

4.01 RIVAROXABAN, Tablet 2.5 mg, Xarelto[®], Bayer Australia Limited.

1 Purpose of Application

- 1.1 The minor submission requested an Authority Required (STREAMLINED) listing of rivaroxaban in combination with aspirin for the treatment of patients at high risk of recurrent cardiovascular events with coronary artery disease (CAD) or peripheral artery disease (PAD) who meet certain conditions.
- 1.2 The PBAC previously considered rivaroxaban for this indication in March 2019 (rejected) and March 2020 (deferred).
- 1.3 The submission made the following changes, which were requested by the PBAC in its March 2020 deferral of rivaroxaban:
- revised the restriction based on the PBAC’s March 2020 advice;
 - an █% price reduction, which resulted in an incremental cost-effectiveness ratio (ICER) of \$15,000 - \$45,000 per QALY using the economic model provided in the pre-PBAC response as requested by the PBAC in March 2020;
 - revised the financial estimates to incorporate the reduced price and reduced uptake rates; and
 - a risk share arrangement (RSA) was proposed with a █ rebate over the caps.
- 1.4 Listing was requested on a cost-effectiveness basis compared with aspirin alone.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with chronic coronary artery disease (CAD) and peripheral artery disease (PAD); or Patients with CAD or PAD and at least one additional risk factor of: <ul style="list-style-type: none"> • Heart failure (LVEF ≥ 30% to < 50%); or • Chronic kidney disease defined by an eGFR 15 to <60 mL/min; or • Diabetes mellitus and: age ≥ 60; concomitant microalbuminuria; or of Aboriginal or Torres Strait Islander descent.
Intervention	Rivaroxaban 2.5 mg twice daily, plus aspirin 100 mg daily
Comparator	Aspirin 100 mg daily
Outcomes	Reductions in cardiovascular events (cardiovascular death, ischaemic stroke) and peripheral vascular events. Increases in major bleeding events.
Clinical claim	In patients with atherosclerotic disease of the coronary and/or peripheral arteries at high risk of cardiovascular events, rivaroxaban 2.5 mg in combination with aspirin is superior in terms of efficacy and inferior in terms of safety compared to aspirin.

Source: Table 1.1-1, p.8 of the previous submission

2 Background

Registration status

- 2.1 Rivaroxaban 2.5 mg was TGA registered on 11 January 2019 for use in combination with aspirin with an indication of ‘Prevention of major cardiovascular events (composite of stroke, myocardial infarction and cardiovascular death) in patients with CAD and/or PAD’.

Previous PBAC consideration

- 2.2 A summary of the key matters of concern arising from the PBAC consideration of the March 2020 submission for rivaroxaban, and how the current submission addresses these concerns, is presented in Table 2.

Table 2: Summary of key matters of concern from PBAC’s March 2020 consideration

Matters of concern	How the submission addressed it
Include the updated restriction based on the PBAC’s advice, which was to target use to a higher risk PAD population and to include diabetes as a risk factor.	Updated PBS restriction as per March 2020 Public Summary Document (PSD); included diabetes in the eligibility criteria.
A further price reduction would be required to achieve an ICER in the range of around \$15,000 - \$45,000 per QALY, using the pre-PBAC response economic model.	AEMP reduced from \$ [redacted] to \$ [redacted], a reduction of [redacted]% compared with the previous submission. The additional price reduction resulted in an ICER of \$15,000 - \$45,000 per QALY
The financial estimates should be revised to reflect the lower price (derived from the economic model outlined above) and reduced uptake rate estimates. Uptake rates of 15% to 30% over six years would be more reasonable (rather than 15% to 40% as proposed in the pre-PBAC response).	Uptake rates changed: Current submission: 9.6% in Year 1, increasing to 20.4% in Year 3, and then decreasing to 19.4% in Year 6. Pre-PBAC response: 9.6% in Year 1, increasing to 30% in Year 6.
An RSA with a [redacted] rebate above the caps would be required given the uncertain patient numbers and the potential for use outside the restriction	Addressed Pre-PBAC response: RSA capped expenditure at [redacted] per year from Year 3 onwards.

Source: Compiled during preparation of the Minor Overview based on Table 1, p.1 of the minor submission and the pre-PBAC response. Paragraph references refer to the March 2020 rivaroxaban PSD.

For more detail on PBAC’s view, see section 6 PBAC outcomes.

3 Requested listing

- 3.1 The submission updated the restriction in line with PBAC’s previous advice, including by targeting use in patients with PAD to a higher risk population, and including diabetes as a risk factor. The listing requested by the submission is outlined below. The restriction recommended by the PBAC is presented in Section 7.

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Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Dispensed Price Max Qty	Proprietary Name and Manufacturer	
RIVAROXABAN rivaroxaban 2.5 mg tablet, 60	NEW	1	60	5	Public: \$84.83 Effective: \$ [REDACTED]	Xarelto	Bayer Australia Ltd

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 (SCM) <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Type / Method: <input checked="" type="checkbox"/> Authority Required – Streamlined
Episodicity: Chronic
Severity: stable
Condition: atherosclerotic disease
Indication: Chronic stable atherosclerotic disease
Clinical criteria:
The treatment must be in combination with aspirin
AND
Clinical criteria:
The treatment must not be in combination with any other anti-platelet therapy
AND
Clinical criteria:
Patient must have a diagnosis of coronary artery disease and must have one or more of the following risk factors: <ul style="list-style-type: none"> • Diagnosed heart failure (left ventricular ejection fraction greater than or equal to 30% but less than 50%); • Diagnosed kidney disease classified by an eGFR 15-60ml/min. • Diabetes Mellitus and at least one of the following: age 60 years or more; concomitant microalbuminuria; or be of Aboriginal or Torres Strait Islander descent. OR Patients must have a diagnosis of peripheral artery disease and must have one or more of the following risk factors: <ul style="list-style-type: none"> • Concomitant coronary artery disease • Diagnosed heart failure (left ventricular ejection fraction greater than or equal to 30% but less than 50%) • Diagnosed kidney disease classified by an eGFR 15-60ml/min • Diabetes Mellitus and at least one of the following: age 60 years or more; concomitant microalbuminuria; or be of Aboriginal or Torres Strait Islander descent.
AND
Clinical criteria:
Patient must have, if coronary artery disease is present, one or more of the following: <ul style="list-style-type: none"> i) Previous multi-vessel coronary revascularisation procedure; ii) Significant stenosis in 2 or more coronary arteries; iii) Previous single vessel coronary revascularisation procedure with significant stenosis in more than 1 coronary artery. OR Patient must have, if peripheral arterial disease is present, one or more of the following: <ul style="list-style-type: none"> i) Previous peripheral artery or carotid revascularisation intervention; ii) Intermittent claudication with ankle-brachial index less than 0.9; iii) Asymptomatic carotid artery stenosis greater than 50%.
AND
Clinical criteria:
The condition must be diagnosed by angiography or non-invasive imaging where peripheral artery disease, peripheral artery stenosis, stenosis of the carotid artery, or coronary artery stenosis is present.
AND
Clinical criteria:
Patient must not be, or have any of the following: <ul style="list-style-type: none"> i) At high risk of bleeding; ii) A history of stroke within one month of treatment initiation or any history of haemorrhagic or lacunar stroke; iii) Severe heart failure with a known ejection fraction less than 30% or New York Heart Association class III or IV symptoms; iv) An estimated glomerular filtration rate less than 15 mL/min; v) A requirement for dual antiplatelet therapy, other non-ASA antiplatelet therapy, or higher dose oral anticoagulant therapy

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Treatment criteria:
Must be treated by or in consultation with a specialist physician.
Administrative Advice:
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.

- 3.2 The submission proposed a special pricing arrangement for rivaroxaban 2.5 mg (quantity 60), with an effective ex-manufacturer price (AEMP) of \$ [REDACTED], which was [REDACTED] % lower than proposed in the previous submission’s pre-PBAC response (\$ [REDACTED]).
- 3.3 The restriction proposed by the submission was consistent with the PBAC’s previous advice (paragraph 3.1, rivaroxaban PSD, March 2020). The PBAC previously considered that the patient population encompassed by this restriction adequately defined the high-risk subgroups who would derive the most benefit from treatment with rivaroxaban (paragraph 7.3, rivaroxaban PSD, March 2020).
- 3.4 The PBAC considered that separate initial and continuing listings would be required to simplify the continuing treatment listing.
- 3.5 The PBAC considered that treatment with rivaroxaban for this condition must be initiated by a specialist physician or in consultation with a specialist physician. The PBAC considered that treatment could be continued (after the initial PBS prescription) by non-specialist prescribers.
- 3.6 The submission stated that approximately less than 10,000 patients require transition from non-PBS to PBS-subsidised supply (‘grandfather access’) in Year 1 and requested a grandfather listing (not previously requested), but did not propose any restriction wording. The ESC previously emphasised that any grandfather restriction would need to ensure that patients had met the PBS initiation criteria at the time of commencement of rivaroxaban (paragraph 3.8, rivaroxaban PSD, March 2020). The PBAC considered that a separate grandfather restriction would not be required given that grandfather patients would be eligible under the initial restriction (if they meet the PBS initiation criteria).
- 3.7 The submission requested prescribing by nurse practitioners. The existing PBS-listings for rivaroxaban are ‘suitable for prescribing by nurse practitioners’ (in the context of a shared care model). However, unlike the existing listings, the requested initial restriction requires that the patient must be treated by, or in consultation with, a specialist/cardiologist. Thus, the PBAC considered that prescribing by nurse practitioners (shared care model) would only be appropriate for continuing use.

For more detail on PBAC’s view, see section 6 PBAC outcomes.

4 Comparator

- 4.1 The PBAC previously considered that aspirin alone, the nominated main comparator, was appropriate.

For more detail on PBAC’s view, see section 6 PBAC outcomes.

5 Consideration of the evidence

Sponsor hearing

5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

5.2 The PBAC noted and welcomed the input from an individual, but noted that this comment related to the treatment of pulmonary embolism, for which rivaroxaban is already PBS-listed.

Clinical trials

5.3 No new clinical data were provided in the submission. The previous submission was based on the COMPASS trial, details of which are provided in the table below.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
COMPASS	A Randomized Controlled Trial of Rivaroxaban for the Prevention of Major Cardiovascular Events in Patients With Coronary or Peripheral Artery Disease (COMPASS - Cardiovascular Outcomes for People Using Anticoagulation Strategies).	Internal study report; 16 October 2017
	Eikelboom et al. (2017). Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease.	NEJM 377(14): 1319-1330
	Anand et al. (2019) Rivaroxaban plus aspirin in relation to vascular risk in the COMPASS trial.	J Am Coll Cardiol 73(25): 3271-3280
	Anand et al. (2018). Major Adverse Limb Events and Mortality in Patients With Peripheral Artery Disease: The COMPASS Trial.	J Am Coll Cardiol 71 (20): 2306-2315
	Anand et al. (2017). Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: An international, randomised, double-blind, placebo-controlled trial.	The Lancet S0140-6736(17): 32409-1.
	Connolly et al., Rivaroxaban with or without aspirin in patients with stable coronary artery disease: An international, randomised, double-blind, placebo-controlled trial.	The Lancet S0140-6736(17): 32458-3.
	Fox et al. (2019b) Rivaroxaban plus aspirin in patients with vascular disease and renal dysfunction: From the COMPASS trial.	J Am Coll Cardiol 73(18): 2243-2250.
	Branch et al. (2019) Rivaroxaban with or without aspirin in patients with heart failure and chronic coronary or peripheral artery disease.	Circulation 140: 529-537.
	Eikelboom et al. (2019). Major Bleeding in Patients With Coronary or Peripheral Artery Disease Treated With Rivaroxaban Plus Aspirin.	J Am Coll Cardiol 74 (12): 1519-1528.
	Lamy et al. (2019). Rivaroxaban, Aspirin, or Both to Prevent Early Coronary Bypass Graft Occlusion: The COMPASS-CABG Study.	J Am Coll Cardiol 2019; 73 (2): 121-130.
	Sharma et al. (2019). Stroke Outcomes in the COMPASS Trial.	Circulation 2019; 139 (9): 1134-1145.
	Moayyedi et al. (2019a). Safety of Proton Pump Inhibitors Based on a Large, Multi-Year, Randomised Trial of Patients Receiving Rivaroxaban or Aspirin.	Gastroenterology 157 (3): 682691.e2.
	Moayyedi et al. (2019b). Pantoprazole to Prevent Gastrointestinal Events in Patients Receiving Rivaroxaban and/or Aspirin in a Randomised, Double-Blind, Placebo-Controlled Trial.	Gastroenterology 157 (2): 403-412.e5.

Source: Table 2.2-1, p.67; Table 2.2-2, p.67; Table 2.2-3, p.68 of the previous submission.

Clinical claim

- 5.4 The PBAC reiterated its previous advice that the claim of superior comparative effectiveness of rivaroxaban in combination with aspirin versus aspirin alone was reasonable, but that the magnitude of the benefit in the proposed PBS population was uncertain (paragraph 6.37, rivaroxaban PSD, March 2020).
- 5.5 The PBAC reiterated its previous advice that the claim of inferior comparative safety of rivaroxaban in combination versus aspirin alone was reasonable. However, the PBAC considered that the magnitude of the risk of bleeding was uncertain, noting that the risk was likely to vary depending on age, renal function, baseline risk and co-morbidities (paragraph 6.38, rivaroxaban PSD, March 2020).

Economic analysis

- 5.6 The model submitted with the previous pre-PBAC response (March 2020) resulted in an ICER of \$15,000 - \$45,000 per QALY gained. This model had removed both non-cardiovascular death treatment effects and non-cardiovascular death transition probabilities, and proposed a lower effective price (█% reduction versus the price proposed in the submission).
- 5.7 The March 2020 PSD states ‘given the uncertain safety and efficacy in clinical practice, particularly the risk of bleeding and the likely overestimation of the clinical benefit in the trial (due to the premature stopping of the trial), and in the context of a secondary prevention medicine for a broad patient population, the PBAC considered that an ICER in the range of around \$15,000 - \$45,000 per QALY would be required for rivaroxaban to be considered suitably cost-effective. The PBAC was particularly concerned that the risk of bleeding would be higher in the proposed PBS population than in the COMPASS trial (which likely underestimated the bleeding risk) and considered that this contributed to uncertainty regarding the ICER and the need for the ICER to be more conservative than proposed in the submission and the pre-PBAC response. The PBAC considered that this ICER should be based on the model submitted with the pre-PBAC response’ (paragraph 7.11, rivaroxaban PSD, March 2020).
- 5.8 The only change to the economic model, compared with the model presented in the previous pre-PBAC response, was that a further reduction to the price of rivaroxaban was proposed (AEMP reduced from \$█ to \$█).
- 5.9 The results of the modelled economic evaluation are summarised below.

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Table 4: Results of economic evaluation of rivaroxaban with aspirin compared to aspirin alone

Outcome	Rivaroxaban with aspirin	Aspirin alone	Increment
Revised economic model			
Costs	\$ [REDACTED]	\$14,211	\$ [REDACTED]
LYs	10.191	10.117	0.074
QALYs	7.996	7.920	0.076
Incremental cost per QALY (Effective DPMQ \$ [REDACTED])			\$ [REDACTED]
March 2020 pre-PBAC response			
Costs	\$ [REDACTED]	\$14,211	\$ [REDACTED]
LYs	10.191	10.117	0.0747
QALYs	7.996	7.920	0.076
Incremental cost per QALY (Effective DPMQ \$ [REDACTED])			\$ [REDACTED]

Source: Table 4 of the submission, Attachment 2_ Xarelto Econ Eval Updated pre-PBAC base case_new price.xlsx

LY = life years; QALYs = quality-adjusted life years

5.10 The submission’s model estimated an ICER of \$15,000 - \$45,000 per QALY.

Drug cost/patient /year: \$ [REDACTED]

5.11 Based on the financial estimates, the estimated drug cost for rivaroxaban would be \$ [REDACTED] per patient per year, based on the requested DPMQ of \$ [REDACTED] and an average of 8.8 scripts per patient per year (assuming: 76% compliance; all patients who experience an event will cease rivaroxaban for 12 months; and negligible incremental aspirin costs). The drug cost per patient was lower in the economic model due to the persistence estimates applied.

Estimated PBS usage & financial implications

5.12 The only changes to the financial estimates compared with the March 2020 pre-PBAC response were that the uptake rates and the proposed price of rivaroxaban were reduced.

5.13 The table below summarises the key inputs into the utilisation estimates.

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Table 5: Key inputs for financial estimates

Parameter	Value applied and source	Compared with previous submission
Prevalent population	Prevalence of 0.77% to 0.83% based on eligible patients in an analysis of hospital data from 2010 in Western Australia, extrapolated to Australian prevalence based on ABS population statistics, and extended to current year based on projected growth in prevalence of cardiovascular disease (Sarink 2016).	Unchanged
Uptake rate	9.6% in Year 1, increasing to 20.4% in Year 3, and then decreasing to 19.4% in Year 6. To address concerns that it does not seem plausible for uptake rates to decline from Year 3 to Year 6, the pre-PBAC response proposed uptake rates that steadily increased from 9.6% in Year 1 to 30% in Year 6.	Previous pre-PBAC response: 15% in Year 1 increasing to 40% in Year 6. Based on the lower limit of the 95% CI from the market research.
Compliance rate	76.4% compliance (9.3 scripts per patient per year) based on 10% sample data for rivaroxaban in the non-valvular atrial fibrillation indication	Unchanged from previous pre-PBAC response.
Treatment interruptions	Patients were assumed to cease rivaroxaban for 12 months if they have an event (based on event rates from the economic model). This reduced the average scripts per patient per year from 9.3 to 8.8 in Year 1.	Unchanged from previous pre-PBAC response

Source: Table 18, rivaroxaban PSD, March 2020; and Attachment 3_ Xarelto (rivaroxaban) Utilisation and Cost – revised.xlsx
ABS, Australian Bureau of Statistics.

- 5.14 The previous submission (March 2020 pre-PBAC response) assumed uptake rates of 15% in Year 1 increasing to 40% in Year 6 and, in March 2020, the PBAC considered that it ‘would be more reasonable to assume uptake rates of 15 to 30% over six years’ (paragraph 7.12, rivaroxaban PSD, March 2020). To address this, the submission estimated uptake rates of 9.6% in Year 1 increasing to 20.4% in Year 3 then decreasing to 19.4% in Year 6.
- 5.15 The submission stated that it expected that the Year 3 cost to the PBS/RPBS of \$10 - \$20 million would be the peak PBS/RPBS cost, due the expected loss of exclusivity in 2023 and the anticipated statutory F2 25% price reduction. The submission (p.3) proposed to maintain the Commonwealth payment stable for Years 3 to 6, by reducing the uptake rates from a peak of 20.4% in Year 3 to 20.0% Year 4, 19.7% in Year 5 and 19.4% in Year 6. As it would have been implausible for uptake to decline from Year 3 to Year 6, the pre-PBAC response provided revised uptake rates which assumed a steady increase in uptake from 9.6% in Year 1 to 30% by Year 6 in order to derive more accurate financial estimates. The pre-PBAC response proposed a risk sharing arrangement (RSA) that would cap Commonwealth expenditure at [REDACTED] from Year 3 onwards (noting that this is lower than estimated expenditure).
- 5.16 The estimated cost to the PBS/RPBS is summarised in the table below.

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Table 6: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Australian population	25,873,480	26,301,274	26,727,025	27,147,199	27,562,195	27,970,435
Prevalence rate	%	%	%	%	%	%
Total eligible patients						
Uptake rates						
Current submission	9.6%	16.9%	20.4%	20.0% ^a	19.7% ^a	19.4% ^a
Pre-PBAC response	9.6%	16.9%	20.4%	23.6%	26.8%	30.0%
March 2020 (pre-PBAC response)	15%	26%	32%	36%	40%	40%
Estimated extent of use						
Grandfather patients		-	-	-	-	-
Number of patients treated						
Number of scripts (pre-PBAC response) ^b						
Estimated financial implications of rivaroxaban						
Cost to PBS/RPBS less copayments (pre-PBAC response)	\$	\$	\$	\$	\$	\$
Net impact after RSA rebate (pre-PBAC response)	\$	\$	\$	\$	\$	\$
March 2020 (pre-PBAC response)	\$	\$	\$	\$	\$	\$
March 2019	\$	\$	\$	\$	\$	\$

Source: Table 4, p5 of the submission; Attachment 3_Xarelto (rivaroxaban) Utilisation and Cost – revised.xlsx

^a The submission assumed loss of patent exclusivity would occur from Year 4 and thus reduced the uptake rates to maintain PBS/RPBS expenditure at

^b Assuming 9.3 scripts/patient/year based on compliance of 76.39%, and assuming that patients cease rivaroxaban for 12 months if they have an event (based on event rates from the economic model) which results in average of 8.8 scripts/patient/year.

The redacted table shows that at Year 6, the estimated number of patients treated was 10,000 – 50,000.

- 5.17 The pre-PBAC response estimated a net cost to the PBS/RPBS of \$30 - \$60 million in Year 6 of listing, with a total net cost to the PBS/RPBS of more than \$100 million over the first 6 years of listing. The pre-PBAC response also proposed RSA expenditure caps that would cap PBS/RPBS expenditure at over the first 6 years of listing.
- 5.18 This expenditure was lower than estimated in previous submissions, which estimated costs over 6 years of: more than \$100 million in the previous pre-PBAC response, more than \$100 million in the previous submission and more than \$100 million in the March 2019 submission.
- 5.19 The submission stated that the sponsor plans to commence a special access program for rivaroxaban. There were less than 10,000 grandfather patients included in the submission's estimates of uptake in Year 1 of listing.
- 5.20 The previous pre-PBAC response also estimated the impact on utilisation due to the ESC's suggested changes to the restriction (inclusion of patients with CAD and diabetes which may increase patient numbers, and further targeting of the PAD only population which may reduce patient numbers) based on data from the Western Australia linked

data analysis. The pre-PBAC response estimated that the restriction changes would lead to an overall increase of less than 10,000 patients, comprising an increase of less than 10,000 patients with CAD and diabetes, and a reduction of less than 10,000 patients with PAD only (i.e. without concomitant diabetes, HF, or CKD). The pre-PBAC response did not include these additional patients in the revised financial estimates nor the revised RSA caps. In March 2020, the PBAC considered that this was likely conservative in the context of an RSA with [REDACTED] rebate above the caps. (paragraph 6.73, rivaroxaban PSD, March 2020). These additional patients were also not included in the submission.

Financial Management – Risk Sharing Arrangements

- 5.21 In its previous consideration, ‘the PBAC considered that a RSA with a [REDACTED] rebate for use above the caps would be required given the uncertain patient numbers and the potential for use outside the restriction. The PBAC emphasised that the financial estimates underpinning this RSA would need to be based on conservative assumptions to provide confidence that the utilisation estimates reflect only the intended high-risk population in order to ensure cost-effectiveness’ (paragraph 7.13, rivaroxaban PSD, March 2020).
- 5.22 The revised estimates proposed in the submission were based on the conservative assumptions as requested by the March 2020 PBAC.
- 5.23 The pre-PBAC response proposed a RSA with cap as outlined in Table 6 above. The proposed RSA caps were set at [REDACTED] per year from Year 3 onwards, noting this was lower than estimated expenditure, which the pre-PBAC response stated was due to rivaroxaban being anticipated to lose exclusivity late in 2023 (Year 3 of the financial estimates). The pre-PBAC response stated that the caps proposed ‘resulted in Commonwealth expenditure estimates below the current cabinet threshold’.

For more detail on PBAC’s view, see section 6 PBAC outcomes.

6 PBAC Outcome

- 6.1 The PBAC recommended the Authority Required listing of rivaroxaban for the treatment of patients at high risk of recurrent cardiovascular events with coronary artery disease (CAD) or peripheral artery disease (PAD) and additional high-risk factors. The PBAC’s recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of rivaroxaban would likely be acceptable at the price proposed in the minor submission. The PBAC further considered that the financial impact estimated in the pre-PBAC response was reasonable, noting that the Risk Sharing Arrangement (RSA) proposed in the pre-PBAC response would appropriately mitigate the risk of any excess financial impact of the listing due to uncertain patient numbers, as well as potential use outside the restriction.
- 6.2 The PBAC was satisfied that rivaroxaban in combination with aspirin provides, for

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some patients, a significant improvement in efficacy over aspirin alone.

- 6.3 The PBAC considered that there is a moderate clinical need for effective treatments for the secondary prevention of thrombotic events in patients with a high risk of cardiovascular events.
- 6.4 The PBAC considered that the restriction proposed in the submission adequately defined the high-risk subgroups who would derive the most benefit from treatment with rivaroxaban.
- 6.5 The PBAC considered that treatment with rivaroxaban for this condition must be initiated by a specialist physician or in consultation with a specialist physician. The PBAC considered that treatment could be continued (after the initial PBS prescription) by non-specialist prescribers.
- 6.6 The PBAC reiterated its previous advice that aspirin alone, the nominated main comparator, was appropriate.
- 6.7 The PBAC considered that rivaroxaban is associated with important clinical benefits in the intended population, noting that the key trial, COMPASS, which comprises a broader population than requested for listing, found that rivaroxaban plus aspirin was associated with a statistically significant reduction in the proportion of patients who experienced myocardial infarction, stroke, or cardiovascular death (the primary outcome) compared with aspirin alone (HR: 0.76 (95% CI: 0.66, 0.86)).
- 6.8 The PBAC noted the submission had amended the economic model and adequately addressed the Committee's previous concerns by proposing a █% price reduction, which resulted in an incremental cost-effectiveness ratio (ICER) of \$15,000 - \$45,000 per QALY. The PBAC considered that rivaroxaban was likely cost-effective at the proposed price in the requested population.
- 6.9 The PBAC noted that the submission's financial estimates had been revised to incorporate the reduced price (outlined in the paragraph above) and reduced uptake rates, with the pre-PBAC response proposing a clinically plausible steady increase in uptake over the first six years of listing. The PBAC considered that the financial estimates proposed in the pre-PBAC response were reasonable and reflected the intended population.
- 6.10 The PBAC considered that the RSA proposed in the pre-PBAC response, which included a █ rebate for use above the caps and capped expenditure at █ per year from Years 3 to 6 would appropriately mitigate the risk of any excess financial impact of the listing due to uncertain patient numbers, as well as potential use outside the restriction.
- 6.11 The PBAC advised that rivaroxaban is suitable for prescribing by nurse practitioners (shared care model) in the continuing listing only.
- 6.12 The PBAC recommended that the Early Supply Rule should apply as it applies to other long-term oral prophylactic antithrombotic agents.

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6.13 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically the PBAC found that the circumstances of its recommendation for rivaroxaban:

- a) Treatment with rivaroxaban is expected to provide a substantial and clinically relevant improvement in efficacy over alternative therapies.
- b) Treatment with rivaroxaban is not expected to address a high and urgent unmet clinical need.
- c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

6.14 The PBAC advised that this submission would not meet the criteria for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

7 Recommended listing

7.1 *Add new indication to new strength (2.5 mg) only as follows:*

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
RIVAROXABAN rivaroxaban 2.5 mg tablet, 60	NEW	1	60	5	Xarelto

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Initial treatment

Restriction Summary [new] / Treatment of Concept: [new]

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction Type / Method: <input checked="" type="checkbox"/> Authority Required – Streamlined [new 4-digit code]
Episodicity: Chronic
Severity: stable
Condition: atherosclerotic disease
Indication: Chronic stable atherosclerotic disease
Treatment phase: Initial treatment
Clinical criteria:
The treatment must be in combination with aspirin, but not with any other anti-platelet therapy
AND
Clinical criteria:
Patient must have a diagnosis of coronary artery disease in addition to at least one of the following risk factors: (i) diagnosed heart failure (left ventricular ejection fraction of at least 30% but less than 50%) (ii) diagnosed kidney disease classified by an eGFR in the range of 15-60 mL/minute (iii) diabetes mellitus combined with at least one of the following: age at least 60 years / concomitant microalbuminuria / Aboriginal/Torres Strait Islander descent; OR
Patients must have a diagnosis of peripheral artery disease in addition to at least one of the following risk factors: (i) concomitant coronary artery disease (ii) diagnosed heart failure (left ventricular ejection fraction of at least 30% but less than 50%) (iii) diagnosed kidney disease classified by an eGFR in the range of 15-60 mL/minute (iv) diabetes mellitus combined with at least one of the following: age at least 60 years / concomitant microalbuminuria / Aboriginal/Torres Strait Islander descent
AND
Clinical criteria:
Patient must have, if coronary artery disease is present, at least one of the following: (i) a previous multi-vessel coronary revascularisation procedure (ii) significant stenosis in at least 2 coronary arteries (iii) a previous single vessel coronary revascularisation procedure with significant stenosis in more than 1 coronary artery; OR
Patient must have, if peripheral arterial disease is present, at least one of the following: (i) a previous peripheral /carotid artery revascularisation intervention (ii) intermittent claudication with an ankle-brachial index less than 0.9 (iii) asymptomatic carotid artery stenosis greater than 50%
AND
Clinical criteria:
The condition must be diagnosed by one of: (i) invasive (selective) angiography; (ii) noninvasive imaging (CT / ultrasound).
AND
Clinical criteria:
Patient must have evidence of an absence of each of the following: (i) high risk of bleeding (ii) prior stroke within one month of treatment initiation (iii) prior haemorrhagic / lacunar stroke (v) severe heart failure with a known ejection fraction less than 30% (vi) New York Heart Association class III / IV heart failure symptoms (vii) an estimated glomerular filtration rate less than 15 mL/minute (viii) a requirement for dual antiplatelet therapy (ix) a requirement for non-acetylsalicylic acid antiplatelet therapy (x) a requirement for a higher dose of oral anticoagulant therapy
Treatment criteria:
Must be treated by a specialist physician; OR
Must be treated by a physician who has consulted with a specialist physician

Continuing treatment

Restriction Summary [new] / Treatment of Concept: [new]

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners (SCM)
Restriction Type / Method: <input checked="" type="checkbox"/> Authority Required – Streamlined [new 4-digit code]
Episodicity: Chronic
Severity: stable
Condition: atherosclerotic disease
Indication: Chronic stable atherosclerotic disease
Treatment phase: Continuing treatment
Clinical criteria:
Patient must have received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
The treatment must be in combination with aspirin, but not with any other anti-platelet therapy
Administrative advice
Treatment may be continued by non-specialist prescribers
Administrative advice
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.

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

Bayer welcomes the PBAC decision to recommend the PBS listing of Xarelto 2.5mg in combination with aspirin for the treatment of patients at high risk of recurrent cardiovascular events with coronary artery disease (CAD) or peripheral artery disease (PAD) who meet certain conditions.