on the management of stable angina. This is due to be published in July 2011[8].

## 3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFICACY

Four randomised, placebo-controlled trials are included in the company submission, comprising one primary study and three supportive studies.

The supportive study MARISA (Study 3031; Monotherapy Assessment of Ranolazine In Stable Angina) was a four week trial evaluating the use of ranolazine as monotherapy. Patients were randomised to ranolazine (500 mg, 1000 mg or 1500 mg 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[2]. 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.

The supportive study MERLIN-TIMI-36 (Metabolic Efficiency with Ranolazine for Less Ischaemia in Non-ST-elevation acute coronary syndromes) was a clinical outcome study of ranolazine (1000 mg twice daily) in patients with acute coronary syndromes, treated for approximately 12 months. Only 54% of patients had stable angina; in this sub-group ranolazine was associated with reduced need for additional anti-anginal medications, prolonged exercise tolerance and reduced frequency of angina attacks[9]. However, the study was not primarily intended to investigate symptomatic control of angina, and the sub-group analysis performed was not part of the original study design. Given these factors, and the fact that the ranolazine dose is outside of the current licensed range, this study will not be discussed further.

### 3.1 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 750 mg, 1000 mg or placebo twice daily as add-on therapy to a chosen baseline regimen of commonly prescribed anti-anginals: atenolol 50 mg once daily, diltiazem prolonged-release 180 mg once daily or amlodipine 5 mg 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 after dosing (trough levels). For the licensed 750 mg ranolazine dose, the mean difference from baseline was 115.4 seconds, 23.7 seconds longer than the mean change for placebo (p = 0.03). Ranolazine 750 mg 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 reduced the need for use of glyceryl trinitrate. Results were comparable for the 1000 mg dose.

Following the concern raised by the Committee for Medicinal Products for Human Use (CHMP) that the baseline treatments were not optimised at maximally tolerated doses, the company submitted a *post hoc* subgroup analysis for patients who were considered to be maximally dosed. Change in exercise duration from baseline for ranolazine 750 mg was slightly higher for this subgroup when compared to the whole group (difference from placebo: 34.2 seconds) but this difference was not statistically significant. Results were similar for the 1000 mg dose[11].

### 3.2 ERICA (Efficacy of Ranolazine In Chronic Angina)[12]

ERICA compared ranolazine 1000 mg twice daily with placebo in 565 patients with stable angina who were experiencing three or more angina attacks per week for over three months, despite receiving a maximum dose of amlodipine (10 mg once daily). Around 45% 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 during the six week treatment phase. Patients receiving ranolazine had a significantly lower rate of angina episodes compared with placebo (trimmed mean rates 2.88 and 3.31 respectively, p = 0.028). Use of the trimmed mean—removing the top 2% and bottom 2% of results—to reduce the influence of extreme outliers removed the data for patients who reported very frequent attacks (ranging from 47–160 angina attacks per week). It should be noted that when the conventional mean was used no significant difference was found between treatment groups. Furthermore, 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), however it should be noted that this study was not powered for testing treatment effects within subgroups[12]. The benefit of ranolazine in this subgroup therefore remains uncertain.

## 4.0 SUMMARY OF EVIDENCE ON COMPARATIVE SAFETY

Safety data is based primarily on the findings of the long-term study MERLIN-TIMI-36[11].

The most commonly reported adverse events with ranolazine are constipation, nausea, dizziness, vomiting and headache[1]. Syncope is an infrequent (0.1–1%) but potentially serious adverse event reported with ranolazine; the majority of cases are vasovagal or orthostatic in aetiology and not due to ventricular arrhythmias[1,2,11].

The $QT_c$ interval increases by a mean of 2.4 milliseconds with every 1000 nanograms/mL increase in plasma concentration of ranolazine[11]. 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[11]. Nevertheless, the summary of product characteristics (SPC) currently advises caution when treating patients with a family history of long QT interval, in patients with congenital or acquired QT interval prolongation, and in patients treated with drugs affecting the $QT_c$ interval[1].

Ranolazine is metabolised via CYP3A4 and CYP2D6 to a number of metabolites, one of which may be active[11]. It displays saturable pharmacokinetics: an increase in dose results in more than a proportional increase in plasma concentration. Ranolazine is contraindicated in any patient taking concomitant potent CYP3A4 inhibitors. Careful dose titration and monitoring is required in any patients receiving moderate CYP3A4 inhibitors, P-glycoprotein inhibitors, or who are poor CYP2D6 metabolisers[1].

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 (New York Heart Association class III–IV), the elderly, and patients weighing 60 kg or less. In patients with a combination of these factors frequent monitoring is required; dose reduction or drug discontinuation may be necessary[1].

Although the safety profile of ranolazine at 1000 mg doses is acceptable, intolerable adverse events have been observed at doses only two or three times above this[11]. This finding, in combination with the many factors that can result in increased ranolazine exposure, prompted a reduction of the maximum dose to 750 mg from the initially proposed 1000 mg[11].

As an additional safety measure, the company have introduced a patient alert card to be carried by patients treated with ranolazine. This contains information about adverse events as well as the risk of increased drug exposure under certain circumstances[11].

## 5.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

- Unlike other anti-anginal medicines, there is no evidence that ranolazine significantly affects blood pressure or heart rate. This is advantageous, as it allows ranolazine to be used in combination with other therapies, particularly where the patient is unable to tolerate further dose increases of their conventional anti-anginal therapies. The company assert that where patients do not gain symptom relief from standard alternatives, where low cardiac output precludes their use, or where side effects limit patient tolerability, there is a strong case for the use of ranolazine[2].
- No clinical studies of ranolazine versus any potential comparator were included in the company submission.
- Despite the reduction in maximum ranolazine dose from 1000 to 750 mg to increase the safety margin, dose reductions are still required for subgroups at risk of increased exposure (see section 4.0), and drug discontinuation may be necessary. This may limit the population of patients eligible for this treatment.
- Only one study has been carried out using the licensed dose of ranolazine. However, the reasons for this are transparent—withdrawal of the proposed maximum dose of 1000 mg due to safety concerns—and the 750 mg and 1000 mg doses showed comparable efficacy in the pivotal clinical trial[11].
- Clinical data on patients treated with ranolazine whilst also maximised on other anti-anginal therapies is limited to a *post hoc* subgroup analysis in the CARISA trial. However, this analysis did show that ranolazine treatment was at least as effective in this patient group as the overall population.
- Although ranolazine improves angina frequency and exercise duration in the population of patients included within the clinical trials, the overall difference reported compared to placebo is clinically modest. The company have outlined in their submission that the magnitude of benefit seen in CARISA is at least as

great as that seen with other anti-anginals used as an add-in to first-line therapy, both in terms of exercise tolerance and angina frequency[2].

- Both the clinical studies of ranolazine conducted within its licensed indication were short (maximum duration 12 weeks). The only evidence for long-term efficacy comes from a subgroup of patients with angina in the study MERLIN-TIMI-36; this study was not primarily intended to investigate symptomatic control of angina[2].

## 6.0 SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

### 6.1 Cost effectiveness evidence

#### 6.1.1 Context

The company submission[2] describes a cost utility analysis of ranolazine used as routine add-on therapy in patients with stable angina who are inadequately controlled with first line agents (beta-blockers or calcium channel blockers). The comparator in the base case analysis is 'standard care' add-on therapy, which is considered to be composed of beta-blockers, calcium channel blockers and nitrates, as classes of agents, and ivabradine and nicorandil. A simplistic clinical pathway is represented, in which patients in need of add-on therapy to first line treatment receive a second line agent, which is continued until withdrawal of that treatment due to adverse effects or death. Patients who do not withdraw or die while on second line treatment are assumed to continue with dual therapy for the full time-horizon of analysis.

In the absence of direct comparative trial data, unadjusted indirect comparisons have been made of data derived from the CARISA trial of ranolazine and data identified via a systematic review of trials of the comparators. There are assumed to be no differential mortality effects between treatments, and the key efficacy data in the model relate to the reduction in angina frequency with add-on therapy, which drives the quality adjusted life years (QALYs) that are modelled for each treatment. Further details are provided in Table 1A in Appendix 1.

The company submission indicates that the target population for ranolazine is patients with a clinical profile that limits therapeutic choice, or if standard first line treatments have proved ineffective or poorly tolerated. The company asserts that the results of this cost utility analysis can be extrapolated to this population based on *post hoc* sub-group analysis of the pivotal clinical trial CARISA, in which patients deemed to have relative contra-indications to maximising first-line treatment dose achieved a similar response to ranolazine treatment as the remainder of the trial population[2,11].

#### 6.1.2 Results

The results of the base-case analyses as presented in the company submission are displayed in Table 1. The incremental cost per QALY gained for ranolazine versus standard care is estimated to be £12,887, based on additional costs of £1,830 and a gain of 0.142 QALYs over the five year time horizon of analysis. The company reports that the most important driver of the cost difference is the higher acquisition cost of ranolazine versus standard care (£2,251 versus £404), and that the costs of adverse events, withdrawals and referrals offset the additional cost to only a minor extent (£33 for ranolazine versus £54 for standard care). The difference in QALYs is due to a higher proportion of patients modelled to remain on ranolazine treatment (54% versus 38%) and a greater reduction in angina attack frequency (38% versus 29%) compared with standard care over the five year time horizon.

**Table 1. Company-reported cost utility analyses over 5 year time horizon[2].**

| Treatment arm | Mean cost | Mean QALY | Incremental cost | Incremental QALY | Incremental cost/QALY |
|---|---|---|---|---|---|
| Ranolazine | £2,284 | 2.642 | £1,830 | 0.142 | £12,887 |
| Standard care | £454 | 2.500 | - | - | - |
| QALY = quality-adjusted life years | | | | | |

The limited one-way sensitivity analyses presented in the company submission suggest that the model is relatively insensitive to the time horizon of analysis (tested as 20 years), the baseline angina attack frequency (range two to seven per week), drug costs estimated from prescription costs analyses, baseline utility, utility associated with a reduction in attack frequency, and adverse event utility. Sensitivity analyses around relative reductions in angina attack frequency were conducted by varying the mean relative reductions for each individual agent or class within the range of its 95% confidence interval, while holding all other agents/class estimates constant. When varying the relative reduction in angina attack frequency for ranolazine (range 0.50 to 0.66) the incremental cost effectiveness ratio (ICER) ranged from £9,946 to £18,673 per QALY gained. For the beta-blocker class (range in relative reduction of angina attack frequency 0.34 to 0.90), the ICER ranged from £21,279 to £9,581 per QALY gained. Estimation of the probabilities of cost effectiveness at specific willingness to pay thresholds has not been undertaken.

The company has subsequently provided additional analyses of ranolazine compared against the individual agents/classes of agents (unverified data, see Table 1B in Appendix 1). These analyses are based on the same limited data used to derive the base case model and indicate that the ICERs range from ranolazine being dominated by ivabradine (i.e. ranolazine is both more expensive and less effective than ivabradine) to £23,962 per QALY gained for ranolazine compared against beta-blockers. One-way sensitivity analyses indicate the model is sensitive to the assumed relative reductions in angina attack frequency, and the assumed adverse event rates[13].

### 6.1.3 WMP critique of the company's economic evidence

Strengths of the economic evidence include:

- In the absence of direct comparative data for ranolazine and the comparators in the model, a systematic review was conducted to identify relevant comparator trial data.
- The company has made efforts to provide relevant data for the simplistic clinical pathway that is modelled.

Limitations of the economic evidence include:

- The comparator in the base case analysis is standard care, which is considered to be a composite of several classes and individual agents and limits interpretation of the cost-effectiveness of ranolazine relative to individual agents or classes of agents. Supplementary analyses provide a limited indication of the contribution of each of the individual comparators to the overall model outputs (see Table 1B, Appendix 1).
- Baseline patient characteristics and efficacy outcomes with ranolazine are based primarily on the CARISA trial, which was conducted in a wider population than the licensed population and in which first line treatment was not optimised. It is possible that baseline angina attack frequency and potential to benefit from add-on therapy may differ in patients in practice.

- There are no direct comparative data for ranolazine and the comparators, and so indirect comparisons have been conducted using unadjusted data. Such naïve indirect comparisons are subject to significant uncertainty and potential bias.
- Adverse event and treatment withdrawal rates over time are limited for ranolazine and the comparators. It is unclear whether or not the methods employed to model adverse event and withdrawal rates favour ranolazine against the comparators (see Appendix 1).
- The sensitivity analyses as reported in the submission are limited to one-way analyses that do not fully address the uncertainty associated with efficacy estimates derived from unadjusted indirect comparisons. In addition, rates of withdrawal from treatment, which determine time on treatment, have not been subjected to sensitivity analysis. Collectively, there would appear to be significant uncertainty in the modelled outputs.

### 6.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have not identified any published evidence on the cost effectiveness of ranolazine relative to comparators used as routine second line agents. An economic analysis of ranolazine compared against no-add-on therapy over a one-year time horizon in Italy has been published[14], but is of limited relevance to the current analysis and decision problem due to differences in the modelled clinical pathways and the absence of comparators.

## 7.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

### 7.1 Budget impact evidence

#### 7.1.1 Context and Methods

The company's budget impact analysis relates only to the treatment of patients with stable angina who are intolerant of standard second line therapies[2]. In the absence of reported Welsh epidemiological data, published prevalence and incidence data from a 2001–2 survey of Scottish primary care practices[15] have been applied to mid-2008 Welsh population estimates. Incidence is assumed to increase by 2% per year, and patient mortality is derived from a 20-year follow up of Scottish patients[16], which reported near-linear rates. The company estimates that 90% of patients with angina in Wales are currently receiving treatment. Based on a UK audit of 500 patients attending six hospitals[17], 56% of patients use monotherapy, and therefore 44% of treated patients are assumed to receive combination therapy.

Around 31% of patients entering the CARISA study had bradycardia, hypotension or extended PR interval, and the company suggests these patients would be less suitable for treatment with cardiodepressive agents. Based on *post hoc* sub-group analyses, treatment outcomes in these patients were similar to outcomes in the remainder of the CARISA trial population[2,11]. Therefore, the company suggests that 31% of patients that are candidates for combination therapy would have potential intolerance of standard second line therapies. Of these, the company simply assumes that 15% will not be able to achieve adequate dose adjustment of standard treatment options and so may be eligible for ranolazine treatment (equivalent to 1.8% of all angina patients)[2]. The company further assumes that uptake will be 20% in these patients in year one, rising to 100% in year five.

No direct savings are anticipated and, as it is assumed that only patients who are not suitable for treatment with other anti-anginal agents would receive ranolazine, there are no drug costs offset.

### 7.1.2 Results

The company-estimated annual budget impact is summarised in Table 2.

**Table 2. Company estimates of budget impact[2].**

| Year | Net patients | Patients on ranolazine | | Net cost of ranolazine* |
|---|---|---|---|---|
| | n | % | n | £ |
| 2010 | 99,374 | 0.36 | 358 | **£106,670** |
| 2011 | 101,269 | 0.72 | 729 | **£430,552** |
| 2012 | 103,245 | 1.08 | 1,115 | **£766,651** |
| 2013 | 105,301 | 1.44 | 1,516 | **£1,116,158** |
| 2014 | 107,436 | 1.80 | 1,934 | **£1,479,669** |
| *Treatment costs for new patients are assigned mid-year and therefore on average reflect half of the first year costs. | | | | |

### 7.1.3 WMP critique of the company's budget impact estimates

The budget impact estimates are based upon the assumption that only patients who are not candidates for, or are not tolerant of, standard add-on therapy with beta-blockers, calcium channel blockers, nitrates, ivabradine, nicorandil will receive ranolazine. The company acknowledges that there is a lack of data to accurately estimate eligible patient numbers, and consequently the estimates of uptake of ranolazine, and budget impact, must be viewed with caution.

### 7.2 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. Table 3 provides example costs of individual agents that may be used; it should be noted that these agents may be used in combination in some patients.

**Table 3. Example annual costs of selected anti-anginal therapies.**

| **Drug** | **Example dose** | **Annual cost[18]** |
|---|---|---|
| **Beta-blockers** | | |
| Atenolol (non-proprietary) | 100 mg once daily | £11.96 |
| Bisoprolol (non-proprietary) | 10 mg once daily | £16.38 |
| **Calcium channel blockers** | | |
| Amlodipine (non-proprietary) | 5–10 mg once daily | £14.56–£16.38 |
| Felodipine (non-proprietary) | 5–10 mg once daily | £55.90–£75.14 |
| Diltiazem (Adizem SR®) | 90–180 mg twice daily | £112.06–£186.68 |
| **Nitrates (long-acting)** | | |
| Isosorbide mononitrate (Monomil XL®) | 60–120 mg once daily | £56.16–£112.32 |
| **Other anti-anginal agents** | | |
| Nicorandil (Ikorel®) | 10–20 mg twice daily | £99.52–£189.07 |
| Ivabradine (Procoralan®) | 5–7.5 mg twice daily | £507 |
| **Ranolazine (Ranexa®▼)** | **500–750 mg twice daily** | **£595.92** |
| *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[1]). See the individual SPCs and BNF for recommendations. All costs are calculated from BNF list prices[18].* | | |

## 8.0 ADDITIONAL INFORMATION

### 8.1 Shared care arrangements

WMP is of the opinion that ranolazine may be suitable for shared care in accordance with appropriate local guidance. Although patients with angina would routinely be managed in the primary care setting, ranolazine should be initiated by a cardiologist.

---

**This assessment report is based on evidence submitted by A Menarini Pharma UK SRL on 12 July 2010.**

**This report should be cited as:**
**AWMSG Secretariat Assessment Report – Advice no. 1710: ranolazine (Ranexa®▼) November 2010**

## REFERENCES


1 A Menarini Pharma UK SRL. Summary of product characteristics. Ranexa®▼. Mar 2009. Available at: http://www.medicines.org.uk/EMC/medicine/21402/SPC/Ranexa+prolonged-release+tablets. Accessed Aug 2010.

2 A Menarini Pharma UK SRL. Form B: detailed appraisal information (resubmission). Jul 2010.

3 Fox K, Garcia MA, Ardissino D et al. Guidelines on the management of stable angina pectoris. Executive summary: the task force on the management of stable angina pectoris of the European Society of Cardiology. *European Heart Journal* 2006; 27 (11): 1341-81.

4 Scottish Intercollegiate Guidelines Network. Clinical guideline no. 96: management of stable angina. Feb 2007. Available at: http://www.sign.ac.uk/pdf/sign96.pdf.

5 The Information Centre. Health Survey for England 2006 Volume 1: Cardiovascular disease and risk factors in adults. 2008. Available at: http://www.ic.nhs.uk/webfiles/publications/HSE06/HSE%2006%20report%20VOL%201%20v2.pdf.

6 Belardinelli L, Shyrock JC, Fraser H. The mechanism of ranolazine action to reduce ischemia-induced diastolic dysfunction. *European Heart Journal Supplements* 2006; 8: A10-A13.

7 The cardiac disease national service framework for Wales. Jun 2009. Available at: http://howis.wales.nhs.uk/sites3/Documents/338/090706cardiacNSFen%5B1%5D1.pdf.

8 National Institute for Health and Clinical Excellence. Clinical Guideline: management of stable angina. Aug 2010. Available at: http://guidance.nice.org.uk/CG/Wave17/25. Accessed Aug 2010.

9 Wilson SR, Scirica BM, Braunwald E et al. Efficacy of ranolazine in patients with chronic angina observations from the randomized, double-blind, placebo-controlled MERLIN-TIMI (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Segment Elevation Acute Coronary Syndromes) 36 Trial. *Journal of the American College of Cardiology* 2009; 53 (17): 1510-6.

10 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: The Journal Of the American Medical Association* 2004; 291 (3): 309-16.

11 European Medicines Agency. European Public Assessment Report: Latixa. Jul 2008. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000805/WC500045942.pdf.

12 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. *Journal of the American College of Cardiology* 2006; 48 (3): 566-75.

13 A Menarini Pharma UK SRL. Supplementary Cost Effectiveness analyses. Sep 2010.

14 Lucioni C, Mazzi S. Economic evaluation of ranolazine for the treatment of chronic angina in Italy. *PharmacoEconomics - Italian Research Articles* 2009; 11: 141-52.

15 Murphy NF, Simpson CR, MacIntyre K et al. Prevalence, incidence, primary care burden and medical treatment of angina in Scotland: age, sex and socioeconomic disparities: a population-based study. *Heart* 2006; 92 (8): 1047-54.

16 Murphy NF, Stewart S, Hart CL et al. A population study of the long-term consequences of Rose angina: 20-year follow-up of the Renfrew-Paisley study. *Heart* 2006; 92 (12): 1739-46.
17 Elder DH, Pauriah M, Lang CC et al. Is there a Failure to Optimize theRapy in anGina pEcToris (FORGET) study? *QJM: An International Journal of Medicine* 2010; 103 (5): 305-10.
18 British Medical Association, Royal Pharmaceutical Society of Great Britain. *British National Formulary No. 59.* Mar 2010.
19 Koren MJ, Crager MR, Sweeney M. Long-term safety of a novel antianginal agent in patients with severe chronic stable angina: the Ranolazine Open Label Experience (ROLE). *Journal of the American College of Cardiology* 2007; 49 (10): 1027-34.

## Appendix 1. Additional Health Economic Analysis Information

### Table 1A. Health economic analysis detail[2].

| | Base Case Model | Appropriate? |
|---|---|---|
| **Comparator(s)** | Ranolazine is compared against standard care add-on treatment, which is composed of calcium channel blocker, beta-blocker, nitrate, ivabradine or nicorandil as add-on treatment to first line beta-blocker or calcium channel blocker. The proportion of each class of agent in standard care is based on market research data. | The base case analysis covers the comparators requested by WMP, but as a composite of standard care rather than as individual agents or classes.<br><br>Additional analyses have subsequently been provided by the company to compare ranolazine against the individual agents/classes of agents (see Table 1B). |
| **Population** | Patients with symptomatic stable angina requiring add-on treatment to first line beta-blocker (64%) or calcium channel blocker (36%). Baseline angina attack frequency reflects rate in the CARISA trial for patients randomised to receive ranolazine 750 mg twice daily.<br><br>The company submission indicates that the target population for ranolazine is patients with a clinical profile that limits therapeutic choice, or if standard first line treatments have proved ineffective or poorly tolerated. | Modelled population reflects the licensed indication in terms of patients inadequately controlled on first line treatment[1], but is synthesised from several sources. The proportion of patients taking first line beta-blocker or calcium channel blocker therapy is derived from a market research project, which appears to be based on a small sample of UK patients, and differs from the proportions observed in the CARISA trial (approximately 43% beta-blocker and 57% calcium channel blocker)[10]. The proportion of each of the second line comparator agents used by this population is also based on this project. Baseline angina attack frequency on first line treatment is derived from the CARISA trial in the subset of patients randomised to receive ranolazine 750 mg twice daily. However, the CHMP noted that first line treatment in the CARISA trial was not optimised[11], and so baseline angina attack frequency and potential to benefit from add-on therapy may differ in patients in practice. The company asserts that the results of this cost utility analysis can be extrapolated to this population based on *post hoc* sub-group analysis of the CARISA trial, in which patients deemed to have relative contra-indications to maximising first line treatment dose achieved a similar response to ranolazine treatment as the remainder of the trial population[2,11]. |
| **Analysis type** | Cost utility analysis (CUA) conducted using a Markov model. Patients in need of add-on therapy to first line treatment receive a second line agent, which is continued until withdrawal of that treatment due to adverse effects or death. Patients who withdraw from second line treatment are assumed to then receive a nitrate in addition to their first line treatment unless a nitrate was the second line agent, in which case they receive nicorandil. Patients who do not withdraw or die while on second line treatment are assumed to continue with dual therapy for the full time horizon of analysis. | CUA is the preferred analysis type. The model represents a simple clinical pathway in that it assumes that all patients who can tolerate their second line treatment receive continual adequate symptom control on dual therapy, and that no patients progress to triple therapy or other interventions such as PCI/CABG. |
| **Perspective** | Considers direct medical costs only, from the perspective of NHS Wales. | Yes. |

**Table 1A. Health economic analysis detail[2]. Continued.**

| | Base Case Model | Appropriate? |
|---|---|---|
| **Time horizon** | Five year time horizon of analysis in base case model, with 20 year horizon explored in the sensitivity analysis. | The company considers that the available data are not sufficiently robust to extrapolate over a life-time horizon, and so a five year horizon of analysis has been used in the base case. A five year death-rate of 25% is applied, and the implicit assumption is that there is no difference in mortality risk across treatments. |
| **Discount rate** | 3.5% for both costs and outcomes in the base case model. | Yes, but no sensitivity analyses conducted around discount rates. |
| **Efficacy** | The main outcome measure is treatment-specific rates of angina following add-on treatment. Treatment withdrawals for adverse events are considered, but as the modelled clinical pathway is very simplistic, there are no other outcomes considered (for example hospitalisations or revascularisations).<br><br>Angina frequency with ranolazine treatment is based on the 12 week CARISA trial data for patients randomised to receive ranolazine 750 mg twice daily. A systematic review has been conducted to identify trials of the comparators used as add-on treatment to first line agents. Relative reductions in angina frequency with add-on treatment are assumed to remain constant throughout treatment with that agent. | There are several limitations to the source of relative outcomes data. The CARISA trial was conducted in a wider population than the licensed population.. First line treatment was not optimised before addition of ranolazine in the CARISA trial; this is in contrast to several (but not all) of the trials conducted using comparators, which employed higher doses of first line treatments. In addition, there are no direct, head-to-head studies of ranolazine against the comparators. Therefore, indirect comparisons have been made across the data derived from 12 week CARISA data and the comparator trial data identified via the systematic review. Meta-analysis has been undertaken to pool all beta-blockers together and all calcium channel blockers together. Relative reductions in angina attacks with the addition of second line agents have been derived by expressing the weekly angina attack frequency with add-on treatment versus baseline weekly attack frequency, and these have been simply compared across studies. Results from such unadjusted, indirect comparisons are subject to considerable uncertainty and potential bias. This is compounded by the potential for different expressions of angina attack frequency in some studies (for example: from the trial of ivabradine identified in the systematic review, relative reductions in angina attack frequency have been estimated based on the whole trial population, including asymptomatic patients, which would yield lower relative risk reductions than analyses based on symptomatic patients, who may more closely reflect the intended population for ranolazine treatment). Collectively, there would appear to be significant uncertainty in the extent to which these data reflect relative outcomes in clinical practice, and this may not be adequately addressed within the limited one-way sensitivity analyses that have been conducted. |

**Table 1A. Health economic analysis detail[2]. Continued.**

| | Base Case Model | Appropriate? |
|---|---|---|
| **Adverse effects** | Focus on withdrawals and incidence of any other treatment-related adverse events (irrespective of type or severity). Specific adverse events are not considered individually. | Available adverse event data are limited for ranolazine and the comparators. For ranolazine, withdrawal rates due to adverse events in the first three months are based on the 12 week CARISA data, from which an average monthly rate of withdrawal is estimated, and for subsequent months are derived from the ROLE two year open-label follow up study[19]. Rates of adverse events that do not lead to withdrawal of treatment post-three months are unavailable and so are estimated based on the ratio of adverse events to withdrawals observed with ranolazine in the 12 week CARISA trial. It should be noted that the implicit assumption of the approach adopted to estimate short term adverse events for ranolazine is linear rates of withdrawals and adverse events over a 12 week period. There are no data provided to support this, and it is possible that withdrawal rates could be higher in early weeks of treatment compared with later weeks (as was observed in the trial providing adverse event data for nicorandil). For comparators, a meta-analysis has been identified to provide rates of withdrawals due to adverse events for beta-blockers, calcium channel blockers and nitrates, over periods of four to eight weeks. Estimation of the monthly rate of withdrawals for these comparators is therefore based on a reduced period compared with for ranolazine. It is possible that consideration of withdrawal events for ranolazine over 12 weeks may reduce the estimated monthly rate of withdrawals for ranolazine, compared with the estimates generated for the comparators based on four to eight weeks. In the absence of longer term adverse event and withdrawal data for these comparators, the ratios of adverse events to withdrawals observed in the 12 week CARISA trials have been employed, which compounds the uncertainty in the assumed adverse event and withdrawal rates.<br><br>Individual one year trials provide adverse event and treatment withdrawal rates for ivabradine and nicorandil. The ratio of withdrawal rates to adverse events from the CARISA trial is also applied to these data to derive longer term adverse event and withdrawal rates.<br><br>Therefore, there are a number of uncertainties with the adverse event data employed in the model, which are used to determine length of time on treatment for ranolazine and the comparators. Sensitivity analyses around adverse events are limited to variation of ±25% change in rates applied equally across all treatments, which does not address potential uncertainty in the adverse event and withdrawal rates for ranolazine relative to the comparators. Modelled withdrawal rates have not been subjected to sensitivity analysis. |

**Table 1A. Health economic analysis detail[2]. Continued.**

| | Base Case Model | Appropriate? |
|---|---|---|
| **Utility values** | Baseline utility weight is based on an estimate from the literature. Utility decrements associated with angina attacks are derived from a regression model developed using survey data from 405 patients in Cardiff and Vale NHS Trust in 2008, who completed the EQ-5D questionnaire and the Seattle Angina Questionnaire. Disutility due to an adverse event is simply represented by an arbitrary 0.01 decrement in utility for the month in which the adverse event occurred. | In the reported absence of alternative utility data, the approach to estimate utility values for given states seems reasonable and has been tested in sensitivity analyses. |
| **Resource use** | Relates to drug costs and health professional contact time associated with adverse events and treatment withdrawal. | Adverse events are assumed to result in one GP appointment, with an additional GP appointment if withdrawal of treatment occurs. Those who subsequently withdraw from replacement add-on therapy are assumed to be referred to a consultant, but the modelled clinical pathway ends following this. |
| **Unit costs** | Direct medical costs of drugs are based on BNF list prices[18] for those with flat pricing structures (ranolazine and ivabradine). For other classes of agents the mean costs estimated from Welsh Prescription Cost Analysis data. Health professional contact times are based on relevant published unit costs data. | The company acknowledges that the use of prescription cost analysis data to estimate average daily costs of the beta-blocker, calcium channel blocker and nitrate classes is open to error due to the wide range of potential indications. |
| **Model Provided?** | Yes. | - |
| CABG: coronary artery bypass graft; CHMP: Committee for Medicinal Products for Human Use; CUA: cost-utility analysis; PCI: percutaneous coronary infusion. | | |

**Table 1B. Additional analyses of ranolazine compared against the individual comparator agents/classes of agents[13]**

| Treatment arm | Mean cost | Mean QALY | Incremental cost (ranolazine vs. comparator) | Incremental QALY (ranolazine vs. comparator) | Incremental cost/QALY (ranolazine vs. comparator) |
|---|---|---|---|---|---|
| **Ranolazine** | **£2,284** | **2.642** | | | |
| Beta-blocker | £391 | 2.563 | £1,893 | 0.079 | £23,962 |
| CCB | £403 | 2.436 | £1,881 | 0.206 | £9,131 |
| Nitrate | £469 | 2.421 | £1,815 | 0.221 | £8,213 |
| Ivabradine | £1,965 | 2.683 | £319 | -0.041 | -£7,780 (i.e. Ranolazine is dominated by Ivabradine) |
| Nicorandil | £679 | 2.559 | £1,605 | 0.083 | £19,337 |