NHS
South London
Cardiovascular and Stroke Network

Guidance on the use of rivaroxaban for stroke prevention in atrial fibrillation (AF)

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.

Rivaroxaban is a novel oral anticoagulant recently licensed for use for stroke prevention in atrial fibrillation (SPAF). NICE has approved the use of rivaroxaban as an option for SPAF, for patients with additional risk factors.

In south London, rivaroxaban should be considered, in line with its licensed indications, as an alternative to warfarin for SPAF in patients with $CHADS_2 \geq 1$ who:

- **have a warfarin allergy, warfarin specific-contraindication or are unable to tolerate warfarin therapy due to severe adverse effects[1]**
- **are unable to comply with the specific monitoring requirements of warfarin[2]**
- **are unable to achieve a satisfactory INR after an adequate trial of warfarin (usually at least 3 months) despite compliance with drug therapy. Patients at particular risk are those that remain sub-therapeutic (INR persistently <2), those where the INR regularly fluctuates above 4 and those requiring dosages at the extreme ends of the dose range.**

Patients currently stable on warfarin therapy should not usually be considered for a switch to rivaroxaban.

Initiation of rivaroxaban should only be undertaken by clinicians with expertise in initiating anticoagulant therapy for SPAF.

The initiating clinician is responsible for ensuring patient follow up and providing medicine supplies 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 may be considered for transfer back to the patient's own GP, provided the patient meets the criteria for use of rivaroxaban (as above), the GP agrees to take over prescribing responsibility and SLCSN transfer of care guidance is followed. If rivaroxaban is prescribed for patients / indications that do not meet the criteria above, prescribing responsibility will remain with the initiating clinician / organisation.

Contraindications	Cautions
-Hypersensitivity to the active substance or to any of the excipients -Clinically significant active bleeding -Hepatic disease associated with coagulopathy and clinically relevant bleeding risk -Pregnancy and breast feeding -Patients with severe renal impairment(CrCL< 15 ml/min / eGFR<15ml/min; CKD stage 5)	-Use not recommended where liver enzymes are elevated > 2 x upper limit of normal (ULN) -People at increased risk of bleeding due to co-morbidities such as active ulcerative gastrointestinal disease, congenital or acquired bleeding disorders -Rivaroxaban should be used with caution in renal impairment. ***See below for dose adjustments***. -Rivaroxaban should be used with caution in patients on concomitant drugs that increase rivaroxaban plasma levels such as drugs that are potent inhibitors of CYP3A4 (e.g. clarithromycin, telithromycin) -Concomitant use of medicines such as NSAIDs, aspirin, clopidogrel, prasugrel, ticagrelor or other antithrombotic agents will increase bleeding risk.

Dosing

- The recommended dose is 20 mg once daily (recommended maximum dose) with food, at the same time each day. No dose adjustment is required in the elderly.
- For patients at risk of ulcerative gastrointestinal (GI) disease, the co-prescription of a low cost PPI may be considered to reduce the risk of GI bleed.
- Once initiated, rivaroxaban therapy should be continued long term.

Renal impairment

Increased plasma rivaroxaban levels (1.6 fold on average) are expected in severe renal impairment (CrCl < 30ml/min CKD stages 4 and 5). Renal function should be assessed at least annually in all patients and more frequently if clinically appropriate.

Creatinine clearance as stated in SPC	Approximate equivalent eGFR (CKD stage)	Recommendation
CrCl<15ml/min	eGFR <15ml/minute (CKD stage 5)	Rivaroxaban is contraindicated
CrCL 15-29ml/min (severe)	eGFR 15-29ml/minute (CKD stage 4)	Maximum rivaroxaban dose is 15mg once daily
CrCL 30-49ml/min (moderate)	eGFR 30-45ml/minute (CKD stage 3b)	

[1] Such as intolerable rash, significant alopecia, skin necrosis

[2] Inability to comply with warfarin monitoring may be due to lack of understanding of the monitoring process or inability to access any local monitoring service (this should be discussed with the patient's own GP, before a NOAC is initiated).

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

- Bleeding occurs commonly during treatment with rivaroxaban, patients should be monitored for signs of bleeding or anaemia. In the ROCKET-AF study with rivaroxaban 20mg daily (15mg daily in moderate renal impairment) bleeding rates were reported as 3.6% major bleeds including 0.82% critical organ bleeds and 0.49% intracranial haemorrhage and 11.8% minor bleeds, such as epistaxis. 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.
- Common side effects include: dyspepsia, diarrhoea, nausea, vomiting, hypotension, oedema, tachycardia, thrombocytopenia, syncope and dizziness.

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

Drug / Drug class	Recommendation
Concomitant administration of P-gp inducers - such as rifampicin, St. John`s wort (Hypericum perforatum), Phenobarbital, carbamazepine or phenytoin	Will result in decreased rivaroxaban plasma concentrations, and the SPC recommends should be co-administered with caution. The co-administration of rivaroxaban with any of these agents should only be considered under specialist haematology supervision.
NSAIDs, aspirin, platelet aggregation inhibitors, other antithrombotic agents or any medicinal products affecting haemostasis	May increase the risk of bleeding when used concomitantly close monitoring required. Promptly review any signs or symptoms of blood loss
Anticoagulants	Increased risk of bleeding, avoid concurrent use
Clopidogrel	May increase the risk of bleeding when used concomitantly close monitoring required. Promptly review any signs or symptoms of blood loss
Systemic ketoconazole, voriconazole, itraconazole or posaconazole	Concomitant use is not recommended due to increased plasma rivaroxaban levels
Clarithromycin	Concomitant use of clarithromycin will 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 4/5.
HIV Protease inhibitors e.g. lopinavir/ritonavir, indinavir	Not recommended for concomitant treatment with rivaroxaban
Dronedarone	Not recommended for concomitant treatment with rivaroxaban

Roles and responsibilities

Initiating clinician / organisation	Patient's own GP
• To initiate rivaroxaban, in line with SLCSN position statement • To supply rivaroxaban for the first 3 months of treatment • To provide counselling to improve adherence and deal with any early adverse effects • To ensure the patients GP and current anticoagulant service is informed about the cessation of warfarin therapy (if previously treated with warfarin) • To seek agreement from the patient's own GP at 3 months to take over prescribing of rivaroxaban. Ensure GPs are given sufficient information and time to consider and respond to the request (at least two weeks) • To transfer care to the GP in line with SLCSN transfer of care guidance (in progress)	• To ensure use of rivaroxaban is line with the SLCSN position statement • 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 emphasise the importance of adherence to rivaroxaban therapy and address any patient concerns • To ensure renal monitoring is undertaken at least annually throughout therapy and review treatment in line with contra-indications and cautions should renal function decline (see overleaf). 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
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 undergoing invasive treatments, including elective surgery and dental treatment
4. If a dose is missed the patient should take rivaroxaban immediately and continue the following day with once daily intake as recommended. Patients should take no more than one dose per day!
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 any special storage requirements[3].

References
-NICE TA256: rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation. May 2012
-SPC Xarelto. Bayer. May 2012. Accessed 11th July 2012 at http://www.medicines.org.uk/EMC/medicine/25586/SPC/Xarelto+20mg+film-coated+tablets/
-BNF No 63 March 2012

[3] **Please note Bayer are unable to recommend rivaroxaban is included in a MCA as stability has not been analysed by the company**