Prescribing RIVAROXABAN for the acute treatment and secondary prevention of venous thromboembolism (VTE) (Pulmonary Embolism (PE) or Deep Vein Thrombosis (DVT))

Note: Rivaroxaban is also licensed for the prevention of stroke in patients with non-valvular atrial fibrillation and at a lower dose for acute coronary syndrome. Guidance for use for these indications can be found at: SEL APC CVD Guidelines

Rivaroxaban▼(Xarelto®) is a direct oral anticoagulant (DOAC) licensed for the acute treatment of VTE (PE or DVT) and for the secondary prevention of VTE in patients at risk of recurrent events. The National Institute for Health and Care Excellence (NICE) has approved the use of rivaroxaban as an option for the acute management and secondary prevention of VTE.

In South London, rivaroxaban may be considered as an option for any patient experiencing a provoked or unprovoked DVT or PE, except those patients in whom there is an underlying malignancy or those who are pregnant or breast-feeding where a low molecular weight heparin (LMWH) is preferred, or patients with renal impairment (creatinine clearance (CrCl) < 30ml/min) in whom warfarin is preferred (rivaroxaban is contra-indicated when CrCl < 15ml/min).

- Patients with provoked VTE events (e.g. caused by surgery, trauma, long distance travel, immobility, pregnancy or hormone replacement therapy) usually require 3 - 6 months of rivaroxaban therapy.
- Patients with unprovoked events or where there are on-going risk factors for recurrence may require a longer duration, as advised by the initiating clinician.

Additional resources have been developed to support implementation including:

- Overview summary of VTE treatment
- Screening checklist and Notification of initiation of a DOAC for the treatment of VTE This document **must be completed and sent to the General Practitioner (GP) on 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.

Rivaroxaban should only be initiated by clinicians with expertise in managing anticoagulant therapy. 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 requiring longer term anticoagulant 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 • Prosthetic heart valves requiring anticoagulant treatment - the effect of rivaroxaban has not been studied in this patient group • 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*) • Pregnancy and/ or breast feeding • For contra-indications for use with other medicines see overleaf	• 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), vascula retinopathy bronchiectasis or history of pulmonary bleeding • Active cancer- efficacy and safety of rivaroxaban in the treatment and/or prevention of VTE in patients with active cancer was moderate and more data is needed – LMWH preferred • Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy- not recommended since the safety and efficacy of rivaroxaban have not been established in these clinical situations • Liver enzymes elevated > 2 x upper limit of normal • Moderate (CrCl 30-49ml/min) or severe (CrCl 15-29 ml/min) renal impairment • 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 circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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South East London Area Prescribing Committee. A partnership between NHS organisations in South East London: Bexley/ Bromley/ Greenwich/ Lambeth/ Lewisham & Southwark Clinical Commissioning Groups (CCGs) & GSTFT/KCH/SLAM/Oxleas NHS Foundation Trusts & Lewisham & Greenwich NHS Trust

Dosing

The recommended dose of rivaroxaban for management of acute DVT or PE is 15mg twice daily for three weeks, then 20mg once daily thereafter. (In the maintenance phase, the initiating clinician may recommend a reduced dose of 15mg daily in patients with moderate (CrCl 30–49 ml/min) or severe (CrCl 15–29 ml/min) renal impairment if their risk of bleeding is considered high

- The dose should be taken with food, at the same time each day
- No dose adjustment is required in the elderly

- Patients with provoked VTE events (e.g. caused by surgery, trauma, long distance travel, immobility, pregnancy or hormone replacement therapy) usually require 3 - 6 months of rivaroxaban therapy.
- Patients with unprovoked events or where there are on-going risk factors for recurrence may require a longer duration, as advised by the initiating clinician.

For patients identified as at risk of upper GI bleeding the co-prescription of a proton pump inhibitor *(e.g. lansoprazole/omeprazole) may be considered.*

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 **at least annually** to assess benefits and risks of on-going therapy weighing the risk for thrombotic events against the bleeding risks.
- Patients should be monitored for signs of bleeding or anaemia; treatment should be stopped if severe bleeding occurs.
- A baseline renal function test is required and consequent re-testing should take place at least annually (frequency determined by the patient's baseline renal function as guided by the initiating clinician).
- For patients on long-term therapy clinicians will need to monitor patients and make any other dose adjustments necessary based on renal function and bleeding risk (see dosage section above).

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 and headache.

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, LMWHs, or oral anticoagulants)	Concomitant use is contraindicated due to increased risk of bleeding, except when UFH is given at doses necessary to maintain a patent catheter or if switching with other anticoagulants
Use of fibrinolytic agents for the treatment of acute ischaemic stroke	May be considered by hyper-acute stroke units if the clinician can be certain that there is no anticoagulant effect present based on laboratory testing of clotting
Aspirin and other antiplatelet agents	Increased risk of bleeding – use with caution; should be stopped if clinically appropriate (seek advice from cardiologist); if required to continue close monitoring required and gastro-protection is advised
Non-steroidal anti-inflammatory drugs (NSAIDs)	Increased risk of bleeding if used long-term. Avoid where possible; if required use at the lowest dose and for the shortest duration possible; close monitoring required and gastro-protection is advised
Any other medicinal products affecting haemostasis	May increase the risk of bleeding when used concomitantly, close monitoring required
CYP3A4 or P-glycoprotein 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-administration 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 renal impairment. In these patients alternative antibiotic therapy is preferred. Avoid use in CKD stage 4/5
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 • If treatment is required for longer than three months; to transfer care to the GP in line with local transfer of care guidance • If treatment is required for longer than three 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 ongoing 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 ensure monitoring of renal and hepatic function is undertaken as directed by the initiating clinician and at least annually. If results fall outside normal range then refer to contraindication, caution and dosing sections in the prescribing guidelines and/or seek specialist advice as appropriate • 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 (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 accident and emergency 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 during the 15 mg twice daily treatment phase (day 1 - 21), the patient should take rivaroxaban immediately to ensure intake of 30 mg rivaroxaban per day. In this case two 15 mg tablets may be taken at once. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day.
    - If a dose is missed during the once daily treatment phase (day 22 and onwards), the patient should take rivaroxaban immediately, and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.
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 TA261: Rivaroxaban for the treatment of DVT and the prevention of recurrent DVT / PE. July 2012. Accessed April 2016 via: https://www.nice.org.uk/guidance/ta261/resources/rivaroxaban-for-the-treatment-of-deep-vein-thrombosis-and-prevention-of-recurrent-deep-vein-thrombosis-and-pulmonary-embolism-82600546953157
2. NICE TA287: Rivaroxaban for Pulmonary Embolism and recurrent VTE. June 2013. Accessed April 2016 via: https://www.nice.org.uk/guidance/ta287/resources/rivaroxaban-for-treating-pulmonary-embolism-and-preventing-recurrent-venous-thromboembolism-82600677963205
3. SPC Xarelto. Bayer. July 2015. Accessed April 2016 via: http://www.medicines.org.uk/emc/medicine/25586
4. The Einstein Investigators. Oral Rivaroxaban for symptomatic Venous Thromboembolism. N Eng J Med 2010;363:2499-510. Accessed April 2016 via http://www.nejm.org/doi/pdf/10.1056/NEJMoa1007903