This policy statement is approved by Halton, Knowsley, Liverpool, South Sefton, Southport and Formby, St Helens, Warrington, and Wirral CCGs

Ha Kn Li SS SF SH Wa Wi

NHS
Pan Mersey
Area Prescribing Committee

RIVAROXABAN 2.5mg tablets (Xarelto® ▼)
for the prevention of atherothrombotic events

The Pan Mersey Area Prescribing Committee recommends the prescribing of RIVAROXABAN 2.5mg tablets (Xarelto® ▼) plus 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, in accordance with NICE TA607.

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NICE technology appraisal (TA) 607 (17 October 2019) recommends rivaroxaban 2.5mg tablets plus aspirin, within its marketing authorisation, as an option for preventing atherothrombotic events in adults with CAD or symptomatic PAD who are at high risk of ischaemic events.[1]

For people with CAD, high risk of ischaemic events is defined as:

- aged 65 or over, or
- atherosclerosis in at least 2 vascular territories (such as coronary, cerebrovascular, or peripheral arteries), or
- two or more of the following risk factors:
  - current smoking
  - diabetes
  - kidney dysfunction with an estimated glomerular filtration rate (eGFR) of less than 60ml/min
  - heart failure
  - previous non-lacunar ischaemic stroke[1]

Clinicians should assess the person's risk of bleeding before considering rivaroxaban. Treatment should only be started after an informed discussion with them about the risks and benefits of rivaroxaban, weighing up the risk of atherothrombotic events against the risk of bleeding. The risks and benefits of continuing treatment with rivaroxaban should be regularly reviewed.[1]

Note: Patients who are not eligible for treatment under this statement may be considered on an individual basis where their GP or consultant believes exceptional circumstances exist that warrant deviation from the rule of this policy. In this situation, follow locally defined processes.

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Effectiveness

Rivaroxaban is a highly selective direct factor Xa inhibitor, inhibiting both thrombin formation and development of thrombi. No effects on platelets have been demonstrated.[2]

In the COMPASS phase III double blind study,[3] 27,395 participants who met the study eligibility criteria with stable CAD, PAD or both CAD and PAD were randomized to receive rivaroxaban 2.5mg twice daily plus aspirin 100mg once daily, rivaroxaban 5mg twice daily, or aspirin 100mg once daily. The primary outcome was a composite of cardiovascular (CV) death, stroke, or myocardial infarction (MI). The study was stopped after a mean follow-up of 23 months.

The primary outcome occurred in fewer patients in the rivaroxaban plus aspirin group than in the aspirin alone group (379 patients [4.1%] vs. 496 patients [5.4%]; hazard ratio, 0.76; 95% confidence interval [CI], 0.66 to 0.86; P<0.001; z=−4.126), but major bleeding events occurred in more patients in the rivaroxaban plus aspirin group (288 patients [3.1%] vs. 170 patients [1.9%]; hazard ratio, 1.70; 95% CI, 1.40 to 2.05; P<0.001). There was no significant difference in intracranial or fatal bleeding between these two groups. There were 313 deaths (3.4%) in the rivaroxaban plus aspirin group as compared with 378 (4.1%) in the aspirin-alone group (hazard ratio, 0.82; 95% CI, 0.71 to 0.96; P=0.01; threshold P value for significance, 0.0025). Overall, patients who received rivaroxaban 2.5mg twice daily plus aspirin had better CV outcomes and more major bleeding events than those assigned to aspirin alone. Rivaroxaban 5mg twice daily alone did not result in better CV outcomes than aspirin alone and resulted in more major bleeding events.

Safety[2]

The most commonly reported adverse reaction was bleeding including epistaxis (4.5 %) and gastrointestinal (GI) tract haemorrhage (3.8 %).

Contraindications include active clinically significant bleeding; concomitant treatment with any other anticoagulants; concomitant treatment of CAD or PAD with aspirin in patients with previous haemorrhagic or lacunar stroke, or any stroke within a month; hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C; pregnancy; and breast-feeding.

Rivaroxaban is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics or HIV protease inhibitors. These are strong inhibitors of both CYP3A4 and P-gp and may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6 fold on average) and lead to an increased bleeding risk.

Serious skin reactions, including Stevens-Johnson syndrome/toxic epidermal necrolysis and DRESS syndrome, have been reported.

Refer to SPC for full cautions, contraindications, side effects and potential drug interactions.

Cost

Total annual cost per patient: £666.38 (excluding VAT) [4]

- Rivaroxaban (Xarelto®) 2.5mg tablet twice daily: £655.20
- Aspirin 75mg dispersible tablet once daily: £11.18

NICE estimates the overall additional resource impact of implementing NICE TA607 to be £7,177 per 100,000 population in 2019/20, rising to £48,976 per 100,000 population by the end of 2020/21. This is when NICE assumes that steady state will have been achieved.[1]

Patient factors[2]

Use in renal impairment: No dose adjustment necessary in mild or moderate renal impairment (CrCl 30-80ml/min). Use rivaroxaban with caution in patients with severe renal impairment (CrCl 15-29ml/min). Rivaroxaban is not recommended in patients with CrCl < 15 ml/min.

Rivaroxaban should be used with caution in patients with CAD with severe symptomatic heart failure; in patients with CAD or PAD ≥ 75 years of age if co-administered with aspirin; and also in patients with CAD or PAD with body weight < 60kg if co-administered with aspirin.

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Prescribing information[2]

- The recommended dosage for rivaroxaban is 2.5 mg twice daily in combination with a daily dose of 75mg aspirin, taken orally.
- Rivaroxaban may be crushed and administered in a small amount of water to be given via a gastric tube, which should then be flushed with water.
- Rivaroxaban should preferably be taken with food.

Implementation notes[2]

- Patients should be carefully monitored for signs of bleeding. Rivaroxaban should be discontinued if severe haemorrhage occurs.
- Rivaroxaban should be discontinued at the first appearance of a severe skin rash or any other sign of hypersensitivity in conjunction with mucosal lesions.
- Duration of treatment should be determined for each individual patient based on regular evaluations and should consider the risk for thrombotic events versus the bleeding risks.
- Rivaroxaban is not licensed for use with other antiplatelet agents, e.g. clopidogrel, for the prevention of atherothrombotic events.
- Dual antiplatelet therapy has not been studied in combination with rivaroxaban 2.5 mg twice daily (i.e. triple therapy) in patients with CAD/PAD.

References

1. National Institute for Health and Care Excellence. NICE TA607: Rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease. Accessed online 24 October 2019.
2. Bayer plc. Summary of Product Characteristics, Xarelto 2.5 mg film-coated tablets, July 2019. Accessed online 21 August 2019.
3. Eikelboom J, Connolly S, Bosch J et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med 2017; 377:1319-1330 Accessed online 21 August 2019.
4. NHSBA Dictionary of Medicine and Devices (dm+d Browser). Accessed online 04 November 2019.