7.03 RIVAROXABAN, Tablet 2.5 mg, Xarelto®, Bayer Australia Limited.

1 Purpose of submission

1.1 The resubmission requested a Section 85 (Authority Required) PBS listing for low dose rivaroxaban in combination with aspirin for the prevention of recurrent cardiovascular events in patients at high risk of recurrent thrombotic events, specifically patients with peripheral artery disease (PAD), PAD with coronary artery disease (CAD), CAD with heart failure (HF), or CAD with chronic kidney disease (CKD).

1.2 The PBAC previously considered rivaroxaban for this indication in March 2019.

1.3 Listing of rivaroxaban (for use in combination with aspirin) was requested on a cost-effectiveness basis compared to aspirin alone.

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

Component	Description
Population	Patients with peripheral artery disease (PAD) defined as: • Previous peripheral artery or carotid revascularisation intervention or • Intermittent claudication with an ABI < 0.90 or • Asymptomatic carotid artery stenosis OR Patients with chronic coronary artery disease (CAD) and at least one additional risk factor of: • Heart failure (LVEF ≥ 30%) or • Chronic kidney disease defined by an eGFR 15 to <60 mL/min. These patient populations were further refined in the ESC Advice and pre-PBAC response (refer to Section 3).
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 resubmission

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 2019 major submission for rivaroxaban, and how the current resubmission addresses these concerns, is presented in Table 2.

Table 2: Summary of key matters of concern

Matter of concern, rivaroxaban Public Summary Document, March 2019 PBAC meeting	How the resubmission addresses it
The PBAC considered that the patient population should be more highly targeted to those patients who are likely to achieve the most favourable risk-benefit profile given the differing levels of absolute incremental benefits between patient groups which needs to be balanced against the high bleeding risk in some patients. …a population with a more favourable risk-benefit profile may include patients with CAD and PAD, or patients with CAD or PAD who have other high risk factors such as diabetes or recurrent events. (para 7.1 and 7.4) The PBAC noted there are a lack of treatment options for patients with PAD and considered there is a clinical need for effective treatments in this patient group, particularly treatments that reduce the risk of amputation. (para 7.2)	Addressed. The resubmission's proposed PBS restriction defines specific subgroups to address the unmet needs of patients with PAD, and to identify patients at higher risk of recurrent events who would receive the greatest absolute benefit: - PAD (with or without CAD) - CAD & HF (LVEF ≥ 30%) - CAD & CKD (defined as eGFR 15 to <60 mL/min). The target population was further refined by the ESC and pre-PBAC response.
The PBAC accepted that whilst aspirin was an appropriate comparator, it agreed with the ESC that there is some use of long-term (i.e. longer than 12 months) dual anti-platelet therapy following acute coronary syndromes and considered that clopidogrel may be a suitable comparator in a group of patients (e.g. those with high cardiovascular risk but low bleeding risk). (para 7.6)	Not changed. The resubmission argued that aspirin is the standard treatment for patients with CAD and/or PAD unless there is reason for DAPT treatment (clopidogrel + aspirin) for example post percutaneous revascularisation. The resubmission further stated that there does not appear to be clinical data clearly establishing a benefit for DAPT as secondary prevention in patients with CAD and additional risk factors such as PAD, HF and/or CKD.
The PBAC considered that the COMPASS trial, which had a median follow-up of 23 months, was relatively short in the context of a long-term treatment. …it was unclear whether the treatment effect would be maintained over time. (para 7.8) Provide further information about the results of the PPI component of the COMPASS trial	Unable to be addressed – no further clinical efficacy data were available. The ESC noted the Kaplan-Meier curves for the primary outcome did not indicate a convergence in the treatment effect over time, but noted the number of patients at risk was relatively low toward the end of the curves. Addressed. The results of the PPI sub-study were presented in the resubmission.

Matter of concern, rivaroxaban Public Summary Document, March 2019 PBAC meeting	How the resubmission addresses it
The ESC considered that a microsimulation approach may have been more appropriate as it would have a greater ability to track events over time … The ESC further considered that a microsimulation approach may be appropriate given the baseline heterogeneity of the patient population (para. 6.45). The economic model submitted did not provide a reliable basis for estimating the cost-effectiveness of rivaroxaban in combination with aspirin. In particular: - Up to 4 years of trial data were extrapolated to 30 years - The model assumed all patients would remain fully adherent and persistent - There were sparse clinical data informing transition probabilities resulting in implausible null transitions for some subsequent events and highly uncertain non-zero transitions for other subsequent events. (para 7.11)	Partially addressed. A microsimulation modelling approach was used in the resubmission, compared to a multi-state Markov model presented in the previous submission. However, the revised microsimulation approach does not account adequately for heterogeneity at baseline or over time in the patient population. Addressed. The resubmission assumes convergence of treatment effect after 4 years, with full convergence at 30 years (includes imperfect adherence). The resubmission estimated persistence based on a 10% Medicare sample of rivaroxaban use for stroke prevention in patients with atrial fibrillation. The switch from a cohort model to a microsimulation model reduced the number of required health states and therefore the number of transition probabilities required.
Estimated utilisation and financial impacts were high, with a total cost to the PBS/RPBS of more than $100 million over the first 6 years of listing (including the proposed risk sharing arrangement (RSA) rebate) (para 7.13) The PBAC considered that the uptake rates were likely significantly overestimated (para 7.14)	Addressed. Eligible patient subgroups were changed, resulting in a higher risk population of the COMPASS trial being eligible. A Special Pricing Arrangement proposed to reduce the cost per patient. Pooled uptake rates were higher in the resubmission compared to the March 2019 submission, but the smaller eligible patient population resulted in a smaller estimate of treated patients.
Any resubmission would need to propose an RSA with a 100% rebate over the cap to mitigate the uncertain patient population, the potential for use outside the restriction and the high overall financial impact (para 7.17)	Addressed. The eligible population was reduced by the selection of higher risk subgroups, and so total patient numbers were reduced. RSA amended to a proposed [redacted]% rebate over expected expenditure for the pooled patient population.

CAD, coronary artery disease; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; ESC, Economic Sub-Committee, HF, heart failure; PAD, peripheral arterial disease; PPI, proton pump inhibitor; RSA, risk share arrangement.

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

3 Requested listing

3.1 The restriction requested in the submission is outlined below. The PBAC's suggested additions 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
RIVAROXABAN 2.5 mg tablet, 60	1	5	Public: $92.99 ($84.84)* Effective: $[redacted]*	Xarelto® Bayer Australia Ltd.

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☐Dental ☒Medical Practitioners ☒Nurse practitioners (SCM) ☐Optometrists ☐Midwives
Restriction Level / Method: ☐Unrestricted benefit ☐Restricted benefit ☐Authority Required – In Writing

☐Authority Required – Telephone/Electronic/Emergency ☒Authority Required - Streamlined
Episodicity: ~~Secondary prevention~~ *Chronic*
Severity: ~~Chronic~~ *Stable*
Condition: Atherosclerotic disease
Indication: ~~Prevention of recurrence of atherothrombotic events~~ *Chronic stable atherosclerotic disease*
Treatment Phase: [nil]
Clinical criteria:
The treatment must be in combination with aspirin.
AND
Clinical criteria: ~~Patient must not require concomitant dual anti-platelet therapy.~~ *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: • 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:* ~~AND~~ ~~Patient must have one or more risk factors:~~ • *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.* • ~~Previous peripheral artery or carotid revascularisation intervention;~~ • ~~Intermittent claudication with ankle-brachial index less than 0.9;~~ • ~~Asymptomatic carotid artery stenosis greater than 50%.~~
AND
Clinical criteria: Patient *must have,* if coronary artery disease *is present,* one or more of the following: 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: 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* ~~Patients with~~ peripheral artery disease, peripheral artery stenosis, stenosis of the carotid artery, or coronary artery stenosis ~~must be diagnosed by angiography or non-invasive imaging~~ *is present.*
AND

Clinical criteria: *Patient must not be, or have any of the following:* ~~Not for patients with any one of the following characteristics:~~ 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.
Treatment criteria: ~~Patient initiation must be by a specialist or in consultation with a specialist.~~ *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.*

Source: Requested restriction, Tables 1.4-1 and 1.4-2, pp.51-54 of the resubmission
*Effective DPMQ shown is post 10% anniversary price cut

3.2 The resubmission proposed a special pricing arrangement. No special pricing arrangement was offered in the March 2019 submission. The effective DMPQ represents a discount of approximately [redacted]% after adjusting for an expected 10-year F1 anniversary price cut (from April 2020). The pre-PBAC response proposed a further [redacted]% price reduction, resulting in a revised effective DPMQ of $[redacted], and a revised approved ex-manufacturer price (AEMP) of $[redacted] (reduced from $[redacted] in the resubmission).

3.3 The restriction proposed in the resubmission attempts to define groups at higher baseline cardiovascular risk, who will derive greater benefit from treatment, using specific clinical characteristics (including PAD (with or without CAD), CAD with heart failure, and CAD with CKD). However, these groups differ in their levels of risk and may exclude some high risk patients (e.g. with diabetes, with multiple prior events). The commentary considered that alternative methods to identify high risk patients who would derive the highest absolute benefit could be considered, for example use of a cardiovascular risk score that identifies patients at similar levels of baseline risk. However, the ESC recognised (as did the Pre-Sub-Committee Response (PSCR)) that there is no validated scoring system in this population.

3.4 When compared to the previous submission, the ESC considered the nominated patient subgroups were more representative of those who would benefit most from rivaroxaban, but that some further refinement would be required to define the optimal patient population, and to increase consistency with the recommended restrictions for other secondary prevention strategies, especially lipid lowering therapy. As such, the PBAC agreed with the following advice that ESC had provided regarding the proposed criteria:

- Inclusion of an additional risk factor to the CAD criteria to allow use in patients with diabetes mellitus and at least one of the following: age ≥ 60 years; microalbuminuria; or patients of Aboriginal or Torres Strait Islander descent.
- For patients with heart failure, the addition of an upper limit of 50% for left ventricular ejection fraction (LVEF) in order to exclude heart failure with preserved

ejection fraction (HFpEF), which is not the intended population (i.e. LVEF must be 30% or greater, but less than 50%).

3.5 The requested restriction (in the resubmission) included all patients with PAD, which is a heterogeneous group at substantially different levels of cardiovascular risk including patients with carotid artery stenosis at increased risk of stroke, and patients with lower extremity arterial disease at increased risk of limb events. In March 2019, the PBAC considered that a population with a more favourable risk-benefit profile may include patients with CAD and PAD, or patients with CAD or PAD who have other high risk factors such as diabetes or recurrent events (paragraph 7.4, rivaroxaban Public Summary Document, March 2019 PBAC meeting). Although there may be a clinical need for effective treatments for PAD, the ESC considered that the absolute benefit in the whole PAD population was the same or lower than the ITT population in COMPASS and therefore that the optimal population with PAD who would derive the highest absolute benefit from treatment with rivaroxaban needed to be more clearly defined. The ESC considered that it would be appropriate for the restriction to require that patients with PAD have concomitant CAD or have additional risk factors that replicate the criteria for CAD, that is that patients with PAD must have one or more of the following risk factors:

- Concomitant CAD;
- 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; or
- Diabetes mellitus and: age greater than or equal to 60; concomitant microalbuminuria; or of Aboriginal or Torres Strait Islander descent.

3.6 The pre-PBAC response (p1) accepted the revisions to the restriction proposed by the ESC in the paragraphs above, but noted that the sponsor was unable to undertake any further analyses of the COMPASS trial in these revised patient populations due to a 'lack of data accessibility'.

3.7 The requested restriction in the March 2019 submission excluded use in patients with acute coronary syndrome, and specified that use should be in the chronic or stable phase of atherosclerotic disease. In the resubmission, the requested restriction was amended to specify that rivaroxaban with aspirin should not be used in patients who require dual antiplatelet therapy, which implies patients will be in the chronic or stable phase of disease. The commentary considered that it was unclear in the proposed restriction at what point treatment should be initiated. However, the ESC considered that the duration of use of dual antiplatelet therapy following an acute event, such as an acute coronary syndrome or percutaneous revascularisation, was covered in appropriate guidelines and subject to evolution, but that clinicians would generally be aware of, and would follow, these guidelines.

3.8 The resubmission estimated that 3,600 patients would require grandfathered access in Year 1, however the resubmission did not propose a separate grandfathered restriction. The ESC emphasised that any grandfathered restriction would need to

ensure that patients had met the PBS initiation criteria at the time of commencement of rivaroxaban.

3.9 The ESC considered that a separate continuing restriction may also be required given that a patient's renal function and LVEF may change over time and thus, without a continuing restriction, some patients who initially meet the criteria would no longer continue to do so.

3.10 There is a significant potential for leakage as the requested restriction is narrower than the TGA indication (PAD and/or CAD), and the resubmission requested a streamlined authority restriction, consistent with the current rivaroxaban listings.

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

4 Population and disease

4.1 Atherosclerosis is a progressive disease characterised by the accumulation of lipids and fibrous elements in the large arteries. Stable CAD is predominantly an atherosclerotic disease with narrowing of coronary arteries that give rise to episodes of myocardial ischaemia causing angina pectoris. PAD is also typically caused by atherosclerosis and is broadly defined as a progressive stenosis or occlusion of any of the arteries except the coronary and intracranial arteries. CAD and PAD share the same risk factors; both increase with increasing age and the variable clinical characteristics and presentations result in variable overall risk of future major cardiovascular events.

4.2 Atherosclerosis can have long, stable periods interrupted by unstable periods, typically due to an acute atherothrombotic event. The risk of future major cardiovascular events varies considerably between patients with stable disease as compared to those with unstable disease and also based on evidence of more generalised atherosclerotic disease and previous atherothrombotic events.

4.3 The resubmission positions rivaroxaban 2.5 mg in combination with low dose aspirin as an alternative to low dose aspirin monotherapy for the secondary prevention of thrombotic cardiovascular events for patients with CAD and/or PAD with additional risk factors that place them at high risk of future events, referred to as the 'pooled target population'. Treatment is initiated at any time following resolution of acute events but is not to be administered in patients who are also eligible for dual antiplatelet therapy.

4.4 The pooled high risk population identified in the resubmission was based on an analysis of the key COMPASS trial (Anand et al, 2019). The authors applied a modified version of the Reduction of Atherothrombosis for Continued Health (REACH) registry cardiovascular risk score to the COMPASS trial patients and used the median score to divide patients into low- (<13) or high-risk (≥13) groups. The publication identified components of the REACH score that had a 30-month incidence risk at least equivalent or greater than those with a REACH score of 13+, which included patients with ≥2 vascular beds affected, those with low eGFR, and those with a history of HF. The

results of this study were based on the application of the REACH risk score to a highly selected trial population. Any deviations from the population in practice will alter the baseline risk, and the corresponding absolute risk reduction.

4.5 The pre-PBAC response stated that the analyses by Anand et al, 2019 also identified patients with diabetes as a distinct subgroup who are at high risk.

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

5 Comparator

5.1 The resubmission nominated aspirin alone as the main comparator for rivaroxaban plus aspirin, which was consistent with the previous submission. The PBAC previously accepted aspirin as an appropriate comparator (paragraph 7.6, Rivaroxaban Public Summary Document, March 2019 PBAC meeting).

5.2 Alternative comparators such as antiplatelet therapies (aspirin in combination with clopidogrel, or clopidogrel monotherapy) were not considered to be relevant comparators in the resubmission. The resubmission argued that these are indicated for short term management of acute coronary syndromes, and patients with an indication for dual antiplatelet therapy are excluded from the proposed restriction.

5.3 In most guidelines dual antiplatelet therapy (clopidogrel + aspirin) is indicated for 12 months following the short term management of acute coronary syndromes. Previously, the ESC and the PBAC considered that the use of long-term dual anti-platelet therapy following ACS (e.g. for longer than twelve months after an acute event) is increasing in clinical practice in patients at low risk of bleeding, who would likely represent a key part of the rivaroxaban target population. Thus, the ESC and PBAC previously considered that clopidogrel may be a relevant comparator in a sub-group of patients (paragraph 5.4, rivaroxaban Public Summary Document, March 2019 PBAC meeting).

5.4 This corresponds with the observed use of antiplatelet agents in the proposed high risk subgroups in the COMPASS trial, with up to 11% of patients in the high risk subgroups reporting use of clopidogrel at baseline. Collectively, the evaluation considered that this suggests clopidogrel could be considered an alternative comparator, particularly in populations with a higher level of baseline cardiovascular risk. While the ESC considered that clopidogrel (in combination with aspirin) may be a relevant comparator, the extent of the overlapping population would likely be small particularly if current clinical guidelines for use of dual anti-platelet therapy are followed.

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 and welcomed the input from health care professionals (3) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with rivaroxaban in combination with aspirin including improved cardiovascular outcomes (e.g. myocardial infarction, stroke and cardiovascular death) and reduction in amputation rates for patients with PAD, noting that there are limited therapeutic options for the treatment of PAD in Australia, with Indigenous Australians being most at risk. The comments from Diabetes Australia noted that reducing the complications of diabetes (such as stroke, heart disease and vascular disease) is a major element of the Australian National Diabetes Strategy 2016-2020.

Clinical trials

6.3 The resubmission was based on one head-to-head trial, in which patients were randomised in a 1:1:1 ratio to rivaroxaban 2.5 mg twice daily in combination with aspirin 100 mg once daily, or rivaroxaban 5 mg monotherapy twice daily, or aspirin 100 mg monotherapy (n=27,395; COMPASS). The COMPASS trial has previously been considered by the PBAC.

6.4 The resubmission presented additional subgroup analyses based on cardiovascular risk factors. Data from the CAD & HF and the CAD & CKD subgroup analyses have not previously been considered by PBAC.

6.5 The COMPASS trial used a partial factorial design. Patients who successfully completed the run-in phase were randomised 1:1:1 to rivaroxaban 2.5 mg twice daily in combination with aspirin 100 mg once daily, rivaroxaban 5 mg twice daily, or aspirin 100 mg once daily. Additionally, patients without an existing continuous need for treatment with a proton pump inhibitor (PPI) were randomised to pantoprazole or placebo. The ESC noted that the baseline use of non-study PPIs in this population was high (36%). The objective for pantoprazole randomisation was to determine whether pantoprazole 40 mg once daily compared with placebo reduces the risk of upper gastrointestinal bleeding, ulceration, or obstruction or perforation in patients receiving antithrombotic study medications. The ESC considered there may be lower levels of PPI use in Australian clinical practice than in the COMPASS trial.

6.6 Details of the trial presented in the resubmission are provided in Table 3 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 Gastroduodenal 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 resubmission.

6.7 The key features of the COMPASS trial are summarised in Table 4 below.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Rivaroxaban in combination with aspirin versus aspirin monotherapy						
COMPASS	27,395	MC, R, DB, PC 1.7 years	Low	Adults with stable atherosclerotic disease of the coronary and/or peripheral arteries, following resolution of one or more acute episodes	Composite of time to first event including myocardial infarction, stroke, or cardiovascular death; major bleeding	Major adverse cardiovascular events; major bleeding; other vascular events

Source: Table 2.3-2, pp.76-77; Table 2.4-1, p.81; Table 2.4-5, p.100; Table 2.4-8, pp.107-112 of the resubmission
Abbreviations: DB, double blind; MC, multi-centre; PC, placebo controlled; R, randomised.

6.8 The COMPASS trial was stopped prematurely, due to a recommendation for early termination from the independent data and safety monitoring board at the first formal interim analysis for efficacy (50% of planned events), due to a consistent difference in the primary efficacy outcome in favour of rivaroxaban plus aspirin.

Historically, trials that are terminated prematurely have been at risk of overestimating the treatment effect, an issue which is acknowledged in the discussion of the primary COMPASS publication. The corresponding reduction in the number of overall events available for analysis reduces the statistical power of the subgroup analyses presented by the resubmission, as well as reducing the duration of the trial and hence the median duration of therapy with rivaroxaban.

6.9 It is likely that there will be differences in the demographics and disease characteristics between the pooled target subgroup identified from the COMPASS population, and Australian patients under the proposed PBS restriction. This may have two possible implications: 1) possible differences in the underlying risk of having an event between the populations and 2) if these characteristics are treatment effect modifiers, then the treatment effect of rivaroxaban in the Australian population may be different to that observed in COMPASS. Based on the comparison of patient demographics and disease characteristics presented in the submission, the evaluation considered that the underlying risk of having an event may be different between the Australian population and COMPASS as there are differences in the proportions of patients with known risk modifiers such as myocardial infarction, coronary revascularisation, diabetes and smoking. The comparisons in the resubmission were based on the Western Australian linked health dataset and the Australian subgroup of the REACH registry. The ESC considered that, despite having significant limitations, these provided the most reliable data on the likely Australian PBS population.

6.10 The PBAC previously considered that the magnitude of the incremental treatment benefit when added to ideal medical management of cardiovascular risk is unknown (paragraph 7.7, rivaroxaban PSD, March 2019). The PSCR provided a comparison of the baseline medication use in COMPASS compared with that reported in the Australian sub-study of the REACH registry and stated there was high use of therapies for the standard management of modifiable CV risk factors in COMPASS compared with the Australian registry data. The ESC considered that while specific background therapies were not mandated in COMPASS, overall patients appeared to be well treated with background medications generally matching those reported in the Australian registry data.

6.11 The PSCR stated that patients in COMPASS who were on lipid lowering agents at baseline had a lower risk of major adverse cardiovascular events than those who were not (event rate in the aspirin alone arm was 5.25% versus 7.02%, respectively). The PSCR stated that use of lipid-lowering agents was not a treatment effect modifier (interaction p = 0.4685). However, the ESC noted that evolocumab was recommended by the PBAC in November 2019 for the treatment of non-familial hypercholesterolaemia in patients who have atherosclerotic cardiovascular disease and additional high-risk factors[1]. The ESC considered that the potential availability of

[1] https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2019-11/positive-recommendations-11-2019.docx.pdf

evolocumab for a proportion of the eligible population may lead to further differences in the baseline risk of the COMPASS trial population subgroups and the target Australian population.

6.12 The COMPASS trial excluded patients who were a high bleeding risk; those who had experienced a recent stroke or previous haemorrhagic or lacunar stroke; severe heart failure; and advanced stable kidney disease (estimated GFR <15 mL per minute). The ESC noted that these are listed as exclusions in the proposed restriction. However, the ESC also considered that in clinical practice, it will be essential to carefully screen for other factors that increase bleeding risk, such as prior bleeding, older age, less advanced kidney disease, anaemia, and low body weight when considering the overall risk-benefit ratio with the addition of rivaroxaban to established regimens.

Comparative effectiveness

6.13 The resubmission noted that the COMPASS trial was only powered to detect a difference for the primary composite outcome in the ITT population. The resubmission relied on the results of a number of secondary and tertiary outcomes conducted across various prespecified and posthoc subgroups to make its clinical claim. Due to the premature stopping of the COMPASS trial, the total number of events was lower than predicted in the protocol. This further reduced the available power to make subgroup comparisons, particularly for those subgroups which were defined posthoc. Further, the resubmission did not conduct treatment by subgroup interaction testing for the new subgroups presented, and did not correct for multiple statistical testing, despite a large number of statistical tests being conducted to inform the subgroup comparisons presented here. The PSCR outlined that subgroup analyses were required to address the PBAC's previous concerns that utilisation should be more highly targeted to patients who are likely to achieve the most favourable risk-benefit profile. The ESC recognised the limitations of the subgroup analyses and considered that the results of these subgroup comparisons would need to be interpreted with caution.

6.14 The results of the primary outcome (proportion of patients who experienced myocardial infarction, stroke, or cardiovascular death), and key cardiovascular outcomes, for the ITT and key high-risk subgroups presented by the resubmission, are summarised in Table 5.

Table 5: Results of cardiovascular outcomes in the COMPASS trial (ITT) and relevant subgroups

	Rivaroxaban 2.5 mg + aspirin 100 mg, n/N (%)	Aspirin 100 mg, n/N (%)	Absolute risk difference %	NNT/NNH	Hazard ratio (95% CI)
Primary outcome (composite of myocardial infarction, any stroke, or cardiovascular death)					
ITT population	379/9251 (4.1)	496/9126 (5.4)	-1.3382	75	**0.76 (0.66, 0.86)**
Pooled subgroup					
PAD					
PAD only[a]					
CAD & PAD					
CAD & HF					
CAD & CKD					
Complement of pooled subgroup					
Myocardial infarction					
ITT population	178/9152 (1.9)	205/9126 (2.2)	-0.3014	332	0.86 (0.70, 1.05)
Pooled subgroup					
PAD					
PAD only[a]					
CAD & PAD					
CAD & HF					
CAD & CKD					
Complement of pooled subgroup					
Ischaemic stroke					
ITT population	64/9152 (0.7)	125/9126 (1.4)	-0.6704	149	**0.51 (0.38, 0.69)**
Pooled subgroup					
PAD					
PAD only[a]					
CAD & PAD					
CAD & HF					
CAD & CKD					
Complement of pooled subgroup					
Cardiovascular death					
ITT population	160/9152 (1.7)	203/9126 (2.2)	-0.4762	210	**0.78 (0.64, 0.96)**
Pooled subgroup					
PAD					
PAD only[a]					
CAD & PAD					
CAD & HF					
CAD & CKD					
Complement of pooled subgroup					

Source: Table 2.6-1 (p 145), Table 2.6-2 (p 146), Table 2.6-4 (p 148) of the resubmission; Table 9-2 (p 124) of the COMPASS trial report
Abbreviations: CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; HF, heart failure; NNH, number needed to harm; NNT, number needed to treat; NR, not reported; PAD, peripheral artery disease.
[a] PAD only represents patients who have PAD without CAD. This patient group was included in the resubmission's proposed restriction, but was further refined in the ESC Advice and pre-PBAC response.

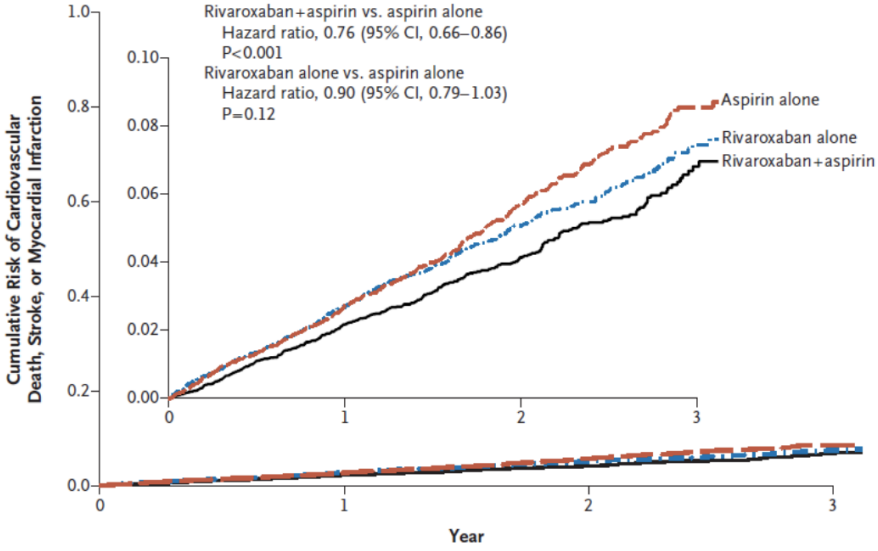
6.15 Treatment with rivaroxaban plus aspirin was associated with a statistically significant reduction in the proportion of patients who experienced the composite primary efficacy outcome compared with aspirin alone in the ITT population and most of the high risk subgroups. Statistically significant reductions were also observed in the ITT

population for ischaemic stroke and cardiovascular death. The results for myocardial infarction were less certain (wide confidence intervals, did not reach statistical significance) across the populations, but the study was not powered for this and the point estimate result favoured rivaroxaban plus aspirin.

6.16 The hazard ratios for the individual high risk subgroups (and the pooled subgroup) were generally lower than those for the ITT population, with the noticeable exception of the PAD only subgroup, however the wider confidence intervals reflect the increased uncertainty associated with these estimates.

6.17 Figure 1 shows the cumulative incidence of the primary outcome over time in COMPASS.

Figure 1: Cumulative incidence of the composite primary outcome among participants receiving rivaroxaban 2.5 mg plus aspirin 100 mg, rivaroxaban 5 mg alone, or aspirin 100 mg alone



No. at Risk				
Aspirin alone	9126	7808	3860	669
Rivaroxaban alone	9117	7824	3862	670
Rivaroxaban+aspirin	9152	7904	3912	658

Source: Figure 1, p8 Eikelboom et al (2017)
Note: The inset shows the same data on an expanded y-axis

6.18 The ESC noted there were limited long-term data available (median follow-up of 23 months). The ESC further noted the Kaplan-Meier curves did not indicate a convergence in the treatment effect over time, however noted the number of patients at risk was relatively low toward the end of the curves.

6.19 The results of peripheral outcomes in the COMPASS trial, including acute limb ischaemia, major and minor amputations, and venous thromboembolism, for the ITT and key high-risk subgroups presented by the resubmission, are summarised in Table 6.

Table 6: Results of peripheral outcomes in the COMPASS trial (ITT) and relevant subgroups

	Rivaroxaban 2.5 mg + aspirin 100 mg, n (%)	Aspirin 100 mg, n (%)	Absolute risk difference (%)	NNT/NNH	Hazard ratio (95% CI)
Acute limb ischaemia					
ITT population	22/9152 (0.2)	40/9126 (0.4)	-0.1979	505	**0.55 (0.32, 0.92)**
[redacted]					
Major amputation					
ITT population	15/9152 (0.2)	26/9126 (0.3)	-0.1210	826	0.57 (0.30, 1.09)
[redacted]					
Minor amputation					
ITT population	17/9152 (0.2)	26/9126 (0.3)	-0.0991	1009	0.65 (0.35, 1.20)
[redacted]					
Venous thromboembolism					
ITT population	25/9152 (0.3)	41/9126 (0.4)	-0.1761	568	0.61 (0.37, 1.00)
[redacted]					

Source: Table 2.6-9 (p 153) of the resubmission; Table 2/1, p. 217 '15786_query22_compass_add_heor_australia2new', Appendix 5 of the resubmission; Table 9-30 (p 181) and Table 9-35 (p 188) of the COMPASS trial report

Abbreviations: CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; HF, heart failure; NE, not estimated; NNH, number needed to harm; NNT, number needed to treat; NR, not reported; PAD, peripheral artery disease

[a] PAD only represents patients who have PAD without CAD; CAD yes includes patients who have PAD with CAD or CAD only (complement of PAD only). Results were calculated during the evaluation as the incidence of events in the PAD yes subgroup minus the incidence of events in the CAD & PAD subgroup.

6.20 In populations which explicitly include patients with PAD, there was a consistent reduction in acute limb ischaemia events in favour of treatment with rivaroxaban in combination with aspirin compared with aspirin monotherapy. The results for minor and major amputation and venous thromboembolism were less certain across the populations, but results favoured rivaroxaban plus aspirin. The total number of events for peripheral outcomes were low, including in the PAD only population. The confidence intervals in the individual subgroups were wide, reflecting uncertainty associated with these estimates. Hazard ratios were broadly not estimable for the CAD & HF and CAD & CKD subgroups, due to very low event rates.

6.21 Non-cardiovascular death was included in the base case of the resubmission's economic model. The results for non-cardiovascular death in the ITT and nominated high risk subgroups are summarised in Table 7.

Table 7: Results of non-cardiovascular death in the COMPASS trial (ITT) and relevant subgroups

	Rivaroxaban 2.5 mg + aspirin 100 mg, n (%)	Aspirin 100 mg, n (%)	Absolute risk reduction (%)	NNT/NNH	Hazard ratio (95% CI)
Non-cardiovascular death					
ITT population	153/9152 (1.7)	175/9126 (1.9)	-0.2458	407	0.87 (0.70, 1.08)
[redacted]					

Source: Tables 2/1 to 2/11 (pp 217-257), Subgroup analyses for Australia report; Table 14.2.4/4 (p 18), Section 4 Tables and Figures, Appendix 5 of the resubmission

Abbreviations: CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; HF, heart failure; NNH, number needed to harm; NNT, number needed to treat; NR, not reported; PAD, peripheral artery disease

[a] PAD only represents patients who have PAD without CAD; CAD yes includes patients who have PAD with CAD or CAD only (complement of PAD only). Results were calculated during the evaluation as the incidence of events in the PAD yes subgroup minus the incidence of events in the CAD & PAD subgroup.

6.22 In the ITT and nominated high risk subgroups, there was no statistically significant difference between treatment arms for non-cardiovascular death.

6.23 The resubmission presented the results of the proton pump inhibitor sub-study of the COMPASS trial. As anticoagulants and antiplatelets are associated with an increased risk of upper gastrointestinal bleeding, this sub-study of COMPASS assessed the effect of pantoprazole versus placebo in reducing GI bleeding, ulceration, obstruction or perforation. The results for the effect of pantoprazole on clinically significant upper GI events are summarised in Table 8.

Table 8: Clinically significant upper gastrointestinal bleeding events by pantoprazole randomisation (ITT)

	Pantoprazole 40 mg	Placebo	HR (95% CI)
GI bleeding events, n/N (%)	102/8791 (1.2)	116/8807 (1.3)	0.88 (0.67, 1.15)

Source: Table 2.5-25, p.143 of the resubmission

6.24 The proportion of patients who experienced significant upper gastrointestinal events was not statistically significantly different between the pantoprazole arm (1.2%) and

the placebo arm (1.3%) (HR 0.88; 95% CI: 0.67, 1.15). The publication reporting on this study, Moayyedi et al. (2019b), stated that although there was no significant difference between treatment groups for upper gastrointestinal events, there was a significant reduction in bleeding of gastroduodenal lesions. However, this conclusion was based on a very small number of events (16-31 in each arm), and the resulting number needed to treat was high (n=982).

Comparative harms

6.25 In the COMPASS trial, there were more study medication-related treatment-emergent adverse events, serious adverse events, and permanent discontinuation of anti-thrombotic study medication due to adverse events associated with rivaroxaban in combination with aspirin compared with aspirin alone.

6.26 A summary of the results for the primary safety outcome, treatment-emergent modified International Society on Thrombosis and Haemostasis (ISTH) major bleeding events, is presented in Table 9. The ESC noted that the modified definition (as requested by the FDA) of ISTH major bleeding, used as the primary safety endpoint, is broader than the standard definition as it included any bleed that resulted in a presentation to an acute care facility (with or without transfusion), in addition to the standard ISTH definition which includes bleeds that result in death, are life threatening, cause chronic sequelae or consume major healthcare resources.

Table 9: Results of modified ISTH major bleeding events in the COMPASS trial (ITT) and relevant subgroups

	Rivaroxaban 2.5 mg + aspirin 100 mg, n (%)	Aspirin 100 mg, n (%)	Absolute risk difference (%)	NNT/NNH	Hazard ratio (95% CI)
Modified ISTH major bleeding events					
ITT population	288/9152 (3.1)	170/9126 (1.9)	1.2840	78	**1.70 (1.40, 2.05)**
[redacted]					

Source: Table 2.6-12, p 168 of the resubmission; COMPASS additional HEOR subgroup analyses, Appendix 5 of the resubmission
Abbreviations: CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; HF, heart failure; NNH, number needed to harm; NNT, number needed to treat; NE, not estimated; PAD, peripheral artery disease
[a] PAD only represents patients who have PAD without CAD; CAD yes includes patients who have PAD with CAD or CAD only (complement of PAD only)

6.27 Treatment with rivaroxaban in combination with aspirin was associated with a statistically significantly higher incidence of major bleeding overall, compared with the aspirin monotherapy group, primarily driven by gastrointestinal bleeding (and hospitalisations). The evaluation considered that the risk of major bleeding in clinical practice in the proposed high-risk subgroups remains uncertain. The COMPASS trial excluded patients at high risk of bleeding, and patients with poor renal function (eGFR < 15 mL/min). Further, the mean age of patients in the COMPASS trial was 68 years. Safety results may not be applicable to elderly patients, patients with different risk

factors for bleeding, or patients with deteriorating renal function. In particular, due to the exclusion of patients with poor renal function (eGFR < 15 mL/min) from the COMPASS trial, the safety of rivaroxaban in combination with aspirin in the CAD and CKD subgroup is unclear.

6.28 An extended assessment of harms presented in the resubmission acknowledged that the administration of rivaroxaban is associated with an increased risk of haemorrhage, including surgical and extra-surgical site bleeding, or fatal or critical organ bleedings. Higher rates of major bleeding associated with treatment with rivaroxaban occurred in COMPASS, and across other rivaroxaban clinical trials. Patients at high risk of bleeding were not eligible for enrolment in the COMPASS trial. The additional benefit of adding rivaroxaban 2.5 mg to low dose aspirin in stable atherosclerotic disease must be weighed against the bleeding risk for each individual at the point of care. The assessment of bleeding risk in the target patient population is complex and undertaken on an individual patient basis by the treating clinician. The ESC recognised that there is no bleeding risk scoring system that has been validated in this clinical scenario.

Benefits/harms

6.29 A summary of the comparative benefits and harms for rivaroxaban in combination with aspirin versus aspirin monotherapy is presented in the table below.

Table 10: Differences in numbers of patients with outcomes per 1000 patients with stable atherosclerotic disease who have CAD and/or PAD, who are treated with low dose rivaroxaban and aspirin compared with aspirin over mean duration of 1.84 years

	Benefits		Harms
	Reduction in major adverse cardiovascular event (myocardial infarction, any stroke or cardiovascular death); n. patients	**Reduction in acute limb-threatening ischaemic event requiring medical intervention (pharmacological, surgery or amputation); n. patients**	**Increase in major bleeding event (fatal or non-fatal bleeding requiring hospitalisation); n. patients**
ITT population	13	2	13
Pooled subgroup			
PAD			
PAD only			
CAD & PAD			
CAD & HF			
CAD & CKD			

Source: Table 2.6-1, p 145, Table 2.6-2, p 146, Table 2.6-9, p 153, Table 2.6-12, p 168 of the resubmission; Table 9-2 of the COMPASS trial report; COMPASS additional HEOR subgroup analyses, Appendix 5 of the resubmission

Abbreviations: CAD, coronary artery disease; CKD, chronic kidney disease; HF, heart failure; ITT, intention to treat; PAD, peripheral artery disease

6.30 On the basis of direct evidence presented in the resubmission, every 1000 patients with stable atherosclerotic disease who have PAD, CAD and PAD, CAD & HF, or CAD & CKD, who are treated with low dose rivaroxaban and aspirin compared with aspirin over mean duration of 1.84 years would result in:

- Approximately [redacted] fewer patients with a major adverse cardiovascular event (myocardial infarction, any stroke or cardiovascular death), primarily due to a difference in ischaemic stroke events;
- Approximately [redacted] fewer patients with an acute limb-threatening ischaemic event requiring medical intervention (pharmacological, surgery or amputation);
- Approximately [redacted] more patients with a major bleeding event (fatal or non-fatal bleeding requiring hospitalisation).

Clinical claim

6.31 The resubmission described rivaroxaban in combination with aspirin as superior in terms of efficacy and inferior in terms of safety compared with aspirin monotherapy in the pooled target population. The ESC considered this claim was reasonable and consistent with the previous claim for the broader PAD and/or CAD population, which was accepted by the PBAC at the March 2019 meeting (paragraph 7.7, Rivaroxaban Public Summary Document, March 2019 PBAC meeting).

6.32 The PBAC previously considered that the magnitude of the clinical benefit was likely to have been overestimated in the trial (due to the premature stopping of the trial) and may not be reflected in clinical practice (due to potential differences between the trial population and likely PBS population in terms of: baseline risk; and compliance to rivaroxaban plus aspirin).

6.33 The resubmission claimed that the revised pooled target population, which has a higher risk than the ITT population, would increase the absolute benefit associated with using rivaroxaban with aspirin compared to aspirin alone, and that this is achieved without an increase in the risk of major bleeding compared with the ITT population.

6.34 Overall, the resubmission claimed that the pooled target population had a better risk-benefit profile than the ITT population. The ESC considered that this may not have been reasonable as the PAD only population had a less favourable risk-benefit profile than the other subgroups and the ITT. However, the PBAC noted that the pre-PBAC response had further refined the PAD population to include higher risk patients as per the ESC's advice. Although the pre-PBAC response stated that clinical efficacy data were not available for the new higher risk PAD subgroup population, the PBAC accepted the revised PAD population would likely have a more favourable risk-benefit profile than the ITT population.

6.35 The clinical claim in the high-risk subgroups is based on some outcomes with very low event rates, due to both the premature stopping of the COMPASS trial, and the numbers of patients in each subgroup. Further, many of the analyses were specified post hoc, no treatment by subgroup tests for interaction were run and no correction was applied for multiplicity despite a very high number of statistical tests being run to support the clinical claim. The ESC acknowledged the PSCR's claim that subgroup analyses were necessary in order to target use to patients who are likely to achieve

the most favourable risk-benefit profile, but considered that the results of these subgroup analyses must be interpreted with caution.

6.36 The evaluation considered it was unclear whether the baseline risk in the COMPASS trial population subgroups would be similar to the target Australian population, as comparisons in the submission identified a number of potential differences in cardiovascular/bleeding risk factors (e.g. history of prior stroke, MI, coronary revascularisation, diabetes, etc.). As a consequence it is unclear whether similar absolute treatment benefit would be observed in the Australian population.

6.37 The PBAC reiterated its previous consideration 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.

6.38 The PBAC reiterated its previous consideration 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.

Economic analysis

6.39 The resubmission presented a stepped economic evaluation of the additive effects of using rivaroxaban with aspirin compared to aspirin alone for the prevention of atherothrombotic events in patients at high cardiovascular risk. The economic evaluation was based on a direct randomised trial (COMPASS) with additional modelled data. The economic evaluation was presented as a cost-effectiveness/cost-utility analysis**.**

6.40 The current resubmission substantially revised the economic analyses compared to the analysis presented in the March 2019 submission with major changes to: model structure/computational method (switch to microsimulation model), transition probabilities (removed risk multipliers, included non-cardiovascular death in addition to background mortality, reduced the number of possible transitions), treatment effects (included a non-cardiovascular death treatment effect, convergence of treatment effect) and measures of compliance (included treatment persistence and interruptions). Other changes were also made to the patient population, costs and utility values.

Table 11: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Low dose rivaroxaban with aspirin; aspirin alone
Time horizon	30 years (lifetime). The ESC considered this was reasonable.
Outcomes	Major cardiovascular event avoided; life years; quality adjusted life years
Methods used to generate results	Discrete event simulation model. The ESC considered this method was appropriate, but noted that it did not adequately adjust for all baseline heterogeneity (it only accounts for heterogeneity in baseline age and gender, and their impact on background mortality).
Health states	Alive health state and 7 death event states (MI death, IS death, ICH death, bleeding death, other CV death, non-CV death, background mortality death)
Cycle length	1 month
Transition probabilities	Transition probabilities for fatal/non-fatal cardiovascular events, fatal/non-fatal bleeding events, other non-fatal vascular events and non-cardiovascular death were derived from post hoc analysis of individual patient data from the COMPASS trial. Background mortality was based on Australian life tables. Treatment effect estimates were derived from the COMPASS trial.
Extrapolation method	The underlying risk of events was assumed to remain constant over time. Based on a median follow-up in the trial of 23 months, the model assumed a constant treatment effect for the first four years of the model (maximum follow-up of the COMPASS clinical trial) and then a declining difference in hazards over the remaining 26 years of the model (full convergence at 30 years). The ESC noted that convergence was achieved by declining the adherence rate, rather than declining effectiveness, which may underestimate costs, however the ESC considered this was unlikely to significantly impact the results.
Health related quality of life	Utility/disutility values derived from the COMPASS trial Pooled target population Baseline: [redacted], acute MI: [redacted], chronic MI: [redacted], acute IS: [redacted], chronic IS: [redacted], acute ICH: [redacted], chronic ICH: [redacted]
Circumstances of use	Adherence implicitly included in the assumption of a decline in efficacy. Full drug costs were assumed for all patients remaining on treatment Treatment persistence estimated based on rivaroxaban use for stroke prevention in atrial fibrillation patients using 10% Medicare data Treatment interruption for 12 months following any event. Permanent discontinuation for patients experiencing intracranial haemorrhage or major bleed

Source: Table 3.1-1 (p 197) of the resubmission

Abbreviations: CV, cardiovascular; ICH, intracranial haemorrhage; IS, ischaemic stroke; MI, myocardial infarction

6.41 Patients enter the model in the alive health state. In each monthly cycle, patients can have no event or experience non-fatal/fatal events (patients can experience multiple different types of events in the same month):

- Non-fatal myocardial infarction
- Non-fatal ischaemic stroke
- Non-fatal intracranial haemorrhage
- Acute limb ischaemia
- Major amputation
- Minor amputation
- Major bleed
- Venous thromboembolism
- Fatal myocardial infarction
- Fatal ischemic stroke
- Fatal intracranial haemorrhage
- Fatal bleeding
- Other cardiovascular death
- Non-cardiovascular death
- Background mortality

6.42 The model tracks the time since an event in order to model treatment interruptions and adjust costs and utilities over time (acute phase < 3 months, chronic phase > 3 months). Additionally, the model tracks time on treatment to model treatment persistence and convergence of treatment effect. Patients experiencing multiple cardiovascular events accrue the ongoing cost and utility of the most severe event (ischaemic stroke > intracranial haemorrhage > myocardial infarction > alive health state), which the ESC considered to be a conservative assumption. The costs and utility losses associated with other non-fatal events were assumed to be additive to cardiovascular events. The model structure allowed patients in the low dose rivaroxaban with aspirin treatment arm to discontinue rivaroxaban treatment and continue with aspirin alone.

6.43 The changes to the economic analysis (particularly the switch from a cohort model to a microsimulation model and the removal of risk multipliers) improved the robustness of the model by reducing the impact of data sparseness. However, the data informing transition probabilities remains sparse for many events in the subgroup populations.

6.44 The resubmission included a new clinical outcome of non-cardiovascular death in the current model compared to the previous March 2019 model. The inclusion of this outcome was not appropriate as it overlapped with background mortality estimates (which have only been adjusted for cardiovascular death) and led to double-counting of non-cardiovascular mortality risk in the model. Further, the inclusion of this outcome was not adequately supported by available clinical data and strongly biases the economic evaluation in favour of rivaroxaban with aspirin. The PSCR argued that COMPASS patients have many additional comorbidities and are at increased risk of non-cardiovascular death compared to the general population (and thus not adequately captured in background mortality alone). The PSCR further argued that the 'reduction in risk of non-cardiovascular death is thought to be due to synergistic effects of atherosclerosis on underlying vascular comorbidities (e.g. chronic kidney disease) by stabilising existing atherosclerotic plaques with rivaroxaban'. The HR for

non-cardiovascular death in COMPASS for the ITT population was not statistically significant (HR: 0.87; 95% CI: 0.70, 1.08), which the PSCR stated was due to the trial not being adequately powered for this outcome. The ESC agreed with the evaluation that the inclusion of non-cardiovascular mortality was not appropriate as it would result in double-counting between non-cardiovascular death and background mortality. Further, the ESC considered it was unclear whether the data supported a 'real' difference in non-cardiovascular outcomes as the proposed mechanism was not adequately supported and the differences were not statistically significant. Overall, the ESC considered that excluding non-cardiovascular death may be a more appropriate base case. To address this, the pre-PBAC response proposed a revised base case that removed both non-cardiovascular death treatment effects and non-cardiovascular death transition probabilities.

6.45 The ESC noted that other non-statistically significant events were also included in the model, including non-fatal myocardial infarction, non-fatal intracranial haemorrhage, amputation (major and minor), venous thromboembolism and bleeding death. The resubmission acknowledged that not all treatment effects were statistically significant but argued that many of the analyses were underpowered and there was a general trend towards improved cardiovascular and peripheral vascular outcomes and worse bleeding outcomes in patients treated with rivaroxaban and aspirin.

6.46 The targeted population comprised high-risk subgroups of COMPASS, while the hazard ratios (HRs) applied in the economic model were based on the ITT population (not the pooled subgroup). The ESC considered this was appropriate given the aforementioned uncertainties with the subgroup analyses, but also noted this approach may be conservative as the HR point estimates for the pooled subgroup were more favourable to rivaroxaban plus aspirin (than the ITT results) for most of the modelled outcomes.

6.47 A comparison between the outcomes observed in the trial versus those modelled in the economic evaluation (for patients with PAD plus CAD) indicated that the incremental number of events (between the treatment arms) observed in the trial was typically higher than estimated in the model over the first three years, which was conservative.

6.48 The revised estimates of treatment compliance and long-term treatment effects were more conservative than the previous submission (perfect compliance with no treatment interruption and no loss of effect over time) but estimates were still highly uncertain as they were dependent on poorly documented utilisation data and additional assumptions.

6.49 Key drivers of the economic model are summarised in the table below.

Table 12: Key drivers of the model

Description	Method/Value	Impact
Treatment effect estimates	Treatment effects were based on secondary/exploratory analyses of population-level data from the COMPASS trial. The resubmission acknowledged that not all treatment effects were statistically significant but argued that many of the analyses were underpowered and there was a general trend towards improved cardiovascular and peripheral vascular outcomes and worse bleeding outcomes in patients treated with rivaroxaban and aspirin.	High, favours rivaroxaban
Extrapolation	The model assumed a constant treatment effect for the first four years of the model (maximum follow-up of the COMPASS clinical trial) and then a declining difference in hazards over the remaining 26 years of the model (full convergence at 30 years). 94% of incremental QALYs; 94% of incremental life years; and 63% of incremental costs are accrued in the extrapolated period beyond 1.84 years.	High, favours rivaroxaban

Source: Constructed during the evaluation

6.50 The results of the modelled economic evaluation are summarised below.

Table 13: Stepped economic evaluation of rivaroxaban with aspirin compared to aspirin alone (pooled target population)

Type of resource item	Rivaroxaban with aspirin	Aspirin alone	Incremental difference
Step 1: Trial based efficacy/safety for high cardiovascular risk subgroup; 1.84 year horizon; drug costs only; incremental cost per major cardiovascular event avoided (myocardial infarction, ischaemic stroke, intracranial haemorrhage, cardiovascular death)			
Costs	$[redacted]	$0	$[redacted]
Patients with MI, IS, ICH or CV death	[redacted]	[redacted]	-[redacted]
Incremental cost per event avoided			$[redacted]
Step 1a: Converting to cost per life year gained			
Costs	$[redacted]	$0	$[redacted]
LYs	[redacted]	[redacted]	[redacted]
Incremental cost per life year gained			$[redacted]
Step 2: Extending to 30 years			
Costs	$[redacted]	$0	$[redacted]
LYs	[redacted]	[redacted]	[redacted]
Incremental cost per life year gained			$[redacted]
Step 2a: Extrapolated efficacy/safety for high cardiovascular risk subgroup; 30 year horizon; age simulation, general population mortality, treatment interruptions for any event, discontinuations due to bleeding, modelled treatment persistence, declining treatment effect over time; drug costs only; incremental cost per life year gained			
Costs	$[redacted]	$0	$[redacted]
LYs	[redacted]	[redacted]	[redacted]
Incremental cost per life year gained			$[redacted]
Step 3: Adding acute event costs and disease management costs			
Costs	$[redacted]	$12,835	$[redacted]
LYs	[redacted]	[redacted]	[redacted]
Incremental cost per life year gained			$[redacted]
Step 4: Base case ICER for pooled subgroup. Adding quality adjusted life year gained conversion			
Costs	$[redacted]	$12,835	$[redacted]
QALYs[a]	[redacted]	[redacted]	[redacted]
Incremental cost per QALY gained			$[redacted]

Source: Table 3.8-1 (p 273) of the resubmission

Abbreviations: ACS, acute coronary syndrome; CV, cardiovascular; ICH, intracranial haemorrhage; IS, ischaemic stroke; LY, life years; MI, myocardial infarction; QALYs, quality-adjusted life years

[a] Quality of life estimates were corrected during the evaluation to have a standardised 3 month duration for acute events in both treatment arms

6.51 Based on the economic model, treatment with rivaroxaban and aspirin was associated with a cost per QALY gained of $15,000 - $45,000 (base case ICER for pooled subgroup).

6.52 The pre-PBAC response proposed a revised base case that removed both non-cardiovascular death treatment effects and non-cardiovascular death transition probabilities, and with a lower effective price (% reduction versus the price proposed in the resubmission). This resulted in an ICER of $15,000 - $45,000 per QALY gained.

6.53 The difference in health outcomes between treatment arms was primarily driven by a small delay in the time to other cardiovascular death and time to non-cardiovascular death (in the resubmission base case). The extrapolation of treatment benefits beyond the clinical trial data had the largest impact on the stepped economic evaluation.

6.54 Figure 2 below summarises the proportions of patients with non-fatal cardiovascular events over the 30 year duration of the model.

Figure 2: Proportions of patients with non-fatal cardiovascular events in the model over the 30 year time horizon

Source: Constructed during the evaluation using the 'Xarelto (rivaroxaban) Economic Evaluation - POOLED' Excel spreadsheet provided in the resubmission

6.55 The proportions of patients with non-fatal peripheral events over the duration of the model are summarised in Figure 3 below.

Figure 3: Proportions of patients with non-fatal peripheral events in the model over the 30 year time horizon

Source: Constructed during the evaluation using the 'Xarelto (rivaroxaban) Economic Evaluation - POOLED' Excel spreadsheet provided in the resubmission

6.56 Figure 4 below summarises the proportions of patients with non-fatal bleeding events over the 30 year duration of the model.

Figure 4: Proportions of patients with non-fatal bleeding events in the model over the 30 year time horizon

Source: Constructed during the evaluation using the 'Xarelto (rivaroxaban) Economic Evaluation - POOLED' Excel spreadsheet provided in the resubmission

6.57 The proportions of patients with fatal events over the duration of the model presented in the resubmission are summarised in Figure 5 below. As outlined above, non-cardiovascular death treatment effects and transitions were removed in the pre-PBAC response.

Figure 5: Proportions of patients with fatal events in the model over the 30 year time horizon (resubmission model)

Source: Constructed during the evaluation using the 'Xarelto (rivaroxaban) Economic Evaluation - POOLED' Excel spreadsheet provided in the resubmission

6.58 Table 14 compares the incremental outcomes of the model over the trial duration (1.84 years mean follow-up) with the outcomes over the 30 year time horizon (based on the resubmission base case).

Table 14: Comparison on modelled results within trial period and over 30 year time horizon (resubmission base case)

	Model results over trial duration (1.84 years)	Model results over 30 year time horizon	Proportion accrued in extrapolated period
Incremental cost	$	$	63.4%
Incremental LYs			94.2%
Incremental QALYs			94.0%
Incremental patients with events per 1000 patients treated			
Non-fatal cardiovascular events[1]			45.3%
Non-fatal peripheral events[2]			57.3%
Non-fatal extracranial bleed			62.9%
Cardiovascular death			28.6%
Non-cardiovascular death[3]			175.0%
Bleeding death			-

Source: Constructed during the evaluation using the 'Xarelto (rivaroxaban) Economic Evaluation - POOLED' Excel spreadsheet provided in the resubmission

Abbreviations: LYs, life years; QALYs, quality adjusted life years

[1]Non-fatal cardiovascular events include myocardial infarction, ischaemic stroke and intracranial haemorrhage

[2]Non-fatal peripheral events include venous thromboembolism, acute limb ischaemia, minor amputation and major amputation

[3]The changing relationship between treatment arms between the two periods in non-cardiovascular death is due to the changing relationship between cardiovascular death, non-cardiovascular death and background mortality over time. Non-cardiovascular death transitions and treatment effects were removed in the revised base case proposed in the pre-PBAC response.

6.59 In the model, a substantial proportion of events occur within the trial period, but the ongoing consequences of these events (life years, QALYs) occur in the extrapolated period.

6.60 A summary of the modelled comparative benefits and harms for rivaroxaban in combination with aspirin versus aspirin monotherapy over the 30 year model duration is presented in the table below. This was based on the resubmission base case and does not include the refinement of the PAD population or the inclusion of diabetes as a risk factors that were proposed by ESC and agreed by the pre-PBAC response.

Table 15: Modelled differences in numbers of patients with outcomes per 1000 patients with stable atherosclerotic disease who have CAD and/or PAD, who are treated with low dose rivaroxaban and aspirin compared with aspirin over the 30 year model duration (resubmission base case)

Population	Benefits					Harms	
	Increase in overall survival	Reduction in MI events	Reduction in ischaemic stroke events	Reduction in acute limb ischaemia events[1]	Reduction in VTE events	Increase in intracranial haemorrhage events	Increase in major bleeding events
Pooled subgroup	[redacted]						
PAD							
CAD & PAD							
CAD & HF							
CAD & CKD							

Source: Constructed during the evaluation using the model spreadsheets provided with the resubmission
Abbreviations: MI, myocardial infarction; VTE, venous thromboembolism
[1]Acute limb ischaemia events may include amputation

6.61 In the resubmission base case, treatment of 1,000 patients with rivaroxaban with aspirin compared to aspirin alone over 30 years in the pooled target population was associated with an average increase in survival of [redacted] months. Treatment with rivaroxaban was also associated with [redacted] fewer myocardial infarction events, [redacted] fewer ischaemic stroke events, [redacted] fewer acute limb ischaemia events (which may include amputation) and [redacted] fewer venous thromboembolism events. However, treatment with rivaroxaban was also associated with [redacted] more intracranial haemorrhage event and [redacted] major bleeding events.

6.62 The health outcomes modelled for each of the subgroup populations in the economic analysis were relatively homogeneous over the 30 year time horizon. This may have been due to the high degree of overlap between target populations which confounds the interpretation of any specific subgroup result by the inclusion of patients already eligible under a different clinical criterion. Alternatively, the COMPASS trial may have been of insufficient duration to clearly differentiate the underlying risk between populations. Overall, the ESC considered that the apparent homogeneity between populations may not reflect the underlying differences between these patient groups.

6.63 The results of the sensitivity analyses indicated that the model was most sensitive to time horizon and treatment effects (primarily the inclusion of non-statistically significant differences).

Table 16: Results of sensitivity analyses (pooled target population) based on resubmission model

Analyses	Incremental cost	Incremental QALY	ICER
Base case in resubmission	$		$
Time horizon (base case: 30 years)			
5 years	$		$
10 years	$		$
20 years	$		$
Treatment effects (base case: point estimate difference from COMPASS trial, using HR for ITT population)			
Exclude non-CV death treatment effect	$		$
Only include statistically significant differences (non-fatal IS, CV death, acute limb ischaemia and major bleeds)	$		$
Full treatment effect to 22 months (average trial duration), full convergence at 5 years; no drug costs beyond 5 years	$		$
Treatment effects (HR) based on pooled subgroup population [a]	$		$
Multivariate sensitivity analysis			
Only include statistically significant differences Treatment effect (HR) based on pooled subgroup population	$		$

Source: Table 3.9-1 (p 276) of the resubmission

Abbreviations: ACS, acute coronary syndrome; CV, cardiovascular; ICER, incremental cost effectiveness ratio; ICH, intracranial haemorrhage; IS, ischaemic stroke; MI, myocardial infarction; QALY, quality-adjusted life year

[a] The HR for the ITT was used for bleeding death as the pooled HR was not available.

6.64 The resubmission included four scenario analyses with baseline risks from the COMPASS trial for the following subgroups: PAD; PAD with CAD; CAD with heart failure; and CAD with chronic kidney disease. While the estimated cost-effectiveness of rivaroxaban was consistent across each of the individual subgroups, the ESC considered that the scenario analyses did not adequately account for the baseline risk of each of the subgroups, as the microsimulation approach only accounted for heterogeneity in baseline age and gender, and their impact on background mortality. Further sensitivity analyses by the evaluators indicated that use of rivaroxaban and aspirin in the PAD without CAD population is unlikely to be cost-effective unless a treatment effect on cardiovascular death is assumed. The PBAC considered that the further refinement of the PAD population helped address this issue.

Drug cost/patient/year

Table 17: Drug cost per patient for rivaroxaban

	Trial	Economic analysis	Financial estimates
Compliance	Yr 1: 83.9%[a] Yr 2: 77.6% Yr 3: 72.1%	-	87.52% in each year[b] (Pre-PBAC response: 76%)
- Adherence	Yr 1: 96.4%[c] Yr 2: 97.2% Yr 3: 98.1%	Not explicitly modelled	-
- Persistence	Yr 1: 87.1%[d] Yr 2: 79.9% Yr 3: 73.5%	Yr 1: 57%[e] Yr 2: 46% Yr 3: 40% Yr 4: 36% Yr 5: 32% Yr 6: 29%	-
Treatment interruptions	Duration of interruptions not reported[f]	All events in the rivaroxaban and aspirin arm were associated with at least a 12 month treatment interruption	Not included in the resubmission's estimates, but were included in revised estimates provided in the PSCR.
Average number of scripts per year	-	Yr 1: 6.94[g] Yr 2: 5.60 Yr 3: 4.87 Yr 4: 4.39 Yr 5: 3.90 Yr 6: 3.53	10.66 in resubmission (Pre-PBAC response: 8.8 in Yr 1 decreasing to 8.4 in Yr 6)
Cost/patient/year	-	Resubmission: Yr 1: $[redacted][h] Yr 2: $[redacted] Yr 3: $[redacted] Yr 4: $[redacted] Yr 5: $[redacted] Yr 6: $[redacted] (Pre-PBAC response: Yr 1: $[redacted] to Yr 6: $[redacted])	$[redacted][h] in resubmission (Pre-PBAC response: $[redacted])

Source: Table 14.1.4/3 of the COMPASS trial report; Xarelto (rivaroxaban) Utilisation and Cost Excel workbooks, Section 4 Spreadsheets of the resubmission

[a] Proportion of patients taking at least 80% of the study drug; of patients who completed each visit

[b] Based on reported compliance in the COMPASS trial, weighted by each visit (10 visits from Month 1 to Month 42). In the pre-PBAC response: based on PBS 10% sample data for rivaroxaban in non-valvular atrial fibrillation.

[c] Defined as patients taking at least 80% of the study drug; of patients who were still on the study drug

[d] These proportions were based on patients still taking the study drug at each visit; of patients who completed each visit

[e] 10% Medicare sample analysis of rivaroxaban for stroke prevention in atrial fibrillation patients

[f] COMPASS trial report noted that treatment interruptions could not be calculated, because the number of days off study drug could not be determined from the data

[g] Calculated using persistence estimates, assuming no treatment interruptions and 12.18 scripts/patient/year

[h] Calculated using average number of scripts/year and the proposed effective price of $[redacted] in the resubmission (and $[redacted] in the pre-PBAC response)

6.65 The estimation of treatment adherence, persistence and interruption was not consistent between different sections of the resubmission. The ESC considered that these parameters may not have been adequately accounted for in the financial estimates. The assumptions around persistence and interruptions were amended in the PSCR and the pre-PBAC response.

6.66 The resubmission assumed that the drug cost for aspirin was negligible and did not include this cost in the economic model or financial implications. The ESC noted that patients would be taking aspirin anyway.

Estimated PBS usage & financial implications

6.67 This resubmission was not considered by DUSC. The resubmission took a similar epidemiological approach to the previous submission. The total eligible population from the pooled and individual subgroups of PAD, PAD & CAD, CAD & HF and CAD & CKD were estimated from the same source as used in the previous submission, an analysis of Western Australian linked health data. An updated analysis was conducted to identify patients within the newly specified subgroups. The resubmission used a 15 year lookback period to define the prevalent population of patients with atherothrombotic cardiovascular disease. Patients meeting the eligibility criteria for the eligible disease subgroups on 1 July 2010 ('prevalence date') were included in the analysis. Key inputs are summarised in the table below.

Table 18: Key inputs for financial estimates

Parameter	Value applied and source	Comment
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).	Para 7.15 of March 2019 PSD: "The PBAC noted that DUSC had identified issues with the prevalence rates used in the financial estimates. However, the PBAC considered that, while the prevalence was highly uncertain, there were unlikely to be better data available and considered the prevalence used in the submission was reasonable." The ESC considered there is remaining uncertainty with respect to the eligible population.
Uptake rate	Resubmission base case: [redacted]% in Year 1 increasing to [redacted]% in Year 6 for the pooled patient group. Based on market research conducted by the sponsor. Pre-PBAC response base case: [redacted]% in Year 1 increasing to [redacted]% in Year 6 for the pooled patient group. Based on the lower limit of the 95% CI from the market research.	The ESC noted that uptake rates were based on assumptions from a clinician survey and therefore subject to considerable uncertainty. The ESC considered the uptake rates may be significantly overestimated, due to patient and/or clinician reluctance to prescribe long-term antiplatelet and anticoagulant agents together, at least until considerable clinical experience using this combination of antithrombotics is attained.
Compliance rate	Resubmission base case: 87.5% compliance, based on weighted average compliance across all months of the COMPASS trial. Pre-PBAC response base case: 76% compliance, based on 10% sample data for rivaroxaban in the non-valvular atrial fibrillation indication.	The ESC considered compliance was likely overestimated because compliance estimates reported in the clinical trial setting are unlikely to be representative of clinical practice, particularly given that patients with poor adherence were excluded from the COMPASS trial during the run-in period. The ESC further noted that the compliance rates in the trial decreased over time (per Table 18).

Source: Table 4.1.1, p279 of the resubmission.
ABS, Australian Bureau of Statistics.

6.68 Table 20 presents the estimated utilisation and total cost of rivaroxaban for the overall pooled patient population (accounting for overlap). The PSCR revised the estimates to account for treatment interruptions and permanent treatment discontinuations, and the pre-PBAC response provided revised estimates to account for a price reduction, reduced uptake rates, and reduced compliance. These revised estimates are also presented in Table 20.

Table 19: Estimated use and financial implications, pooled subgroup population

	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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total eligible patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake rate (pooled)	18%	31%	36%	40%	43%	43%
Total treated patients [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total script numbers [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs (Effective DMPQ $)						
Total cost	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Patient co-payments [c]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total cost excl co-pay	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Revised estimates in PSCR						
Total cost excl co-pay	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Revised estimates in pre-PBAC response						
Uptake rate (pooled)	15%	26%	32%	36%	40%	40%
Total cost excl co-pay	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total cost from March 2019 submission (inclusive of [redacted]% rebate)[d]						
Total cost excl co-pay	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Table 4.2.1, Table 4.2.2, p287 of the resubmission.
DPMQ, dispensed price for maximum quantity.
[a] uptake rate x total eligible patients. Year 1 also includes [redacted] grandfathered patients, which are assumed to be accounted for as part of the uptake rate in Years 2-6.
[b] 10.66 scripts/patient/year based on compliance of 87.5%
[c] Weighted average patient co-payment of $5.06 for PBS and $4.81 for RPBS.
[d] Based on previous submission's proposed risk share arrangement with [redacted]% rebate applied to patients with CAD only and PAD only.

The redacted table shows that at Year 6, the estimated number of patients was 100,000 – 200,000 per year and the net cost to the PBS would be $30 - $60 million.

6.69 The resubmission estimated that the total cost to the PBS/RPBS of listing rivaroxaban (less patient co-payments) would be $60 - $100 million in Year 6, and a total of more than $100 million in the first 6 years of listing. This was reduced in the pre-PBAC response to $30 - $60 million in Year 6, and a total of more than $100 million in the first 6 years of listing.

6.70 The utilisation/financial estimates were uncertain due to the following issues:

- The PBAC previously considered that the Western Australian linked health data were likely to be the best available data to inform epidemiology estimates. However, the reliability of hospital administrative data to predict underlying cardiovascular disease prevalence is unclear. The resubmission acknowledged that the estimated eligible population may have been underestimated due to reliance on hospital admission records for case identification. The PSCR acknowledged the limitations of the dataset but argued that it continues to provide the best information to inform epidemiology estimates. The ESC considered there is remaining uncertainty with respect to the eligible population.
- Compliance rates used in the resubmission's financial impact estimates were based on weighted average numbers of compliant patients across 42 months of

the COMPASS trial. Compliance estimates reported in the clinical trial setting are unlikely to be representative of clinical practice, particularly given that patients with poor adherence were excluded from the COMPASS trial during the run-in period, and are therefore potentially overstated. The ESC further noted that the compliance rates in the trial decreased over time (per Table 18) which may not have been adequately accounted for in the weighted average approach used, given no data were available beyond 42 months. The approach used in the financial estimates was inconsistent with the economic model, which did not explicitly model compliance but did model persistence. The persistence rates applied in the economic model (based on a 10% PBS sample of rivaroxaban for stroke prevention in atrial fibrillation) were lower than the compliance rate applied in the financial estimates, which contributed to a large difference in the average number of scripts per patient between the economic model and financial estimates (refer to Table 18 in the 'Drug cost/patient/year' section). The pre-PBAC response provided updated estimates (based on 10% sample data for rivaroxaban in the non-valvular atrial fibrillation indication) which reduced the compliance rate from 87.5% to 76%.

6.71 The PBAC previously considered that uptake rates in the March 2019 submission were likely to have been substantially overestimated. The ESC considered that the addition of another antithrombotic agent on a twice daily basis would add considerably to the overall "pill burden" on these patents, which is already high in patients on secondary prevention strategies, as well as add minor and major bleeding risks. The PBAC previously considered that uptake was also likely to be lower than forecast due to some uncertainty in the risk/benefit profile of rivaroxaban for individual patients and a general reluctance from GPs to prescribe rivaroxaban without considerable guidance from specialists (paragraph 7.14, Rivaroxaban Public Summary Document, March 2019 PBAC meeting). This reluctance would be higher given that patients would be on both an antiplatelet agent and an anticoagulant, a combination that has historically been discouraged. Despite this, estimated uptake rates in the pooled population were higher in the current resubmission compared to the previous submission, which the resubmission justified based on market research (from both GPs and specialists) for the four individual subgroup populations. Faster uptake was assumed in the PAD populations due to a perceived unmet clinical need for treatments to manage PAD. The ESC considered that any market research would likely overestimate enthusiasm to prescribe both rivaroxaban and aspirin due to likely bias in the sampling and the likely higher enthusiasm for new therapies in those who answer surveys as opposed to those who do not. The pre-PBAC response reduced the uptake rates for the pooled target population (in Year 6 the uptake rates were [redacted]% in the resubmission versus [redacted]% in the pre-PBAC response). The reduced estimates in the pre-PBAC response were based on the lower limit of the 95% CI from the market research.

6.72 Overall, the ESC considered that the financial estimates were high and uncertain, with the greatest uncertainty being the likely overestimated uptake rate. The ESC considered that conservative assumptions would be required for the financial

estimates, which are being used to inform a risk sharing arrangement, in order to provide a greater level of confidence that utilisation reflects only the intended high risk population on which the economic model was based.

6.73 The 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. This was likely conservative in the context of an RSA with [redacted]% rebate above the caps.

6.74 The resubmission stated that the sponsor plans to commence a special access program for rivaroxaban in line with the proposed clinical criteria. There were less than 10,000 grandfathered patients included in the resubmission's estimates of uptake in Year 1 of listing. The ESC considered this may be double-counting as these patients may already be included in the prevalence-based financial estimates.

Quality Use of Medicines

6.75 The sponsor listed the following activities to support the quality use of medicines, which were the same as detailed in the previous submission:

- Optimised labelling and packaging to reduce dispensing and administration errors. Administration of higher than recommended doses of rivaroxaban may occur due to erroneous prescribing or administration of higher doses of rivaroxaban. There may be potential for use of rivaroxaban without aspirin (i.e. low-dose rivaroxaban monotherapy), resulting in suboptimal disease management.
- Provision of a prescriber guide. The ESC was concerned that the different treatment regimens and indications for rivaroxaban (atrial fibrillation, venous thromboembolic disease management and prophylaxis, stable atherosclerotic disease) across a wide range of doses raises considerable potential for incorrect dosing and administration. This is particularly likely when the indication for rivaroxaban changes within an individual patient necessitating a change in dose.
- Provision of a patient alert card to increase awareness and understanding among patients about the potential bleeding risk during treatment.
- Routine risk minimisation activities, including warning statements and notification of undesirable effects in the Australian Product Information to ensure healthcare professionals are fully informed of the identified safety concerns in order to undertake an individualised risk benefit evaluation for the patient.

Financial Management – Risk Sharing Arrangements

6.76 In response to a request from the PBAC, the resubmission proposed an updated risk sharing arrangement (RSA) which takes the form of capped Commonwealth expenditure with a [redacted]% rebate for all expenditure beyond the agreed annual expenditure caps (based on the total cost excluding co-payments in Table 20 above). The pre-PBAC response proposed that the capped Commonwealth expenditure be based on the pre-PBAC response's revised estimates as outlined in Table 20 above.

6.77 The ESC considered that the proposal for an RSA with a [redacted]% rebate over the cap was appropriate to mitigate the uncertain patient population, the potential for use outside the restriction and the high overall financial impact.

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

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation on the listing of rivaroxaban for the prevention of cardiovascular events in patients at high risk of recurrent thrombotic events, specifically patients with CAD and /or PAD, and additional high-risk factors. The PBAC considered there were important clinical benefits associated with rivaroxaban and that the patient groups who are likely to achieve the most favourable risk-benefit profile had been identified appropriately. The PBAC acknowledged the reductions in the price and the financial estimates since the previous submission, but considered that the proposed price and ICER were still unacceptably high and there remained considerable uncertainty regarding the financial estimates.

7.2 The PBAC considered there is a clinical need for effective treatments for the secondary prevention of thrombotic events in patients with a high risk of cardiovascular events.

7.3 The PBAC considered that the patient population suggested by ESC and accepted in the pre-PBAC response adequately defined the high-risk subgroups who would derive the most benefit from treatment with rivaroxaban, that is, patients with:

- CAD and PAD, or
- CAD or PAD with one or more of the following risk factors:
    - 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; or
    - Diabetes mellitus and: age greater than or equal to 60; concomitant microalbuminuria; or of Aboriginal or Torres Strait Islander descent.

7.4 The PBAC considered that aspirin alone, the nominated main comparator, was appropriate. The PBAC considered that while clopidogrel (in combination with aspirin) may also be a relevant comparator, the extent of the overlapping population would likely be small, particularly if current clinical guidelines for the use of dual anti-platelet therapy are followed.

7.5 The key clinical evidence presented was the COMPASS trial (unchanged from the previous submission), which 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 in the ITT population (HR: 0.76 (95% CI: 0.66, 0.86)), which comprises a broader population than requested for listing. The HRs were generally more favourable in the individual high-risk subgroups (and the pooled subgroup), except the PAD only population, which had been refined in the restriction proposed by ESC and agreed by the pre-PBAC response.

7.6 In the pooled subgroup specified in the resubmission, the HR for myocardial infarction, stroke, or cardiovascular death (the primary outcome) was [redacted]. As noted above, this population was further refined by the ESC and the pre-PBAC response to target use to a higher risk PAD population and to include diabetes as a risk factor.

7.7 The PBAC reiterated its previous consideration that the claim of inferior comparative safety was reasonable. Rivaroxaban in combination with aspirin was associated with a higher incidence of major bleeding overall compared with the aspirin monotherapy group, primarily driven by gastrointestinal bleeding and hospitalisations. The hazard ratio for major bleeding events was 1.70 (95% CI: 1.40, 2.05) in the ITT population and [redacted] in the pooled subgroup population (noting the latter was based on the resubmission's proposed population and did not account for refinement of the PAD population or inclusion of diabetes as a risk factor). The PBAC considered that the risk of bleeding in the target population was unlikely to be higher than in the ITT population.

7.8 Overall, the PBAC accepted the resubmission's claim that the revised target population would increase the absolute benefit associated with using rivaroxaban with aspirin compared to aspirin alone without an increase in the risk of major bleeding compared with the ITT population. However, the PBAC considered that some uncertainties remained with the clinical data including:

- The magnitude of the clinical benefit may have been overestimated in the trial (due to the premature stopping of the trial) and may not be reflected in clinical practice (due to potential differences between the trial population and likely PBS population in terms of baseline risk and compliance);
- While acknowledging that subgroup analyses were necessary given the narrower population, the PBAC considered that the subgroup analyses need to be interpreted with caution (as many of the analyses were specified post hoc and were not adjusted for multiple statistical testing despite the high number of statistical tests conducted);
- There were limited long term data (median follow up of 23 months) in the context of a long-term treatment; and
- The risk of bleeding with rivaroxaban was likely underestimated in the COMPASS trial because patients at high risk of bleeding were excluded, and patients treated

in clinical practice may be older and at a higher risk of bleeding than patients in the trial.

7.9 The pre-PBAC response presented a revised base case for the economic analysis that addressed the ESC's concerns that it was not appropriate to include non-cardiovascular death transition probabilities (in addition to background mortality, which would result in double-counting) and non-cardiovascular death treatment effects (no proposed mechanism and differences between arms were not statistically significant). The pre-PBAC response's revised base case also included a further [redacted]% price reduction, which resulted in an ICER of $15,000 - $45,000 per QALY.

7.10 The PBAC considered that a number of outstanding issues remained with the economic model including that: the data informing transition probabilities were sparse; and non-statistically significant cardiovascular benefits were included. The PBAC acknowledged there were some conservative assumptions in the economic model including that: patients experiencing multiple cardiovascular events accrue the ongoing cost and utility of the most severe event only; and the hazard ratios applied were based on the ITT (not the pooled subgroup). However, on balance the PBAC considered that the ICER remained uncertain and likely overestimated. The PBAC acknowledged that it would not be possible to address these uncertainties in a revised economic model.

7.11 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.

7.12 The PBAC noted that the resubmission had estimated a net cost to the PBS/RPBS of more than $100 million over 6 years, which was reduced to more than $100 million over 6 years in the pre-PBAC response. The PBAC accepted the changes in the pre-PBAC response's revised financial estimates, with the exception of the estimated uptake rate. The PBAC considered that the uptake rates remained overestimated given that rivaroxaban would add considerably to the overall "pill burden" in patients on secondary prevention strategies, and the uncertainty in the risk/benefit profile of rivaroxaban for individual patients. The PBAC considered that it would be more reasonable to assume uptake rates of [redacted] to [redacted]% over six years (rather than [redacted] to [redacted]% over six years, as estimated in the pre-PBAC response).

7.13 The PBAC considered that a risk sharing arrangement (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.

7.14 The PBAC advised that a minor resubmission would be required that addresses the following issues:

- Include the updated restriction based on the PBAC's advice (i.e. per the amended restriction under paragraph 3.1).
- 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.
- The financial estimates should be revised to reflect the lower price (derived from the economic model outlined above) and reduced uptake rate estimates.
- 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.

Outcome:
Deferred

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 will continue to work with the PBAC and the Department of Health on the listing of rivaroxaban 2.5mg.