Rationale for Initiation, Continuation and Discontinuation (RICaD)

Rivaroxaban▼

- For the prevention of stroke and systemic embolism within its licensed indication, that is, in people with nonvalvular atrial fibrillation (NICE TA 256)

This document supports the use and transfer of an agent which is classified as **AMBER**.
It is intended for completion by specialist in order to give Primary Care prescribers a clear indication of the reason for recommending an **AMBER** medication together with suggested criteria for its subsequent continuation or discontinuation. This RICaD should be provided as a supplement to the specialist's clinical letter.

Patient details		**GP details**		**Specialist details**	
Name		**GP name**	**Dr**	**Specialist name**	
PID		**GP address**		**I confirm that this patient is eligible to receive rivaroxaban under the restrictions listed below**	
DOB				**Signature**	
Patient address				**Date**	
				Contact details	

Rationale for Choice

Relevant Diagnosis:	Non-valvular atrial fibrillation ☐
Agreed Indication(s) for inclusion in the BSSE APC Formulary:	**NICE TA 256** Rivaroxaban is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with nonvalvular atrial fibrillation with one or more risk factors such as: • congestive heart failure☐ • hypertension☐ • age 75 years or older☐ • diabetes mellitus, ☐ • prior stroke or transient ischaemic attack☐
Reason why rivaroxaban has been chosen in preference to drugs without Formulary restrictions:	Specialists please type text below and check boxes: I can confirm that an informed discussion about the benefits and risks of rivaroxaban compared with warfarin has taken place with the patient. Rivaroxaban has been selected for this patient because: ☐Patient has an allergic reaction/intolerance of coumarins (warfarin, phenindione, sinthrome) ☐Patient has an important and unavoidable drug interaction(s) that favour rivaroxaban over warfarin ☐Patient would find it difficult to cope with a variable dose regimen and subsequent monitoring, but is able to comply with a fixed dose drug regime. ☐Patient has had a significant bleed on warfarin and bleed is associated with poor INR control in despite patient being adherent with prescribed medication. ☐Poor INR control (e.g. more than 2 INRs >8.0 or more than 3 INRs >5.0 in 6 months) ☐Poor TTR (Time in therapeutic range). List TTR value: …… ☐Patients who, following informed discussion of risks and benefits of rivaroxaban and warfarin, request rivaroxaban as their preferred choice in terms of a favourable lifestyle in comparison to warfarin
Special precautions	**Contraindications** • Hypersensitivity to the active substance or to any of the excipients listed • Active clinically significant bleeding. • Lesion or condition, if considered to be a significant risk for major bleeding. This may include 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. • Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under specific circumstances of switching anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child-Pugh B and C • Pregnancy and breast feeding **Cautions** Haemorrhagic risk

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment This may be done by regular physical examination of the patients, close observation of the surgical wound drainage and periodic measurements of haemoglobin.
Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.
Although treatment with rivaroxaban does not require routine monitoring of exposure, rivaroxaban levels measured with a calibrated quantitative anti-factor Xa assay may be useful in exceptional situations where knowledge of rivaroxaban exposure may help to inform clinical decisions, e.g., overdose and emergency surgery

Elderly population

Increasing age may increase haemorrhagic risk.

Renal impairment

In patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6-fold on average) which may lead to an increased bleeding risk. Rivaroxaban is to be used with caution in patients with creatinine clearance 15-29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min

In patients with moderate renal impairment (creatinine clearance 30-49 ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations rivaroxaban is to be used with caution

Interaction with other medicinal products

The use of rivaroxaban is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6 fold on average) which may lead to an increased bleeding risk

Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory medicinal products (NSAIDs), acetylsalicylic acid (ASA) and platelet aggregation inhibitors. For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered

Other haemorrhagic risk factors

As with other antithrombotics, rivaroxaban is to be used with caution in patients with an increased bleeding risk such as:

- congenital or acquired bleeding disorders
- uncontrolled severe arterial 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.

Dosing recommendations before and after invasive procedures and surgical intervention other than elective hip or knee replacement surgery

If an invasive procedure or surgical intervention is required, rivaroxaban should be stopped at least 24 hours before the intervention, if possible and based on the clinical judgement of the physician.
If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.
Rivaroxaban should be restarted as soon as possible after the invasive procedure or surgical intervention provided the clinical situation allows and adequate haemostasis has been established as determined by the treating physician.

Pre-treatment test results	Specialists please complete the information in table below: Date of test | eGFR | • *Note: Rivaroxaban* is to be used with caution in patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentration. • *Rivaroxaban* is to be used with caution in patients with creatinine clearance 15-29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min. *See full SPC for prescribing information.* • The patient has been informed of the need for annual (or more frequent if clinically appropriate) renal function tests in order to assess suitability for ongoing treatment. ☐

Guidance on initiation (to be completed by the specialist)

Initiation dose:	The recommended dose is 20 mg once daily, which is also the recommended maximum dose. **Renal Impairment** | **Recommended dose** Mild (Creatinine clearance 50-80 ml/min) | No dose adjustment is necessary Moderate (Creatinine clearance 30-49 ml/min) | 15 mg once daily Severe (Creatinine clearance 15-29 ml/min) | Use rivaroxaban with caution in these patients 15 mg once daily Creatinine clearance < 15 ml/min | Rivaroxaban not recommended
Additional info:	• There is no known antidote to rivaroxaban. • The tablets are to be taken with food. • For patients who are unable to swallow whole tablets, rivaroxaban tablets may be crushed and mixed with water or apple puree immediately prior to use and administered orally. After the administration of the crushed tablets, the dose should be immediately followed by food. • The crushed rivaroxaban tablet may also be given through gastric tubes after confirmation of the correct gastric placement of the tube. The crushed tablet should be administered in a small amount of water via a gastric tube after which it should be flushed with water. After the administration of the crushed tablets, the dose should be immediately followed by food. • Rivaroxaban can be transferred to "monitored dose systems". • Tablets must be swallowed whole. A liquid formulation is not available. • Rivaroxaban ▼ is a black triangle drug. All suspected adverse effects should be reported to the CHM www.yellowcard.gov.uk
Drug interaction (significant interaction as outlined in BNF, please see BNF and SPC for more detail)	**Rivaroxaban** has the following interaction information: Anticoagulants | increased risk of haemorrhage when rivaroxaban given with other anticoagulants (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency) Carbamazepine | plasma concentration of rivaroxaban possibly reduced by carbamazepine —manufacturer of rivaroxaban advises monitor for signs of thrombosis Cobicistat | anticoagulant effect of rivaroxaban possibly enhanced by cobicistat —avoid concomitant use Fosphenytoin | plasma concentration of rivaroxaban possibly reduced by fosphenytoin —manufacturer of rivaroxaban advises monitor for signs of thrombosis Ketoconazole | plasma concentration of rivaroxaban increased by ketoconazole —avoid concomitant use Phenobarbital | plasma concentration of rivaroxaban possibly reduced by phenobarbital —manufacturer of rivaroxaban advises monitor for signs of thrombosis Phenytoin | plasma concentration of rivaroxaban possibly reduced by phenytoin —manufacturer of rivaroxaban advises monitor for signs of thrombosis Primidone | plasma concentration of rivaroxaban possibly reduced by primidone —manufacturer of rivaroxaban advises monitor for signs of thrombosis Rifampicin | plasma concentration of rivaroxaban reduced byrifampicin —manufacturer of rivaroxaban advises monitor for signs of thrombosis

Ritonavir	plasma concentration of rivaroxaban increased by ritonavir —avoid concomitant use
St John's Wort	plasma concentration of rivaroxaban possibly reduced by St John's wort —manufacturer of rivaroxaban advises monitor for signs of thrombosis

Rivaroxaban belongs to **Anticoagulants** and will have the following interactions:

Apixaban	increased risk of haemorrhage when other anticoagulants given with apixaban (avoid concomit when switching with other anticoagulants or using heparin to maintain catheter patency)
Dabigatran	increased risk of haemorrhage when other anticoagulants given with dabigatran (avoid concom when switching with other anticoagulants or using heparin to maintain catheter patency)
Diclofenac	increased risk of haemorrhage when anticoagulants given with *intravenous* diclofenac (avoid co including low-dose heparins)
Ketorolac	increased risk of haemorrhage when anticoagulants given with ketorolac (avoid concomitant us dose heparins)
Rivaroxaban	increased risk of haemorrhage when other anticoagulants given with rivaroxaban (avoid concor when switching with other anticoagulants or using heparin to maintain catheter patency)

Monitoring:	Deterioration of renal function can significantly increase plasma concentration. Renal function should be assessed in all patients **before starting rivaroxaban and at least once a year or more frequently** as needed in clinical situations when it is suspected that the renal function could decline or deteriorate. The patient should be questioned periodically regarding any abnormal bleeding such as nosebleeds and encouraged to report any such events to the GP.

Suggested Criteria for Continuation or Discontinuation (to be completed by the specialist)

Assessment of Efficacy	
Frequency	At routine appointments but at least annually
Location	GP practice
Method (what tests are required)	Renal and hepatic function tests Discussion with patient regarding compliance and any factors that may affect compliance (i.e. need for monitored dose system or swallowing difficulties) Reassess bleeding risk, including risk of falls, and use of medication associated with gastro-intestinal bleeding Review hepatic function
Test results and action	Renal function • Mild to moderate renal impairment: No dosage adjustment necessary • Severe renal impairment (creatinine clearance 15-29 ml/min): Use with caution – seek specialist advice • Creatinine clearance < 15 ml/min: Discontinue and seek specialist advice Compliance • As indicated Reassessment of bleeding risk • As indicated. If elevated from initiation, seek specialist advice. Hepatic function • Discontinue if patient has developed hepatic disease associated with coagulopathy and clinically relevant bleeding risk
Continuation Criteria	Appropriate renal and hepatic function, assessment of bleeding risk, and compliance confirmed
Discontinuation Criteria	• When recommended duration of treatment reached following review. • Renal function – CrCl <15 ml/min – discontinue • CrCl 15-49 ml/min – reconsider use and dose - see dose section above • Poor compliance • Unacceptable bleeding risk • Severe hepatic impairment • Use with interacting medication with significant interactions as SPC.
Follow up action	Specialists to complete
Shared Care read code	In the patients notes, using the appropriate Read Code listed below, denote that the patient is receiving treatment under a shared care agreement

GP Prescribing System	Read Code	Description
EMIS and Vision	8BM5.00	Shared care prescribing
SystmOne	XaB58	Shared care