

Guidelines for the use of Rivaroxaban (Xarelto®)

Information for GPs at Northamptonshire PCT

Introduction

Patients undergoing major orthopaedic surgery including total hip replacement (THR) and total knee replacement (TKR) have a particularly high risk for venous thromboembolism (VTE), with the risk extending to post discharge if thromboprophylaxis is not continued. All patients undergoing surgery must be risk assessed with the Thromboprophylaxis prescribed as appropriate.^{1, 2}

The new oral anticoagulant Rivaroxaban (Xarelto®) made by Bayer Healthcare directly inhibits factor Xa, which by interrupting the pathway of blood coagulation, inhibits the thrombin formation and development of thrombi. It is only licensed for use in THR and TKR surgery³.

All patients undergoing THR or TKR will be risk assessed before prescribing thromboprophylaxis to ensure the risk of bleeding and other contraindications are taken into account.

- Rivaroxaban is one of two new oral anticoagulants which have been recently licenced for this indication.
- Dabigatran was shown to be equivalent to enoxaparin, not superior (as rivaroxaban was).
- Rivaroxaban studies:
 - Record 1 (extended thromboprophylaxis (TP) post THR) compared = 35 days enoxaparin).
 - Record 2 (extended TP with rivaroxaban compared with 14 days enoxaparin).
 - Record 3 (14 days extended TP post TKR compared with 14 days enoxaparin).
 - Record 4 (American regimes rivaroxaban 14 days compared with enoxaparin 30 mg BD in TKR).All showed equal or superior efficacy to enoxaparin.
- Bleeding risk was more than with enoxaparin however results are very small and not significant. Incidences of major bleeding ranged from <0.1%-0.6% in the rivaroxaban group compared with <0.1%-0.5% in the enoxaparin group for Record 1, 2, 3.
- The rivaroxaban studies included older patients (up to 90 years) and a variety of bodyweights. The dabigatran studies excluded patients over 75 years, those with renal insufficiency, extremities of weight and previous VTE patients. It was felt this was not truly representative of the TKR, THR population.
- The NGH Thrombosis Committee have recommended the use of rivaroxaban predominantly for its straightforward dosing strategy (10mg od). Dabigatran has an initial dose of 110mg then further dosing at 220mg od. There are also dosing reductions for >75 years; patients on amiodarone and patients with renal failure 30-50mL/ minute.
- The use of an oral agent will improve compliance compared to subcutaneous enoxaparin for the extended TP which NICE has directed must be done.
- **Prescribing responsibility will be with Secondary Care.** No further monitoring of rivaroxaban is required post discharge (unlike enoxaparin which requires platelet monitoring).

Pharmaceutical Preparation

Light red, round tablets marked with the BAYER-cross on one side, with '10' and a triangle on the other side.

Supply Information (from NGH)

The total duration of treatment for the THR post operatively is 35 days and for TKR 14 days. If a patient is discharged before day 4 (knee) or before day 5 (hip) they will only receive one of the appropriate pack size, and that will complete the course.

Rivaroxaban will be held as stock on the elective orthopaedic ward at NGH (Abington Ward).

- On day 5 post THR, the patients will receive an over-labelled pack (TTO pre-pack) of 30 rivaroxaban 10 mg tablets.
- On day 4 post TKR, the patients will receive an over-labelled pack (TTO pre-pack) of 10 rivaroxaban 10 mg tablets.
- Patients will also be given a Xarelto® Patient Information Leaflet (PIL).

No further supplies are needed from primary care. TTOs will state not to continue on discharge.

Discharge

On discharge the patient will take home the remaining supply of Rivaroxaban to complete the full course (14 days TKR and 35 days THR).

Two pairs of graduated compression stockings will be supplied for use. No further monitoring is required.

Patients will be given the NORTH Team details to contact if they experience any problems with their anticoagulation while under their care; usually 2 weeks post-discharge. After which, they are advised to see their GP.

Prescribing of Rivaroxaban

For full prescribing information, see summary of product characteristics³
<http://emc.medicines.org.uk/document.aspx?documentId=21265>

The daily dose of rivaroxaban is 10mg once a day.

All rivaroxaban prescriptions should be written for administration post operatively at **22.00hrs**, it must be started no earlier than **6 hours after** the removal of an epidural catheter.

If the patient's operation involved a traumatic insertion or removal of epidural catheter, the first dose of rivaroxaban will be **delayed for 24 hrs** post operation.

Contra-indications

- Clinically significant active bleeding.
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
- Pregnancy and lactation.
- Hypersensitivity to the active substance or any excipients.

Patients with contra-indications to rivaroxaban will be prescribed enoxaparin (40mg od subcutaneously) unless contra-indicated.

Caution

Renal failure: If the creatinine clearance <15mL/minute do not use rivaroxaban. If the creatinine clearance 15-29mL/minute use with caution (plasma levels may be increased which may lead to an increased bleeding risk).

Hepatic impairment: In cirrhotic patients with moderate hepatic impairment, rivaroxaban plasma levels may be significantly increased which may lead to an increased bleeding risk.

Interactions

- Avoid with systemic azole-antimycotics (eg, ketoconazole) use with caution with fluconazole.
- Avoid with HIV protease inhibitors (eg, ritonavir).
- Care with concomitant use of NSAIDs, aspirin, clopidogrel.
- Use with caution with strong CYP3A4 inducers (eg, rifampicin, carbamazepine, phenytoin, St John's Wort) as it may lead to a reduced rivaroxaban plasma concentration.

No additional monitoring is required with rivaroxaban.

Reversal of Rivaroxaban

Overdose following administration of rivaroxaban may lead to haemorrhagic complications due to its pharmacodynamic properties. A specific antidote antagonising the pharmacodynamic effect of rivaroxaban is not available.

The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered.

Appropriate symptomatic treatment, eg mechanical compression, surgical interventions, fluid replacement and haemodynamic support, blood product or component transfusion should be considered.

If life-threatening bleeding cannot be controlled by the above measures, administration of recombinant factor VIIa may be considered after discontinuation of rivaroxaban and above symptomatic treatment.

Protamine sulphate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban

Patients on Aspirin, Clopidogrel or Dipyridamole

Antiplatelets are not adequate prophylaxis for VTE; additional VTE prophylaxis must be given to patients who are having antiplatelet agents to treat other conditions and who are assessed to be at increased risk of VTE. Take into account the risk of bleeding and of co-morbidities such as arterial thrombosis

In elective THR and TKR, patients are usually well and their co-morbidities managed such that antiplatelets can be stopped for surgery. If Clopidogrel is being used post-stent insertion or recent stroke/ACS it is very rare they would be considered for elective surgery.

With prolonged therapy of enoxaparin or rivaroxaban, aspirin/clopidogrel will be stopped temporarily at least until the sutures are removed. Restarting the antiplatelet can be considered after suture removal or after 14 days, provided there are no signs of bleeding into the joint or at the wound site. The withholding of antiplatelet therapy may be continued for the duration of the course of rivaroxaban at the consultant's discretion.

Patients on Warfarin

Patients on warfarin will be managed according to the NGH Bridging Guidelines (currently under review).

Patients will not be prescribed rivaroxaban if taking therapeutic warfarin or enoxaparin post-operatively.

References

1. NICE Clinical Guideline 46. Venous thromboembolism. Reducing the risk of venous thromboembolism in in-patients undergoing surgery. April 2007.
2. NICE draft Clinical Guidance. Venous thromboembolism reducing the risk: NICE guidance for Consultants. March 2009.
3. SPC Rivaroxaban Xarelto® Bayer, Sept 2008
<http://emc.medicines.org.uk/document.aspx?documentId=21265>
4. Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK et al, for the RECORD 1 study group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Eng J Med 2008; 358: 2765-75.
5. Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J et al, for the RECORD 2 investigators. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind randomised controlled trial. Lancet 2008; 372: 31-39.
6. Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ et al, for the RECORD 3 investigators. Rivaroxaban versus enoxaparin for Thromboprophylaxis after total knee arthroplasty. N Eng J Med 2008; 358: 2776-86.
7. Turpie AGG, Lassen MR, Davidson BL, Bauer KA, Gent M, Kwong LM et al, for the RECORD 4 investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty: A randomised trial. Lancet 2009; 373: 1673-80.