Medicines Management Programme

Managed Access Protocol – Rivaroxaban 2.5 mg for the prevention of atherothrombotic events in adult patients

Medicine	Date of addition to Managed Access Protocol
Rivaroxaban 2. 5mg tablets	01/10/2022

Approved by	**Professor Michael Barry, Clinical Lead, MMP**	
Date approved	Version 1.0	28/09/2022
Date updated	Version 1.1	01/09/2024

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List of Abbreviations

BP	Blood pressure
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CDS	Community Drug Schemes
HbA1c	Glycated haemoglobin
HSE	Health Service Executive
LLT	Lipid–lowering therapy
LDL	Low-density lipoprotein
MAP	Managed Access Protocol
MMP	Medicines Management Programme
NYHA	New York Heart Association
PAD	Peripheral artery disease
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
SmPC	Summary of Product Characteristics

1. Rivaroxaban

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability.

1.1 Licensed indications

Rivaroxaban 2.5 mg tablets are indicated for:

1) co-administration with acetylsalicylic acid (aspirin) alone or with aspirin plus clopidogrel or ticlopidine, for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome with elevated cardiac biomarkers;
2) co-administration with aspirin, for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events.

1.2 Reimbursement

Reimbursement of rivaroxaban 2.5 mg tablets under the Community Drug Schemes (CDS) for the prevention of atherothrombotic events when co-administered with aspirin is supported only for adult patients with CAD or symptomatic PAD at high risk of ischaemic events, who meet the criteria outlined in this Managed Access Protocol (MAP). All criteria must be satisfied in order for reimbursement to be supported.

An application for reimbursement approval is required to be submitted on an individual patient basis through the online application system.

Table 1 outlines the licensed therapeutic dosage of rivaroxaban 2.5 mg tablets when co-administered with aspirin, for the prevention of atherothrombotic events in adult patients with CAD or symptomatic PAD at high risk of ischaemic events. Please refer to the Summary of Product Characteristics (SmPC) for further prescribing information.

Table 1: Licensed therapeutic dosage of rivaroxaban 2.5 mg tablets

Patient population	Route of administration	Dosage
Adults aged 18 years and older who are co-administered aspirin	oral	2.5 mg twice daily

mg: milligrams

If a patient is recommended for reimbursement of rivaroxaban 2.5 mg tablets, reimbursement is supported in line with the licensed therapeutic dosage specified in Table 1. Reimbursement of dosages in excess of the licensed therapeutic dosage (as outlined in Table 1) is not supported.

See Section 3 for further details on Reimbursement Criteria – Requirement for outcome data.

1.3 Reimbursement details

The scope of this MAP includes all medicinal products containing rivaroxaban 2.5 mg per dosage unit on the reimbursement list.

2. Reimbursement criteria – Initiation

This section outlines the criteria that must be satisfied in order for patients to be recommended for reimbursement of rivaroxaban 2.5 mg tablets when co-administered with aspirin, for the prevention of atherothrombotic events in adult patients with CAD or symptomatic PAD at high risk of ischaemic events under the CDS.

2.1 Submission of applications

Due to the information that is required to be submitted, the clinician responsible for the initiation of treatment should complete the online application. Approval for reimbursement support should be in place prior to issuing a prescription for reimbursement under the CDS.

Clinicians are responsible for ensuring that the patient or their representative/guardian is aware that the application for reimbursement approval is being made on their behalf.

2.2 Patient age

Applications for reimbursement approval will only be considered for adults aged 18 years and older at the time of application.

2.3 Patient diagnosis

For reimbursement approval, prescribers will be required to confirm a diagnosis of CAD, PAD or both conditions at the time of application.

2.3.1 Coronary artery disease

In line with the COMPASS clinical trial (NCT01776424) eligibility and inclusion criteria, CAD is defined as one of the following:

- myocardial infarction within the last 20 years
- multi-vessel coronary disease* with symptoms or with history of stable or unstable angina
- multi-vessel percutaneous coronary intervention (PCI)
- multi-vessel coronary artery bypass graft (CABG) surgery.

**Refers to stenosis of greater than or equal to 50% in two or more coronary arteries, confirmed by invasive coronary angiography, or non-invasive imaging or stress studies (e.g. exercise or pharmacologic) suggestive of significant ischaemia in two or more coronary territories; or in one coronary territory if at least one other territory has been revascularised.*

For patients with CAD, the patient must also meet one of the following criteria at the time of application:

i. be aged 65 years or older

ii. be aged under 65 years with one of the following:
    - documented atherosclerosis
    - revascularisation involving at least two vascular beds†
    - at least two additional risk factors:
        a) current smoker (has smoked within the previous 12 months)
        b) diabetes mellitus
        c) renal dysfunction with an estimated glomerular filtration rate < 60 ml/min
        d) heart failure
        e) non-lacunar ischemic stroke at least one month prior to date of application.

†*As CAD involves disease in the coronary vasculature, only one additional vascular bed is required: e.g., the aorta, arterial supply to the brain, gastro-intestinal tract, lower limbs, upper limbs, kidneys.*

2.3.2 Peripheral artery disease

In line with the COMPASS clinical trial (NCT01776424) eligibility criteria, PAD is defined as one of the following:

- previous aorto-femoral bypass surgery, limb bypass surgery, or percutaneous transluminal angioplasty revascularisation of the iliac, or infra-inguinal arteries
- previous limb or foot amputation for arterial vascular disease

- history of intermittent claudication and one or more of the following:
  a) an ankle/arm blood pressure (BP) ratio < 0.90
  b) significant peripheral artery stenosis (≥ 50%) documented by angiography, or by duplex ultrasound
- previous carotid revascularisation or asymptomatic carotid artery stenosis ≥ 50% as diagnosed by duplex ultrasound or angiography.

2.4 Patient clinical history/status

In line with the exclusion criteria for the COMPASS clinical trial (NCT01776424) and information contained within individual product SmPCs[¥] for rivaroxaban 2.5 mg tablets, applications for reimbursement approval will not be considered in the following circumstances:

- patients with active clinically significant bleeding or at high bleeding risk[∞]
- patients with a recent history of stroke (within one month of date of application) or any history of haemorrhagic or lacunar stroke
- patients with severe heart failure with known ejection fraction < 30% or New York Heart Association (NYHA) class III or IV symptoms
- patients with a creatinine clearance < 15 ml/min
- patients with known hepatic disease associated with coagulopathy
- patients who have a need for dual antiplatelet therapy, other non-aspirin antiplatelet therapy, or other anticoagulant therapy (except under specific circumstances of switching anticoagulant therapy or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter)
- patients who are pregnant or currently breast-feeding.

[¥]*This list is not exhaustive; please refer to individual product SmPC for rivaroxaban 2.5 mg tablets for full prescribing information.*

∞ For example current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.

2.5 Patient medical treatment and optimisation of cardiovascular risk factors

2.5.1 Aspirin therapy

Reimbursement will only be supported when co-administered with aspirin for the prevention of atherothrombotic events. The prescriber will be required to confirm that rivaroxaban 2.5 mg tablets are co-prescribed with aspirin at the time of application.

2.5.2 Optimisation of cardiovascular risk factors

Prior to reimbursement approval for rivaroxaban 2.5 mg tablets, prescribers will be required to provide information to confirm cardiovascular risk factors have been optimised including lipids, blood pressure and diabetes mellitus. Applications submitted with clinical parameters outside of those specified in this MAP may be considered for reimbursement support if sufficient clinical justification is provided.

2.5.2.1 Lipid management

The lipid lowering therapies (LLTs) available for reimbursement under the CDS in Ireland include statins, ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.

For the purposes of this MAP, a low-density lipoprotein (LDL) cholesterol level of < 3 mmol/L is considered optimised.

The following information concerning lipid management is required as part of a reimbursement application for rivaroxaban 2.5 mg tablets:

1. Confirmation that lipid levels have been optimised at the time of application.
2. A current LDL cholesterol level and the date of the corresponding blood test. This level must have been taken within 30 days of the date of application.
3. Details of LLTs the patient is taking at the time of application. Information required includes name of medication, dose and duration of treatment.

2.5.2.2 Blood pressure management

For the purposes of this MAP, systolic and diastolic blood pressure readings of < 140 mmHg and < 90 mmHg, respectively, are considered optimised.

The following information concerning BP management is required as part of a reimbursement application for rivaroxaban 2.5 mg tablets:

1. Confirmation that blood pressure has been optimised at the time of application.
2. Current systolic and diastolic blood pressure measurements and the date of the corresponding measurements. These measurements must have been taken within 30 days of the date of application.
3. Details of antihypertensive medication the patient is taking at the time of application. Information required includes name of medication, dose and duration of treatment.

2.5.2.3 Diabetes mellitus management

For the purposes of this MAP, a glycated haemoglobin (HbA1c) level of < 53 mmol/mol is considered to be optimised.

The following information concerning diabetes mellitus management is required as part of a reimbursement application for rivaroxaban 2.5 mg tablets:

1. Confirmation that HbA1c level has been optimised at the time of application.
2. Current HbA1c level and the date of the corresponding blood test. This measurement must have been taken within 30 days of the date of application.
3. Details of any glucose lowering therapies the patient is taking at the time of application. Information required includes name of medication, dose and duration of treatment.

3. Reimbursement criteria – Requirement for outcome data

Follow-up data may be requested by the Health Service Executive (HSE)-Medicines Management Programme (MMP) for audit purposes and provision of same is a condition of ongoing reimbursement. It is the responsibility of the clinician to ensure that the patient or their representative/guardian is aware that the provision of follow-up data is a condition of reimbursement, and that audits may occur during which their personal data will be reviewed.

4. Prescribing of rivaroxaban 2.5 mg for approved patients

Please refer to the relevant SmPCs for rivaroxaban 2.5 mg tablets for full prescribing information including monitoring and patient counselling requirements.

Prior to issuing a prescription for reimbursement on the CDS, the clinician should ensure that the individual has been approved for reimbursement support, following review of an application submitted to the MMP.