NHS

City and Hackney Clinical Commissioning Group
Homerton University Hospital Foundation Trust

DRUG NAME: RIVAROXABAN (XARELTO®)
Transfer of Care document
Treatment of acute venous thromboembolism and prevention of recurrent venous thromboembolism

INTRODUCTION – Indication and Licensing

Rivaroxaban is a non-vitamin K antagonist oral anticoagulant (NOAC) that works through highly selective inhibition of factor Xa. It is licensed for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE. For patients treated for venous thromboembolism (VTE) rivaroxaban is an attractive and cost effective treatment option. Initiation would be by secondary care only and in accordance with its licensed indication and NICE guidelines.

Due to its selective inhibition of one clotting factor, the anticoagulation effects are more predictable and as such there is no requirement for regular monitoring, unlike vitamin K antagonists (VKA) such as warfarin. Other potential advantages compared to VKAs include a standard dosing regimen and a lower likelihood of drug interactions. Disadvantages of rivaroxaban are its higher cost (partially offset by the reduced need for INR monitoring) and limited clinical experience of long-term use. Additional disadvantages are; there is no antidote as yet in case of life threatening bleeding, no available test for measuring residual activity before operation and no test for monitoring of patient adherence. However, in studies comparing against warfarin, less fatal bleeding was shown in comparison to warfarin in both atrial fibrillation and acute VTE and unlike warfarin has far shorter half-life and is therefore cleared quicker than warfarin, which may explain the less fatal bleeding seen in clinical trials.

PATIENT PATHWAY

Clinical Speciality / Indication	**Prescribing Initiated by**	**Prescribing Continued by *(detail when suitable for transfer to occur)***	**Monitored by *(detail when suitable for transfer to occur IF APPROPRIATE)***	**Duration of treatment**
Haematology	Secondary care prescriber	Hospital after 3 weeks of initiation, where a further 4 weeks supply will be issued to patients	GP after 7 weeks	Individualised for each patients. All VTE patients will be seen by haematologist within 6 months of initiation to confirm duration of treatment.

(N.B. a temporary discontinuation for surgical procedures is advised, see below for further details).

Patients are to be initiated in the first instance by a clinician in secondary care. If rivaroxaban is suitable 3 weeks supply will be issued alongside the anticoagulation alert card and patient booklet.

The patient will return to anticoagulation clinic after the initial 3 weeks to ensure adequate follow up during the initiation phase providing adherence counselling addressing any patients concerns regarding therapy. If rivaroxaban is tolerated, then a further 4 weeks of dose adjusted treatment will be supplied by the hospital, after which the GP will continue the supply and monitoring. If the patient has concerns prior to commencing continuation with the GP they should contact the hospital anticoagulant team. The patient will be advised to contact their GP within 7 weeks of initiation. A NOAC initiation letter will also be forwarded to GP confirming transfer of care.

Duration of treatment will be advised initially by the anticoagulation team. A follow up within 3-6 months would then be carried out by a haematologist to assess the patient and extend the duration in treatment, if needed. Long-term treatment should be reviewed at least annually by GP and an assessment made for new contraindications to ongoing anticoagulation with rivaroxaban (e.g. temporary discontinuation for surgery, marked decline in renal function and increased bleeding risk - see below for further advice on bleeding risk). Where new contraindications are found, treatment is to be reviewed and anticoagulation therapy withdrawn if risks are deemed to outweigh benefits. Ongoing adherence should be reviewed on a regular basis, the duration and method of adherence assessment should be determined by the GP, taking into account individual patient circumstances and factors. The GP is to re-educate the patient each time for the need to stop their rivaroxaban and seeing any doctor as soon as possible in case of bleeding.

ORAL DOSE AND ADMINISTRATION

Rivaroxaban film coated tablets are available in 2 strengths for this indication: 15mg and 20mg.

Usual dose:

	Renal function*		
	CrCl ≥50ml/min	**CrCl: 15 to 49ml/min**	**CrCl <15ml/min**
First 3 weeks (Day 1 to 21)	**15mg twice daily**	**15mg twice daily**	**Not recommended**
Day 22 onwards	**20 mg once daily**	****20 mg once daily**	

*Cockroft and Gault to be used – see below for formula
**A reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on pharmacokinetic modeling and has not been studied in this clinical setting.

Increased risk of bleed:

- If bleeding risk is assessed as high, patients are to be considered for 15mg tablet once daily after the first three weeks and discussed with a haematologist. Clear documentation should be made as to reason for dose reduction.
- Patients with an increased bleeding risk should be closely monitored clinically (looking for signs of bleeding or anaemia, more details below). Dose adjustment should be decided at the discretion of the physician, following assessment of the potential benefit and risk to an individual patient.
- If clinically relevant bleeding occurs, treatment should be interrupted and reviewed prior to re-initiation.

Cockroft and Gault formula to calculate CrCl (ml/min)

$$\frac{K \times (140\text{-age}) \times \text{weight (kg)}}{\text{Serum Creatinine } (\mu\text{mol/L})}$$

K = 1.23 in males
K = 1.04 in females

MONITORING

Parameter	**Renal function (Creatinine clearance - CrCl)** Using Cockroft and Gault equation (see above)
Action Required	CrCl 15-49ml/min: Dose 15mg twice a day for 3 weeks and then increase dose to 20mg once a day, OR maintain at 15mg once a day where patient considered to be at a high risk of bleeding. CrCL <15mls/min; contraindicated – avoid use.
Frequency of monitoring	Assess renal function prior to treatment to ensure appropriate starting dose. Then: • Annually (alongside Hb and liver function tests) • 6 monthly o >75yrs o Frail (defined as ≥3 of the following criteria: unintentional weight loss, self-reported exhaustion, weakness assessed by handgrip test, slow walking speed/gait apraxia, low physical activity) o If CrCl 30–60ml/min • 3 monthly o If CrCl 15-29ml/min More frequent renal function monitoring maybe needed as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate such as hypovolemia and dehydration.
Further Action	Dose reduction may be required based on initial renal function. If renal function declines rapidly may need to temporarily withhold therapy and review prior to restarting.

Parameter	**Minor bleeding (or those at high risk of bleed on treatment)**
Haematological tests	Dose-dependent inhibition of Factor Xa activity was observed in humans. Routine clotting tests (PT and APTT) are not very reliable indicators of the level of rivaroxaban and should not be used for monitoring purposes. If measurement of a rivaroxaban level is required it should be with an anti-Xa assay following discussion with the haematology.
Action	If numerous episodes of minor bleeding are observed or patient at high risk of bleed discuss with haematology.

Parameter	**Adherence**
Target level	100%
Frequency of monitoring	Prior to initiation, likely adherence should be considered and discussed with the patient. Following initiation, adherence should be reinforced at a minimum of annually although this is left at the discretion of the physician
Action	If adherence likely to be low, consider alternative anticoagulation that can be monitored, i.e. warfarin.

Please note: Rivaroxaban has an inverted Black Triangle ▼displayed in the patient information leaflet and in the summary of product characteristics (SPC). This means that it is a medicine subject to additional monitoring by regulatory authorities in the European Union (EU).

KEY ADVERSE EFFECTS & ACTIONS

Adverse effects	Symptoms/signs	Actions)
Minor Bleeding	Self-terminating minor bleeding from scratches, cuts, nosebleeds, gum bleeding etc. may be experienced. If these are frequent or patient / physician concerned - contact local haematology department for advice	The degree of bleeding will dictate action. If minor bleeding is infrequent and self terminates, patient can be reassured. If concerns are raised - liaise with haematology for advice.
Clinically significant bleeding	Bleeding that does not stop with reasonable intervention should be referred to local A&E, if in doubt contact local haematology department for advice	The degree of bleeding will dictate the action. If bleeding stops spontaneously consider omitting a dose. If concerns are raised - liaise with haematology for advice. For bleeding that does not stop with intervention, send patient to local A&E.
Gastrointestinal	Dyspepsia	Consider gastro protection in accordance with local guidance. If no further improvement, consider alternatives or referral to specialist.

This only lists the key important ADRs-For comprehensive information on cautions, contra-indications and interactions please refer to the current British National Formulary and Summary of Product Characteristics.

Important cautions: Surgery and invasive procedures

Patients on rivaroxaban who undergo surgery or invasive procedures are at increased risk for bleeding. Therefore surgical interventions may require temporary discontinuation of rivaroxaban. If an invasive procedure or surgical intervention is required, rivaroxaban should be stopped at least 24hours before the intervention. See SPC for further details. If surgery cannot be delayed the case should be discussed with haematology for advice on reversal if required.

PREGNANCY AND BREAST FEEDING

The safety of rivaroxaban has not been established in pregnant or lactating women; as such use in these patients is to be avoided.

For comprehensive information please refer to the current British National Formulary and Summary of Product Characteristics.

Evidence

Rivaroxaban has been shown to be as effective as standard anticoagulant therapy comprising of low molecular weight heparin in combination with a vitamin K antagonist (VKA) e.g. warfarin; it has similar levels of bleeding and a similar adverse effect profile.

Use of rivaroxaban to reduce the incidence of recurrent VTE has been studied in 2 large multinational, randomised control trials; EINSTEIN-DVT and EINSTEIN-PE. A pooled analysis showed that at least 8,000 patients were enrolled with DVT or PE. The primary efficacy endpoint was recurrent symptomatic venous thromboembolism. The results demonstrated noninferiority of rivaroxaban to warfarin with respect to the primary endpoint (2.1% vs 2.3% ($P<0.001$) rivaroxaban and warfarin respectively) with less major bleeding (1.0% vs 1.7% ($P=0.002$) for rivaroxaban and warfarin respectively).

TRANSFER OF CARE

This document provides information allowing patients to be managed safely by primary care, secondary care and across the interface. It assumes a partnership and an agreement between a hospital specialist, GP and the patient and also sets out responsibilities for each party. The transfer of care should be explained to the patient. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. The prescribing doctor should be appropriately supported by a system of communication and cooperation in the management of patients. The doctor who prescribes the medicine has the clinical responsibility for the drug and the consequence of its use.

Consultant/Anticoagulant team

1. Ensure that the patient/carer is an informed recipient of rivaroxaban.
2. Ensure that patients understand rivaroxaban treatment and monitoring (e.g. renal function) and follow up that is required (using advocacy if appropriate).
3. Ensure baseline investigations are satisfactory before commencing treatment. Give the patient an anticoagulant alert card and patient booklet.
4. Counsel the patient on the risks and benefits of treatment with rivaroxaban as well as importance of adherence to treatment.
5. Initiate treatment, prescribe and monitor for the first 7 weeks.
6. Send a NOAC initiation letter to the GP.
7. Clear documentation should be made as to reason for dose reduction.
8. Report any abnormal blood results to the GP where appropriate.
9. Evaluation of any reported adverse effects by GP or patient.
10. Advise GP on review, duration or discontinuation of treatment where necessary.
11. Ensure a 3 to 6 months follow up is arranged with haematologist.
12. Ensure that backup advice is available at all times.
13. Inform the patient to make a GP appointment between weeks 5-7 for further supplies.

General Practitioner

1. Reinforce the patient understands the nature, effect and potential side effects of rivaroxaban before prescribing and contact the specialist for clarification where appropriate.
2. Monitor patient's overall health and well-being.
3. Report any adverse events to the consultant, where appropriate.
4. Report any adverse events to the CSM, where appropriate.

5. Help in monitoring the progression of disease.
6. Prescribe and monitor the drug treatment as described and stop the drug at the specified time. Consider managing the drug as an acute prescription as oppose to a repeat.

Clinical Commissioning Group

1. To provide feedback to trusts via Joint Prescribing Group.
2. To support GPs to prescribe rivaroxaban safely and effectively.
3. To support trusts in resolving issues that may arise as a result of transferred care.

Patient/ Carer

1. Report any adverse effects to their GP and/or specialist.
2. Ensure they have a clear understanding of their treatment (rivaroxaban).
3. Carry an anticoagulation card with them at all times.
4. Report any changes in disease symptoms to GP and/or specialist.
5. Alert GP and/or specialist of any changes of circumstance which could affect management of disease.
6. Administer rivaroxaban as prescribed and attend hospital/GP for assessment and monitoring as required.

Costs

Drug Product	**Cost in primary care**
Rivaroxaban tablets [15mg and 20mg]	£810.60 / year*

Based on BNF February 2016

Relevant contact details	
Doctor via switchboard Registrar on-call out of hours	Dr Neil Chauhan (clinical lead for anticoagulation) via switchboard Contact on-call haematology registrar out of hours via switchboard
Clinical Nurse Specialist/pharmacist	020 8510 4413 or 020 8510 4114 or via email huh-tr.Antico@nhs.net
Trust Homerton University Hospital NHS Foundation Medicines Information	020 8510 7000 or via email mipharmacy@homerton.nhs.uk
City and Hackney Medicines Management Team	020 3816 3224

References

With thanks to Barts Health NHS Trust,

- Barts Health NHS Trust SCG adapted for local use.
- Prins HM, et al. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. *Thrombosis Journal*. September 2013; 11:21.
- Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism, July 2012, NICE technology appraisal guidance [TA261]. Available at: https://www.nice.org.uk/guidance/ta261, accessed 20/12/15.
- Summary of Product Characteristics, Xarelto 20mg film-coated tablets, Bayer plc, Date of revision of the text Jul 2015, accessed 20/12/15.

SCG template adopted from NELMMN and Barts Health NHS Trust (updated by JPG February 2015)

Amended for use at HUHFT by: N. Chauhan, R.Holland S.Hashi: 06/2016
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