

**5.06 RANOLAZINE,
Tablet (modified release), 375 mg, 500 mg, 750 mg,
Ranexa[®], A. Menarini Australia Pty Ltd.**

1 Purpose of Application

- 1.1 Section 85, Authority Required (Streamlined) listing for ranolazine for add-on symptomatic treatment of stable angina pectoris in patients with inadequate symptom control despite taking the maximum tolerated dose of a beta-blocker or a calcium channel blocker.

2 Requested listing

- 2.1 The proposed restriction for ranolazine is provided below. The ESC considered that it would be appropriate to include wording in the restriction to specify that use of ranolazine should be as add on, rather than as monotherapy.
- 2.2 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Public Summary Document – March 2017 PBAC Meeting

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
RANOLAZINE Tablet 375 mg, 500 mg, 750 mg, 60	1	5	\$ [REDACTED]	Ranexa® Menarini
Category / Program	GENERAL – General Schedule (Code GE)			
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives			
Condition:	Stable angina pectoris			
PBS Indication:	In adults as add-on therapy for the symptomatic treatment of stable angina pectoris in patients taking maximum tolerated doses of a beta-blocker or a calcium channel blocker and have inadequate symptom control			
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required (STREAMLINED) or <input type="checkbox"/> Authority Required?			
Clinical criteria:	in patients taking maximum tolerated doses of a beta-blocker or a calcium channel blocker and have inadequate symptom control Patient must have failed to achieve adequate symptom control with maximum tolerated doses of a beta-blocker or a calcium channel blocker AND Treatment must be used in combination with other medicines for angina.			
Administrative Advice	The recommended initial dose of RANEXA is 375 mg twice daily. After 2-4 weeks, the dose should be titrated to 500 mg twice daily and, according to the patient's response, further titrated to a recommended maximum dose of 750 mg twice daily. Shared Care Model: For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further information can be found in the Explanatory Notes for Nurse Practitioners.			

- 2.3 The submission presented a cost-effectiveness analysis of ranolazine compared with placebo as add-on therapy to beta-blockers and calcium channel blockers in symptomatic stable angina. The proposed price for ranolazine was based on a weighted comparison with placebo, nicorandil and perhexiline. The ESC considered that many of the patients considered in the placebo group would actually be receiving long acting nitrates, and that long-acting nitrates were a relevant comparator.

For more detail on PBAC's view, see section 7 "PBAC outcome"

3 Background

- 3.1 **TGA status at time of PBAC consideration:** Ranolazine was approved for registration by the TGA delegate on 12 May 2016. The approved indication was: "in adults as add-on therapy for the symptomatic treatment of stable angina pectoris in patients taking maximum tolerated doses of a beta-blocker or a calcium channel blocker and have inadequate symptom control." At the time of the ESC advice, ranolazine had not yet been added to the ARTG.

3.2

[REDACTED] The ESC also noted that the pharmacokinetic profile of ranolazine could lead to some potential drug interactions and complexities in management of patients with coronary artery disease. The pre-PBAC response noted that an ARTG listing for ranolazine would occur if a positive PBAC recommendation is received.

3.3 This was the PBAC's first consideration of ranolazine for PBS listing.

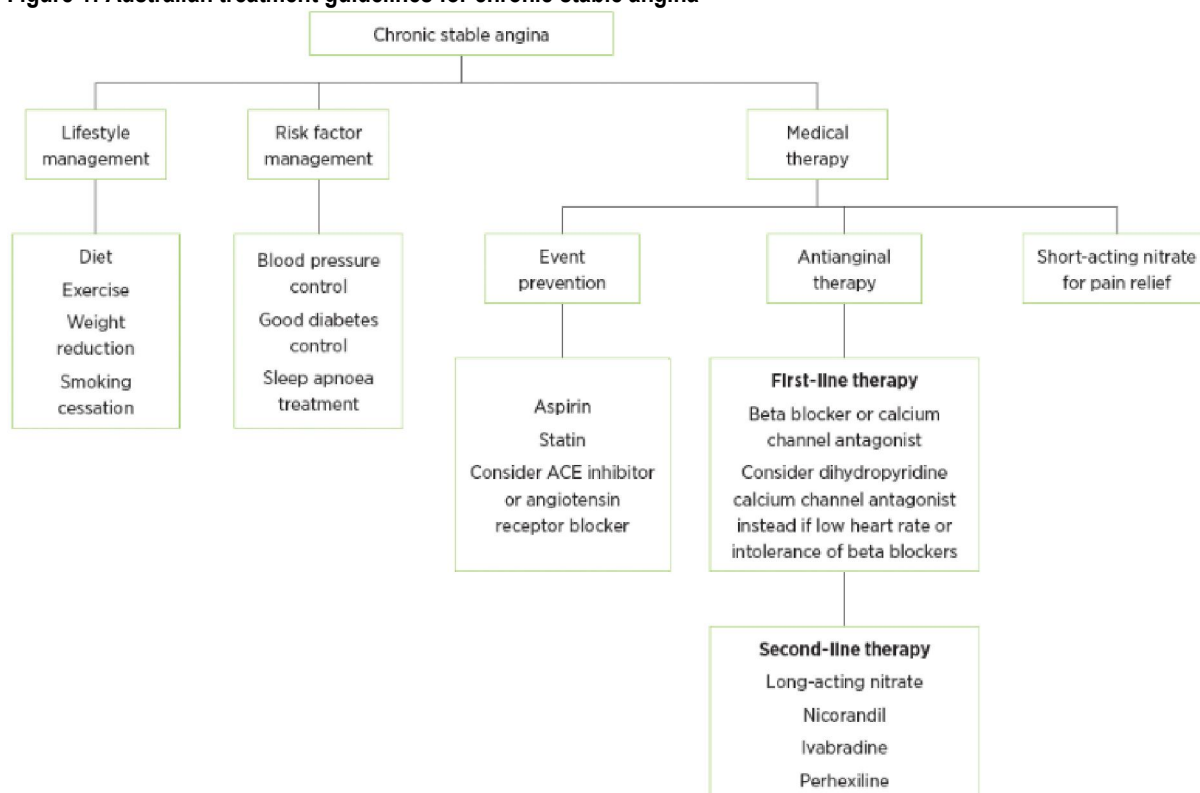
For more detail on PBAC's view, see section 7 "PBAC outcome".

4 Clinical place for the proposed therapy

4.1 Angina pectoris, or stable angina, is a form of coronary heart disease resulting from coronary artery obstruction by a stable atherosclerotic plaque. An angina attack is usually triggered by exertion or other stresses, and is characterised by chest pain or discomfort, which may radiate to other areas of the body. Patients may also experience gastrointestinal discomfort, shortness of breath and nausea. Patients with stable angina are at an increased risk of acute coronary events.

4.2 Current first-line treatment options include drug therapy with beta-blockers and calcium channel blockers, the management of reversible risk factors such as hypertension and dyslipidaemia, and lifestyle modifications. Guidelines from the American College of Cardiology Foundation (US), and European Society of Cardiology recommend ranolazine as second-line treatment of chronic stable angina in some clinical situations; long acting nitrates, nicorandil and perhexiline are also recommended as second-line therapy. The ESC noted that nitrates, both oral and cutaneous, are often used as second line therapy, as shown in the Australian treatment guidelines for chronic stable angina (Figure 1).

Figure 1: Australian treatment guidelines for chronic stable angina



Source: Wee et al (2015), Australian Prescriber "Medical management of chronic stable angina", Aug 2015
<https://www.nps.org.au/australian-prescriber/articles/medical-management-of-chronic-stable-angina>

- 4.3 The submission stated that, based on the current clinical management algorithm for angina management in Australia, ranolazine is to be used as add-on therapy for patients with stable angina pectoris who remain symptomatic despite being on the maximum tolerated dose of a beta-blocker and/or calcium channel blocker. This is in line with the TGA approved indication.

For more detail on PBAC's view, see section 7 "PBAC outcome".

5 Comparator

- 5.1 The submission nominated placebo as the main comparator, and nicorandil and perhexiline as secondary comparators.
- 5.2 The submission did not consider long-acting nitrates as a comparator. This was inappropriate. Long-acting nitrates, nicorandil and perhexiline are all PBS-listed for the management of angina amongst patients who are symptomatic despite therapy with the maximum tolerated dose of beta-blockers or calcium channel blockers, though it was acknowledged by the ESC and PBAC that perhexiline has very limited use in clinical practice.
- 5.3 The submission's nomination of placebo as the main comparator was inappropriate. The submission contended that placebo was the appropriate main comparator based on an analysis of a 10% sample of PBS prescriptions, whereby patients prescribed a

nitrate were assumed to represent patients with angina. For patients not receiving either nicorandil or perhexiline, uncontrolled angina was considered to be present in patients who had reduced their treatment dose or increased their utilisation of short-acting nitrates. Of the identified patients, approximately █% were considered by the submission to be uncontrolled on a beta-blocker and/or a calcium channel blocker and either naïve or refractory to add-on treatment, with █% of patients treated with nicorandil and █% treated with perhexiline. Insufficient information was presented in the submission for the results from the analysis of the 10% PBS sample to be verified. No information was provided on long acting nitrate use in the █% of the PBS sample that were not prescribed perhexiline or nicorandil. The criteria used to define the patient population with uncontrolled angina and the population refractory to nicorandil or perhexiline, in the PBS sample were likely to overestimate the uncontrolled angina population and underestimated the population suitable for treatment with nicorandil or perhexiline. The ESC did not consider it was plausible that █% of patients eligible for second-line therapy had no current alternative therapy on the PBS for stable angina as long acting nitrates could be used.

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on the CARISA trial, a randomised, double-blinded head-to-head trial comparing ranolazine 750mg, ranolazine 1000mg, and placebo (n=823). The submission also presented the ROLE single arm open-label extension study, and the ARETHA single arm open-label study in support of long-term ranolazine safety and efficacy. The IONA and COLE (1990) randomised trials were presented as evidence for the safety and efficacy of nicorandil and perhexiline, respectively.

6.4 Details of the trials presented in the submission are provided in the table below.

Table 1: Trials and associated reports presented in the submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Direct randomised trial		
CARISA	Primary Clinical Study Report – CVT 3033 – A Double-Blind, Randomized, Stratified, Placebo-Controlled, Parallel Study of Ranolazine SR at Doses of 750 mg Twice a Day and 1000 mg Twice a Day in Combination with Other Anti-Anginal Medications in Patients with Chronic Stable Angina Pectoris. CV Therapeutics, Incorporated.	30 July 2002
Chaitman	Chaitman BR, Pepine CJ, Parker JO, Skopal J, Chumakova G, Kuch J, Wang W, Skettino SL, Wolff, MD for the Combination Assessment of Ranolazine In Stable Angina (CARISA) Investigators. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial.	<i>JAMA</i> 2004; 291 (3):309-316
Subgroup analysis of CARISA: Lopez-Sendon	Lopez-Sendon J, Lee S, Cheng ML, Ben-Yehuda O. Effects of ranolazine on exercise tolerance and angina frequency in patients with severe chronic angina receiving maximally-tolerated background therapy: analysis from the Combination Assessment of Ranolazine In Stable Angina (CARISA) randomized trial.	<i>Eur J Prev Cardiol</i> 2012; 19(5): 952-959
Supplementary non-randomised trials		
ARETHA (Diedrichs)	Diedrichs H, Wollenberg U, Schmerbach K, Limberg R, Schiffhorst G, Zeiher AM. Application of Ranolazine in Stable Angina Pectoris Therapy (ARETHA): Real-World Data from an Observational Study.	<i>Journal of Clinical & Experimental Cardiology</i> (online) 2015; 6 (12):412
Studies used in the indirect comparison with nicorandil		
ROLE ^a	Primary Clinical Study Report – CVT 3034 – A Phase 3, Open-Label, Long-Term, Safety Study of Ranolazine SR for Chronic Stable Angina Pectoris at Doses of 500 mg, 750 mg and 1000 mg Twice a Day Administered in Combination with Background Anti-anginal Therapy.	24 January 2007
Koren ^b	Koren MJ, Cramer MR, Sweeney M. Long-term Safety of a Novel Anti-anginal Agent in Patients With Severe Chronic Stable Angina: The Ranolazine Open Label Experience (ROLE)	<i>J Am Coll Cardiol</i> 2007; 49 (10):1027-1034
IONA	IONA Study Group. Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomised trial.	<i>Lancet</i> 2002; 359 (9314):1269-1275
Studies used in the indirect comparison with perhexiline		
Cole	Cole PL, Beamer AD, McGowan N, Cantillon CO, Benfell K, Kelly RA, Hartley LH, Smith TW, Antman EM. Efficacy and safety of perhexiline maleate in refractory angina. A double-blind placebo-controlled clinical trial of a novel anti-anginal agent.	<i>Circulation</i> 1990; 81 (4):1260-1270
CARISA	SEE ABOVE	

Source: pp49-55 of the submission

The ROLE study is based on the CARISA and ERICA populations

The Koren (2007) study, also called ROLE, was based on the CARISA and MARISA populations

- 6.5 The primary efficacy outcome for the CARISA trial was change from baseline in exercise treadmill test (ETT) duration. The ETT was conducted on a treadmill and the

duration was the exercise time required to reach symptoms, which would normally cause cessation of exercise. The ESC considered that the clinical importance of ETT was unclear. ETT was not used in the economic model; the reduction in weekly angina episodes based on a post-hoc analysis of the CARISA trial by Lopez-Sendon (2012) was used to inform the economic model. The PBAC also noted that the CARISA trial was an older publication and may not be reflective of current practice.

- 6.6 The key features of the pivotal CARISA trial, and other trials presented by the submission, are summarised in Tables 2 and 3 below.

Table 2: Key features of the included evidence of the direct comparison of ranolazine vs placebo

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Ranolazine vs Placebo						
CARISA	823	R, DB, MC 12 wks	Low	Refractory stable angina	Improvements to ETT	Weekly angina episodes used in CUA
Lopez-Sendon (2012)	258	Subgroup analysis of CARISA	Unclear			

CUA = cost-utility analysis; DB=double blind; ETT = exercise tolerance test; MC=multi-centre; R=randomised; wks = weeks.

Source: Table B-5 and Table B-9 of the submission

Table 3: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Indirect comparison with nicorandil						
Ranolazine						
Koren (2007)	746	OL, prospective single- arm (mixed dosage) observational study	High	Symptomatic angina	Safety and tolerability assessments	CMA
Nicorandil vs Placebo						
IONA (2002)	5,126	R, DB, 1.6 yrs	Low	Angina patients refractory to optimum background angina therapy	Composite of Coronary heart disease death, or non-fatal myocardial infarction, or unplanned hospital admission for cardiac chest pain	CMA
Indirect comparison vs. perhexiline						
Ranolazine vs placebo						
CARISA	See Table 2					
Perhexiline vs Placebo						
Cole (1990)	19	R, DB crossover trial, 6 mths	Unclear	Angina patients refractory	Change in ETT (s)	CMA

CMA = cost-minimisation analysis; CUA = cost-utility analysis; DB=double blind; ETT = exercise tolerance test; mths = months; OL=open label; R=randomised; s = seconds; yrs = years

Source: compiled during the evaluation

- 6.7 The submission's clinical claim was based on evidence from two of the three arms included in the CARISA trial (750mg ranolazine and placebo), while the clinical efficacy used in the cost-utility model was based on results reported in a post-hoc published subgroup analysis of the CARISA trial (Lopez-Sendon (2012)). This subgroup analysis was based on patients who were assumed to be treated on maximally-tolerated doses of first-line anti-anginal therapies based on clinical

parameters, and was selected on the basis that the population was more reflective of the proposed PBS-population.

6.8 There were a number of issues with the applicability of the CARISA trial results to the proposed PBS population:

- Patients were not required to be taking maximum tolerated doses of a beta-blocker or a calcium channel blocker nor have inadequate symptom control.
- Patients were treated with either 750 mg or 1,000 mg twice daily ranolazine rather than 375 mg twice daily to be titrated upwards to a maximum dose of 750 mg twice daily based on patient tolerance (as recommended in the PI).

The population had a high rate of angina attacks at the start of the trial and therefore it was unclear whether the population was adequately treated with first line agents. If the population was under-treated at baseline, and hence more receptive to active therapy, the effect of ranolazine may have been overestimated in the trial compared to what would be achieved in clinical practice.

6.9 Additional applicability issues in the post-hoc subgroup analysis of the CARISA trial (Lopez-Sendon (2012)) include:

- the characteristics used to identify patients being treated with maximum tolerated doses of background anti-anginal therapy were not necessarily consistent with those used in clinical practice; and
- the subgroup analyses were not pre-specified, and not adjusted for multiplicity.

Comparative effectiveness

Direct comparison with placebo

6.10 The submission provided the results of the intent-to-treat population for the CARISA trial. Supportive safety and efficacy data from the Koren (2007) and ARETHA studies were provided.

6.11 Table 4 summarises the primary efficacy outcome of change from baseline in ETT duration for ranolazine 750 mg twice daily, compared with placebo from the CARISA trial.

Table 4: Results of increase in ETT duration from baseline in the direct randomised trial

Trial ID	Ranolazine 750 mg BID LS mean (SE) ^a	Placebo LS mean (SE) ^a	Mean difference (s) (95% CI)	P-value ^b
CARISA	115.4 (8.0)	91.7 (8.3)	23.7 (2.3, 45.1)	0.030

Source: Table B-31, p83 of the submission and 2.0.0.1, p383 of the clinical study report.

BID = twice daily; ETT = exercise tolerance test; s = seconds; CI = confidence interval; standard error = SE

Bold = statistically significant

^a Mean and corresponding standard error are least-square mean estimates from the analysis of covariance model

^b P-values obtained from analysis of covariance model adjusted for stated effects

6.12 The mean increase in ETT for patients treated with twice daily ranolazine at a dose of 750 mg was approximately 24 seconds longer compared with patients in the placebo comparator arm. These ETT results were used in the submission to support the clinical claim of superior efficacy over placebo. The clinical relevance of ETT as an outcome, and whether an improvement of approximately 24 seconds would represent a clinically significant patient outcome in the management of chronic, symptomatic

stable angina, is unclear. The ESC considered that the clinical significance of an improvement in ETT by 24 seconds was questionable.

- 6.13 In the economic evaluation, the submission modelled improvements in angina frequency and nitroglycerin frequency as reported in Lopez-Sendon (2012). As with ETT, the clinical relevance of these outcomes, and whether the reported improvements would represent clinically significant patient outcomes in the management of chronic, symptomatic stable angina, is unclear.
- 6.14 Table 5 summarises the change from baseline in normalised angina frequency over 12 weeks.

Table 5: Change from baseline in normalised angina frequency (per week) over 12 weeks

Trial ID	Ranolazine 750 mg BID mean (SE)	Placebo mean (SE)	Mean difference (95% CI)	P-value
CARISA	-1.8 (0.03)	-1.3 (0.02)	-0.54 (-0.61, -0.47)	NE
Lopez-Sendon (2012) ^a	-2.3 (0.3)	-0.9 (0.6)	-1.4 (-1.54, -1.26)	<0.001

Source: Table B-32, pp84-85 of the submission, Lopez-Sendon (2012) text pp196-197

For the change from baseline CARISA analysis baseline data was extracted from Chaitman (2004).

BID = twice daily; NE = not estimated; SE = standard error; CI = confidence interval.

^a Subgroup analysis of the CARISA trial

- 6.15 In the ITT population of the CARISA trial, the mean reduction in the number of angina episodes per week was approximately 0.5 greater in the ranolazine group compared with the placebo group. The difference was greater in the subgroup population (1.4 episodes per week), which ESC noted was the basis of the cost-effectiveness modelling.
- 6.16 Table 6 summarises the change from baseline in normalised nitroglycerin consumption (per week) over 12 weeks.

Table 6: Change from baseline in normalised nitroglycerin frequency (per week) over 12 weeks

Trial ID	Ranolazine 750 mg BID mean (SE)	Placebo mean (SE)	Mean difference (95% CI)	P-value
CARISA	-1.89 (0.53)	-0.86 (0.56)	-1.03 (-1.12, -0.94)	Not estimated
Lopez-Sendon (2012) ^a	-2.5 (0.5)	-0.4 (0.9)	-2.1 (-2.24, -1.96)	0.009

Source: Table B-32, pp84-85 of the submission, Lopez-Sendon (2012) text pp196-197

For the change from baseline CARISA analysis baseline data was extracted from Chaitman (2004).

BID = twice daily; NE = not estimated; CI = confidence interval; SD = standard deviation

^a Subgroup analysis of the CARISA trial

- 6.17 In the ITT population of the CARISA trial, the mean reduction in the nitroglycerin consumption over 12 weeks was greater in the ranolazine group compared with the placebo group (difference of approximately 1.0 per week). The difference was greater in the subgroup population (reduction of 2.1 applications per week).

Indirect comparisons vs nicorandil and perhexiline

- 6.18 Table 7 summarises the naïve indirect comparison between ranolazine and nicorandil.

Table 7: Naïve comparison of annualised mortality rates from the ROLE (Koren 2007) and IONA studies

Cause of mortality	Study	Annualised mortality rate (95% CI)
All-cause mortality	Koren (2007) – ranolazine	2.87% (2.27% to 3.62%)
	IONA – nicorandil	2.70% (2.25% to 3.25%)
CV-related mortality	Koren (2007) – ranolazine	2.28% (1.75% to 2.96%)
	IONA – nicorandil	1.46% (1.14% to 1.88%)

Source: Table B-33, p86 of the submission.

CI = confidence interval; CV = cardiovascular; RR = relative risk

6.19 The submission contended that the overall mortality associated with treatment with ranolazine was similar to patients treated with nicorandil based on an indirect, naïve comparison. This claim was not well supported because:

- The majority of the Koren (2007) population (58%) were treated with a higher dose of ranolazine than the maximum dose recommended by the TGA;
- Koren (2007) was a single-arm, open-label extension study of the CARISA and MARISA populations;
- There was a large number of patients that discontinued (almost 40%) in the Koren (2007) study; and,
- There may have been considerable heterogeneity between the two study populations.

The ESC considered that it was not possible to make a reliable estimate of comparative risks and benefits of ranolazine versus nicorandil based on the available data.

6.20 Table 8 summarises the indirect comparison between ranolazine and perhexiline.

Table 8: Indirect comparison of change in exercise duration at peak between CARISA and Cole (1990)

Trial ID	Trial(s) of proposed drug			Trial(s) of main comparator			Indirect change in Exercise duration (s) (95% CI)
	Mean difference in change in exercise duration (s) (95% CI)	Ranolazine mean Exercise duration (s) (SE)	Placebo mean Exercise duration (s) (SE)	Placebo Change in Exercise duration (s) (SE)	Perhexiline Change in Exercise duration (s) (SE)	Mean difference in change in exercise duration (s) (95% CI)	
CARISA	34.0 (13.1, 55.0)	99.4 (7.8)	65.4 (8.1)	-	-	-	-
Cole (1990)	-	-	-	-84.7 (63.1)	-5.5 (61.8)	79.3 (-29.2, 187.7)	-
Pooled							-45.3 (-155.7, 65.2)

Source: Tables B-32, p84; B-39, p94; and B-42, p96 of the submission and Table 2.1.0.1, p461 of the CARISA clinical study report

CI = confidence interval

Bold = statistically significant

6.21 The submission concluded that ranolazine had a similar level of efficacy to perhexiline. The evidence supporting the submission’s claim that ranolazine was associated with a similar level of efficacy to perhexiline was not well supported because:

- The population included in Cole (1990) had more severe disease. The placebo population in the ranolazine trial showed an improvement in exercise duration

whereas the placebo population in the perhexiline trial showed a worsening of their duration at peak exercise.

- The population included in Cole (1990) matched the proposed ranolazine PBS population, whereas the population in CARISA did not;
- Cole (1990) was conducted more than 10 years prior to the CARISA trial; and,
- The submission used results at the time of peak plasma ranolazine concentration (secondary outcome) rather than the primary outcome time, which favoured ranolazine.
- The ESC noted for the indirect comparison for the mean change in ETT, the 95% confidence intervals were wide and hence the claim of similar efficacy was inadequately supported.

6.22 The indirect comparisons with alternative agents were flawed. Overall, the data presented were not reliable as only one study (CARISA) had partial relevance to the proposed PBS population. The indirect comparison of perhexiline and ranolazine was not appropriate as the perhexiline study was no longer consistent with current clinical practice and the management strategy of uncontrolled angina has changed significantly since the study was conducted. While the treatment algorithms utilised in the submission are valid and appropriate for medically treated patients with angina, most patients would undergo evaluation with coronary angiography and implementation of a revascularisation strategy with continuing angina symptoms. The sponsor's PSCR noted that further randomised evidence is not planned and that clinical evidence has not been generated with the sole intention of replacing nicorandil or perhexiline.

Comparative harms

6.23 Based on the CARISA trial, the most common adverse events occurring amongst patients treated with ranolazine were constipation (6.5%), dizziness (3.6%), headaches (2.5%), nausea (3.2%) and asthenia (1.8%). For patients in the placebo comparator arm, the most common adverse events were angina pectoris (4.5%), asthenia (2.2%), and dizziness (1.9%). There were no statistically significant differences in the rate of adverse events between the placebo and ranolazine treatment groups in the CARISA trial. The adverse events occurring in patients treated with ranolazine were consistent with those described in the ranolazine Product Information.

6.24 The submission also presented long-term safety data from the ROLE study, based on the CARISA and ERICA populations. Overall, the most common adverse events reported in the total study population were constipation (9.0%), angina pectoris (7.4%), dizziness (7.1%), peripheral oedema (5.7%), unstable angina (4.7%) and hypertension (4.3%). The study population for ROLE was different to the intended PBS population. However, it was an appropriate source for the extended assessment of the safety of ranolazine, given the large patient population drawn from both the CARISA and ERICA trials.

6.25 The submission did not attempt an indirect comparison of safety between ranolazine and nicorandil or perhexiline. This was appropriate due to the heterogeneity between the studies.

- 6.26 The submission presented a number of studies to identify the adverse events that are associated with nicorandil. The ESC considered that the submission significantly overstated the potential harms of nicorandil. Although the ESC noted that ranolazine has few side effects and appears to be generally well tolerated, there was a high withdrawal rate (40%) in the Koren (2007) study. The conclusions about safety in these studies were based on non-comparative observational studies and narrative reviews of the literature, and did not add to the comparative safety of ranolazine compared with nicorandil.

Benefits/harms

- 6.27 A summary of the comparative benefits and harms for ranolazine versus placebo is presented in Table 9 below.

Table 9: Summary of comparative benefits and harms for ranolazine and placebo

Trial	Ranolazine 750 mg BID			Placebo			Mean difference ^a : Ranolazine vs. Placebo (95% CI)
	n	Mean Δ baseline (s)	SD	n	Mean Δ baseline (s)	SD	
Continuous Outcome I: change from baseline ETT duration							
CARISA	279	115.4	8	269	91.7	8.3	23.7 (2.3, 45.1)
Continuous Outcome II: change from baseline weekly angina frequency							
CARISA	279	-1.8	0.4	269	-1.3	0.5	-0.54 (-0.61, -0.47)
Lopez-Sendon (2012)	89	-2.3	0.6	84	-0.9	0.6	-1.4 (-1.54, -1.26)
Continuous Outcome III: Change from baseline in normalised nitroglycerin frequency							
CARISA	262	-1.89	0.53	252	-0.86	0.56	-1.03 (-1.12, -0.94)
Lopez-Sendon (2012)	89	-2.5	0.5	84	-0.4	0.9	-2.1 (-2.24, -1.96)
Harms							
	Ranolazine 750 mg BID	Comparator/ Placebo	RR (95% CI)	Event rate/100 patients ^a		RD (95% CI)	
				Ranolazine 750 mg BID	Comparator/ Placebo		
Adverse event I: Patient with severe adverse event							
CARISA	21/279	13/269	1.56 (0.8, 3.05)	7	5	2.7 (-1.3, 6.7)	

Source: compiled from Tables B-31, p83; B-32, pp84-85; B-45, p99 of the submission and Tables 12E, p131; 2.0.0.1, p383 of the clinical study report.

RD = risk difference; CI = confidence interval; SD = standard deviation.

^a Maximum duration of exposure: CARISA/Lopez-Sendon (2012) = 12 weeks.

- 6.28 On the basis of the head-to-head direct trial, the comparison of ranolazine with placebo resulted in approximately 0.54 fewer angina attacks per week for patients treated with ranolazine compared with patients in the placebo arm. The ESC noted the reduction in angina frequency is a relevant measure, however the magnitude of the reduction presented here may not be clinically meaningful.

Clinical claim

- 6.29 The submission described ranolazine as superior in terms of comparative effectiveness and slightly inferior in terms of comparative safety over placebo.

- 6.30 The claim of superior efficacy of ranolazine compared with placebo was not well supported for the requested PBS population, as the population in the pivotal trial (CARISA) was different to the requested PBS restriction. The submission provided a subgroup analysis from Lopez-Sendon (2012) for patients who may be more similar to the proposed PBS population; however, differences between the sub group and PBS populations remained, and the analysis was post hoc.
- 6.31 While the data presented in the submission suggested an effect compared to placebo, the magnitude of any benefit remained unclear.
- 6.32 The claim that ranolazine was inferior to placebo in terms of comparative safety was reasonable.
- 6.33 The submission described ranolazine as being similar to nicorandil and perhexiline in terms of comparative effectiveness and safety. The ESC considered this claim was inadequately supported based on the data presented in the submission.
- 6.34 Overall, the PBAC did not consider placebo an appropriate primary comparator, and that the evidence presented for the indirect comparison of ranolazine to nicorandil and perhexiline was not sufficient to support the clinical claims.

Economic analysis

- 6.35 The submission presented:
- a stepped, modelled cost utility economic evaluation versus placebo for patients assumed to be naïve or refractory to second-line therapy;
 - a cost analysis versus nicorandil; and
 - a cost analysis versus perhexiline.
- 6.36 The PBAC did not agree that placebo was an appropriate comparator. This meant that the model did not reflect current clinical practice, making the cost analysis presented unreliable.

Cost utility vs placebo

- 6.37 A Markov model using micro-simulation methods was used to model the cost-effectiveness of ranolazine versus placebo. The economic evaluation was based on the CARISA trial of ranolazine versus placebo. A stepped analysis was presented. Step 1 incorporated patient withdrawal from placebo or ranolazine treatment, and extrapolated the trial-based data to the one-year time horizon. Subsequently, Step 2 incorporated background death and Step 3 incorporated hospitalisations to the model. Step 4, whereby revascularisations were incorporated in the model, was included as a sensitivity analysis by the submission.
- 6.38 Table 10 summarises the inputs and assumptions used in the economic evaluation.

Table 10: Summary of inputs and assumptions used in the economic evaluation

Input Description	Value		Source and Notes
Model duration	1 year		
Discounting (costs and outcomes)	NA		Not applicable as model is 1 year
Cycle length	1 month (12 cycles)		-
Compliance to ranolazine	80%		Published literature
Demographics			
Age	Mean 64		CARISA
Gender (% male)	77.5%		CARISA
Efficacy	Ranolazine	Placebo	
Angina episodes per week	-2.3	-0.9	Lopez Sendon et al 2012
Nitroglycerin use per week	-2.5	-0.4	Lopez Sendon et al 2012
Adverse Events (rate/month)			
Months 1 to 3	12.5%	2.9%	CARISA
Months 4 to 12	1.2%	0.5%	CARISA + open label follow-up. Placebo rate extrapolated
Withdrawals due to AEs			
Months 1 to 3	54%	94%	CARISA
Months 4 to 12	54%	54%	CARISA + open label follow-up. Placebo rate extrapolated
Hospitalisations	5.2%	6.6%	Phelps et al 2012
Revascularisation	1.7%	2.8%	Phelps et al 2012 – sensitivity only
Proportion of revascularisations that are PCI	80.2%	74.8%	Phelps et al 2012 – sensitivity only
Background Death	As per ABS life tables by age and gender		
Quality of life			
Symptomatic stable angina	0.60	0.60	Longworth et al 2005
Death	0.00	0.00	-
<i>Change in utility</i>			
Per angina event avoided	0.035	0.035	Wijeysundera et al 2011 and ERICA
Adverse event (cycle of)	-0.01	-0.01	Estimate – explored in sensitivity analysis
Hospitalisation (cycle of)	-0.01	-0.01	Estimate – explored in sensitivity analysis
Revascularisation (cycle of)	-0.01	-0.01	Estimate – explored in sensitivity analysis
Post revascularisation	+0.1	+0.1	Cohen et al 2011

Source: Table D-3, p158 of the submission

- 6.39 The ESC questioned whether the utility decrements applied in the model were plausible. For example, the utility decrement of 0.035 per angina event avoided is equivalent to an absolute utility decrement of 0.5 for 12 hours per angina attack, eg. a drop in utility from 0.8 to 0.3 for 12 hours, which appeared to be a large change, and may therefore overestimate the benefit of ranolazine. Furthermore, a utility decrement of 0.01 was applied for each month in which an adverse event or hospitalisation (or revascularisation, in sensitivity analyses) occurred. Hospitalisation and revascularisation effects were already captured in the estimated angina event utility decrement.
- 6.40 The approach used to estimate the utility decrement per angina event assigned all utility effects to angina frequency and so may overestimate utility gains.
- 6.41 The ESC considered that the submission's assumption of 80% compliance to ranolazine was inappropriate in the base case, given that this was not reported in the CARISA trial. This assumption reduced the cost of ranolazine in the model without considering any effect of compliance on the benefit.

- 6.42 The angina frequency estimates were derived from a post-hoc analysis of the CARISA trial and were subject to the clinical relevance and statistical validity of that analysis.
- 6.43 Hospitalisation rates (and revascularisation rates in the sensitivity analysis) were based on observational data from a large managed care organisation in the US in a population that did not match the target population. The values used in the model were based on the unadjusted comparison of the percentage of patients having an inpatient stay in the ranolazine and beta blocker/calcium channel blocker groups. The ESC proposed that it would have been more meaningful to compare the mean number of inpatient stays rather than the percentage of patients having an inpatient stay. This would reduce the monthly absolute difference from 1.4% to 1%.
- 6.44 However, the unadjusted results are not valid due to significant differences in baseline age, gender, dyslipidaemia and diabetes between the groups and pre-index use of short-acting nitrate and number of medications (higher in the ranolazine group). Pre-index resource use profiles also differ.
- 6.45 Adjusted analyses are presented in the paper for revascularisation rates, showing a significant increase in the BB/CCB group, but the adjusted results are subject to significant uncertainty due to the potential for unobserved confounding.
- 6.46 Key drivers of the economic model are presented in Table 11 below.

Table 11: Key drivers of the model

Description	Method/Value	Impact
Compliance	Assumed compliance rate of 80% based on literature review.	Moderate, favours ranolazine
Hospitalisations rate	5.2% for ranolazine and 6.6% for placebo, sourced from Phelps (2012).	Moderate, favours ranolazine
Utility gain	Gain in utility of 0.035 for each angina attack avoided per week based on literature review.	Moderate

Source: compiled during the evaluation

DPMQ = dispensed price for maximum quantity; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

- 6.47 Table 12 summarises the results of the stepped economic evaluation.

Table 12: Modelled economic evaluation

Step and component	Ranolazine	Placebo	Increment
Trial based economic evaluation			
Costs	\$	\$	\$
Angina events	24	41	-17
Incremental cost per angina event avoided			\$
Step 1: Preliminary economic evaluation plus withdrawals, full time horizon			
Costs	\$	\$	\$
QALYs	0.663	0.627	0.036
Incremental cost/extra QALY gained			\$
Step 2: Added background death			
Costs	\$	\$	\$
QALYs	0.658	0.622	0.036
Incremental cost/extra QALY gained			\$
Step 3: Base case evaluation (hospitalisations added)			
Costs	\$	\$	\$
QALYs	0.657	0.622	0.036
Incremental cost/extra QALY gained			\$

Source: Ranexa, Section D workbook.xlsx

QALY = quality-adjusted life year

- 6.48 The submission estimated that ranolazine would result in an incremental cost of less than \$15,000 per quality-adjusted life year gained.
- 6.49 Table 13 summarises the key sensitivity analyses conducted by the submission and evaluators. Two additional sensitivity analyses were performed by the ESC, as indicated by the italic font in the table below.

Table 13: Results of univariate and multivariate sensitivity analyses

	Δ costs	Δ QALYs	ICER
Base case	\$ [REDACTED]	0.036	\$ [REDACTED]
Univariate sensitivity analyses			
Addition of revascularisations (Step 4)	-\$ [REDACTED]	0.030	Dominant
Compliance to 100% (base case 80% compliance)	\$ [REDACTED]	0.036	\$ [REDACTED]
Halved rate of hospitalisations (base case: 5.2% in treatment arm)	\$ [REDACTED]	0.036	\$ [REDACTED]
Reduction in utility gain from angina avoidance by 25% (base case: +0.035 gain in utility)	\$ [REDACTED]	0.027	\$ [REDACTED]
Adverse events utility decrement of -0.05 (base case: -0.01)	\$ [REDACTED]	0.035	\$ [REDACTED]
<i>Difference in weekly angina frequency halved</i>	\$ [REDACTED]	0.017	\$ [REDACTED]
Multivariate sensitivity analysis			
Compliance to 100% and no hospitalisations	\$ [REDACTED]	0.036	\$ [REDACTED]
Compliance to 100% halve rate of hospitalisations, reduce utility by 25%	\$ [REDACTED]	0.027	\$ [REDACTED]
<i>Compliance to 100%, difference in hospitalisations reduced to 0.5% per month, reduce angina utility effect by 50%, hospitalisations disutility removed</i>	\$ [REDACTED]	0.018	\$ [REDACTED]

Source: Ranexa, Section D workbook and calculated or corrected during the evaluation and by the ESC.
QALY = quality-adjusted life year

- 6.50 The model was most sensitive to patient compliance, hospitalisation rates frequency of angina attacks and the assumed gain in utility from avoiding an angina attack.

Cost-minimisation analyses vs nicorandil and perhexiline

- 6.51 The equi-effective doses were estimated as ranolazine 750 mg twice daily and nicorandil 20 mg twice daily, or perhexiline 100 mg twice daily based on the doses used in the clinical trials. Whether these doses were equi-effective could not be determined based on the evidence provided in the submission and this affects the robustness of a cost minimisation approach. The cost minimisation approach was not well justified.
- 6.52 The submission calculated the AEMP/day for nicorandil as \$ [REDACTED] based on the price of nicorandil and the costs associated with ulceration events due to nicorandil treatment. The PBAC considered that the submission had overstated the adverse events associated with nicorandil. Table 14 summarises the costs of nicorandil related ulceration (per year) which were included in the submission's calculation of the cost/day of nicorandil.

Table 14: Summary of costs for ulceration events relating to nicorandil

Resource	Skin	Anal	GI	GI + perforation	Cost
	Assumed number of events (per year)				
GP visit					\$37.05
Specialist visit (initial)					\$85.55
Specialist visit (follow-up)					\$43.00
Rectogesic					\$29.99
Antibiotics					\$44.61
Dressing (daily)					\$2.19
Endoscopy ± biopsy					\$177.10
Emergency surgery for perforation					\$4,021.66
Total cost per event	\$	\$	\$	\$	
Proportion of patients per annum	1.90%	0.37%	6.85%	0.32%	
Average cost per patient per year	\$	\$	\$	\$	
Average annual per patient cost of ulcers					\$
Cost per 30 days					\$

Source: Table D-16, p164 of the submission
 GI = gastro intestinal; GP = general practitioner.

- 6.53 The submission calculated the AEMP/day for perhexiline as \$ based on the price of perhexiline and the costs associated with health care resource utilisation for monitoring treatment with perhexiline. This may not have been appropriate as health care resource utilisation costs (for monitoring in high-risk patients) were not included for ranolazine in the comparison. The PBAC considered that the costs attributed to monitoring with perhexiline were overestimated. Table 15 summarises the costs of health care resources used with perhexiline.

Table 15: Summary of costs for perhexiline

Resource	Units/year	Cost per unit	Source	Total cost
Liver function test		\$17.70	MBS 66512	\$
Monitoring test		\$34.80	MBS 66812	\$
Patient episode initiation		\$2.40	MBS 73929	\$
GP visits		\$37.05	MBS 23	\$
Total per year				\$
Total per 30 days				\$

Source: Table D-18, p167 of the submission
 GP = general practitioner; MBS = Medicare Benefits Schedule.

Calculation of weighted price for ranolazine

- 6.54 The submission used 10% PBS sample data to estimate the number of patients with uncontrolled angina who were currently untreated (%) or receiving nicorandil (%) or perhexiline (%), and weighted the price based on these estimates. Within the 10% PBS sample, patients prescribed any type of nitrate were identified as having angina. The submission defined uncontrolled angina as patients that satisfied one of four categories. The commentary considered that insufficient information was presented in the submission for the results from the analysis of the 10% PBS sample to be verified. The commentary stated that the criteria used in the determination of the patient population suitable for ranolazine treatment were not clearly defined. The clinical basis for the chosen criteria were unclear and may be inappropriate for defining patients with uncontrolled stable angina on beta-blockers and/or calcium channel blockers.

- 6.55 Overall, the submission’s approach to determining the relative weighting of the comparator components was inappropriate, and overestimated the proportion of untreated patients. Additionally, the submissions failure to consider long-acting nitrates as a comparator was inappropriate.
- 6.56 Table 16 summarises the weightings and AEMP used to calculate the weighted cost.

Table 16: Weightings and AEMP used by the submission to calculate the price of ranolazine

Drug	Weighting	AEMP/day	DPMQ ^
Placebo	█%	\$█	-
Nicorandil	█%	\$█	10 mg: \$24.54 20 mg: \$30.03
Perhexiline	█%	\$█	\$59.09
Proposed Price		\$█	\$█
Isosorbide mononitrate (long acting nitrate)			60 mg: \$14.24 120 mg: \$18.74

Source: Section D of the submission.

AEMP = approved ex-manufacturer price; DPMQ = dispensed price per maximum quantity

*AEMP/day at which ranolazine was assumed by the submission to be cost effective, based on results of the cost effectiveness model and cost minimisation analyses.

^Price at 1 March 2017

- 6.57 The submission proposed a DPMQ of \$█ for a 30-day supply of ranolazine based on the comparisons with placebo, perhexiline and nicorandil. This was significantly higher than the current prices of alternative therapies nicorandil and perhexiline (and long acting nitrates).
- 6.58 Overall, the weighted cost analysis was not appropriate:
- The submission failed to consider long-acting nitrates, which was a relevant comparator;
 - The approach used to estimate the weightings of the comparator components was not adequately justified in the submission; and,
 - Placebo was included as a comparator and given the greatest weight (█%) in the analysis, which increased the proposed price of ranolazine.

Drug cost/patient/year: \$█ per patient per year

- 6.59 The drug cost per patient per year of ranolazine therapy was based on the requested DPMQ of \$█, with full compliance over 365 days (60 tablets per pack, █ scripts per year).

Estimated PBS usage & financial implications

- 6.60 This submission was considered by DUSC.
- 6.61 Both a market share and an epidemiological approach were used to estimate the extent of use of ranolazine. The submission presented the financial impacts for the epidemiological approach only. The market share approach was used as a sensitivity

analysis. The DUSC considered the estimates presented in the submission to be overestimated.

- 6.62 Table 17 presents the estimated use and financial implications of ranolazine utilisation.

Table 17: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Epidemiological approach					
Net cost to PBS/RPBS	\$	\$	\$	\$	\$
Net cost to MBS	-\$	-\$	-\$	-\$	-\$
Net cost to PBS/RPBS/MBS	\$	\$	\$	\$	\$
Market share approach (PBS 10% sample)					
Net cost to PBS/RPBS/MBS	\$	\$	\$	\$	\$

Source: Tables E-13 - E15, pp184-5 of the submission and calculated or corrected during evaluation

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

- 6.63 The submission estimated that ranolazine was associated with a cost to the PBS/RPBS/MBS of \$60-100 million in Year 5 and a total cost of more than \$100 million in the first five years of listing based on the epidemiological approach.

- 6.64 Overall, the DUSC considered the net cost to the government was unreliable using both approaches because:

- The number of patients who would take ranolazine was overestimated. The DUSC noted that it was assumed that all prevalent coronary heart disease patients have stable angina and the sources used to estimate the eligible population were not consistent with the population in the requested PBS restriction.
- The overall uptake for ranolazine was likely overestimated, as some patients assumed to be taking no add-on therapy would be on long-acting nitrates.
- The number of ranolazine prescriptions per patient per year was overestimated as full compliance was assumed.
- MBS offsets for monitoring of perhexiline were likely overestimated due to the inclusion of GP visits, the overestimation of blood test costs, and the use of an inappropriate MBS Item for monitoring plasma levels of perhexiline;
- Hospitalisation rates were based on a higher risk population than that requested; and
- The cost per hospitalisation was overestimated for coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) because these were based only on the Australian Refined Diagnosis Related Groups (AR-DRG) code with catastrophic complications and/or comorbidities.

For more detail on PBAC's view, see section 7 "PBAC outcome".

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of ranolazine for the treatment of stable angina pectoris in certain patients on the basis of uncertain, and possibly high, cost-effectiveness. In making this decision, the PBAC considered that the comparator nominated by the submission was inappropriate.

- 7.2 The PBAC considered that the weighted comparator nominated by the submission was inappropriate, noting that the submission proposed a weighting of ■% to placebo. The PBAC acknowledged that there may be some patients currently not receiving add-on therapy (in whom placebo would be an appropriate comparator), but considered that this population had not been adequately clinically defined by the submission. Furthermore, the PBAC considered that the assumption that this group would make up such a large proportion of the overall population was not well justified, and in reality this was likely to be much less than ■%. The PBAC noted that ranolazine has a number of pharmacokinetic and pharmacodynamics concerns including variable bioavailability, affected by hepatic and renal impairment and it is a CYP3A4 inhibitor with multiple drug interactions. The PBAC considered that ranolazine may potentially have a small role in the treatment of stable angina given its lack of haemodynamic effects.
- 7.3 The PBAC considered that the justification provided by the submission and pre-PBAC response for not considering long-acting nitrates as a comparator was not adequate. Although the pre-PBAC response argued that some patients are limited in their choice of treatment combinations because all of the available anti-anginal therapies have haemodynamic effects on heart rate or blood pressure making them contraindicated or potentially poorly tolerated, the PBAC noted the requested indication does not specify any haemodynamic requirements. Also, long acting nitrates are normally considered as part of angina treatment in clinical practice. Therefore, the PBAC considered that the omission of long acting nitrates was inappropriate.
- 7.4 The PBAC further noted that the treatment algorithm presented in the submission did not consider revascularisation and that percutaneous or surgical revascularisation would be commonly applied in the population considered appropriate for ranolazine in the submission.
- 7.5 The PBAC noted that there were applicability issues with the clinical trial and post-hoc subgroup analysis presented, as there were differences in baseline characteristics and ranolazine dosing compared to the proposed PBS population. The PBAC also noted that the CARISA trial was performed many years ago and is not reflective of current practice.
- 7.6 The PBAC noted that there was a statistically significant improvement in ETT duration of 24 seconds with ranolazine compared with placebo, but considered the clinical relevance of this improvement unclear. The PBAC noted there was also a reduction in angina attacks and use of short-acting nitrates with ranolazine.
- 7.7 The indirect comparisons of ranolazine to nicorandil and perhexiline were not sufficient to support the clinical claims. The comparison with nicorandil used a different outcome (annual mortality) to the CARISA trial. For the comparison with perhexiline, the Cole (1990) trial included a population with more severe disease and the trial was performed many years ago and is not reflective of current clinical practice. The PBAC noted that no further clinical data was being collected to compare ranolazine with nicorandil and perhexiline.
- 7.8 The PBAC agreed that ranolazine was likely to be superior in terms of effectiveness

over placebo, but considered that the magnitude of benefit remained unclear.

- 7.9 In terms of comparative safety, the PBAC considered the claim that ranolazine was inferior to placebo was reasonable.
- 7.10 In relation to the indirect comparisons to nicorandil and perhexiline, the PBAC did not accept the claims of non-inferiority efficacy and safety of ranolazine as the comparisons were not adequately supported by the data. The PBAC considered that the rate of adverse events for nicorandil and cost of monitoring of perhexiline had been overstated.
- 7.11 The PBAC considered the utilisation to be overestimated and the net cost to government was unreliable given the assumptions presented in the submission.
- 7.12 The PBAC considered there may be a clinical role for ranolazine for add-on symptomatic treatment of stable angina pectoris, especially in the population where revascularisation was not an option and haemodynamic concerns limited other anti-anginal options. The PBAC proposed that any future submission should address the role of long acting nitrates in therapy, and as a relevant comparator in the requested PBS population. The PBAC considered the substantially higher price for ranolazine compared with long acting nitrates and nicorandil was not justified.
- 7.13 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

Menarini will continue to work with the PBAC as we believe there are patients in Australia who could benefit from this treatment