NHS
Dorset
Clinical Commissioning Group

NHS DORSET CLINICAL COMMISSIONING GROUP POSITION STATEMENT ON ANTICOAGULANTS IN VENOUS THROMBOEMBOLISM AND PULMONARY EMBOLISM (TREATMENT AND PREVENTION OF RECURRANCE)

NICE Technology Appraisal (TA) 261 recommends;
'Rivaroxaban is recommended as an option for treating deep vein thrombosis and preventing recurrent deep vein thrombosis and pulmonary embolism after a diagnosis of acute deep vein thrombosis in adults.'

NICE Technology Appraisal (TA) 287 recommends;
'Rivaroxaban is recommended as an option for treating pulmonary embolism and preventing recurrent deep vein thrombosis and pulmonary embolism in adults.'

For these indications rivaroxaban is categorised as amber
The shared care guideline recommends that treatment is initiated by the specialist and that the GP will not be asked to prescribe until the patient is stabilised usually after a minimum of 21 days

N.B. Dabigatran, rivaroxaban and apixaban for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation (AF) (as covered by NICE Technology Appraisals TA249, TA256 and TA275 respectively) are outside the scope of this Guidance.

N.B. Dabigatran and rivaroxaban for the prevention of Venous Thromboembolism (VTE) after hip and knee replacement surgery in adults (as covered by NICE Technology Appraisals 157 and 170 respectively), is outside the scope of this guidance.

Existing treatment options for people with suspected deep vein thrombosis (DVT) or pulmonary embolism(PE) is with immediate parental anticoagulation, most commonly with a low molecular weight heparin (LMWH) delivered by subcutaneous injection, and when the diagnosis has been confirmed, an oral vitamin K antagonist such as warfarin. Duration of treatment is on average six months for DVT but may be longer for PE.

Cardiovascular Clinical Commissioning Programme (CCP) and Health Technologies Forum (HTF) Recommendation

Patients, who do not have active cancer, with **transient risk factors (provoked DVT)**, requiring **short term anticoagulation** i.e. 3 months treatment: **rivaroxaban** is recommended as a first line treatment option (excluding patients with an artificial heart valve).
Patients, who do not have active cancer, with **long-term/permanent risk factors or idiopathic (unprovoked) DVT or PE** and requiring **treatment for greater than 3 months**: **LMWH/warfarin** is recommended as the first line treatment option.

Rivaroxaban may be considered as a longer-term treatment option where patients are found to be unable to tolerate warfarin i.e. true allergy or significant adverse reaction or have poor INR control in the absence of any reversible cause but, only if non-compliance with warfarin treatment is excluded.
(see http://www.dorset.nhs.uk/WS-Pan-Dorset/Downloads/Shared-Content/Pan-Dorset%20Formulary/Other%20Guidelines/NOACs%20in%20AF%20final_final%20pan%20dorset%20determination.pdf for the Forum statement regarding its use in AF)

For **patients who have active cancer**, treatment with **LMWH** is recommended as the first line treatment option and is subject to the shared care guideline.
http://www.dorset.nhs.uk/WS-Pan-Dorset/Downloads/Shared-Content/Pan-Dorset%20Formulary/Shared%20Care%20Guidelines/Shared%20Care%20LMWH%20Aug%2012.pdf

Monitoring of patients treated with rivaroxaban

Monitor renal function prior to commencing treatment and after the first month's treatment (see shared care guideline for full recommendation).

Caution

Syncope and dizziness have been reported to be common adverse reactions with rivaroxaban; patients experiencing these adverse reactions should be advised not drive or use machines.

SHARED CARE GUIDELINE FOR PRESCRIBING RIVAROXABAN IN THE TREATMENT OF DVT AND PE AND PREVENTION OF RECURRENT DVT AND PE IN ADULTS.

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INDICATION

Rivaroxaban is a treatment option in the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

NICE Technology Appraisal (TA) 261 recommends;
'Rivaroxaban is recommended as an option for treating deep vein thrombosis and preventing recurrent deep vein thrombosis and pulmonary embolism after a diagnosis of acute deep vein thrombosis in adults.'
Existing treatment options include the use of low molecular weight heparin (LMWH) short term with warfarin.

NICE Technology Appraisal (TA) 287 recommends;
'Rivaroxaban is recommended as an option for treating pulmonary embolism and preventing recurrent deep vein thrombosis and pulmonary embolism in adults.'

Cardiovascular Clinical Commissioning Programme (CCP) Recommendation:

Patients who do not have active cancer:

Patients with transient risk factors (provoked DVT), requiring short term anticoagulation i.e. 3 months treatment: rivaroxaban is recommended as a first line treatment option (excluding patients with an artificial heart valve).

Patients with permanent risk factors or idiopathic (unprovoked) DVT and requiring treatment for greater than 3 months: LMWH/warfarin is recommended as the first line treatment option.

Patients unable to tolerate warfarin i.e. true allergy or significant adverse reaction: rivaroxaban is recommended as an alternative treatment option.

Patients with poor INR control and in the absence of any reversible cause, consider treatment with rivaroxaban, but, only if non-compliance with warfarin treatment is excluded. (see http://www.bp.nhs.uk/WS-Pan-Dorset/Downloads/Shared-Content/Pan-Dorset%20Formulary/Formulary/Cardiovascular%20system/Dabigatran%20and%20rivaroxaban%20in%20AF.pdf , for the Forum statement regarding its use in AF)

Patients who have active cancer:

Treatment with LMWH is recommended as the first line treatment option *and is subject to the shared care guideline*
http://www.dorset.nhs.uk/WS-Pan-Dorset/Downloads/Shared-Content/Pan-Dorset%20Formulary/Shared%20Care%20Guidelines/Shared%20Care%20LMWH%20Aug%2012.pdf
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Remit of this guideline:

Although rivaroxaban is also licensed for the prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery and for prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation, these indications fall outside of the remit of this guideline.

Traffic Light Categorisation

Rivaroxaban is categorised as amber; in the case of its use in VTE (treatment and long term secondary prevention) the CCP strongly recommends that treatment is initiated (at least first 21 days supply) in a specialist setting (which may be primary, intermediate or secondary care based) and who has experience in the management of anticoagulation.

For full prescribing information see the manufacturer's SPC at

http://www.medicines.org.uk/EMC/medicine/25592/SPC/Xarelto+15mg+film-coated+tablets/#CLINICAL_PRECAUTIONS

AREAS OF RESPONSIBILITY FOR SHARED CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of rivaroxaban can be shared between the specialist setting and the patient's GP (if different). GPs are invited to participate. If the GP is not confident to undertake these roles, then he or she is under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.

Sharing of care assumes communication. The intention to share care is usually explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

REFERRAL AND INITIATION

Specialist Responsibilities which may be primary, intermediate or secondary care based	
1	To assess the patient and establish the diagnosis, determine a management strategy and ensure appropriate follow-up in conjunction with the GP.
2	To initiate the patient on the therapy.
3	Where applicable, to send a letter to the GP requesting shared care for a particular patient. This letter will contain the following information: • Diagnosis • Name and dose of treatment • Results of d-dimer and any other applicable blood tests • Advice on dose alterations (where appropriate) • Results of any other appropriate investigations The specialist will only ask the GP to continue prescribing once the treatment has been initiated and stabilised (usually after a minimum of **21 days**). **Communication needs to be clear and correct dose stated.**
4	For patients with a first provoked pulmonary embolism with a temporary risk factor, to review the patient and their therapy at 3months. .
5	To be available for advice if the patient's condition changes, including providing contact telephone numbers for urgent matters.
6	To ensure that procedures are in place for the rapid re-referral of the patient by the GP.
7	To ensure the patient has given informed consent to their treatment.
8	To discontinue treatment if no longer thought to be beneficial at assessment at any point during treatment.

General Practitioner Responsibilities (where initiation is within a specialist setting and prescribing has been transferred	
1	Initially, to refer the patient for specialist advice.
2	To contact the referring consultant without delay if they do not wish to enter into a shared care agreement.
3	Where appropriate to continue prescriptions of rivaroxaban (usually after a minimum of 21 days) for a total of three months treatment
4	To undertake any necessary monitoring of the patient.
5	To monitor side effects of treatment and seek urgent advice from the consultant as necessary.
6	To review the patient at three monthly intervals and stop therapy after three months of treatment for a first provoked VTE or maintain longer term therapy where a patient is unable to tolerate warfarin or has poor INR control.
7	To monitor concordance with treatment.
8	To liaise with the consultant regarding any complications of treatment.
9	To check for possible drug interactions when newly prescribing or stopping concurrent medication.

Patient's role (or that of carer)	
1	Report to the specialist or GP if he or she does not have a clear understanding of the treatment.
2	Attend appropriate consultant and GP appointments.
3	Share any concerns in relation to treatment with rivaroxaban.
4	Use written and other information on the medication.
5	Seek help urgently if suffering suspected side effects, or otherwise unwell.

SUPPORTING INFORMATION

Dosage and Administration

The initial treatment of acute DVT or PE is 15 mg twice daily for the first three weeks. This is followed by 20 mg once daily for the continued treatment and prevention of recurrent DVT and PE, as indicated in the table below.

	Dosing schedule	Maximum daily dose
Day 1 - 21	15 mg twice daily	30 mg
Day 22 and onwards	20 mg once daily	20 mg

The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding.

Duration of treatment

Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT or PE.

Missed doses

If a dose is missed during 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.

Contraindications

Rivaroxaban is contraindicated in the following situations:

- Hypersensitivity to the active substance or to any of the excipients
- Clinically significant active bleeding
- Lesion or condition at significant risk of major bleeding such as:
    - 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 anticoagulant agent e.g. unfractionated heparin, low molecular weight heparins, heparin derivatives, oral anticoagulants **except** under the circumstances of switching therapy to or from rivaroxaban or when unfractionated heparin is given at doses necessary to maintain a patent 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 (see below).

Special Warnings

Women of childbearing potential / pregnancy / breastfeeding

Safety and efficacy of rivaroxaban have not been established in pregnant women. Studies in animals have shown reproductive toxicity. Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, rivaroxaban is contraindicated during pregnancy.

Women of child-bearing potential should **avoid becoming pregnant** during treatment with rivaroxaban.

Safety and efficacy of rivaroxaban have not been established in breast feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore rivaroxaban is contraindicated during breast feeding. A decision must be made whether to discontinue breast feeding or to discontinue/abstain from therapy.

Haemorrhagic risk

As with other anticoagulants, patients taking rivaroxaban are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage.

Rivaroxaban is not recommended in patients with an increased bleeding risk such as:

- congenital or acquired bleeding disorders

- uncontrolled severe arterial hypertension
- active ulcerative gastrointestinal disease
- vascular retinopathy
- bronchiectasis or history of pulmonary bleeding.

There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests.

In addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate.

Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

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 recommend**ed in patients with creatinine clearance < 15 ml/min.

Rivaroxaban should be used with caution in patients with renal impairment concomitantly receiving other medicinal products that are potent inhibitors of CYP3A4 (e.g. clarithromycin, telithromycin) as PK modelling shows increased rivaroxaban concentrations in these patients.

Hepatic impairment

Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C.

Patients with prosthetic valves

Safety and efficacy of rivaroxaban have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that rivaroxaban adequate anticoagulation in this patient population. Treatment with rivaroxaban is **not recommended** for these patients.

Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy

Rivaroxaban is **not recommended** as an alternative to unfractionated heparin in patients with pulmonary embolism who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy since the safety and efficacy of rivaroxaban have not been established in these clinical situations.

Dosing recommendations before and after invasive procedures and surgical intervention

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 after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established.

Information about excipients

Rivaroxaban contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Side Effects

Nausea, vomiting, diarrhoea, constipation, dyspepsia, abdominal pain; hypotension, oedema, tachycardia, syncope, dizziness, headache; haemorrhage, pain in extremities, pruritus, rash; ***less commonly,*** dry mouth, thrombocythaemia, malaise, renal impairment; ***rarely,*** jaundice.

Drug Interactions [Refer to BNF for further information]

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.

The concomitant use of rivaroxaban with other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort) may also lead to reduced rivaroxaban plasma concentrations. Strong CYP3A4 inducers should be co-administered with caution.

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 and platelet aggregation inhibitors. For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered.

Given the limited clinical data available with dronedarone, co-administration with rivaroxaban should be avoided.

This list is not exhaustive. The manufacturer's summary of product characteristics (SPC) and the most current edition of the British National Formulary should be consulted for full information on contra-indications, warnings, side-effects and drug interactions.

Cost (prices correct at February 2013)

- Rivaroxaban (Xarelto®) 15mg tablets x 28 = £58.80
- Rivaroxaban (Xarelto®) 20mg tablets x 28 = £58.80

References

1. Summary of Product Characteristics for Xarelto® 15mg tablets accessed via www.medicines.org.uk/EMC/medicine/25592/SPC/Xarelto+15mg+film-coated+tablets/ 06/02/2013, last updated 06/02/2013

2. Summary of Product Characteristics for Xarelto® 20mg tablets accessed via www.medicines.org.uk/EMC/medicine/25586/SPC/Xarelto+20mg+film-coated+tablets/ 06/02/2013, last updated 04/12/2012

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