

## 5.07 RIVAROXABAN, Tablet 2.5 mg, Xarelto<sup>®</sup>, Bayer Australia Limited

### 1 Purpose of Application

- 1.1 The submission requested a Section 85 (Authority Required) PBS listing for a new form of the listed drug rivaroxaban (2.5mg tablets) in combination with aspirin for the prevention of recurrent cardiovascular events in patients in the stable phase of coronary artery disease (CAD) or peripheral artery disease (PAD). The PBAC has not previously considered rivaroxaban for this indication.
- 1.2 Listing was requested on a cost-effectiveness basis compared to aspirin.

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

Component	Description
Population	Adults with stable atherosclerotic disease of the coronary and/or peripheral arteries, following resolution of one or more acute episodes.
Intervention	Rivaroxaban 2.5 mg twice daily in combination with aspirin 100 mg once daily
Comparator	Aspirin 100 mg once daily
Outcomes	Composite outcome of cardiovascular death, stroke, or myocardial infarction (efficacy); major bleeding (safety)
Clinical claim	In patients with atherosclerotic disease of the coronary and/or peripheral arteries, 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.25 of the submission

Abbreviations: CAD, coronary artery disease; PAD, peripheral artery disease

### 2 Requested listing

- 2.1 The restriction requested in the submission is outlined below (it has been reworded to comply with electronic media requirements only).

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
RIVAROXABAN Tablet 2.5 mg, 60	1	5	\$ [REDACTED]	Xarelto <sup>®</sup>	Bayer Australia Limited

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	Chronic
<b>Severity:</b>	Stable
<b>Condition:</b>	Atherosclerotic disease
<b>PBS Indication:</b>	Chronic stable atherosclerotic disease
<b>Restriction Level / Method:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical Criteria</b>	Patient must have objective evidence of a large burden of atherosclerotic disease in peripheral, carotid or coronary arteries;

Public Summary Document – March 2019 PBAC Meeting

	<p>AND                      Patient must have had previous surgical intervention for vascular disease; OR                      Patient must have intermittent claudication with an ankle-brachial index &lt;0.90 or diagnosed significant peripheral artery stenosis; OR                      Patient must have asymptomatic stenosis <math>\geq 50\%</math> of the carotid artery; OR                      Patient must have had a previous myocardial infarction within the last {x} years; OR                      Patient must have had a multi-vessel coronary revascularisation procedure; OR                      Patient must have symptomatic coronary artery disease with significant stenosis in <math>\geq 2</math> coronary arteries; OR                      Patient must have symptomatic coronary artery disease with significant stenosis in one coronary artery if <math>\geq 1</math> other territory has been revascularised                      AND                      Patient must not have acute coronary syndrome                      AND                      Patient must not require concomitant intensified antiplatelet therapy                      AND                      The treatment must be in combination with aspirin</p>
<b>Prescriber Instructions</b>	<p>Peripheral artery stenosis, stenosis of the carotid artery, or coronary artery stenosis must be diagnosed by angiography or non-invasive imaging</p> <p>Patients under 65 years of age must have documented atherosclerotic disease affecting an additional vascular bed or at least two additional risk factors such as smoking, diabetes, renal dysfunction, heart failure, or history of non-lacunar stroke</p>
<b>Administrative Advice</b>	<p><b>Shared Care Model:</b>                      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.</p> <p><b>Note</b>                      No increase in the maximum quantity or number of units may be authorised.</p> <p><b>Note</b>                      No increase in the maximum number of repeats may be authorised.</p>

- 2.2 The proposed restriction is narrower than the proposed TGA indication in that it specifies stable atherosclerotic disease.
- 2.3 The submission acknowledged that the restriction is complex and may require further input from the Department. The evaluation considered there is a risk of use outside the proposed population (e.g. in populations at lower risk of cardiac events, or populations with recent ACS). The ESC agreed the proposed restriction was complex and open to interpretation. The ESC considered that the restriction would need considerable refinement to ensure the appropriate high-risk population was identified.
- 2.4 The ESC considered that more specific wording around many of the clinical criteria would be required, including regarding disease burden, surgical intervention (e.g. whether this includes percutaneous procedures), and extent of arterial stenosis (e.g. whether this should outline a minimum percent of stenosis on imaging or evidence of functional significance). The ESC considered that the Prescriber Instruction requiring patients to have at least 2 additional risk factors “such as smoking, diabetes, renal dysfunction, heart failure, or history of non-lacunar stroke” was particularly open to interpretation, and could be interpreted to include risk factors such as family history, hyperuricemia, dyslipidaemia. Given the varying clinical significance of different risk

factors, the ESC considered that it may be necessary to outline the particular risk factors that a patient must have in order to be eligible for rivaroxaban.

- 2.5 The ESC also proposed that rivaroxaban treatment should be excluded in patients who have experienced acute coronary syndromes in the previous 12 months. The ESC considered that the proposed criterion 'Patient must not require concomitant intensified antiplatelet therapy' may need to be more specific (e.g. specify dual antiplatelet therapy). With regard to the proposed criterion 'Patient must have had a previous myocardial infarction within the last {x} years', the ESC and PBAC considered that it may be unnecessary to specify the number of years since the patient had a myocardial infarction, provided it was more than 12 months ago, although considered that remote events were likely associated with a lower risk than more recent events.
- 2.6 The proposed restriction defines a large and heterogeneous eligible population, including patients at varying levels of cardiovascular risk. The submission presents the results of a subgroup analysis of patients with both CAD and PAD, as opposed to patients with CAD and/or PAD, who are included in the proposed restriction. In general, baseline medical history data showed that the narrower population with CAD and PAD have more severe disease resulting from a more diffuse atherosclerotic plaque burden. This population forms the basis of a two-tiered risk-sharing arrangement proposed by the submission, designed to address uncertainty associated with uptake within the large eligible population.
- 2.7 The ESC considered that the optimal patient population for treatment with rivaroxaban had not been clearly defined, and that risk factors in addition to the presence of CAD and PAD may need to be considered to better define the optimal population at higher risk of cardiovascular events who would achieve a greater clinical benefit with rivaroxaban.
- 2.8 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 submission noted that there is no established scoring system for assessing bleeding risk in the large and heterogeneous CAD and/or PAD population.
- 2.9 The Pre-Sub-Committee Response (PSCR) proposed that additional criteria be added to the proposed restriction to align more closely with the COMPASS trial, such as excluding patients at high bleeding risk, or who require dual antiplatelet therapy (refer to Paragraph 6.23).

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

### **3 Background**

#### ***Registration status***

- 3.1 Rivaroxaban 2.5 mg was TGA registered on 11 January 2019 for "the prevention of major cardiovascular events (composite of stroke, myocardial infarction and

cardiovascular death) in patients with coronary artery disease (CAD) and/or peripheral artery disease (PAD)". The TGA-approved indication does not require concomitant use of aspirin with rivaroxaban treatment.

- 3.2 The TGA Delegate noted that, for the proposed indication, no data were available for CAD and/or PAD patients requiring dual antiplatelet therapy or non-aspirin antiplatelet therapy, or those with a history of ischaemic stroke within 1 month or any history of haemorrhagic or lacunar stroke. The Delegate also noted that long-term data were limited; the mean duration of treatment in the COMPASS trial was 619 days (20 months), median 615 days. The Delegate also noted that the risk-benefit profile of patients aged  $\geq 75$  years was more finely balanced than in younger patients, primarily due to the increased risk of bleeding in this older age group.

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

## **4 Population and disease**

- 4.1 The target population is patients with a large burden of stable atherosclerotic disease (CAD and/or PAD), who require prevention for a secondary major cardiac event. It is unclear when patients would transition from post-acute treatment (e.g. dual antiplatelet therapy) to re-establish treatment with rivaroxaban in combination with aspirin for the prevention of secondary events in stable atherosclerotic disease in clinical practice. While Guidelines in this area generally recommend a minimum of 12 months after acute coronary syndromes (ACS) or percutaneous revascularisation, the ESC noted that patients are now frequently treated with dual antiplatelet therapy for longer than 12 months, especially post-ACS.
- 4.2 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 the coronary arteries that give rise to episodes of myocardial ischaemia causing angina pectoris. Peripheral arterial disease is also typically caused by atherosclerosis. CAD and PAD share similar risk factors; both increase with increasing age and entail different risks of future major cardiovascular events depending on risk factors, comorbidities and disease modifying or preventative pharmacotherapies. 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 submission positioned rivaroxaban 2.5 mg in combination with aspirin as an alternative to low dose aspirin monotherapy for the secondary prevention of thrombotic cardiovascular events for patients in the stabilised, asymptomatic phase of CAD and/or PAD. Treatment is initiated as long-term secondary prevention in the stable phase of the disease, and may be temporarily interrupted for the management of recurrent events.
- 4.4 The standard of care for the secondary prevention of cardiovascular events depends on the clinical presentation of patients with CAD and/or PAD, and includes other

classes of medications such as other antiplatelet agents, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers, lipid-lowering therapy and beta-blockers. At present, there is no clear therapeutic strategy for intensified antithrombotic treatment in addition to aspirin in stable cardiovascular patients.

- 4.5 The pivotal trial, COMPASS, included carotid atherosclerotic disease as a subcategory of PAD; however, the evaluation considered that this aligned poorly with clinical practice. While both are atherosclerotic conditions, the baseline risks may be quite different. Treatment algorithms for carotid atherosclerotic disease typically include different management strategies for carotid versus other peripheral disease.

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

## 5 Comparator

- 5.1 The submission nominated aspirin as the main comparator.
- 5.2 Alternative comparators such as anti-platelet therapies (aspirin in combination with clopidogrel, or clopidogrel monotherapy) were not considered to be relevant in the submission. The submission argued that these are indicated for short-term management of ACS. Whilst in most guidelines dual antiplatelet therapy (either aspirin and clopidogrel or aspirin and ticagrelor) is recommended for a short duration following an event, single antiplatelet therapy (monotherapy with either aspirin or clopidogrel) is recommended for long-term prevention of secondary events. Aspirin plus dipyridamole is also used long-term in the specific indication of cerebrovascular disease.
- 5.3 Data from a 10% Medicare sample analysis provided in the submission indicated that a significant number of patients initiated on clopidogrel for prevention of cardiac events after experiencing ACS whilst on aspirin remain on treatment beyond 24 months (estimate of 33,600 patients). The ESC considered that there may be a number of explanations for this, including inadvertent failure to stop dual antiplatelet therapy after 12 months, deliberate use of dual antiplatelet therapy after 12 months due to the potential clinical benefit reflected in recent studies and potentially patient preference.
- 5.4 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,<sup>1</sup> who would likely represent a key part of the rivaroxaban target population. Thus, the ESC and PBAC considered that clopidogrel may be a relevant comparator in a sub-group of patients. The Pre-PBAC response argued that clopidogrel is not an appropriate comparator, stating that the

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<sup>1</sup>2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease. A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. JACC 2016. 68:10 (1082-115).  
<https://www.acc.org/~/media/Non-Clinical/Files-PDFs-Excel-MS-Word-etc/Tools%20and%20Practice%20Support/Quality%20Programs/Anticoag-10-14/DAPT/1%20Levine%202016%20DAPT%20Guidelines.pdf?la=en>

sponsor is not aware of any randomised controlled trials demonstrating a risk-benefit for extended use of dual antiplatelet therapy beyond 12 months. However, the PBAC agreed with the ESC that clopidogrel may be a relevant comparator in a sub-group of patients.

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician discussed various aspects of the COMPASS clinical trial including the trial design, the baseline risk of patients in the trial, the risk of bleeding with rivaroxaban, the net clinical benefit observed in the trial, and the risk-benefit profile in the elderly. The clinician also outlined that major adverse limb events were an important trial outcome, given few trials have been conducted in patients with PAD.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from health care professionals (2) 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, an overall net clinical benefit and a reduction in all-cause mortality, but also noted that rivaroxaban was associated with an increased risk of bleeding. The comments noted that this is the first medical treatment for patients with PAD that reduces the risk of amputation for vascular reasons.

### ***Clinical trials***

- 6.3 The submission was based on one head-to-head randomised controlled 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 twice daily or aspirin 100 mg once daily (COMPASS).
- 6.4 The submission presented only the comparison between two arms, rivaroxaban 2.5 mg twice daily in combination with aspirin versus aspirin monotherapy. The rivaroxaban 5 mg twice daily monotherapy comparison was omitted from the submission as it was not proposed for TGA registration or PBS listing, and because compared to aspirin, this regimen did not statistically significantly reduce the hazard for the primary outcome, but increased major bleeding.
- 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 submission stated that the pantoprazole/placebo arms of the COMPASS trial were still ongoing at the time of the first CSR publication, and did not provide results from these arms. In the absence of results being available, the evaluation considered that the use of concomitant PPIs (which are hypothesised to reduce bleeding risk) may potentially have underestimated the risk of bleeding in populations with lower levels of PPI use. The pre-PBAC response stated that “the sub-study regarding the utilisation of PPIs in COMPASS was recently published (Moayyedi et al 2018). The results of the study showed that routine PPI use did not reduce upper GI complications and major bleeds.” The PBAC noted that the publication was not provided in the PSCR or pre-PBAC response, and only limited information about the results were publicly available.

6.6 Details of the trial presented in the submission are provided in the table below.

**Table 2: 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. (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 CAD: An international, randomised, double-blind, placebo-controlled trial.	The Lancet S0140-6736(17): 32458-3.

Source: Table 2.2-1, p.61; Table 2.2-2, p.62 of the submission.

6.7 The key features of the direct randomised trial are summarised in the table below.

**Table 3: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
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.68-69; Table 2.4-1, p.74; Table 2.4-5, p.83; Table 2.4-7, pp.87-92 of the submission  
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 treatment effect, an issue that is acknowledged in the discussion of the primary COMPASS publication. The ESC agreed with evaluation and considered that the cardiovascular benefits presented in the submission may have been potentially overestimated due to the premature termination of the trial. The pre-PBAC response argued that “visual inspection of the estimated treatment effect size before and after the date of the independent data and safety monitoring board’s recommendation for early termination, and the application of a formal statistical method to account for potential overestimation of treatment effect size, indicate that conditional bias is negligible for the COMPASS study”.

### **Comparative efficacy**

6.9 The results of the primary outcome, the proportion of patients who experienced myocardial infarction, stroke, or cardiovascular death, and the individual components, are summarised in Table 4.

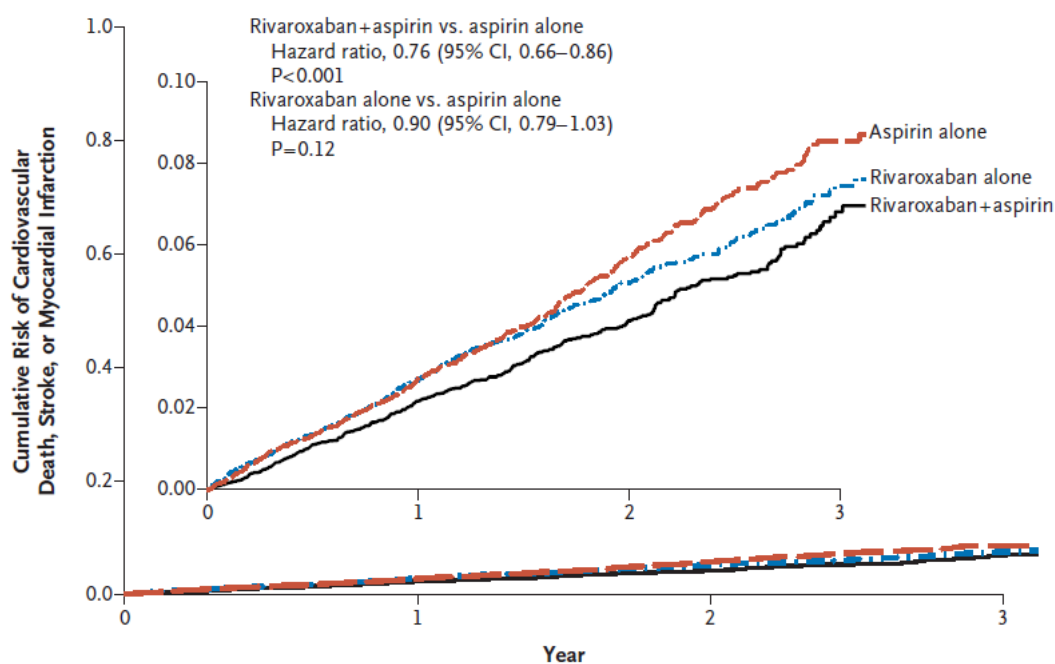
**Table 4: Results of primary efficacy outcome (composite of myocardial infarction, stroke, or death) and its components in the COMPASS trial (ITT)**

	Rivaroxaban 2.5 mg + aspirin 100 mg, n (%) N=9152	Aspirin 100 mg, n (%) N=9126	Mean difference (%)	Hazard ratio (95% CI)
Composite primary outcome	379 (4.1)	496 (5.4)	1.3	<b>0.76 (0.66, 0.86)</b>
Myocardial infarction	178 (1.9)	205 (2.2)	0.3	0.86 (0.70, 1.05)
Stroke	83 (0.9%)	142 (1.6)	0.7	<b>0.58 (0.44, 0.76)</b>
- Definite ischaemic stroke	64 (0.7)	125 (1.4)	0.7	0.51 (0.38, 0.69)
- Definite haemorrhagic stroke	15 (0.2)	10 (0.1)	-0.1	1.49 (0.67, 3.31)
- Uncertain/unknown type of stroke	4 (<0.1)	7 (<0.1)	-	Not calculated
Cardiovascular death	160 (1.7)	203 (2.2)	0.5	<b>0.78 (0.64, 0.96)</b>

Source: Table 2.5-1, p.107 of the submission; Table 9-2, p.124 COMPASS clinical study report

6.10 The Kaplan Meier estimates of the cumulative incidence risk for the composite primary outcome are summarised in Figure 1.

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, p.8 Eikelboom et al. (2017)

Note: The inset shows the same data on an expanded y-axis

- 6.11 Treatment with rivaroxaban in combination with aspirin was associated with a statistically significant reduction in the proportion of patients who experienced the composite primary efficacy outcome compared with the aspirin. A consistent treatment effect was observed for each of the individual components (myocardial infarction, stroke, and cardiovascular death), although the result was not statistically significantly different between treatment groups for myocardial infarction. The stroke result was driven by a reduction in ischaemic stroke.
- 6.12 The PBAC noted the results of a post hoc landmark analysis of the COMPASS trial data for the CAD subgroup for three time periods: from randomization to 1 year; from 1 to 2 years; from 2 years until the end of the trial. This analysis showed that for the primary outcome (myocardial infarction, stroke and cardiovascular death), the hazard ratio was not statistically significant beyond two years (HR: 0.82 (95% CI: 0.58, 1.16)). The PBAC noted the limitations of this analysis (e.g. there were fewer patient numbers with longer follow-up) but considered that the data indicated that it was unclear whether the treatment effect would be maintained over time.
- 6.13 Treatment with rivaroxaban plus aspirin was also associated with a statistically significant decrease in all-cause mortality compared with aspirin alone, which was driven by a reduction in cardiovascular death (HR = 0.82, 95% CI: 0.71, 0.96).

6.14 The results of other vascular outcomes are summarised in Table 5.

**Table 5: Number of patients with other vascular outcomes in the COMPASS trial (ITT)**

	Rivaroxaban 2.5 mg + aspirin 100 mg, n (%) N=9152	Aspirin 100 mg, n (%) N=9126	Hazard ratio (95% CI)
<b>Limb ischaemia outcomes</b>			
Acute limb ischaemia	22 (0.2)	40 (0.4)	<b>0.55 (0.32, 0.92)</b>
Chronic limb ischaemia	17 (0.2)	27 (0.3)	0.63 (0.34, 1.15)
Peripheral vascular intervention	153 (1.7)	184 (2.0)	0.82 (0.67, 1.02)
<b>Amputation outcomes</b>			
Amputation, vascular reasons	15 (0.2)	31 (0.3)	<b>0.48 (0.26, 0.89)</b>
Major amputation, vascular and other reasons	15 (0.2)	26 (0.3)	0.57 (0.30, 1.09)
Minor amputation, vascular and other reasons	17 (0.2)	26 (0.3)	0.65 (0.35, 1.20)
<b>Other outcomes</b>			
Angina	187 (2.0)	195 (2.1)	0.95 (0.78, 1.17)
Heart failure	212 (2.3)	206 (2.3)	1.02 (0.84, 1.24)
Venous thromboembolism	25 (0.3)	48 (0.5)	<b>0.52 (0.32, 0.84)</b>

Source: Table 2.5.10, p.117; Table 2.5-11, p.119; Table 2.5.12, p.119; Table 2.5-13, p.120 of the submission; Table 9-35, p.188; Table 9-36, p.189 COMPASS clinical study report

Note that the results for major and minor amputation could not be verified during the evaluation

6.15 Treatment with rivaroxaban plus aspirin was associated with a nominally significant decrease in acute limb ischaemia, amputation for vascular reasons and venous thromboembolism, compared with aspirin alone. Relatively small patient numbers informed the results for each component.

6.16 EQ-5D results reported in the COMPASS trial showed that, at each time point, results were nearly identical for each treatment group with most patients reporting no problems for each of the dimensions and very few reporting extreme problems. There were no consistent differences in quality of life outcomes between treatments.

6.17 The submission presented subgroup analyses for patients with both coronary and peripheral artery disease (CAD and PAD subgroup), CAD alone and PAD alone. The results for the primary efficacy outcome by the CAD and/or PAD subgroups are summarised in Table 6.

**Table 6: Subgroup analysis of the composite primary efficacy outcome of myocardial infarction, stroke, or cardiovascular death at data cut off (6 February 2017)**

	Rivaroxaban 2.5 mg + aspirin n/N (%)	Aspirin n/N (%)	Hazard ratio (95% CI)	Interaction p-value*
ITT population	379/9152 (4.1)	496/9126 (5.4)	<b>0.76 (0.66, 0.86)</b>	-
CAD and PAD subgroup	94/1656 (5.7)	138/1641 (8.4)	<b>0.67 (0.52, 0.87)</b>	0.5223
CAD only	253/6657 (3.8)	322/6620 (4.9)	<b>0.79 (0.67, 0.92)</b>	
PAD only	32/836 (3.8)	36/863 (4.2)	0.82 (0.53, 1.29)	

Source: Table 2.6-2, p.137 of the submission

Abbreviations: ITT, intention to treat; CAD, coronary artery disease; PAD, peripheral artery disease

\*P-value (two-sided) for the interaction of treatment group and each baseline subgroup based on the Cox proportional hazards model including the terms treatment group, baseline subgroup, and their interaction

- 6.18 There were statistically significantly fewer patients with CAD and PAD in the rivaroxaban in combination with aspirin treatment group who experienced myocardial infarction, stroke, or cardiovascular death compared to the aspirin monotherapy treatment group (5.7% versus 8.4%, respectively; HR: 0.67 (95%CI: 0.52, 0.87)).
- 6.19 Patients in the CAD and PAD subgroup had a higher baseline risk of having an event as a higher proportion of patients in the aspirin arm of the CAD and PAD subgroup (8.4%) had an event compared with the ITT population (5.4%). This resulted in a larger absolute reduction in the incidence of cardiovascular events in the CAD and PAD subgroup (2.7% ARR) compared to the ITT population (1.3% ARR).
- 6.20 Patients treated with rivaroxaban in combination with aspirin had a lower risk of experiencing myocardial infarction, stroke, or cardiovascular death compared with patients treated with aspirin alone in the CAD only subgroup and the PAD only subgroup, although statistical significance was only reached in the CAD only subgroup. An interaction test for homogeneity of treatment effect was not statistically significant, suggesting similar efficacy across subgroups.
- 6.21 Relative treatment effects were generally consistent across subgroups defined by baseline patient and disease history characteristics, with the exception of coronary artery bypass graft (CABG) surgery, which may be a treatment effect modifier. Baseline risk varied substantially between patient subgroup populations (e.g. 3.9% of aspirin patients with no history of hypertension experienced an event; 11.3% of aspirin patients with a history of stroke experienced an event).
- 6.22 It is likely that there will be differences in the demographics and disease characteristics between the COMPASS population and Australian patients defined by the proposed PBS restriction. This may have two possible implications: 1) possible differences across the populations in the underlying risk of having an event 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 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 prior myocardial infarction, prior coronary revascularisation, diabetes and smoking. The PSCR maintained that the Australian patient population is likely to have a higher baseline risk and thus a higher absolute number of events avoided should be anticipated in Australian clinical practice. This was based on a comparison with an analysis of the Western Australian linked hospital data set and the Australian subgroup of the REACH registry. Due to significant differences between the three sources used to compare populations (i.e. clinical trial population, hospital population, and a registry collated via general practice), it remains difficult to assess how comparable the proposed Australian PBS population will be to the COMPASS trial population.
- 6.23 The COMPASS trial excluded patients who were at high risk of bleeding; 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). Further, the mean age of patients was 68, although the majority of deaths due to cardiovascular disease tend to occur in older patients. In clinical practice, it will be essential to carefully screen for factors that increase bleeding risk, such as prior bleeding, older age, kidney disease, anaemia, and low body weight when considering the addition of rivaroxaban. The PSCR proposed that the restriction should include clinical criteria to prevent use in patients with particular risk factors for bleeding, consistent with the exclusion criteria of the COMPASS trial.

### Comparative harms

- 6.24 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.
- 6.25 A summary of the results for the primary safety outcome, treatment-emergent modified International Society on Thrombosis and Haemostasis (ISTH) major bleeding events for the safety set is summarised in Table 7. The ESC noted that the ISTH criteria distinguish bleeds as ‘major’ when they result in death, are life threatening, cause chronic sequelae or consume major healthcare resources. The modification to the standard ISTH definition (which the submission stated was requested by the FDA) was to also include every bleed that resulted in a presentation to an acute care facility.

**Table 7: Summary of treatment-emergent modified ISTH major bleeding events (safety set)**

	Rivaroxaban 2.5 mg + aspirin 100 mg, n (%) N=9134	Aspirin 100 mg, n (%) N=9107	Hazard ratio (95% CI)
Modified ISTH major bleeding	263 (2.9)	144 (1.6)	<b>1.84 (1.50, 2.26)</b>
Fatal bleeding	12 (0.1)	8 (<0.1)	1.51 (0.62, 3.69)
Critical organ bleeding (non-fatal)	58 (0.6)	43 (0.5)	1.36 (0.91, 2.01)
Requiring re-operation (non-fatal and non-critical organ)	7 (<0.1)	6 (<0.1)	1.17 (0.39, 3.48)
Hospitalisation (non-fatal, non-critical organ, not leading to re-operation)	188 (2.1)	91 (1.0)	<b>2.08 (1.62, 2.67)</b>
Hospitalisation where admission date < discharge date	155 (1.7)	74 (0.8)	<b>2.11 (1.60, 2.78)</b>
Hospitalisation where admission date = discharge date	33 (0.4)	19 (0.2)	1.74 (0.99, 3.07)

Source: Table 10-21, pp.266-267 of the COMPASS clinical study report

Abbreviations: ISTH, International Society on Thrombosis and Haemostasis

- 6.26 The rivaroxaban in combination with aspirin group had a higher incidence of major bleeding overall compared with the aspirin monotherapy group. The hazard ratio was statistically significant for modified ISTH major bleeding, primarily driven by bleeds requiring hospitalisation (non-fatal, non-critical organ, not leading to re-operation, and where patients required an overnight stay or greater). Fatal bleeding events were most frequently due to intracranial bleeding events and, of these, primarily haemorrhagic stroke.

- 6.27 The COMPASS trial included a pre-specified endpoint of net clinical benefit, which included time to first occurrence of safety and efficacy events considered to be significant. Net clinical benefit included both the composite primary efficacy outcome (stroke, myocardial infarction, cardiovascular death) and fatal and symptomatic critical organ bleeding events (two components of the primary safety outcome). The submission claimed that including only fatal and symptomatic critical organ bleeding events was justified because they cause irreversible harm, and therefore the endpoint compares efficacy and safety events of similar severity. The PBAC considered that the clinical utility of this net clinical benefit is not established.
- 6.28 The results for the net clinical benefit outcome, as well as the results for the primary efficacy and safety outcomes for comparison, are summarised in Table 8.

**Table 8: Net clinical benefit and components in the COMPASS trial (ITT)**

	Rivaroxaban 2.5 mg + aspirin 100 mg, n (%) N=9152	Aspirin 100 mg, n (%) N=9126	Hazard ratio (95% CI)
Net clinical benefit	431 (4.7)	534 (5.9)	<b>0.80 (0.70, 0.91)</b>
Primary efficacy outcome	379 (4.1)	496 (5.4)	<b>0.76 (0.66, 0.86)</b>
Primary safety outcome <sup>a</sup>	78 (0.9)	58 (0.6)	1.34 (0.95, 1.88)

<sup>a</sup> Excluding bleedings leading to hospitalisation and bleedings into surgical site associated with re-operation

Source: Table 2.5-24, p.133 of the submission

- 6.29 Overall, treatment with rivaroxaban in combination with aspirin statistically significantly reduced the risk of the net clinical benefit outcome compared with aspirin alone. The evaluation, ESC and PBAC considered that the clinical relevance of this outcome is unclear; net clinical benefit outcome includes events of varying severity, and may underestimate safety by neglecting potential consequences of even minor bleeds. In clinical practice, a range of cardiovascular and bleeding outcomes would need to be considered to determine whether benefits are likely to exceed risks for an individual patient, although the ESC recognised that there is no bleeding risk scoring system that has been validated in this clinical scenario.

### **Benefits/harms**

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

**Table 9: Summary of comparative benefits and harms for rivaroxaban and aspirin**

<b>Composite primary outcome (myocardial infarction, stroke, or cardiovascular death): COMPASS trial</b>						
	<b>Rivaroxaban 2.5 mg + aspirin 100 mg, n=9152</b>	<b>Aspirin 100 mg, n=9126</b>	<b>Absolute mean difference (%)</b>	<b>HR (95% CI)</b>		
Composite primary outcome	379 (4.1)	496 (5.4)	1.3	<b>0.76 (0.66, 0.86)</b>		
Myocardial infarction	178 (1.9)	205 (2.2)	0.3	0.86 (0.70, 1.05)		
Stroke	83 (0.9%)	142 (1.6)	0.7	<b>0.58 (0.44, 0.76)</b>		
Cardiovascular death	160 (1.7)	203 (2.2)	0.5	<b>0.78 (0.64, 0.96)</b>		
<b>Harms</b>						
	<b>Rivaroxaban + aspirin n/N</b>	<b>Aspirin n/N</b>	<b>HR (95% CI)</b>	<b>Event rate/100 patients*</b>		<b>RD</b>
				<b>Rivaroxaban + aspirin</b>	<b>Aspirin</b>	
Modified ISTH major bleeding	263/9134	144/9107	<b>1.84 (1.50, 2.26)</b>	2.9	1.6	1.3
Fatal bleeding	12/9134	8/9107	1.51 (0.62, 3.69)	0.1	<0.1	NE
Hospitalisation (non-fatal, non-critical organ, not leading to re-operation)	188/9134	91/9107	<b>2.08 (1.62, 2.67)</b>	2.1	1.0	1.1

Source: Table 2.5-1, p.107 of the submission; Table 9-2, p.124; Table 10-21, pp.266-267 of the COMPASS clinical study report  
Abbreviations: HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis; NE, not estimable; RD, risk difference

- 6.31 On the basis of the direct evidence presented in the submission, for every 1,000 patients treated with rivaroxaban in combination with aspirin in comparison to aspirin alone and over a median duration of exposure of 23 months:
- Approximately 13 additional patients would avoid a major adverse cardiovascular event (myocardial infarction, stroke, or cardiovascular death)
  - Approximately 13 additional patients would experience a major bleeding event
  - Approximately 11 additional patients would require hospitalisation to manage a bleeding event
- 6.32 When rivaroxaban plus aspirin was compared to aspirin alone, the number needed to treat was 77, indicating that 77 patients would need to be treated with rivaroxaban plus aspirin (rather than aspirin alone) for one additional patient to achieve benefit (major adverse cardiovascular event avoided) over a 23-month period. The number needed to harm was 77, indicating that 77 patients would need to be treated with rivaroxaban + aspirin (rather than aspirin alone) for one additional patient to experience major bleeding over the 23-month period.
- 6.33 In the subgroup of patients with CAD and PAD, the number needed to treat to achieve benefit (major adverse cardiovascular event avoided) was 37 and the number need to treat to harm (major bleeding) was 120 patients over the 23-month period. As a subgroup analysis, the ESC noted that these numbers were highly uncertain.
- 6.34 The PSCR claimed that to fully assess risk-benefit, the cumulative incidence of major adverse cardiovascular events should be compared to the cumulative incidence of bleeding events that have similar irreversible consequences, such as a fatal bleed or bleeding into a critical organ or area. The pre-PBAC response stated that the “relative

major bleeding risk between the two treatment arms were not constant over time, in which bleeding risk was relatively high for rivaroxaban plus aspirin within the first year of treatment and subsequently equivalent relative to aspirin alone in the following years, whereas the benefit of major adverse cardiovascular event reduction was observed to be constant over time". However, the PBAC considered that, with an extended duration of treatment in clinical practice, it was likely that the risk of bleeding would increase as a patient's age increases and/or their renal function declines.

### **Clinical claim**

- 6.35 The submission described rivaroxaban in combination with aspirin as superior in terms of efficacy, and inferior in terms of safety, compared with aspirin monotherapy. The ESC considered the clinical claim was reasonable; however, it advised that the benefit seen in the trial may be overestimated. In terms of inferior safety, the ESC considered the claim was reasonable; however, it advised that the risk of bleeding with rivaroxaban may be underestimated.
- 6.36 While relative treatment effects were broadly consistent across most patient groups (with the exception of CABG), the absolute benefit of treatment varied substantially between subgroup populations due to differences in baseline risk. For the overall CAD and/or PAD population, over the 23 month period, 77 patients would need to be treated with rivaroxaban plus aspirin versus aspirin alone to avoid one major adverse cardiovascular event and 77 patients would need to be treated for one additional patient to experience major bleeding. For the population with CAD and PAD the number needed to treat is 37 and the number needed to harm is 120 patients over the 23 month period.
- 6.37 Additionally it was unclear whether the baseline risk in the COMPASS trial population was 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). Consequently, it is unclear whether similar absolute treatment benefit would be observed in the Australian population.
- 6.38 Subgroup analyses suggest that the benefits and harms of rivaroxaban in elderly patients are more finely balanced as, although event rates tend to be higher in the elderly, the decrease in risk of cardiovascular events with rivaroxaban and aspirin may be offset by an increased risk of major bleeding. Therefore, the applicability of the study results to the elderly, who form a large proportion of cardiovascular patients in clinical practice, is unclear.
- 6.39 The evaluation and the ESC considered it was unclear whether the COMPASS trial results can be generalised to clinical practice as a number of study features were likely to have overestimated cardiovascular benefit (e.g. premature stopping of trial) and underestimated bleeding risk (e.g. patients at high risk of bleeding were excluded from the trial; and patients treated in clinical practice may be older and at a higher risk of bleeding than patients in the trial, where the mean age was 68 years). The PBAC noted

that the COMPASS trial included a factorial randomisation to a PPI, pantoprazole, in patients without a pre-existing indication for a PPI, which resulted in a higher number of patients using a PPI than would be seen in Australian clinical practice. The PBAC noted that the full results from the pantoprazole/placebo arms of the COMPASS trial were not provided, and considered that it remained unclear whether the higher use of PPIs in the trial population would have underestimated the risk of bleeding in the PBS population.

- 6.40 The ESC considered the optimal use of concomitant cardiovascular medications (e.g. statins, beta-blockers, ACE inhibitors or angiotensin II receptor blockers) is likely to affect the baseline risk of different populations and noted the COMPASS trial did not require that patients be on optimal medical therapy. Whilst this may be considered to reflect the situation that exists in the population that rivaroxaban will be used in, it is uncertain how baseline differences in the use of concomitant cardiovascular medications will affect the incremental benefit (and risk) of rivaroxaban. While the baseline use of these medications in COMPASS appeared to be relatively high, nevertheless the magnitude of additional benefit in addition to ideal medical management of cardiovascular risk is unknown.
- 6.41 The PBAC considered that the claim of superior comparative effectiveness of rivaroxaban in combination with aspirin versus aspirin alone was reasonable. However, the PBAC considered that the magnitude of the benefit was uncertain.
- 6.42 The PBAC considered 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***

- 6.43 The submission presented a stepped economic evaluation of the additive effects of using rivaroxaban with aspirin compared to aspirin alone for the prevention of cardiovascular events in patients with CAD and/or PAD. The economic evaluation was based on a direct randomised trial (COMPASS) using the overall trial population (CAD and/or PAD) and a high-risk subgroup (CAD and PAD) with additional modelled data.

**Table 10: Key components of the economic evaluation**

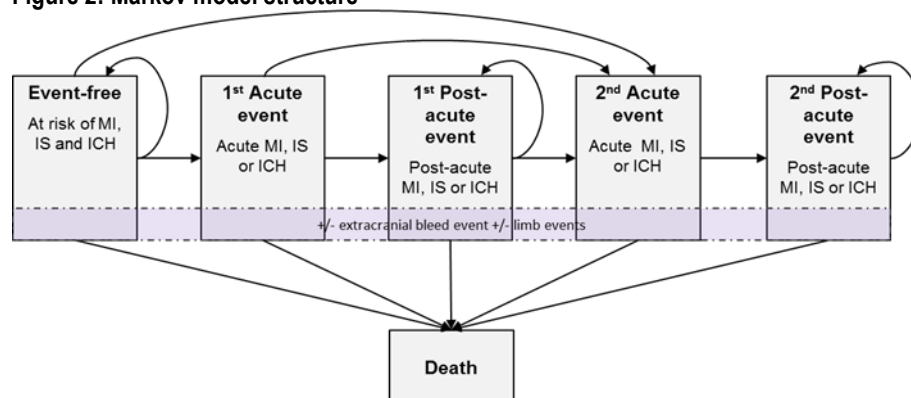
Component	Description
Type of analysis	Cost-effectiveness analysis/cost-utility analysis
Outcomes	Major cardiovascular event avoided; life years; quality adjusted life years
Time horizon	30 years (lifetime)
Methods used to generate results	Markov cohort model with tunnel states (with half-cycle correction)
Treatments	Low dose rivaroxaban with aspirin; aspirin alone
Health states	Baseline health state, 3 single event health states (myocardial infarction, ischaemic stroke, intracranial haemorrhage), 9 double event states (MI + MI, MI + IS, MI + ICH, IS + IS, IS+MI, IS + ICH, ICH+ICH, ICH+MI, ICH+IS) and 9 death event states (MI death, IS death, bleeding death, heart failure death, CV procedure death, sudden cardiac death, other CV death, any CV death, all non-CV death). The non-fatal event health states also include tunnels to differentiate between acute and chronic phases.
Cycle length	3 month
Transition probability	Transition probabilities for fatal/non-fatal cardiovascular events and other vascular events (acute limb ischaemia, major amputation, minor amputation, major extracranial bleeds, venous thromboembolism) were derived from post hoc analysis of individual patient data from the COMPASS trial. Event probabilities were adjusted over time using a cardiovascular risk multiplier and a cardiovascular death multiplier based on the REACH study. Non-cardiovascular death probabilities were based on Australian life tables. Treatment effect estimates were derived from the COMPASS trial.
Discount rate	5% for costs and outcomes
Software package	Microsoft Excel 2016

Source: Table 3.1-1 (p 190) of the submission

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

6.44 The model structure is shown in Figure 2 below. Patients enter the model in the baseline health state. In each quarterly cycle, patients can have no event or experience up to two non-fatal cardiovascular events (myocardial infarction, ischaemic stroke, and intracranial haemorrhage), cardiovascular death (including various sub-categories), bleeding death or non-cardiovascular death. Patients experiencing multiple cardiovascular events accrue the cost and utility of the most severe event (ischaemic stroke > intracranial haemorrhage > myocardial infarction > baseline health state). The modelled health states limit the number of non-fatal cardiovascular events to a maximum of two per patient, which the ESC considered may not be reasonable. The model utilises tunnel states for non-fatal cardiovascular events in order to adjust transition probabilities, costs and utilities over time (acute phase < 3 months, chronic phase > 3 months). Additionally, during any cycle of the model patients can also experience other vascular events (acute limb ischaemia, minor amputation, major amputation, acute major bleed, and acute venous thromboembolism). The model structure allowed patients in the rivaroxaban with aspirin treatment arm to discontinue rivaroxaban treatment and continue with aspirin alone.

Figure 2: Markov model structure



Source: Page 184 of the submission

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

6.45 The ESC considered that a microsimulation approach may have been more appropriate as it would have a greater ability to track events over time (which would assist the validation of estimates) particularly given the need to model time dependent events that have an effect on future events. The ESC further considered that a microsimulation approach may be appropriate given the baseline heterogeneity of the patient population.

6.46 The modelled use of rivaroxaban in patients with acute coronary syndromes is not consistent with the requested restriction (and the submission has not provided any clinical data to support this indication). The circumstances of use for both treatment arms of the model were based on the assumption that all patients would remain fully adherent and persistent to therapy, and there would be no treatment interruptions (i.e. due to acute coronary syndromes or bleeding events). The ESC considered these assumptions were not reasonable as patients are unlikely to be fully adherent and persistent to therapy, with no treatment interruptions, in clinical practice. The ESC considered that this was in particular an issue in the context of the 30-year time horizon and with the assumption of a constant treatment effect. The ESC noted that, while the submission presented sensitivity analyses to attempt to account for these issues, these analyses were not reliable because:

- The sensitivity analyses of persistence were based on discontinuation rates from the COMPASS trial, which the ESC considered would underestimate those in clinical practice, particularly given that the COMPASS trial included a run-in period that excluded patients with poor compliance.
- In the sensitivity analyses of treatment interruptions, only drug costs were changed; however the evaluation and the ESC considered that treatment interruptions should also affect efficacy and safety estimates. The PSCR argued the impact on efficacy and safety would be captured in the observed outcomes from the trial. However, the ESC considered that it was unclear whether the treatment interruptions during the COMPASS trial would reflect clinical practice in the longer-term (particularly as most of the impact of treatment interruptions in the model occurred during the extrapolated period, rather than the trial period).

The appropriate modelling of treatment interruptions may potentially have a major impact on the cost effectiveness estimates given the highest risk of a subsequent cardiovascular event is within one year of a prior event. Further, the sensitivity analysis did not include all relevant causes of treatment interruptions (e.g. it did not include unstable angina, ischaemic stroke and revascularisation procedures).

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

**Table 11: Key drivers of the model**

Description	Method/Value	Impact
Transition probabilities	<p>Transition probabilities for fatal/non-fatal cardiovascular events, fatal/non-fatal bleeding events and other vascular events were based on a post-hoc analysis of individual patient data from the COMPASS trial. Cardiovascular event probabilities were adjusted over time with a cardiovascular risk multiplier and a cardiovascular death multiplier derived from the REACH study. The ESC noted the REACH study, on which this adjustment was based, included participants from 44 countries, and thus the applicability to the relevant Australian population was uncertain. The ESC considered the risk multiplier added considerable additional uncertainty. Non-cardiovascular death probabilities were based on Australian life tables.</p> <p>The clinical data informing the transition probabilities were sparse given the relatively low frequency of events in the COMPASS trial and the large number of health states in the economic model.</p> <p>Due to the lack of data, there were a substantial number of null transitions in the model, which restricted patient transitions in an implausible manner (e.g. patients with two cardiovascular events could not die of cardiovascular causes, with the exception of the acute double MI state). Conversely, data sparseness also affected non-zero transition probabilities as most subsequent transitions were based on a limited number of observations with the event of interest only occurring in a very small number of patients (in most cases based on the experience of a single patient) and therefore cannot be reliably differentiated from random chance.</p> <p>The problems associated with data sparseness were further exacerbated for the CAD and PAD subgroup (18% of overall population) given the smaller number of patients included in this dataset.</p> <p>The submission presented a sensitivity analysis replacing null transitions with transition probabilities from the event-free state. During the evaluation, additional sensitivity analyses were conducted replacing non-zero transitions with transition probabilities from the event-free state and replacing all subsequent event transitions (null and non-zero) with transition probabilities from the event-free state. Overall, the analyses indicate that the economic model was sensitive to different approaches to handling data sparseness.</p>	High, direction unclear
Extrapolation	Up to 4 years of trial data (but with a median follow-up of only 23 months) were extrapolated to 30 years, assuming proportional hazards and with risk multipliers applied for cardiovascular risk and cardiovascular death.	Large impact, likely favours rivaroxaban
Adherence, persistence and treatment interruptions	Base case assumes full adherence and persistent until death, with no treatment interruptions. The sensitivity analyses did not adequately test these assumptions.	Unknown impact (potentially large), favours rivaroxaban

Source: Constructed during the evaluation

6.48 A key issue with the model was the sparse clinical data informing many of the

transition probabilities which resulted in implausible null transitions for some subsequent events and highly uncertain non-zero transitions for other subsequent events (as outlined in the table above). The PSCR acknowledged that few subsequent cardiovascular events were observed in the trial, but stated that the COMPASS trial is the largest cardiovascular disease trial to date. The ESC and PBAC noted that the premature discontinuation of the trial meant that a longer modelled extrapolation was required.

- 6.49 The submission applied the rivaroxaban with aspirin hazard ratios to the underlying risk in the aspirin alone arm to derive transition probabilities for the rivaroxaban with aspirin treatment arm. The submission supported this approach by noting that additional analyses reported in the COMPASS trial report (log-log plot, scaled Schoenfeld residuals and Cox models assessing a treatment by time interaction) did not demonstrate any violation of the proportional hazards assumption. Treatment effects were assumed to remain constant while patients remained persistent with therapy. The ESC noted that the extrapolation to 30 years was based on a median follow-up of 23 months in the trial, which introduced substantial uncertainty given the sparse data informing many of the transition probabilities. The ESC and PBAC considered that, in light of these limitations, a more conservative approach to extrapolation would be required.
- 6.50 From Year 5 onwards, the submission increased the baseline risk in the model to reflect increased cardiovascular risk due to age (based on data from the REACH registry, the economic evaluation assumed a cardiovascular risk multiplier of 1.03 per year and a cardiovascular death multiplier of 1.05 per year. The ESC noted this the REACH registry, on which these multipliers were based, included participants from 44 countries, and the applicability to the relevant Australian population was uncertain). While the treatment effect remained constant over the duration of the model, the baseline risk increased and thus the absolute reduction in events with rivaroxaban increased. The ESC considered that the magnitude of the absolute risk reduction was uncertain, and the approach may have overestimated the number of events avoided during the extrapolation period. The ESC considered that other issues with the risk multipliers included:
- the application of risk multipliers from the REACH study to trial-based transition probabilities further exacerbated the problems associated with sparse data.
  - the model did not apply risk multipliers for the increased risk of bleeding in older patients, which may not have been appropriate.
  - the submission incorrectly applied the multiplier for any event (fatal and non-fatal) to the transition probabilities for non-fatal events.
- 6.51 The ESC considered that many of the clinical issues flowed-on to uncertainties with the economic evaluation including: the COMPASS trial results may potentially have overestimated the cardiovascular benefit and underestimated the bleeding risk; whether the baseline cardiovascular and bleeding risks in the trial population would be similar to the target Australian population; the heterogeneous population with

different risks and benefits; and that dual anti-platelet therapy is a relevant comparator in a group of patients (and would be associated with different efficacy and costs compared with aspirin alone).

6.52 The ESC considered that the model likely double-counted some amputation events due to separately modelling acute limb ischaemia and amputation (i.e. these were not factored as being mutually exclusive), which would favour rivaroxaban.

6.53 The ESC noted the utility values had a limited impact on the economic analysis within the current structure of the model, but noted that the commentary had raised several issues with the utilities (e.g. the limited number of EQ-5D assessments to inform the utility estimates for some events, uncertainties with data handling, potential overestimation of chronic disutility values for cardiovascular events).

6.54 The results of the stepped economic evaluation are summarised below.

**Table 12: Stepped economic evaluation of rivaroxaban with aspirin compared to aspirin alone**

Analysis step	CAD and/or PAD population	CAD and PAD subgroup population
<b>Step 1: Trial based efficacy/safety; 4 year horizon<sup>a</sup>; drug costs only</b>		
Incremental costs	\$ [redacted]	\$ [redacted]
Incremental difference in patients with MI, IS, ICH or CV death	[redacted]	[redacted]
<b>Incremental cost per event avoided</b>	\$ [redacted]	\$ [redacted]
<b>Step 1a: Trial based efficacy/safety; 4 year horizon; drug costs only</b>		
Incremental costs	\$ [redacted]	\$ [redacted]
Incremental difference in LYs	[redacted]	[redacted]
<b>Incremental cost LY gained</b>	\$ [redacted]	\$ [redacted]
<b>Step 2: Model based efficacy/safety including general population mortality; 30 year horizon; drug costs only</b>		
Incremental costs	\$ [redacted]	\$ [redacted]
Incremental difference in LYs	[redacted]	[redacted]
<b>Incremental cost LY gained</b>	\$ [redacted]	\$ [redacted]
<b>Step 3: Model based efficacy/safety including cardiovascular risk multiplier, cardiovascular death multiplier and general population mortality; 30 year horizon; drug costs only</b>		
Incremental costs	\$ [redacted]	\$ [redacted]
Incremental difference in LYs	[redacted]	[redacted]
<b>Incremental cost LY gained</b>	\$ [redacted]	\$ [redacted]
<b>Step 4: As above plus acute event costs, disease management costs, death costs</b>		
Incremental costs	\$ [redacted]	\$ [redacted]
Incremental difference in LYs	[redacted]	[redacted]
<b>Incremental cost LY gained</b>	\$ [redacted]	\$ [redacted]
<b>Step 5: As above plus cardiovascular health state utility values, vascular event disutility values</b>		
Incremental costs	\$ [redacted]	\$ [redacted]
Incremental difference in QALYs	[redacted]	[redacted]
<b>Incremental cost per QALY gained</b>	\$ [redacted]	\$ [redacted]

Source: Table 3.8-1 (p 264) of the submission

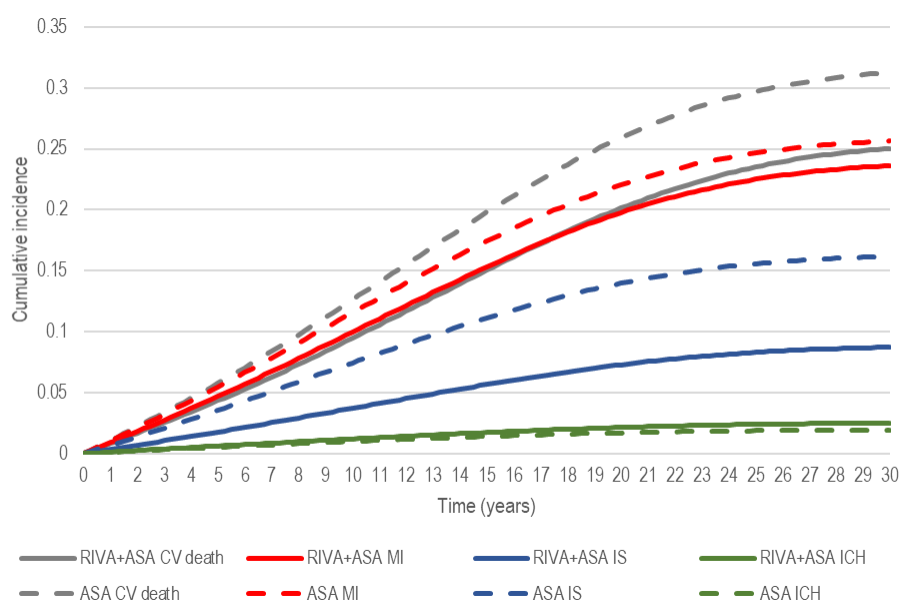
Abbreviations: ICH, intracranial haemorrhage; IS, ischaemic stroke; LY, life years; MI, myocardial infarction; QALYs, quality-adjusted life years

Note: The step order was rearranged during the evaluation with additional steps added to explore the impact of risk multipliers and patient survival.

<sup>a</sup> The submission assumed that the 30 month transition probabilities from the COMPASS trial could be used to inform trial-based estimates up to four years.

- 6.55 Based on the economic model, treatment with rivaroxaban and aspirin was associated with a cost per QALY gained of \$15,000/QALY to 45,000/QALY compared to aspirin alone for the treatment of stable CAD and/or PAD. For the treatment of the subgroup of patients with stable CAD and PAD, the cost per QALY gained was \$15,000 to \$45,000. The submission did not present an economic analysis comparing rivaroxaban with aspirin compared to aspirin alone in a PAD only or CAD only population.
- 6.56 The ESC considered that these results should be interpreted with caution as the economic evaluation may not be sufficiently reliable to inform decision making given: the trial results may have overestimated the cardiovascular benefit and underestimated the risk of bleeding; nearly all of the benefits occurred during extrapolated part of the model, and hence the results of the economic evaluation are inherently uncertain; the extrapolation approach was unlikely to be conservative; there were sparse clinical data informing transition probabilities; and the assumption that patients would remain fully adherent and persistent to therapy with no treatment interruptions was not reasonable.
- 6.57 The extrapolation of treatment benefits beyond the clinical trial data had the largest impact on the stepped economic evaluation (80-90% of the incremental difference occurred during the modelled period beyond 30 months). The incremental difference in life years gained increased from 0.02 years in the trial-based analysis to [redacted] years in the modelled analysis (or [redacted] years undiscounted life years gained) in the CAD and/or PAD population. The impact of the extrapolation is further demonstrated in the figure below. The Markov trace shows that rivaroxaban with aspirin was associated with substantial reductions in ischaemic stroke and cardiovascular death compared with aspirin alone.

Figure 3: Markov traces of the cumulative incidence of cardiovascular events



Source: Xarelto (rivaroxaban) CAD PAD Excel spreadsheet

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

6.58 The results of key sensitivity analyses (presented in the submission or conducted during the evaluation) are summarised below.

**Table 13: Results of key sensitivity analyses**

Analyses	Incremental cost per QALY gained	
	CAD and/or PAD population	CAD and PAD subgroup population
<b>Base case</b>	\$ [REDACTED]	\$ [REDACTED]
<b>Time horizon (base case: 30 years)</b>		
5 years	\$ [REDACTED]	\$ [REDACTED]
10 years	\$ [REDACTED]	\$ [REDACTED]
20 years	\$ [REDACTED]	\$ [REDACTED]
<b>Transition probabilities (base case: individual patient data from COMPASS trial; cardiovascular risk and cardiovascular death multipliers based on the REACH study)</b>		
Replace subsequent zero transition probabilities with event-free transitions and using any CV death from the acute double MI transition to inform the any CV death transition in all double event states	\$ [REDACTED]	\$ [REDACTED]
Replace subsequent zero transition probabilities with event-free transitions and using the sum of all CV death transitions from the event-free state to inform the any CV death transition in all double event states	\$ [REDACTED]	\$ [REDACTED]
Replace subsequent non-zero transition probabilities with event-free transitions (no imputation for zero transition probabilities)	\$ [REDACTED]	\$ [REDACTED]
Replace all subsequent transition probabilities with event-free transitions	\$ [REDACTED]	\$ [REDACTED]
Remove cardiovascular risk and cardiovascular death multipliers	\$ [REDACTED]	\$ [REDACTED]
<b>Treatment effects (base case: point estimate difference from COMPASS trial)</b>		
Only include statistically significant differences (non-fatal IS, CV death, acute limb ischaemia and major bleeds)	\$ [REDACTED]	\$ [REDACTED]
Upper 95% CI for CV death	\$ [REDACTED]	\$ [REDACTED]
Lower 95% CI for CV death	\$ [REDACTED]	\$ [REDACTED]
Upper 95% CI for non-fatal cardiovascular events (MI, IS, ICH)	\$ [REDACTED]	\$ [REDACTED]
Lower 95% CI for non-fatal cardiovascular events (MI, IS, ICH)	\$ [REDACTED]	\$ [REDACTED]
Upper 95% CI for major bleeding events	\$ [REDACTED]	\$ [REDACTED]
Lower 95% CI for major bleeding events	\$ [REDACTED]	\$ [REDACTED]
Upper 95% CI for other vascular events	\$ [REDACTED]	\$ [REDACTED]
Lower 95% CI for other vascular events	\$ [REDACTED]	\$ [REDACTED]
<b>Drug costs (base case: rivaroxaban drug costs based on proposed DPMQ, aspirin costs not included)</b>		
Rivaroxaban drug costs after 10% statutory price reduction	\$ [REDACTED]	\$ [REDACTED]
Rivaroxaban drug costs after 10% statutory price reduction and [REDACTED] % rebate (RSA)	\$ [REDACTED]	\$ [REDACTED]

Source: Table 3.9-1 (p 267) of the submission

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; RSA, risk sharing arrangement

*The redacted table shows ICERs in the range of less than \$15,000/QALY to \$200,000/QALY.*

6.59 The results of the sensitivity analyses indicated that the model was most sensitive to time horizon, transition probabilities (approaches to handling sparse data; use of risk multipliers), treatment effects (particularly CV death) and rivaroxaban drug costs. The

structure of the economic model did not allow sensitivity analyses to adequately assess the impact of the sparse data, the potentially optimistic extrapolation, treatment interruptions (e.g. due to recent ACS event) or changes to baseline risk due to differences in cardiovascular risk factors.

***Drug cost/patient/year***

- 6.60 The estimated drug cost for rivaroxaban per patient per year was \$ [REDACTED] (based on 12.17 scripts using the proposed DPMQ \$ [REDACTED] for 30 days treatment). The submission assumed that the drug cost for aspirin was negligible and did not include this cost in the economic model or financial implications, which the ESC considered was reasonable.

***Estimated PBS usage & financial implications***

- 6.61 This submission was considered by DUSC.
- 6.62 The submission used an epidemiological approach to estimate the utilisation and financial impacts associated with the PBS listing of low dose rivaroxaban for stable CAD and/or PAD. The total eligible CAD and/or PAD population in June 2010 was estimated based on an analysis of Western Australian linked health data.
- 6.63 The table below presents the total utilisation and cost to the PBS of listing low dose rivaroxaban for CAD and /or PAD patients.

**Table 14: Total utilisation and cost to PBS of listing rivaroxaban (CAD and/or PAD population)**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Eligible population</b>						
Australian population	██████████	██████████	██████████	██████████	██████████	██████████
Prevalence rate	██████████%	██████████%	██████████%	██████████%	██████████%	██████████%
Total prevalent patients	██████████	██████████	██████████	██████████	██████████	██████████
Total CAD only (██████████%)	██████████	██████████	██████████	██████████	██████████	██████████
Total PAD only (██████████%)	██████████	██████████	██████████	██████████	██████████	██████████
Total CAD and PAD (██████████%)	██████████	██████████	██████████	██████████	██████████	██████████
Total treated patients <sup>a,b</sup>	██████████	██████████	██████████	██████████	██████████	██████████
Total scripts (██████████ year based on compliance of ██████████%)	██████████	██████████	██████████	██████████	██████████	██████████
<b>Estimated total cost of rivaroxaban (DPMQ \$██████████)</b>						
Total cost to PBS	\$██████████	\$██████████	\$██████████	\$██████████	\$██████████	\$██████████
Total copayments (\$4.95 per script)	-\$██████████	-\$██████████	-\$██████████	-\$██████████	-\$██████████	-\$██████████
Total cost to PBS less copayments	\$██████████	\$██████████	\$██████████	\$██████████	\$██████████	\$██████████
<b>Estimated total cost of rivaroxaban inclusive of ██████████% rebate<sup>c</sup></b>						
Total cost to PBS	\$██████████	\$██████████	\$██████████	\$██████████	\$██████████	\$██████████

Source: Table 4.1-5, p.280; Table 4.1-6, p.280; Table 4.1-7, p.281; Table 4.2-1, p.283 of the submission; Xarelto (rivaroxaban) CAD PAD Predicted Use Excel spreadsheet.

Abbreviations: CAD, coronary artery disease; DPMQ, dispensed price for maximum quantity.

<sup>a</sup> Based on an uptake rate of ██████████% in Year 1 to ██████████% in Year 6 for CAD only and PAD only patients and an uptake rate of ██████████% in Year 1 to ██████████% in Year 6 for CAD and PAD patients

<sup>b</sup> Includes additional 10,000 grandfathered patients (Year 1 only).

<sup>c</sup> Based on proposed RSA with ██████████% rebate applied to patients with CAD only and PAD only.

6.64 Based on the proposed DPMQ of \$██████████, the total cost to the PBS/RPBS of listing rivaroxaban (less patient copayments) for patients with CAD and/or PAD was estimated to be \$30 to \$60 million in Year 1 of listing, increasing to more than \$100 million in Year 6, a total of more than \$100 million in the first 6 years of listing. The estimated cost over the first 6 years of listing including the proposed RSA rebate of ██████████% (applied post copayment to estimated patients with CAD only or PAD only) was more than \$100 million.

6.65 The PBAC noted that, if only patients with both CAD and PAD were included, the estimated cost to the PBS/RPBS would be \$30 to \$60 million in Year 6 and a total of more than \$100 million in the first 6 years of listing.

6.66 Sensitivity analyses indicated that the financial estimates were most sensitive to changes in the prevalence of CAD and/or PAD, compliance rates, and uptake rates.

6.67 DUSC considered that the main issues with the financial estimates were:

- The Western Australian linked health data relied on hospital admission records for case identification, which DUSC considered may underestimate eligible patients.
- The Western Australian linked data analysis prevalence estimates were based on a 10-year lookback period. DUSC discussed the change in the management of CAD over the last 10 years and questioned the applicability of the Western Australia linked data to the current population.

- The submission assumed that the prevalence rate in 2019 was the same as June 2010 (1.44%). DUSC considered this was not reasonable and may underestimate the eligible population.
- The submission did not adequately justify the assumed proportions of eligible patients with CAD only (■%), PAD only (■%) or CAD and PAD (■%) given the uncertainty regarding the prevalence of PAD (with or without CAD) which varied between data sources. The estimated proportion of patients with CAD and PAD is a key variable used to derive the Tier 1 rebate included in the proposed risk share arrangement.
- Uptake rates for patients with CAD only and PAD only may be underestimated and, given the large eligible population, any increase in uptake rates will result in large changes in the treated population. DUSC further considered the uptake rates may be influenced by the uncertain benefit risk profile. DUSC acknowledged the assessment of bleeding risk in the target patient population is complex and should be undertaken on an individual patient basis by the treating clinician. DUSC noted the lack of long-term efficacy and safety data for the combination of aspirin and rivaroxaban and considered that this may influence the uptake of rivaroxaban in practice.
- The PBAC also considered that there was very considerable uncertainty in the eligible population and the uptake rates, noting that use of rivaroxaban in this patient population would represent a major change in clinical management algorithms and that uptake would likely initially be specialist-led. The PBAC also felt that the increased bleeding risk in these patients, especially those aged over 75 years, would affect uptake rates as even minor bleeding when chronic is likely to affect uptake and persistence.

### ***Quality Use of Medicines***

6.68 The sponsor outlined a range of activities to support the quality use of medicines including:

- The different doses and regimens for rivaroxaban in the management of atrial fibrillation, treatment of venous thromboembolic disease, long-term prevention of venous thromboembolism and prevention of recurrent cardiovascular events had considerable potential to cause confusion and erroneous prescribing.
- Optimised labelling and packaging to reduce dispensing and administration errors. Administration of inappropriate doses of rivaroxaban may occur due to erroneous prescribing or administration of higher doses of rivaroxaban (given the dose and frequency differ to other indications). There may be potential for use of rivaroxaban without aspirin (i.e. low-dose rivaroxaban monotherapy) resulting in suboptimal disease management, or with other antiplatelet strategies such as clopidogrel, for which there is no clinical trial data.

- Provision of a prescriber guide clearly identifying the different doses and regimens of rivaroxaban in different antithrombotic indications.
  - Provision of a patient alert card to increase awareness and understanding among patients about the potential bleeding risk during treatment.
- 6.69 DUSC advised that the addition of rivaroxaban would present a paradigm shift in the treatment algorithm for CAD and advised that further education and changes to the current management guidelines would be required. DUSC also highlighted potential medication compliance issues may arise due to twice daily dosing and complications of bleeding (bruising etc). DUSC also noted that, if rivaroxaban is given with inhibitors of CYP3A4 or P-gp, the blood concentration of rivaroxaban and the risk of bleeding may increase.

### **Financial Management – Risk Sharing Arrangements**

- 6.70 The submission proposed a two-tier Risk Sharing Arrangement (RSA) to address uncertainty relating to the absolute uptake of rivaroxaban, as well as the relative distribution between the sub-population at elevated risk (CAD and PAD) and broader eligible patient population.
- 6.71 The RSA consists of a [REDACTED] % rebate on Commonwealth expenditure above Tier 1 (based on the expected uptake of rivaroxaban in combination with aspirin in patients with CAD and PAD), and an [REDACTED] % rebate on Commonwealth expenditure above Tier 2 (based on the expected uptake of rivaroxaban in combination with aspirin in the total CAD and/or PAD population). The ESC, noting the difficulties in determining the number of patients with this condition and the uncertainties around uptake, considered the financial estimates were high and very uncertain. Whilst the proposed RSA may mitigate some financial risk, the ESC considered this was only effective if the estimates of patient and script numbers are reliable.
- 6.72 The proposed Commonwealth expenditure caps presented in the submission incorporate the April 2020 statutory anniversary price reduction. For consistency with the budget impact estimates presented above, the expenditure thresholds were recalculated during evaluation to exclude the anniversary price reduction.
- 6.73 The table below presents the Commonwealth expenditure caps and associated rebates under the proposed RSA.

**Table 15: Commonwealth expenditure caps and associated rebates under the proposed RSA**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Proposed caps (inclusive of anniversary price reduction)</b>						
Tier 1: █% rebate	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Tier 2: █% rebate	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
<b>Recalculated caps (excluding anniversary price reduction, calculated during evaluation)</b>						
Tier 1: █% rebate	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Tier 2: █% rebate	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █

Source: Table 5.1-2, p.295 of the submission; 'Xarelto (rivaroxaban) CAD PAD Predicted Use' Excel spreadsheet.

Abbreviations: RSA, risk sharing arrangement

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

## 7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of rivaroxaban in combination with aspirin for the prevention of recurrent cardiovascular events in patients in the stable phase of coronary artery disease (CAD) or peripheral artery disease (PAD). 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 benefit between patients groups which needs to be balanced against the high bleeding risk in some patients. The PBAC considered that the incremental cost-effectiveness was uncertain as the economic model submitted did not provide a reliable basis for decision-making.
- 7.2 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.
- 7.3 The PBAC considered that the requested population – patients with CAD and/or PAD – was a large and heterogeneous group. The PBAC noted that the pre-PBAC response stated that narrowing the population to patients at heightened cardiovascular risk “would set an arbitrary threshold and result in a large sub-group of patients who have a significant capacity to benefit ... being excluded from subsidised therapy”. However, the PBAC considered that the population with CAD and/or PAD includes patients at varying levels of cardiovascular risk who would likely achieve differing levels of absolute benefit with rivaroxaban, and that the risk of bleeding is not insignificant particularly in some patient groups. For example, the PBAC noted that for the overall CAD and/or PAD population over a 23-month period, 77 patients would need to be treated with rivaroxaban plus aspirin versus aspirin alone to avoid one major adverse cardiovascular event (i.e. stroke, myocardial infarction, cardiovascular death). In addition, 77 patients would need to be treated for one additional patient to experience major bleeding. For the population with both CAD and PAD, the overall risk-benefit profile was more favourable over the 23-month period, with a number needed to treat of 37 and the number needed to harm of 120.

- 7.4 As such, the PBAC considered that rivaroxaban should be restricted to a smaller patient group with the most favourable risk-benefit profile given: the risk of bleeding; the marginal efficacy and small overall benefit in some patient groups, particularly when all bleeding events are taken into account; and the high cost of treatment. 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.
- 7.5 The PBAC considered that the restriction proposed in the submission was complex and open to interpretation. The PBAC advised that a revised restriction would need to clearly identify an appropriate high-risk population, while being easy to interpret. Even with such a restriction, the PBAC considered that there would be a high potential for use outside the restriction and so an RSA with a 100% rebate over the cap would be required.
- 7.6 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).
- 7.7 The PBAC noted that the COMPASS trial found that rivaroxaban plus aspirin was associated with a statistically significant reduction in the proportion of patients who experienced myocardial infarction, stroke, or cardiovascular death (the primary outcome) compared with aspirin alone (HR: 0.76 (95% CI: 0.66, 0.86)). The PBAC accepted the clinical superiority of rivaroxaban in combination with aspirin compared with aspirin alone. However, the PBAC 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; use of concomitant cardiovascular medicines; and compliance to rivaroxaban plus aspirin). The PBAC also considered that the magnitude of incremental benefit in addition to ideal medical management of cardiovascular risk is unknown.
- 7.8 Further, the PBAC considered that the trial, which had a median follow-up of 23 months, was relatively short in the context of a long-term treatment. The PBAC considered that it was unclear whether the treatment effect would be maintained over time.
- 7.9 The PBAC considered the claim of inferior comparative safety of rivaroxaban in combination with aspirin compared with aspirin alone was reasonable. The PBAC considered 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. In particular, the PBAC noted that the mean age of patients in the COMPASS trial was 68 years, and considered that the safety results may not be applicable to elderly patients, who represent a large proportion of cardiovascular

patients in clinical practice. The PBAC noted that the COMPASS trial excluded patients with poor renal function (eGFR < 15 mL/min), and considered it was likely that the risk of bleeding would be higher in patients with deteriorating renal function. The PBAC considered that these safety concerns were a particular issue in the context of the broad population requested for listing, and the chronic nature of the treatment.

- 7.10 The PBAC noted the COMPASS trial included a pre-specified endpoint of net clinical benefit, which included both the composite primary efficacy outcome (stroke, myocardial infarction, cardiovascular death) and fatal and symptomatic critical organ bleeding events (two components of the primary safety outcome). The PBAC considered that the clinical relevance of this outcome was unclear because it includes events of varying severity and may underestimate safety by neglecting potential consequences of other types of bleeds. The PBAC considered that the comparison of risk-benefit outlined in Paragraph 7.3 (number needed to treat and number needed to harm) was more informative as all types of major bleeding were included.
- 7.11 The PBAC considered that the economic model submitted did not provide a reliable basis for estimating the cost-effectiveness of rivaroxaban in combination with aspirin. The PBAC considered that the model included a number of highly optimistic assumptions, as outlined in Section 6 'Economic analysis'. In particular, the PBAC noted that:
- up to 4 years of trial data (but with a median follow-up of only 23 months) were extrapolated to 30 years. Nearly all of the benefits occurred during the extrapolated part of the model, which the PBAC considered was inherently uncertain. For example, the PBAC noted that the modelled survival curves continued to diverge over the 30-year time horizon (see Figure 3), while it was unclear from the clinical data whether the treatment effect would be maintained over time. Overall, the PBAC considered that the assumption of a 30-year treatment effect was not reasonable.
  - the model assumed that all patients would remain fully adherent and persistent while on therapy, and there would be no treatment interruptions. The PBAC considered these assumptions were not reasonable, particularly in the context of a 30-year time horizon.
  - there were sparse clinical data informing transition probabilities which resulted in implausible null transitions for some subsequent events and highly uncertain non-zero transitions for other subsequent events.
- 7.12 The PBAC considered the base case ICER presented in the submission for the CAD and/or PAD population, \$15,000 to \$45,000 per QALY gained, was high in the context of a secondary prevention treatment with an uncertain risk-benefit profile. The PBAC noted that the ICER reduced to \$15,000 to \$45,000 per QALY gained when the subgroup of patients with both CAD and PAD was modelled, but the Committee considered that this ICER was not reliable (as outlined above).
- 7.13 The PBAC considered that the estimated utilisation and financial impacts of listing rivaroxaban for patients with CAD and/or PAD were high, with 100,000 to 200,000

patients estimated to be treated in Year 6, and a total cost to the PBS/RPBS of more than \$100 million over the first 6 years of listing (including the proposed RSA rebate). The PBAC noted that this estimate reduced considerably if use was confined to the group of patients with both CAD and PAD, which had an estimated cost of more than \$100 million in the first 6 years of listing.

- 7.14 The PBAC considered that the financial estimates were uncertain, but likely overestimated because the uptake rates were likely significantly overestimated. The PBAC considered that uptake was likely to be lower than estimated in broad clinical practice due to concerns over the risk of bleeding, the marginal clinical benefit, and the complexity in determining an individual's risk-benefit profile. Further, the PBAC considered that patients who experience bleeding or bruising may be reluctant to remain on treatment long-term. The PBAC felt that general practitioners were unlikely to prescribe rivaroxaban in this population without considerable guidance from specialists.
- 7.15 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.
- 7.16 The PBAC noted the quality use of medicines issues identified by DUSC, and considered that a comprehensive education campaign would be required, particularly for general practitioners. The PBAC considered that this would need to include guidance regarding selection of appropriate patients, dosing, and the need for concomitant aspirin.
- 7.17 The PBAC considered that any resubmission would need to be a major submission and would need to address the following issues:
- target use to a patient population with a higher cardiovascular risk and a more favourable overall risk- benefit profile;
  - provide any further data that may be available regarding the treatment effect over time;
  - provide further information about the results of the PPI component of the COMPASS trial;
  - update the economic model to reflect the revised patient population and to address the issues outlined in Section 6. In particular, the PBAC considered that significantly more conservative assumptions would be required around the extrapolation of treatment effect, and around treatment persistence, adherence and treatment interruptions
  - revise the financial estimates to reflect the revised patient population and assume a significantly lower uptake rate; and
  - 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.

7.18 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

## **8 Context for Decision**

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

## **9 Sponsor's Comment**

Bayer will continue to work with the PBAC to seek a PBS listing of rivaroxaban 2.5mg in combination with aspirin for the prevention of recurrent cardiovascular events in patients in the stable phase of coronary artery disease (CAD) and/or peripheral artery disease (PAD).