PHARMAC
TE PĀTAKA WHAIORANGA

# PHARMACEUTICAL SCHEDULE APPLICATION

**To:** PTAC

**From:** Funding Application Advisor

**Date:** Feb 2021

## Rivaroxaban for the prevention of major cardiovascular events

| SUMMARY OF PHARMACEUTICAL | | | |
|---|---|---|---|
| **Brand Name** | Xarelto | **Chemical Name** | Rivaroxaban |
| **Indications** | Prevention of major cardiovascular events | **Presentation** | 2.5 mg tablet in 60 tablet pack |
| **Therapeutic Group** | Cardiovascular system | **Dosage** | 1 tablet twice daily in combination with a daily dose of 100 mg aspirin |
| **Supplier** | Bayer New Zealand Ltd | **Application Date** | May 2020 |
| **MOH Restrictions** | Prescription medicine | **Proposal type** | Widen listing |
| **Current Subsidy** | NA | **Proposed Restriction** | Special Authority |
| **Proposed Subsidy** | $80.10 per 60 tablets (gross)<br>Withhel* per 60 tablets (net) | **Manufacturer's Surcharge** | Nil |
| **Market Data** | Year 1 | Year 2 | Year 3 |
| **Number of Patients†** | 2,033 | 3,110 | 4,229 |
| **Net Cost to Schedule†** | Withheld | Withheld | Withheld |
| **Net Cost to DHBs (5-year NPV, 8%)** | Withheld | | |

DHBs, District health board; MOH, Ministry of Health; NPV, Net Present Value.
* Proposed net price.
†Supplier estimate.

## QUESTIONS TO PTAC

*Note to PTAC members: These questions have been identified by PHARMAC staff as being particularly relevant to the application. Please feel free to provide additional information as appropriate.*

### Need

1. Does rivaroxaban have the same or similar therapeutic effect to any pharmaceuticals currently listed on the Pharmaceutical Schedule, in the requested indication? If so, which pharmaceutical (or therapeutic subgroup) and at what dose does it have the same or similar effect? Are there currently any problems with access to them, or their availability?
2. How severe is the health need of patients with Peripheral Artery Disease (PAD)/ Coronary Artery Disease (CAD)? Please describe the health need of a person over their lifetime on current treatment with:
   - 2.1. PAD?
   - 2.2. CAD?
   - 2.3. PAD + CAD?
3. What is the Committee's view of the patient number estimates by the applicant and PHARMAC staff?
   - 3.1. What is the Committee's opinion on estimated uptake of rivaroxaban from the eligible patient population?
   - 3.2. How does the Committee consider the proposed Special Authority criteria would limit incident patient uptake for patients with:
     - PAD?
     - PAD + CAD?
4. What are the health needs of families and whānau of people at risk of major cardiovascular events (including long-term effects) or of wider society? How severe are these needs?
5. Does PAD with or without CAD disproportionally affect:
   - Māori?
   - Pacific people?
   - Other groups already experiencing health disparities relative to the wider New Zealand population (eg. NZ Dep 9-10 deprivation, refugees/asylum seekers)?
6. What is the strength and quality of evidence in relation to health needs due to this PAD, PAD+CAD, or CAD alone?

### Health benefit

7. Does rivaroxaban provide any additional health benefit or create any additional risks compared with other funded treatment options? If so, what benefits, or risks are different from alternative treatments?

8. What is the strength and quality of evidence, including its relevance to NZ, for health benefits that may be gained from rivaroxaban for PAD and PAD+CAD patient groups?

9. Would rivaroxaban produce a health benefit for family, whānau or wider society, additional to the health benefits for people with PAD w/wo CAD? If so how, and what is the strength and quality of evidence for this benefit?

10. Should rivaroxaban be funded, are there any consequences to the health system that have not been noted in the application?

## Suitability

11. Are there any non-clinical features of the rivaroxaban tablet formulation (eg size, shape) that may impact on use, either by the patient, by family, or by healthcare workers, that have not been considered in the application?

12. With a more widespread use of rivaroxaban proposed should PHARMAC consider whether funding a dedicated reversal agent (Andexant alfa) is appropriate?

## Costs and savings

13. Does the information in the PICO table (Table 3) accurately reflect the intended population, intervention, comparator and outcome, should rivaroxaban also be funded for patients at high risk of major cardiovascular events due to the presence of:

    13.1. PAD

    13.2. PAD+CAD only?

    13.3. If not, how should this be adjusted?

    13.4. Would there be any change to the PICO if funding for the CAD population was considered?

    13.5. What is the role of the use of clopidogrel in NZ in combination with aspirin?

14. With which pharmaceuticals would rivaroxaban be used in combination, and which pharmaceuticals would it replace, in treating the requested indication?

15. Would the use of rivaroxaban create any significant changes in health-sector expenditure other than for direct treatment costs (e.g. diagnostic testing, nursing costs or treatment of side-effects)? If so, what are these?

## General

16. Is there any data or information missing from the application, in particular clinical trial data and commentary?

17. Does the Committee consider the proposed Special Authority criteria to be appropriate for patients with:

    17.1. PAD

    17.2. PAD + CAD

    17.3. If not, how should these be amended?

    17.4. In which population do you consider the pharmaceutical provides the most benefit to patients:

- PAD only
- PAD + CAD
- CAD only
- How would the funding of each patient group listed above impact patient numbers?
- What additional information would the Committee need to see to make a recommendation on the CAD only patient group, if any?

17.5. What is the Committee's advice on changes that could be made to the Special Authority criteria to restrict access to those patients with the greatest need (ie with 1 or more comorbidities)?

17.6. Do the proposed Special Authority criteria act to address current inequities in medicines access and health outcomes in relation to cardiovascular disease in New Zealand?

- If not, how could they be amended to do so?

## Recommendations

18. Should the listing of rivaroxaban in the Pharmaceutical Schedule be extended to:

18.1. Patients with PAD only?

18.2. Patients with PAD and CAD?

- Name the Factors for Consideration particularly relevant to a positive or negative recommendation for each scenario and explain why each is relevant.

19. If **widened access** is recommended, what priority rating would you give to this proposal (for each scenario listed above)? **[low / medium / high / only if cost-neutral]**?

20. Does the Committee have any recommendations additional to the application?

## PURPOSE OF THIS PAPER

The purpose of this paper is to seek advice from the Committee regarding an application from Bayer for the use of rivaroxaban (Xarelto) for the first-line treatment of Peripheral Artery Disease (PAD) with or without Coronary Artery Disease (CAD).

## DISCUSSION

### BACKGROUND

*Previous consideration of rivaroxaban*

Rivaroxaban is currently listed without restriction on the Pharmaceutical Schedule (all formulations: 10 mg, 15 mg, and 20 mg). Rivaroxaban has previously been considered by PTAC and various Subcommittees for the treatment and prevention of venous thromboembolism, and for stroke prevention in atrial fibrillation, but there has been no consideration for the 2.5 mg formulation or for the requested indication.

### Need

#### Description of the disease

Atherosclerosis is a progressive disease characterised by the accumulation of lipids and fibrous elements in the large arteries. Peripheral artery disease (PAD) and coronary artery disease (CAD) are clinical presentations of atherosclerosis, which is a progressive condition affecting the large and medium-sized arteries. PAD and CAD develop in different vascular beds but can frequently coexist in patients with multi-vessel disease. The main risk factors for atherosclerosis include lack of physical activity, smoking, unhealthy diet, age, and a family history of heart disease.

PAD is caused by atherosclerosis of the arteries of the lower extremities and sometimes the carotid arteries. Clinical presentations of PAD include asymptomatic and symptomatic disease, the latter including intermittent claudication (IC), chronic limb ischemia (CLI), and acute limb ischemia (ALI). CLI and ALI are the most severe manifestations of PAD and can lead to gangrene and amputation. The unstable plaques in PAD can also rupture and trigger acute atherothrombotic events as a result of embolus formation. Atherothrombotic events may present as myocardial infarction (MI), stroke, cardiovascular death, and ALI. PAD is broadly defined as a progressive stenosis or occlusion of any of the arteries except the coronary and intracranial arteries.

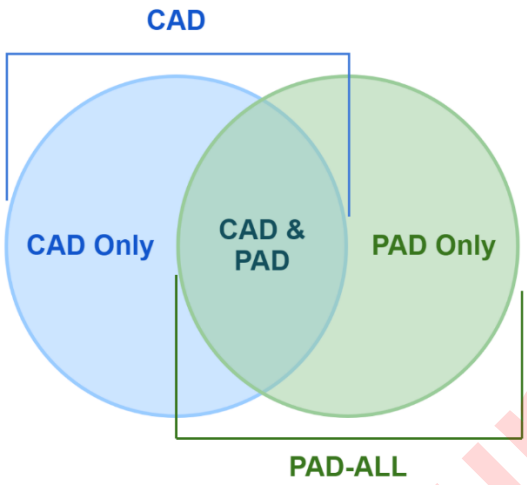
CAD is caused by atherosclerosis of the coronary arteries that leads to a restriction of blood flow to the heart. CAD can be categorised into (1) acute coronary syndrome (ACS) and (2) chronic CAD. ACS refers to a range of conditions associated with a sudden, reduce blood flow to the heart including unstable angina and acute MI. Chronic coronary syndrome includes patients with stable angina and patients who have survived ACS and have ‘restabilised’ although patients remain at risk of recurrent major adverse cardiovascular events (MACE), which includes MI, stroke and cardiovascular death.

For reference, the patient groups proposed by the supplier in this application are defined as follows (Figure 1):

1. The group of patients in the stable phase of PAD (referred to throughout the submission as “PAD-ALL); and

2. The subgroup with diagnoses of PAD and CAD (concurrent). This population is a subset of the PAD-ALL population.

**Figure 1:** Proposed patient population




The proposed target population in New Zealand specified in the submission has been refined to high-risk patient group with 2 or more vascular beds affected and have been presented as the PAD-ALL (including both the PAD only subgroup and the combined PAD with CAD subgroup of patients) population and a separate population, the PAD & CAD subgroup.

PAD and CAD share the same risk factors; both increase with age and could present in different severities entailing different risks of future major cardiovascular events. 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 based on evidence of more generalised atherosclerotic disease and previous atherothrombotic events.

Overall, there is a proven high unmet clinical need in PAD-ALL patients and the PAD & CAD subpopulation with approximately 50 per cent of people with PAD being under-diagnosed and under-treated (Conte & Vale. Heart Lung Circ. 2018;27:427-32). While PAD is not immediately life threatening, someone with PAD is up to six times more likely to have a heart attack or stroke. Both these populations show positive efficacy outcomes in the presented clinical trial data (prevention of cardiovascular events).

While PAD is not immediately life threatening, someone with PAD is up to six times more likely to have a heart attack or stroke. In addition, the reduced blood flow to the limbs can lead to the limb developing gangrene, where it starts to decay and die. There is no cure for gangrene. The only treatment option is to amputate the affected limb to prevent the gangrene from spreading further in the body.

CAD is characterised by atherosclerotic plaque accumulation in the coronary arteries which occurs over decades before becoming clinically apparent. The disease can have long, stable periods interrupted by unstable periods, typically due to an acute atherothrombotic event. The probability of having MACE within 5 years of the onset of stable angina is up to 35%, depending on clinical variables that affect the risk (Fox et al. Eur Heart J. 2019;40:1466-71; Fox et al. Nat Rev Cardiol. 2020;17:9-21)

**Epidemiology**

In 2008, the New Zealand prevalence (over a period of ten years) of PAD was 416 per 100,000. This equated to about 17,000 individuals. Prevalence was higher for men than women (491 and 347 per 100,000 respectively) with prevalence for both groups increasing with age. Prevalence of PAD in non-Māori (438 per 100,000) was higher than that in Māori (269 per 100,000) (National Health Committee, 2013).

**The health need of the person**

The most well recognised symptom of PAD is leg pain experienced during walking (intermittent claudication) which can reduce walking capacity and contribute to mobility loss and is associated with impaired health-related quality of life. In the advanced stages of PAD, events such as ALI may occur, a limb-threatening condition and requires surgical revascularisation for limb salvage in approximately half of cases. Amputees have a poorer quality of life than patients who are successfully revascularized, as amputations have permanent and profound effects.

Effective secondary prevention of MACE and ALI in PAD patients with or without CAD contributes to physical and psychosocial well-being and reduces disability and functional impairment in the target patient population, in addition to avoiding costly hospitalisations.

**The availability and suitability of existing medicines, medical devices and treatments**

Current treatment guidelines from New Zealand and international medical bodies recommend the use of low-dose aspirin indefinitely in the secondary prevention of MACE in patients in the PAD-ALL or PAD & CAD groups.

Lower extremity artery disease (LEAD) affects the lower limbs and is one of the manifestations of PAD. Antiplatelet agents are used in patients with LEAD to prevent limb-related and general cardiovascular events. Long-term single antiplatelet therapy with either aspirin or clopidogrel is recommended in symptomatic patients and patients who have previously undergone revascularisation during the chronic phase of LEAD. However, clopidogrel is not Medsafe registered for the treatment of PAD in New Zealand.

In patients with both LEAD and CAD, clopidogrel plus aspirin treatment duration may be prolonged if patients have a reason for longer treatment in accordance with the CAD treatment guidelines.

**The health need of family, whānau, and wider society**

The impact of a patient with PAD & CAD on family and whānau is expected to be related to the care burden associated with MACE such as myocardial infarction, or ischemic stroke and/or acute limb ischemia or amputation. Following an atherothrombotic event, half of patients with PAD are no longer working, which places a financial burden on the family and whānau (Steg et al. JAMA. 2007;297:1197-206).

If patients suffer from a stroke, it is possible that they will suffer a disability which impedes their ability to carry out daily living activities unassisted such as dressing, transfers in the bathroom, etc.

**The impact on the Māori health areas of focus and Māori health outcomes**

Heart health (including high blood pressure, and stroke), is a Māori health area of focus for PHARMAC.

In 2018, deaths from ischaemic heart disease for Māori was 80.9 per 100,000, compared to the non-Māori populations 44.7 per 100,000.

In 2014-2016, the age standardised rate for hospitalisations due to cardiovascular disease was 2082 per 100,000 for non-Māori males, and 3285 per 100,000 for Māori males. For non-Māori females, the hospitalisation rate was 1161 per 100,000, compared to 2272 per 100,000 for Māori females.

PHARMAC staff were unable to identify hospitalisation and mortality rates by ethnicity for PAD as a subset of cardiovascular disease.

In 2012-2014, Māori males died from stroke at a rate of 46 per 100,000, compared to non-Māori males' rate of 29 per 100,000. For females, the rate was also higher for Māori females than non-Māori females (46 deaths compared to 26 deaths per 100,000).

Gurney et al. (Diabetologia. 2018;61:626-35) in their study to understand the risk factors of lower limb amputations in the New Zealand diabetic population identified that the risk of major amputation among Māori individuals (6.4 cases/1,000 Māori individuals) was substantially higher than for European (3.6 cases/1,000). From their observations they concluded that the individual condition with the strongest association was PAD, which independently increased the risk of major amputation by nearly 13 times, and the risk of minor amputation by more than seven times.

**The impact on the health outcomes of population groups experiencing health disparities**

After adjusting for age, Pacific men and women aged 45−64 years had significantly higher hospitalisation rates from total cardiovascular disease, ischaemic heart disease and stroke than men and women in the total population of the same age. Pacific men aged 45−64 years had almost twice and Pacific women almost three times the mortality rate for total

cardiovascular disease than total men and women respectively of the same age (NZ Ministry of Health, 2012).

Adults living in the most socioeconomically deprived areas have significantly higher levels of most health risks, including cardiovascular disease, diabetes and obesity (NZ Ministry of Health, 2016)

**The impact on Government health priorities**

Cardiovascular disease as a long-term health condition is a government health priority.

Cardiovascular disease remains one of the leading causes of death and disability for the New Zealand population, therefore the economic burden of managing the health of patients with cardiovascular disease/coronary artery disease is substantial.

## Health Benefit

**Details of the pharmaceutical under consideration**

*Clinical Pharmacology and Mechanism of Action*

Rivaroxaban is a direct factor Xa inhibitor that targets both clotting factor and platelet pathways. Factor Xa converts prothrombin to thrombin through the prothrombinase complex which leads to fibrin clot formation and activation of platelets.

*New Zealand Regulatory Approval*

Rivaroxaban is Medsafe approved in combination with aspirin, 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).

*Recommended Dosage*

2.5 mg rivaroxaban twice daily in combination with a daily dose of 100 mg aspirin.

*Proposed Treatment Paradigm*

The supplier is proposing rivaroxaban 2.5 mg, in combination with aspirin, as an alternative to low dose aspirin monotherapy for the prevention of major cardiovascular events (composite of stroke, myocardial infarction and cardiovascular death) for the PAD-ALL patient group, and the PAD + CAD patient group.

The supplier is proposing that treatment using rivaroxaban 2.5 mg 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.

*Proposed Special Authority Criteria*

The supplier has proposed the below Special Authority criteria based on the inclusion criteria from the pivotal trial.

For the prevention of cardiovascular events in patients with PAD:

INITIAL APPLICATION
Applications from any relevant practitioner. Approvals valid for 12 months.
All of the following:

1. Patient has peripheral artery disease; and
   1.1. Previous peripheral artery or carotid revascularisation intervention; or
   1.2. Asymptomatic stenosis ≥ 50% of the carotid artery diagnosed by angiography or non -invasive imaging; or
   1.3. Intermittent claudication and ankle-brachial index (ABI) < 0.90; and
2. Patient must be prescribed rivaroxaban 2.5mg twice daily in combination with 100mg aspirin daily; and
3. Patient must not be in the period immediately following revascularisation when intensified antiplatelet therapy is indicated; and
4. Patient must not be on Dual Anti Platelet therapy

RENEWAL:
Applications from any relevant practitioner. Approvals valid for 12 months.
The treatment remains appropriate and the patient is benefiting from treatment.

For the prevention of cardiovascular events in patients with PAD and CAD:

INITIAL APPLICATION
Applications from any relevant practitioner. Approvals valid for 12 months.
All of the following:

1. Patient has peripheral artery disease and
   1.1. Previous peripheral artery or carotid revascularisation intervention; or
   1.2. Asymptomatic stenosis ≥ 50% of the carotid artery diagnosed by angiography or non -invasive imaging; or
   1.3. Intermittent claudication and ankle-brachial index (ABI) < 0.90; and
2. Patient must be prescribed rivaroxaban 2.5mg twice daily in combination with 100mg aspirin daily; and
3. Patient must not be in the period immediately following revascularisation when intensified antiplatelet therapy is indicated; and
4. Patient must not be on Dual Anti Platelet therapy; and
5. Patient has chronic coronary artery disease (CAD)

RENEWAL:
Applications from any relevant practitioner. Approvals valid for 12 months.
The treatment remains appropriate and the patient is benefiting from treatment.

*PHARMAC staff seek the Committee's advice on the following points:*

- *Does the Committee consider the proposed Special Authority criteria to be appropriate? If not, what should be amended?*
  - *Should the patient population be limited to patients with PAD only, or should patients with PAD + CAD, or CAD only, be able to access rivaroxaban? How would each scenario effect patient numbers?*
  - *Do the proposed Special Authority criteria address current inequities in medicines access and health outcomes in relation to cardiovascular disease in New Zealand? If not, how could they be amended?*

*International Recommendations*

In addition to the recommendations outlined below, the supplier has indicated that rivaroxaban is funded for this indication in the European Union, USA, Switzerland, Chile, Israel, Republic of Korea, Turkey, and Mexico.

**Table 1:** International recommendations regarding the funding of rivaroxaban for the prevention of major cardiovascular events

| Country (HTA Agency) | Meeting Date | Outcome | Reason |
|---|---|---|---|
| Australia (PBAC) | March 2019 | ✗ 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 CAD or PAD. | The PBAC considered that the patient population should be more targeted to patients 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. |
| | March 2020 | 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. |
| | July 2020 | ✓ The PBAC recommended the listing of rivaroxaban for the treatment of patients at high risk of recurrent cardiovascular events with coronary artery disease (CAD) or peripheral artery disease (PAD) and additional high-risk factors | The PBAC recommended listing based on its assessment that the cost-effectiveness of rivaroxaban would likely be acceptable at the price proposed in the resubmission.<br><br>**The clinical criteria for 2.5 mg rivaroxaban for this indication can be found here.** |

| | | | |
|---|---|---|---|
| Canada (CADTH - CDEC) | November 2018 | ✓ The CADTH recommended that rivaroxaban be reimbursed in combination with acetylsalicylic acid (75 mg to 100 mg) for the prevention of stroke, myocardial infarction, and cardiovascular death, and for the prevention of acute limb ischemia and mortality in patients with **concomitant** CAD and PAD. | Clinical trial evidence demonstrated that the use of rivaroxaban in combination with acetylsalicylic acid significantly reduced the risk of composite outcome of stroke, myocardial infarction, and cardiovascular death compared to acetylsalicylic acid alone.<br><br>The CADTH considered the price of rivaroxaban to be cost-effective compared to acetylsalicylic acid alone. |
| Scotland (SMC) | February 2019 | ✓ The SMC accepted rivaroxaban for use together with aspirin (acetylsalicylic acid), for patients with circulatory disease affecting the arteries who are at high risk of ischaemic events (such as heart attack or stroke). | Addition of rivaroxaban to low-dose aspirin (acetylsalicylic acid) reduced the incidence of a composite outcome that included stroke, cardiovascular death and myocardial infarction, mainly due to reductions in stroke and cardiovascular death. It also increased the incidence of major bleeding. |
| UK/Wales (NICE) | October 2019 | ✓ The NICE recommended rivaroxaban plus aspirin as an option for preventing atherothrombotic events in adults with CAD or symptomatic PAD who are at high risk of ischaemic events. | Compared with aspirin alone, rivaroxaban plus aspirin reduces the risk of having an ischaemic stroke, myocardial infarction or dying from cardiovascular disease. However, it increases the risk of bleeding.<br><br>The cost effectiveness of rivaroxaban is within the range that is considered an acceptable use of NHS resources |

**The health benefits to the person, family, whānau and wider society**

*Evidence Summary*

The COMPASS trial gives the primary evidence for the health benefits of rivaroxaban for the prevention of cardiovascular events (PAD and CAD subgroups). The trial design is presented in Figure 2 below. A summary of the papers submitted by the supplier is provided in the table below (Table 2, Appendix 1).

Bosch et al. (Can J Cardiol. 2017;33:1027-1035) describes the rationale, design, and baseline characteristics of the participants of the COMPASS trial (Appendix 1). The primary objectives

for the trial were to: (1) determine whether rivaroxaban 2.5 mg twice daily with aspirin 100 mg once daily compared with aspirin 100 mg once daily reduces the risk of the composite outcome of MI, stroke, or CV death in participants with stable CAD or PAD; and (2) determine whether rivaroxaban 5 mg twice daily compared with aspirin 100 mg once daily reduces the risk of the composite outcome of MI, stroke, or CV death in participants with stable CAD or PAD.

For the purpose of the trial, CAD was defined as previous myocardial infarction or history of angina with evidence of multivessel disease, or multivessel revascularization; and PAD was defined as claudication with objective evidence of arterial disease, previous amputation or revascularization, previous carotid revascularization, or asymptomatic carotid disease with at least 50% stenosis.

**Figure 2:** COMPASS trial design

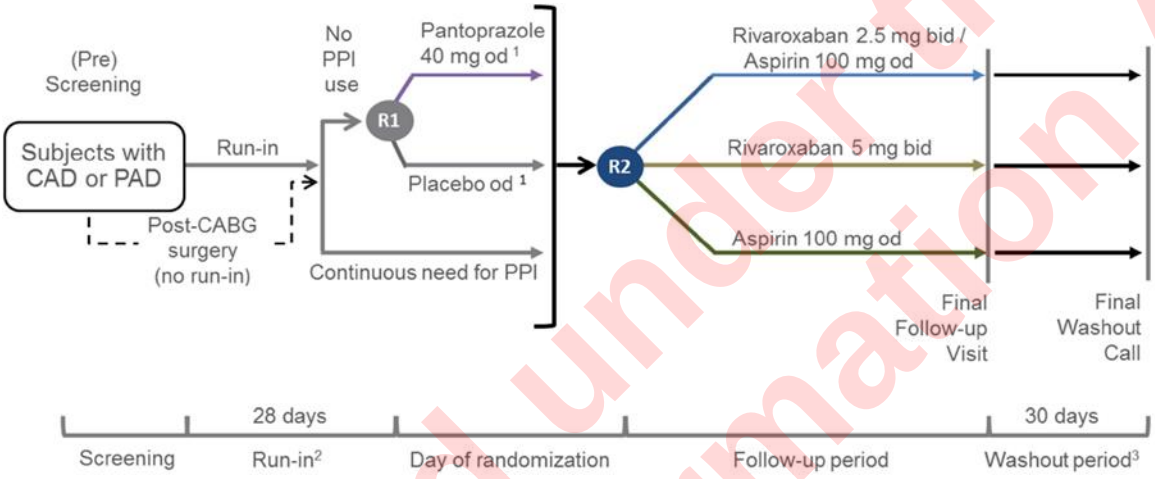


**Table 2**: Summary of evidence for rivaroxaban for the prevention of major cardiovascular events

| Trial | Study Design | Patients Group(s) | No. Patients | Intervention | Duration | Efficacy and safety | Citation |
|---|---|---|---|---|---|---|---|
| COMPASS | Phase III, event-driven, blinded, randomized controlled trial with a 3 x 2 partial factorial design | Stable CAD and/or PAD.<br><br>Patients with CAD: Adults ≥ 65 years, or <65 years | N=27395 | Patients randomised 1:1:1:<br><br>rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily (n=9152)<br><br>rivaroxaban 5 mg twice daily (n=9117),<br><br>aspirin 100 mg once daily (n=9126). | Mean of 23 months. | <u>Death (cardiovascular):</u><br>• 139/8313 (2%) in rivaroxaban 2.5 mg + aspirin group vs 184/8621 (2%) in aspirin alone group: HR 0.75; 95% CI 0.60 to 0.93; p=0.010<br>• 139/8313 (2%) rivaroxaban 2.5 mg + aspirin vs 175/8250 (2%) in rivaroxaban alone 5 mg group: HR 0.95; 95% CI 0.77 to 1.17; p=0.63<br><br><u>Myocardial infarction:</u><br>• 169/8313 (2%) in rivaroxaban 2.5 mg + aspirin group vs 195/8261 (2%) in aspirin alone group: HR 0.86; 95% CI 0.70 to 1.05; p=0.15<br>• 169/8313 (2%) rivaroxaban 2.5 mg + aspirin compared to rivaroxaban alone 5 mg: HR 0.90; 95% CI 0.74 to 1.11; p=0.33<br><br><u>Stroke:</u><br>• 74/8313 (1%) in the rivaroxaban + aspirin group vs 130/8261 (2%) in aspirin alone: HR 0.56; 95% CI 0.42 to 0.75; p<0.0001<br>• Rivaroxaban alone (5 mg) did not show an improvement compared to aspirin alone: HR 0.81; 95% CI 0.62 to 1.05; p=0.10<br><br><u>Heart failure:</u><br>• 178/8313 (2%) in rivaroxaban 2.5 mg + aspirin group vs 182/8261 (2%) in aspirin alone group: HR 0.97; 95% CI 0.79 to 1.19; p=0.78<br>• 178/8313 (2%) rivaroxaban + aspirin compared to rivaroxaban alone 5 mg: HR 0.96; 95% CI 0.78 to 1.18; p=0.66<br><br><u>Major bleeding:</u><br>263/8313 (3%) of the rivaroxaban 2.5 mg + aspirin group vs 158/8261 (2%) aspirin alone group: HR 1.66; 95% CI 1.37 to 2.03; p<0.0001)<br><br><u>Fatal bleeding:</u><br>• 14/8313 (<1%) rivaroxaban 2.5 mg + aspirin group vs 9/8261 (<1%) aspirin alone: HR 1.55; 95% CI 0.67 to 3.58, p=0.30<br><br><u>Other major bleeding:</u><br>• 194/8313 (2%) rivaroxaban 2.5 mg + aspirin group vs 105/8261 (1%) aspirin alone group: HR 1.85; 95% CI 1.46 to 2.34; p<0.0001 | Connolly et al. Lancet. 2018;391:205-218 |

| Trial | Study Design | Patients Group(s) | No. Patients | Intervention | Duration | Efficacy and safety | Citation |
|---|---|---|---|---|---|---|---|
| COMPASS - *effects of rivaroxaban + aspirin compared with aspirin alone on bleeding* | | As above | N=27395 | As above | As above | Major bleeding (as defined by modified or original definition from International Society on Thrombosis and Haemostasis (ISTH)):<br>• Modified: rivaroxaban + aspirin compared with aspirin alone increased bleeding (288 of 9,152 [3.1%] vs.170 of 9,126 [1.9%]; HR: 1.70; 95% CI 1.40 to 2.05; p<0.0001)<br>• Original: (206 of 9,152 [2.3%] vs. 116 of 9,126 [1.3%]; HR: 1.78; 95% CI 1.41 to 2.23; p <0.0001)<br>Common sites of major bleeding included gastrointestinal tract, intracranial, skin, eye, nasal, urinary, respiratory, or genital.<br>Fatal bleeding:<br>• rivaroxaban + aspirin vs aspirin alone (15 of 9,152 [0.2%] vs. 10 of 9,126 [0.1%]; HR: 1.49; 95% CI 0.67 to 3.33; p=0.32)<br>Combination compared with aspirin alone increased major bleeding leading to hospitalization or presentation to acute care facility without overnight stay (259 of 9,152 [2.8%] vs. 147 of 9,126 [1.6%]; HR: 1.76; 95% CI 1.44 to 2.16; p <0.0001)<br>Minor bleeding:<br>• rivaroxaban + aspirin vs aspirin alone: (838 of 9,152 [9.2%] vs. 503 of 9,126 [5.5%]; HR: 1.70; 95% CI: 1.52 to 1.90; p <0.0001) | Eikelboom et al. J Am Coll Cardiol. 2019;74:1519-1528 |
| COMPASS – *safety of proton pump inhibitors* | As above | As above | N=17,598 | Patients in COMPASS trial randomized to receive pantoprazole 40 mg once daily (n=8791) or placebo (n=8807). | 3.01 years | To determine if pantoprazole compared with placebo reduces the risk of upper GI bleeding, ulceration, obstruction, or perforation in COMPASS participants with stable CAD or PAD receiving antithrombotic therapy (rivaroxaban +aspirin).<br>Upper gastrointestinal events: pantoprazole group vs placebo group (HR, 0.88; 95% CI 0.67 to 1.15; p=0.35).<br>Gastroduodenal bleeding: pantoprazole group vs placebo group (HR 0.52; 95% CI 0.28 to 0.94; p=0.03)<br>By antithrombotic treatment arm: pantoprazole use did not affect the occurrence of upper GI events in the rivaroxaban + aspirin arm (HR 1.16; | Moayyedi et al. Gastroenterology. 2019;157:403-412.e5. |

| Trial | Study Design | Patients Group(s) | No. Patients | Intervention | Duration | Efficacy and safety | Citation |
|---|---|---|---|---|---|---|---|
| | | | | | | 95% CI: 0.75, 1.80) but significantly reduced upper GI events in the aspirin alone arm (HR 0.58; 95% CI 0.35 to 0.96). | |
| COMPASS - *Risk factors and clinical outcomes* | As above | As above | N=27117 | Described above | 23 months | Ischemic events (cardiovascular death, stroke, or myocardial infarction) in participants from COMPASS by individual risk factor (blood pressure, smoking status, cholesterol level, presence of diabetes, body mass index, and level of physical activity), and by number of risk factors.<br><br>Compared to optimal control at baseline, HRs for individual risk factor status for ischemic events:<br>• 1.41 (95% CI 1.19 to 1.68) for uncontrolled blood pressure<br>• 1.15 (1.01 to 1.31) for smoking<br>• 1.98 (1.55 to 2.52) for high serum cholesterol<br>• 1.46 (1.31 to 1.63) for presence of diabetes<br>• 1.60 (1.40 to 1.83) for low levels of PA<br><br>Rates of ischemic events were higher both for low BMI (<20 kg/m2; HR 1.32, 0.89 to 1.95) and for high BMI (HR 1.17, 1.00 to 1.36).<br><br>Rates of ischemic events increased with the number of risk factors - 2.2-fold increased risk in patients with four or more risk factors, compared with optimal control.<br><br>Patients with poorest overall risk factor status had a two-fold higher risk of cardiovascular death compared with those with optimal status.<br><br>No statistically significant interaction between risk factor status and treatment effect (rivaroxaban + aspirin vs aspirin alone).<br><br>Absolute reduction in the event rate of rivaroxaban + aspirin as compared with aspirin alone increased with the number of risk factors: 0.27% per year in patients 0-1 unfavourable risk factors to 1.08% per year in patients with >4 risk factors.<br><br>Overall, rates of CV death, stroke, MI, or major adverse limb events were higher in the subgroup of patients with PAD with or without CAD than in | Vanassche et al. Eur J Prev Cardiol. 2020;27:296-307 |

| Trial | Study Design | Patients Group(s) | No. Patients | Intervention | Duration | Efficacy and safety | Citation |
|---|---|---|---|---|---|---|---|
| | | | | | | patients with CAD alone. In PAD patients, the rate of ischemic events increased with the number of risk factors. Within each risk factor category, the effect of rivaroxaban on top of aspirin was conserved. | |

**Literature Search**

PHARMAC staff conducted a PubMed search (search terms: COMPASS and RIVAROXABAN) and identified the following relevant publications not provided by the supplier:

- Anand et al. J Am Coll Cardiol. 2019;73:3271-3280 (Appendix 2): a study to identify subsets of patients in the COMPASS trial at higher risk of recurrent vascular events, which may help focus the use of rivaroxaban and aspirin therapy. Patients were risk stratified (using the REACH (REduction of Atherothrombosis for Continued Health) atherothrombosis risk score and CART (Classification and Regression Tree) analysis) and the absolute risk differences for rivaroxaban with aspirin were compared to aspirin alone for the composite of cardiovascular death, myocardial infarction, stroke, acute limb ischemia, or vascular amputation; for severe bleeding; and for the net clinical benefit. Rivaroxaban + aspirin vs aspirin alone reduced serious vascular event incidence by 25% (4.48% vs. 5.95%, HR 0.75; 95% confidence interval 0.66 to 0.85).

- Anand et al. J Am Coll Cardiol. 2018;71:2306-2315 (Appendix 2): a study assessing the impact of treatment with rivaroxaban + aspirin compared with aspirin alone on the incidence of major adverse limb events (MALE), peripheral vascular interventions, and all peripheral vascular outcomes. Compared with aspirin alone, the combination of rivaroxaban 2.5 mg twice daily and aspirin lowered the incidence of MALE by 43% (p=0.01), total vascular amputations by 58% (p=0.01), peripheral vascular interventions by 24% (p=0.03), and all peripheral vascular outcomes by 24% (p=0.02).

- Fox et al. J Am Coll Cadriol. 2019;73:2243-2250 (Appendix 2): a study to determine the effect of the rivaroxaban + aspirin, compared with aspirin alone in vascular patients with or without moderate renal dysfunction. For the COMPASS trial, CAD patients aged younger than 65 years required additional risk factors were, and these comprised documented atherosclerosis or revascularization involving at least 2 vascular beds, or at least 2 additional risk factors. The additional risk factors included a glomerular filtration rate (GFR) <60 ml/min (but those with a GRF <15 ml/min were excluded); hence, the population was enriched for moderately severe renal dysfunction. Patients in the COMPASS trial were categorized by severity of chronic renal disease according to the estimated GFR <60 and ≥60 ml/min and the relation between renal dysfunction and outcomes was also investigated as a continuous function of GFR.
  Cardiovascular death, MI, or stroke was reduced in those randomized to rivaroxaban plus aspirin compared with aspirin alone (GFR ≥60 ml/min: 3.5% rivaroxaban plus aspirin, 4.5% aspirin alone; HR: 0.76; 95% CI 0.64 to 0.90; GFR <60 ml/min 6.4% rivaroxaban plus aspirin, 8.4% aspirin alone, HR: 0.75; 95% CI 0.60 to 0.94).
  Ischemic stroke occurred in 0.7% of patients taking rivaroxaban + aspirin, and 2.2% of patients taking aspirin alone in the group with a GFR <60 ml/min (HR 0.31; 95% CI 0.17 to 0.57; p<0.0001) and 0.4% vs 1.2% in patients with GFR ≥60 ml/min (HR 0.62; 95% CI 0.44 to 0.87; p=0.005; the P value for the interaction = 0.05).

- Branch et al. Circulation. 2019;140:529-537 (Appendix 2): a study exploring the effects of rivaroxaban with or without aspirin in patients with or without a history of heart failure (HF) and an ejection fraction of <40% or ≥40% at baseline. Rivaroxaban and aspirin had similar relative reduction in major adverse cardiovascular events compared with aspirin in participants with HF (5.5% versus 7.9%; HR 0.68; 95% CI 0.53 to 0.86) and those without HF (3.8% versus 4.7%; HR 0.79; 95% CI 0.68 to 0.93; P for interaction = 0.28) but larger absolute risk reduction in those with HF (HF absolute risk reduction 2.4%, number needed to treat=42; no HF absolute risk reduction 1.0%, number needed to treat=103). The primary major adverse cardiovascular events outcome was not statistically different between those with EF <40% (HR 0.88; 95% CI 0.55 to 1.42) and ≥40% (HR 0.81; 95% CI 0.67 to 0.98; P for interaction = 0.36).

- Lamy et al. J Am Coll Cardiol. 2019;73:121-130 (Appendix 2): a sub-study to determine whether the COMPASS treatments are more effective than aspirin alone for preventing graft failure and major adverse cardiovascular events (MACE) after coronary artery bypass graft (CABG) surgery. The combination of rivaroxaban and aspirin did not reduce the graft failure rates compared with aspirin alone (OR 1.13; 95% CI 0.82 to 1.57; p=0.45). Compared with aspirin, the combination was associated with fewer MACE (HR 0.69; 95% CI 0.33 to 1.47; p=0.34).

- Sharma et al. Circulation. 2019;139:1134-1145 (Appendix 2): an analysis of stroke outcomes in the COMPASS trial. Fewer patients had strokes in the rivaroxaban plus aspirin group than in the aspirin group (HR 0.58; 95% CI 0.44 to 0.76; P<0.0001). Ischemic/uncertain strokes were reduced by nearly half (HR 0.51; 95% CI 0.38 to 0.68; P<0.0001) by the combination in comparison with aspirin alone. The occurrence of fatal and disabling stroke was decreased by the combination (HR 0.58; 95% CI 0.37 to 0.89; P=0.01).

  *PHARMAC seeks the Committee's advice on changes that could be made to the SA criteria to restrict access to those patients with the greatest need (ie 1 or more comorbidities)?.*

  Branch et al. Circulation. 2019;140:529-537 outlines results from the subgroups with or without a history of heart failure, and Fox et al. J Am Coll Cadriol. 2019;73:2243-2250 outlines differences in patients with differing renal functions. PHARMAC staff also identified a study by Bhatt et al (Circulation. 2020;141:1841-1854, Appendix 2) which outlines the comparison of the effects of rivaroxaban plus aspirin versus aspirin + placebo in patients with diabetes mellitus versus without diabetes mellitus in preventing major vascular events. Of the total COMPASS trial population, 10341 had diabetes mellitus. The cumulative hazard for cardiovascular death, myocardial infarction, or stroke with rivaroxaban + aspirin vs aspirin with placebo in patients with diabetes had an HR of 0.74 (95% CI 0.61 to 0.90; absolute risk reduction 2.3%), compared to a HR of 0.77 in patients without diabetes (95% CI 0.64 to 0.93; absolute risk reduction 1.4%) at 36 months. The absolute risk reduction for all cause death for patients with diabetes was 1.9% with rivaroxaban + aspirin compared to aspirin alone (HR 0.81; 95% CI 0.65 to 1.00) versus 0.6% for patients without diabetes (HR 0.84; 95% CI 0.68 to 1.03).

## Suitability

**The features of the medicine or medical device that impact on use**

Rivaroxaban 2.5 mg is a light yellow, round biconvex tablet that does not require special storage (ie refrigeration) or handling. For patients with difficulty swallowing whole tablets, it can be crushed and mixed with water or apple sauce prior to administration, it can also be crushed and administered via a gastric tube.

## Costs and Savings

**PICO (Population, Intervention, Comparator, Outcome)**

Table **3** below summarises PHARMAC staff's interpretation of the PICO for rivaroxaban 2.5mg if it were to be funded in New Zealand for major cardiovascular risk prevention in PAD or PAD+CAD patients.

This PICO captures key clinical contexts, helping review the proposal and frame any future economic assessment by PHARMAC. We seek the Committee's advice on the content in the table below.

Note that the PICO may change as clinical and other features evolve.

**Table 3:** PICO for rivaroxaban if it were to be funded in New Zealand for major cardiovascular risk prevention in patients with PAD or PAD and CAD.

| | |
|---|---|
| **P**opulation | Patients with PAD-ALL or PAD-CAD (see definitions described previously in this paper) who have either had a peripheral artery or carotid revascularisation intervention, have asymptomatic stenosis (stenosis > 50% of the carotid artery) or intermittent claudication and ankle-brachial index (ABI) < 0.90. |
| **I**ntervention | Rivaroxaban 2.5mg twice daily + 100mg Aspirin daily |
| **C**omparator(s) (NZ context) | 100mg Aspirin daily |
| **O**utcome(s) | Improved periods of quality of life with a reduction in subsequent non-fatal MACE and improved overall survival because of a reduction in fatal MACE as described in COMPASS post hoc analysis. |
| *Table definitions:*<br>**P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg. line of therapy, disease subgroup)<br>**I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).<br>**C**omparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).<br>**O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data. | |

**Costs and savings to pharmaceutical expenditure**

**Cost per patient**

We understand that rivaroxaban 2.5 mg is an add-on therapy to current standard of care resulting in each patient incurring an additional cost of $20 per year in pharmacy co-payments.

At a confidential net price of Withheld per pack of 60, 2.5mg tablets, the annual cost of treatment with rivaroxaban assuming 100% treatment adherence is Withheld per person. No material change in the cost of treatment with aspirin is anticipated.

**Estimated Incremental Total Cost of Listing**

PHARMAC staff question the validity of the suppliers estimated patient numbers. The suppliers estimate of eligible patient numbers appears to be solely based on incidence and prevalence figures sourced from the Global Burden Disease National Health Committee Cardiovascular Strategic Overview and do not appear to have been adjusted for the proposed Special Authority criteria. Furthermore, it is unclear from the information provided by the supplier what the anticipated patient numbers are for CAD+PAD group. The supplier's uptake assumption appear very low with 10% starting in year one increasing to 30% in year 5.

PHARMAC staff will construct a full BIA for this proposal following clinical advice on the appropriate patient definition for this indication, estimated patient numbers and uptake assumptions. A preliminary calculation is provided below for indication purposes only. The BIA presented below is for the PAD-ALL group and assumes that all patients with PAD are eligible and that adherence to the treatment is 100%. Patient uptake is assumed as per the supplier's application.  will commence treatment in year 1 of listing increasing to 100% by year 3. Health sector savings from reduce MACE events are not included.

*PHARMAC staff seek the Committee's advice on the estimated patient population for the defined population being considered and an estimated uptake assumption.*

**Table 4:** Back of the envelope budget impact assessment for rivaroxaban for the prevention of major cardiovascular events in PAD-ALL patients.

| Year of listing | 1 | 2 | 3 | 4 | 5 | 5-year NPV | Assumption |
|---|---|---|---|---|---|---|---|
| New Zealand Population (millions | 4.89 | 4.98 | 5.08 | 5.19 | 5.29 | | Statistics NZ. 2% annual population growth |
| Eligible patient population | 20,326 | 20,732 | 21,147 | 21,570 | 22,001 | | NZ prevalence of PAH (416 per 100,000) NHC, 2013 |
| Uptake | 10% | 15% | 20% | 25% | 30% | | Estimate uptake |
| Uptake patient population | 2,033 | 3,110 | 4,229 | 5,393 | 6,600 | | |
| CPB expenditure gross (million) | Withh | Withhe | Withh | Withh | Withh | Withhel | Withhe annual cost per patient |
| CPB expenditure net (million) | Withh | Withh | Withh | Withh | Withh | Withhe | Withheld annual cost per patient |
| DHB expenditure (millions) | $0.06 | $0.09 | $0.13 | $0.16 | $0.20 | $0.54 | Pharmacy margin only. Health sector offsets not included. |

**Costs and savings to the rest of the health system**

Some health system savings are likely to occur as a result of a reduction in subsequent MACE events associated with rivaroxaban use. The supplier notes that specialised hospital level care including further revascularisations procedures and their associated follow-up in particularly are likely to reduce incurring significant health system savings. A reduction in the number of services relating to the ongoing management and follow-up of patients with PAD and CAD including care in the community setting is also likely.

**Cost Effectiveness (combining the Health Benefits and Costs quadrants)**

The supplier has provided an economic model which evaluates the cost-effectiveness of rivaroxaban in combination with aspirin compared to aspirin alone in both populations proposed. The microsimulation model is primarily based on efficacy and quality of life data published in the COMPASS trial, supplemented with background mortality data provided by Statistics New Zealand. The available trial data has a 2-year follow-up so significant extrapolation of trial data was required for the 30-year lifetime horizon model. The outcomes modelled included fatal and non-fatal MACE avoidance. The model contains provisions for treatment persistence, treatment interruptions following subsequent atherosclerotic events and the occurrence of multiple subsequent non-fatal MACE. The supplier claims the model submitted is the model that was accepted by PBAC following several cycles of PBAC review. The model results in an estimated cost-effectiveness for Withheld under section per million dollars spent for PAD-ALL and Withheld under section per million dollars spent on CAD+PAD. The QALY estimate is reduced to approximately Withheld under section per million if it is assumed there is not difference in non-CVD death as a result of treatment (recommended by PBAC).

While the supplier has provided the economic model, an additional piece of software is required to be purchased to enable use of it. PHARMAC staff have not been able to review the model in detail to date and will investigate this further following clinical advice.

United Kingdom (NICE)

In 2019, NICE reviewed the supplier economic model for rivaroxaban for the prevention of atherothrombotic events in people with coronary or peripheral artery disease and considered it was appropriate for decision making. NICE accepted that the base case cost-effectiveness ration for rivaroxaban in combination with aspirin compared to aspirin alone of £14,185 per QALY (NZ$26,800 per QALY or 37 QALYs per million dollars spent) as indication of a cost-effective intervention for those as high risk of ischaemic events as defined by the inclusion criteria of COMPASS.

Scotland and Wales (SMC)

The SMC reviewed the supplier's model in 2019. The model was accepted to demonstrate the economic case of the proposal, but the SMC noted several limitations including underestimation of the risks, costs and utilities associated with bleeding events, insufficient variation in utility values were considered in the sensitivity analyses, the appropriateness of including cardiovascular disease mortality figure used in the model and how age may impact the modelled results over the long term.

Canada (CADTH)

CADTH reviewed the supplier's economic model as part of their 2018 review of the proposal. CADTH report an incremental cost-effectiveness ratio of CA$17,764 per QALY (NZ$19,344 per QALY or 52 QALYs per million dollars spent) for patients with concomitant CAD and PAD and an incremental cost-effectiveness ratio of CA$31,758 per QALY (NZ$34,564 per QALY

or 29 QALYs per million dollars spent) for patients with CAD and/or PAD (COMPASS trial population). CADTH accepted the cost-effectiveness estimates and funded treatment for the most cost-effective group, those with concomitant CAD and PAD. CADTH notes that the model provided by the supplier had limitations in that the analysis considered the COMPASS trail population which did not allow for subgroup stratification, that inclusion criteria of COMPASS limited the models generalisability, particular to those with high risk of bleeds, and that there was limited long term trial data due the early termination of the COMPASS trial due to significant benefit.

Australia (PBAC)

PBAC indicated that an ICER of between AU$15,000 and AU$45,000 per QALY (20-62 QALYs per million NZD spent) would be considered for the funding of rivaroxaban which appears to have been met in July 2020. The model reviewers noted concern that the risk of bleeding would likely be higher in the proposed patient population than in the trial and that this introduced significant uncertainty in the model. Furthermore, the reviewers noted concern with the inclusion of non-statistically significant events including non-CVD death and several non-fatal event as well as the fact that trial evidence may be overstating the true efficacy of the treatment due to the early trial completion. The reviewers recommended that more conservative assumptions and sensitivity analyses be undertaken to consider these limitations.

## APPENDICES

**Appendix 1:**


Bosch et al. Can J Cardiol. 2017;33:1027-1035

Connolly et al. Lancet. 2018;391:205-218

Eikelboom et al. J Am Coll Cardiol. 2019;74:1519-1528

Moayyedi et al. Gastroenterology. 2019;157:403-412.e5.

Vanassche et al. Eur J Prev Cardiol. 2020;27:296-307


**Appendix 2:**


Anand et al. J Am Coll Cardiol. 2019;73:3271-3280

Anand et al. J Am Coll Cardiol. 2018;71:2306-2315

Branch et al. Circulation. 2019;140:529-537

Lamy et al. J Am Coll Cardiol. 2019;73:121-130

Sharma et al. Circulation. 2019;139:1134-1145

Fox et al. J Am Coll Cadriol. 2019;73:2243-2250

Bhatt et al. Circulation. 2020;141:1841-1854

## THE FACTORS FOR CONSIDERATION

Factors are presented here in the order they appear in the paper, without implying any ranking or relative importance.

### NEED

- The health need of the person
- The availability and suitability of existing medicines, medical devices and treatments
- The health need of family, whānau, and wider society
- The impact on the Māori health areas of focus and Māori health outcomes
- The impact on the health outcomes of population groups experiencing health disparities
- The impact on Government health priorities

### HEALTH BENEFITS

- The health benefit to the person
- The health benefit to family, whānau and wider society
- Consequences for the health system

### SUITABILITY

- The features of the medicine or medical device that impact on use by the person
- The features of the medicine or medical device that impact on use by family, whānau and wider society
- The features of the medicine or medical device that impact on use by the health workforce

### COSTS AND SAVINGS

- Health-related costs and savings to the person
- Health-related costs and savings to the family, whānau and wider society
- Costs and savings to pharmaceutical expenditure
- Costs and savings to the rest of the health system