7.18 RANOLAZINE
Tablet (modified release), 375 mg, 500 mg, 750 mg, Ranexa®, A. Menarini Australia Pty Ltd.

1 Purpose of Application

1.1 The minor resubmission sought a Section 85 Authority Required (Telephone) listing for stable angina in patients on a maximum tolerated dose of a beta blocker or calcium channel blocker, and where revascularisation is not an option and haemodynamic concerns limit other anti-anginal treatment options.

2 Requested listing

2.1 The minor resubmission requested the following new listing. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

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:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	*Stable ~~A~~angina* pectoris
PBS Indication:	Stable angina pectoris
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☒Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined
Clinical criteria:	Patient must be one in whose symptoms are not controlled satisfactorily by the maximum tolerated dose~~s~~ of *a* beta-blocker~~s~~ or a calcium channel blocker; AND Patient must be one in whom revascularisation is not an option; AND Patient must be one in whose haemodynamic concerns limit other anti-anginal treatment options

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.

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

3 Background

3.1 Ranolazine was approved for registration by the TGA delegate on 12 May 2016. The approved indication is: "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."

3.2 The first submission for ranolazine was considered by the PBAC in March 2017. The PBAC did not recommend the listing of ranolazine on the basis of the uncertain, and possibly high, incremental cost-effectiveness ratio. In making this decision, the PBAC considered that the comparator nominated by the submission (weighted mix of placebo, nicorandil and perhexiline) was inappropriate as it did not include long acting nitrates.

4 Population and disease

4.1 Angina occurs when myocardial oxygen demand exceeds supply. Angina is categorised as stable if the pattern of symptoms has not changed during the past month, such as the distance walked before the development of angina (allowing for terrain, meals and cold weather).

4.2 Choice of antianginal agents is influenced by the severity of angina and presence of coexisting diseases, and may be limited by adverse effects. Beta-blockers are recommended as initial therapy. Calcium channel blockers, in particular verapamil and diltiazem, are alternatives; they are recommended when beta-blockers are contraindicated. If beta-blockers are ineffective in controlling symptoms, a dihydropyridine calcium channel blocker can be added; if this is inadequate, adding a third agent may be considered if revascularisation is not appropriate or while waiting for revascularisation. When both beta-blockers and calcium channel blockers cannot be used, long-acting nitrates, ivabradine, nicorandil or perhexiline are alternative treatment options.

4.3 At its March 2017 meeting, the PBAC considered 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. 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 (paragraphs 7.4 & 7.12, ranolazine March 2017 PBAC Public Summary Document).

4.4 The minor resubmission narrowed the requested PBS indication compared to the March 2017 submission, for patients who are on a maximum tolerated dose of a beta-blocker or a calcium channel blocker, where revascularisation is not an option and haemodynamic concerns limit other anti-anginal treatment options. The requested PBS indication is narrower than the approved TGA indication.

5 Comparator

5.1 The major submission considered by the PBAC in March 2017 nominated placebo as the main comparator, and nicorandil and perhexiline as secondary comparators. The PBAC considered that the weighted comparator nominated by the submission was inappropriate, noting that the submission proposed a weighting of 85% 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 85% (paragraph 7.2 ranolazine March 2017 PBAC Public Summary Document). The PBAC also considered that any future submission should address the role of long acting nitrates in therapy, and as a relevant comparator in the requested PBS population (paragraph 7.12, ranolazine March 2017 PBAC Public Summary Document).

5.2 The minor resubmission nominated placebo as the comparator. Given the change in the requested PBS listing for a narrower population (in patients on a maximum tolerated dose of a beta blocker or calcium channel blocker and where revascularisation is not an option and haemodynamic concerns limit other anti-anginal treatment options), the PBAC accepted placebo as an appropriate comparator.

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 as it was a minor submission.

Consumer comments

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

Clinical evidence

6.3 The minor resubmission did not present any new clinical data. However, the minor resubmission presented:

- discussion of clinical need and limitations of current treatments;
- rationale for the proposed restriction;
- discussion of mechanism of action of the anti-anginal medicines;
- epidemiology of coronary artery disease and revascularisation rates; and
- results of a survey of 50 cardiologists to help identify patients suitable for ranolazine under the requested PBS restriction.

6.4 At its March 2017 meeting, the PBAC noted that ranolazine has a number of pharmacokinetic and pharmacodynamic concerns including variable bioavailability, affected by hepatic and renal impairment and it is a CYP3A4 inhibitor with multiple drug interactions (paragraph 7.2, ranolazine March 2017 PBAC Public Summary Document). The minor resubmission did not address the PBAC's concerns. The pre-PBAC response stated that since ranolazine's first marketing approval, cumulative exposure is estimated to be 16,475,440 patient-months of treatment and that no major new safety issues have emerged from the latest periodic safety update report. The pre-PBAC response argued that the overall benefit-risk profile of ranolazine is positive.

Comparative effectiveness

6.5 At its March 2017 meeting, the PBAC noted that there was a statistically significant improvement in the exercise treadmill test (ETT) duration of 24 seconds with ranolazine compared with placebo, but considered the clinical relevance of this improvement unclear. The PBAC agreed in March 2017 that ranolazine was likely to be superior in terms of effectiveness over placebo, but considered that the magnitude of benefit remained unclear. In terms of comparative safety, the PBAC considered the claim that ranolazine was inferior to placebo was reasonable (paragraphs 7.6, 7.8 & 7.9, ranolazine March 2017 PBAC Public Summary Document). The PBAC also noted that the CARISA trial was performed many years ago and is not reflective of current practice (paragraph 7.5, ranolazine March 2017 PBAC Public Summary Document).

6.6 The minor resubmission maintained the same clinical claim as the March 2017 major submission: ranolazine is superior in terms of comparative effectiveness and inferior in terms of comparative safety over placebo. In March 2017, the PBAC considered that 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 major 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 (paragraph 6.30, ranolazine March 2017 PBAC Public Summary Document).

6.7 Although the minor resubmission narrowed the requested PBS population, the applicability issues from the March 2017 major submission remain. The population group in the CARISA trial does not match the PBS restriction, as patients did not need to be taking maximum tolerated doses of a beta-blocker or a calcium channel blocker and have inadequate symptom control to be enrolled in the trial. Patients in the CARISA trial were initiated at a twice-daily dose of either 750 mg or 1,000 mg of ranolazine, whereas the requested listing stipulated that patients are to initiate treatment on 375 mg twice daily and titrated upwards to 500 mg twice daily and then to a maximum of 750 mg twice daily depending on patient tolerance and response to ranolazine. Patients in the PBS population may remain on 500 mg twice daily, which is a dose not included in the CARISA trial.

Economic analysis

6.8 The major submission considered by the PBAC in March 2017 presented a cost-utility analysis against placebo. The minor resubmission did not present a revised model. The March 2017 submission estimated that ranolazine would result in an incremental cost of less than $15,000 per quality-adjusted life year gained.

6.9 The minor resubmission did not address the concerns raised by the Economics Subcommittee (ESC) regarding the model presented in the March 2017 major submission (paragraphs 6.39 – 6.46, ranolazine March 2017 PBAC Public Summary Document), including:

- Plausibility of the utility decrements applied in the model:
    - the utility decrement of 0.035 per angina event avoided appeared to be a large change, and may therefore overestimate the benefit of ranolazine;
    - 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.
    - The approach used to estimate the utility decrement per angina event assigned utility effects to angina frequency and so may overestimate utility gains.
- the submission's assumption of 80% compliance to ranolazine was considered 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.
- Hospitalisation rates (5.2% for ranolazine and 6.6% for placebo) were based on observational data from a large managed care organisation in the US in a population that did not match the target population.

6.10 Multivariate sensitivity analyses conducted during the evaluation of the March 2017 major submission, which changed the compliance rate to 100%, reduced the

difference in hospitalisation rates to 0.5% per month, reduced angina utility effect by 50% and removed disutility associated with hospitalisations, resulted in an incremental cost of $15,000 - $45,000 per quality-adjusted life year gained.

6.11 The minor resubmission noted a price of $[redacted]/day was proposed for ranolazine in the March 2017 submission. This was a weighted price based on the cost-utility analysis versus placebo (ranolazine price $[redacted]/day; [redacted]% weighting), and cost analyses versus nicorandil (ranolazine price $[redacted], [redacted]% weighting) and perhexiline ($[redacted], [redacted]% weighting). The same price was proposed in the minor resubmission ($[redacted]/day) even though placebo was the only comparator nominated.

Drug cost/patient/year: $[redacted].

6.12 The drug cost per patient per year of ranolazine was based on the requested DPMQ of $[redacted], with full compliance assumed ([redacted] prescriptions per year).

Estimated PBS usage & financial implications

6.13 The selection of sources of data used by the minor resubmission for the financial analyses is presented below.

Table 1: Overview of data sources used in the financial analysis of ranolazine

	Variable	Value	Source
A	All angina patients on PBS treatment.	502,440[a]	PBS dispensing data[b].
B	Angina patients treated with a beta blocker, calcium channel blocker or both.	[redacted][a]	PBS dispensing data[b].
C	Angina patients treated with a beta blocker, calcium channel blocker or both, and a short acting nitrate.	[redacted][a]	PBS dispensing data[b].
D	Angina patients treated with a beta blocker, calcium channel blocker or both, and a short acting nitrate and an add-on therapy (current & past).	[redacted][a]	PBS dispensing data[b].
E	Angina patients treated with a beta blocker, calcium channel blocker or both, and a short acting nitrate and an add-on therapy (current only).	[redacted][a]	PBS dispensing data[b].
F	Angina patients treated with a beta blocker, calcium channel blocker or both, and a short acting nitrate and an add-on therapy and where revascularisation is not an option.	[redacted][a]; estimated [redacted]% of stable angina patients are revascularised.	PBS dispensing data[b] + cardiologist survey.
G	Angina patients treated with a beta blocker, calcium channel blocker or both, and a short acting nitrate and an-add on therapy and where revascularisation is not an option and haemodynamic concerns limit other anti-anginal treatment options.	[redacted][a]; estimated of patients not suitable for revascularisation, [redacted]% have haemodynamic issues.	PBS dispensing data[b] + cardiologist survey.
H	Uptake rate.	Years 1 – 6: [redacted]	Assumption.
I	Compliance rate.	[redacted]%.	Assumption.
J	Number of patients treated with ranolazine.	Years 1 – 6: [redacted], [redacted].	Based on ABS population projections (ABS, 2013) and proportion of population eligible ([redacted]%[c]) for the proposed PBS indication (estimate).

[a]=in the current year

[b] Based on analysis of the 10% PBS sample. Page 1 of the attachment to the minor resubmission, "PBS angina data methodology" states that the data source included all scripts processed from March 2005 to June 2017, however, page 2 states that the analysis examined script numbers from the period January 2017 – June 2017.

[c] [redacted] (row G) / 24,781,121 (2017 Australian population)

Source: compiled during the minor overview from p42-43 of the minor resubmission and the utilisation and cost model provided with the minor resubmission.

6.14 The minor resubmission presented a simplified, revised financial workbook to estimate the impact of listing ranolazine. The minor resubmission stated that it used the PBS 10% Patient Sample data six months to June 2017, with the description of the methodology and results included in an appendix. However, the estimate of the number of patients eligible for ranolazine presented in the minor resubmission differed from that provided in the appendix. This difference may be the result of the workbook submitted with the minor resubmission used twelve months of PBS dispensing data from October 2016 – September 2017, whereas the appendix stated that the analysis of patient numbers were based on prescriptions from March 2005 to June 2017 (a workbook was not provided with the appendix). The PBAC noted that the pre-PBAC response did not comment on the reason for the discrepancy.

6.15 The estimated use and financial implications of listing ranolazine are presented below.

Table 2: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Eligible patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prescriptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to the PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: compiled during the minor overview from Tables 4.2 – 4.4, p44 of the minor resubmission.

The redacted table shows that at year 6, the estimated number of patients was less than 10,000, the estimated number of prescriptions was less than 10,000, and the cost to the PBS would be less than $10 million.

6.16 The minor resubmission estimated a net cost to the PBS of less than $10 million in Year 6 of listing, with a total net cost to the PBS of less than $10 million over the first six years of listing. Compared to the March 2017 major submission, there was a [redacted]% reduction in the estimated patient numbers ([redacted] vs [redacted]) and cost to the PBS ($[redacted] million vs $[redacted] million) over five years, in the minor resubmission.

6.17 No offsets to the PBS/RPBS or MBS were claimed. The minor resubmission claimed that this is a conservative assumption as the cardiologist survey estimated that [redacted]% of patients unsuitable for revascularisation with haemodynamic issues are treated with a combination of perhexiline, nicorandil, short-acting and long-acting nitrates.

6.18 The PBAC noted that ranolazine requires initial dose titration in order to establish tolerability where patients should take 375 mg twice daily for 2 to 4 weeks, and increase to 500 mg twice daily. Based on the patient's response, further titration is recommended to the maximum dose of 750 mg twice daily. The requested maximum quantity of 60 tablets with 5 repeats will provide 6 months of treatment which is sufficient for the recommended dosing schedule. The PBAC considered however, that there may be wastage of tablets during the dose titration period.

6.19 The requested PBS listing is much narrower than the approved TGA indication and there is a risk of leakage to a wider population if ranolazine became available on the PBS. The pre-PBAC response contended that the risk of leakage can be sufficiently managed with the requested Authority Required (Telephone) listing. It argued that a Risk Sharing Arrangement (RSA) is not warranted for the small population proposed and the estimated low overall cost to government. The pre-PBAC response stated, however, that if a RSA was deemed necessary, the sponsor is open to discussing what the deed would entail. It proposed that the patient cap in a RSA be set at a higher level than the estimated population, due to a possible margin of error in each step of the calculation of the size of the patient population proposed in the minor resubmission, plus a factor for population growth.

6.20 The PBAC noted that as a minor resubmission, the methodology applied to estimate utilisation and financial impact was not evaluated. The PBAC also noted that the estimated patient population and financial impact to government were significantly reduced in the minor resubmission compared to the March 2017 major submission, due to the narrower PBS indication proposed. The PBAC further noted that the proposed PBS indication was narrower than the TGA indication and considered that given the symptomatic nature of the condition, an Authority Required (Telephone) listing was insufficient to mitigate the risk of leakage. The PBAC therefore advised that an RSA, with a hard cap, based on the estimated patient population would be required to ensure financial certainty to government.

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

7 PBAC Outcome

7.1 The PBAC recommended the Section 85 listing of ranolazine. The Committee is satisfied that ranolazine provides, for some patients, a significant improvement in efficacy over placebo. The PBAC also acknowledged the unmet clinical need in patients with stable angina whose symptoms are not controlled satisfactorily by the maximum tolerated doses of a beta-blocker or a calcium channel blocker, where revascularisation is not an option and haemodynamic concerns limit other anti-anginal treatment options. However, the PBAC was concerned that given the symptomatic nature of the condition and the broader TGA indication, that there was a high risk of leakage of using PBS-subsidised ranolazine outside of the PBS eligibility criteria.

7.2 The PBAC considered that given the sponsor was only seeking PBS listing of the 60 tablet pack size, although a 15 tablet pack size is also TGA registered, there may be wastage of tablets during the dose titration period. The PBAC advised that the proposed Authority Required (Telephone) listing is appropriate, given that ranolazine is positioned to be used as a later-line/add-on symptomatic treatment.

7.3 The PBAC accepted placebo as the appropriate comparator for the requested PBS population. The PBAC recalled its March 2017 consideration that ranolazine was likely to be superior in terms of effectiveness over placebo, but considered that the magnitude of benefit remained unclear. However, the PBAC considered that ranolazine may have a small but useful role in the requested PBS population. The PBAC also noted that whilst ranolazine was of inferior safety to placebo, there were no significant safety concerns.

7.4 The PBAC noted that no adjustments were made to the economic model and that the minor resubmission proposed a lower price for ranolazine for the placebo comparison of $[redacted]/day (compared to $[redacted]/day in the March 2017 major submission).

7.5 The PBAC considered that although there was uncertainty in the estimated utilisation and financial impact to government, the overall eligible population and

cost to government was significantly reduced from the March 2017 major submission. The PBAC advised however, that a risk sharing arrangement with a hard cap would be required to manage the risk of leakage.

7.6 The PBAC noted that other PBS listed medicines for angina are not exempt from the Early Supply Rule and are currently included for prescribing by nurse practitioners under a shared care model, and advised that the same should apply to ranolazine. The PBAC further advised that under Section 101(3BA) of the National Health Act 1953, ranolazine should not be treated as interchangeable with any other drugs on an individual patient basis, as ranolazine belongs to a new class of anti-anginal drug with no alternative pharmacological analogues listed on the PBS.

7.7 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item: restriction to be finalised.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
RANOLAZINE TABLET 375 MG, 500 MG, 750 MG, 60	1	5	Ranexa®	Menarini

Category/ Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	*Stable ~~A~~angina* pectoris
PBS Indication:	Stable angina pectoris
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☒Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined
Clinical criteria:	Patient must be one in whose symptoms are not controlled satisfactorily by the maximum tolerated doses of *a* beta-blockers or a calcium channel blocker; AND Patient must be one in whom revascularisation is not an option; AND Patient must be one in whose haemodynamic concerns limit other anti-anginal treatment options

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.

9 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.

10 Sponsor's Comment

The sponsor had no comment.