Prescribing RIVAROXABAN for preventing atherothombotic event after acute management of Acute Coronary Syndrome (unstable angina, non-ST segment elevation myocardial infarction (NSTEMI) or ST segment elevation myocardial infarction (STEMI))

Note: Rivaroxaban is also licensed, at a higher dose for stroke prevention in non-valvular atrial fibrillation, treatment and secondary prevention of venous thromboembolism. Guidance for use for these indications can be found at: Cardiovascular Disease Guidelines

Rivaroxaban▼ (Xarelto®) is a direct oral anticoagulant (DOAC) licensed for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome with elevated cardiac biomarkers. The National Institute for Health and Care Excellence (NICE) has approved the use of rivaroxaban with aspirin alone, or with aspirin plus clopidogrel as an option for adults to prevent further blood clots.

In South London, rivaroxaban may be considered as an option for any patient following an ACS event, except those patients in whom rivaroxaban is contra-indicated. **Local cardiology opinion indicates that it will only be suitable for selected patients (as dual antiplatelet therapy is preferred for the majority).** ***Note: it is not suitable for concomitant use with ticagrelor or prasugrel or in the patients requiring full anticoagulation for any indication (e.g. AF, DVT, PE).***

Additional resources have been developed to support implementation including:

- Screening checklist and Notification of initiation of a rivaroxaban for prevention atherothrombotic events after ACS. This document **must be completed and sent to the General Practitioner (GP) on initiation:** ACS Rivaroxaban Notification of Initiation
- Transfer of prescribing responsibility to primary care for DOACs. This document **must be completed and sent to the GP when transferring the prescribing responsibility** in accordance to South London guidelines: ACS Rivaroxaban Transfer of Care

Treatment must be initiated by a consultant cardiologist, after careful evaluation of the patients risk for ischaemic events and bleeding. The initiating clinician / organisation is responsible for ensuring patient follow up and providing a supply of rivaroxaban for the first three months of treatment. During this time, efforts should be made to reinforce adherence and address any adverse effects.

Transfer of prescribing responsibility to patients own GP

Following the initial 3 month period, patients' therapy may be considered for transfer back to the patient's own GP, provided the transfer of care guidance is followed. If rivaroxaban is prescribed for non-approved / unlicensed indications, prescribing responsibility will remain with the initiating clinician / organisation.

Contraindications (for full details see BNF or **SPC**)	**Cautions** (for full details see BNF or **SPC**)
• Hypersensitivity to the active substance or to any of the excipients • Clinically significant active bleeding • Any Lesion or condition considered a significant risk factor for major bleeding e.g. 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 • Rare hereditary conditions such as galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption as **Xarelto** contains lactose • Prior stroke or transient ischaemic attack (TIA) • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C • Established renal failure (CrCl< 15 ml/min* / chronic kidney disease (CKD) stage 5) • Pregnancy and/ or breast feeding • For contra-indications for use with other medicines see overleaf	• >75 years of age • Low body weight (<60kg) • Patients with an increased bleeding risk such due to: - Congenital or acquired bleeding disorders - Uncontrolled severe hypertension, - Other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease), vascular retinopathy, bronchiectasis or history of pulmonary bleeding • Liver enzymes are elevated > 2 x upper limit of normal • Severe renal impairment (CrCl 15-29ml/min*) • For cautions for use with other medication – see overleaf

Note: BNF=British National Formulary**; SPC=**Summary of Product Characteristics

*** Estimated Glomerular Filtration Rate (eGFR) should NOT be used to guide dosing decisions. Creatinine clearance must be estimated using the Cockcroft-Gault equation calculator or refer to the South London creatinine clearance information sheet.**

This guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the

Dosing

The recommended dose is 2.5mg twice daily with or without food**.** It **must** be co-administered with aspirin 75mg daily (+/- clopidogrel 75mg daily).

- Treatment duration is usually up to 12 months. Decision to continue therapy after 12 months may be considered on an individual basis in those with on-going cardiovascular ischaemic risks. Such an extension must be on advice of a cardiologist, because experience of use between 12-24 months is limited.
- No dose adjustment is needed in patients with mild (CrCl 50-80ml/min) or moderate (CrCl 30-49ml/min) renal impairment. It should be used with caution in patients with severe (CrCl 15-29ml/min) renal impairment in view of limited data.

Initiation

- Treatment should be started >24hours after diagnosis and **after** stabilisation of ACS event (including revascularisation procedure).
- Treatment must only be started at time when parenteral anticoagulation therapy would normally be discontinued. A dose must not be administered concomitantly with any additional anticoagulation.
    - For patients on low molecular weight heparin (LMWH) / fondaparinux – the first dose of rivaroxaban must be given when the next dose of LMWH / fondaparinux is due. The LMWH / fondaparinux must be discontinued prior to administration.
    - For patients on continuous infusion of unfractionated heparin – the first dose of rivaroxaban must be given immediately after discontinuation of the heparin infusion.

For patients at risk of ulcerative gastrointestinal (GI) disease, the co-prescription of a proton pump inhibitor *(e.g. lansoprazole) should be considered to reduce the risk of GI bleed.*

Monitoring

International normalised ratio (INR) monitoring is not required for patients taking rivaroxaban. However, clinical surveillance is recommended throughout the treatment period in line with good anticoagulation practice. All patients prescribed rivaroxaban should be reviewed regularly to assess benefits and risks of on-going therapy weighing the risk of ischaemic events against the bleeding risks.

Side effects (for full details see the BNF or SPC)

- As with any other form of anticoagulation, there is an associated bleeding risk during treatment with rivaroxaban, and patients should be monitored for signs of bleeding or anaemia. Patients should be advised to seek medical advice if they experience persistent or frequent episodes of bleeding. Patients experiencing severe bleeding should seek urgent medical advice.
- Other common side effects include: dyspepsia, diarrhoea, nausea, vomiting, hypotension, oedema, tachycardia, thrombocytopenia, syncope, dizziness.

Rivaroxaban *is a black triangle drug - any adverse effect must be reported to the MHRA using the yellow card system and via the local incident reporting system*

Drug Interactions (for full details on drug interactions – see BNF or SPC)

Drug / Drug class	Recommendation
Other anticoagulant agents (e.g. unfractionated heparin (UFH) or heparin derivatives, low molecular weight heparins, oral anticoagulants)	Concomitant use is contraindicated due to increased risk of bleeding, except when switching with other anticoagulants or using UFH to maintain a patent catheter
Antiplatelet agents	Increased risk of bleeding and lack of data. Concomitant use with antiplatelet agents other than aspirin and clopidogrel must be avoided.
Non-steroidal anti-inflammatory drugs (NSAIDs),	May increased risk of bleeding when used concomitantly. Avoid where possible; if required use at the lowest dose and for the shortest duration possible; close monitoring required and gastro-protection is advised
Other platelet aggregation inhibitors, antithrombotic agents or any medicinal products affecting haemostasis	May increase risk of bleeding when used concomitantly, close monitoring required
CYP3A4 inducers - such as St. John`s wort (Hypericum perforatum), rifampicin, phenobarbital, carbamazepine or phenytoin	Concomitant use will result in decreased rivaroxaban plasma concentrations, and the SPC recommends avoiding co-administeration unless patients can be closely monitored for signs and symptoms of thrombosis. The co-administration of rivaroxaban with any of these agents should only be considered under specialist haematology supervision
Systemic azole-antimycotics (such as ketoconazole, voriconazole, itraconazole or posaconazole)	Concomitant use is not recommended due to increased plasma rivaroxaban levels
HIV Protease inhibitors (e.g. lopinavir/ritonavir, indinavir)	Concomitant use is not recommended due to increased plasma rivaroxaban levels
Clarithromycin, erythromycin, fluconazole	Concomitant use of clarithromycin, erythromycin and fluconazole slightly increase rivaroxaban levels. This is not clinically significant in normal renal

	function, but may be significant in patients with moderate renal impairment (CKD stage 3). In these patients alternative antibiotic therapy is preferred. Avoid use in CKD stage 4 or 5
Dronedarone	Not recommended for concomitant treatment with rivaroxaban

Roles and responsibilities

Initiating clinician / organisation	Patient's own GP
• To initiate / guide the initiation of rivaroxaban in line with NICE and local guidance • To supply rivaroxaban for the first 3 months of treatment • To provide counselling to improve adherence and address any early adverse effects • Following the initial three months of treatment; transfer care to the GP in line with local transfer of care guidance • If treatment is required for longer than 12 months; to give the GP clear guidance about intended duration of treatment or further follow-up required • For patients requiring long-term treatment; to arrange a follow-up at 12 months to review on-going need for therapy	• To ensure use of rivaroxaban is in line with the NICE / local guidance • To agree to take over prescribing responsibility when the patient is stable on therapy (at least 3 months after initiation and in line with the transfer of care guidance) • To agree to take over prescribing earlier in patients with complex medication supply issues e.g. patients using medication compliance aids (MCA) or housebound patients • To emphasise the importance of adherence to rivaroxaban therapy and address any patient concerns • To monitor ongoing risk of bleed and if appropriate, seek specialist advice

Additional information

1. Patients taking rivaroxaban should be encouraged to carry an anticoagulation card in addition to the antiplatelet card. (available from initiating clinician / anticoagulation clinics) at all times or to wear a medic-alert bracelet.
2. There is no specific reversal agent should a patient experience a bleed on rivaroxaban. In the event of a significant bleed, the patient should be referred to A & E for supportive measures.
3. Other healthcare professionals should be made aware that rivaroxaban is prescribed, for any patients who are to undergo invasive treatments, including elective surgery and dental treatment.
4. Missed dose advice should be discussed at initiation: If a dose is missed the patient should continue with regular dose as recommended at the next scheduled time. The dose should not be doubled to make up missed doses.
5. If a patient has been assessed as being appropriate for a multi-compartment compliance aid (MCA), often known as a dosette box, consideration can be given to including rivaroxaban tablets as they do not have special storage requirements.

References

1. NICE TA335: Rivaroxaban for prevention adverse outcomes after acute management of acute coronary syndrome. March 2015. Accessed via: https://www.nice.org.uk/guidance/ta335/resources/rivaroxaban-for-preventing-adverse-outcomes-after-acute-management-of-acute-coronary-syndrome-82602549055429
2. SPC Xarelto. Bayer. July 2015. Accessed April 2016 via: https://www.medicines.org.uk/emc/medicine/29371
3. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. N Eng J Med 2012; 366:9-19