

Implementation of NICE TAs 261 and 287

Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism

Rivaroxaban for the treatment of pulmonary embolus and prevention of recurrent venous thromboembolism

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Letter to Primary Care following initiation of rivaroxaban for DVT or PE and secondary prevention of recurrent DVT and PE

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EMA updated Patient and Prescriber information for rivaroxaban

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Executive summary

NICE has issued a Technology appraisal for rivaroxaban (Xarelto, Bayer) for the treatment of deep vein thrombosis (DVT), and the prevention of recurrent DVT and pulmonary embolism (PE) following an episode of acute DVT in adults in July 2012. This was followed by a Technology Appraisal for rivaroxaban (Xarelto, Bayer) for the treatment of pulmonary embolism and prevention of recurrent venous thromboembolism (VTE) in adults in June 2013. This guidance has been produced to help identify those patients who are most likely to benefit from rivaroxaban and to provide advice on using this drug in the safest possible manner. The guidance does not and should not over-ride the NICE TAs. A clinician may choose to initiate rivaroxaban for a patient within the Technology Appraisals criteria if clinically appropriate.

Rivaroxaban is a direct inhibitor of factor Xa and is orally active. Currently most patients in the UK are anticoagulated with low molecular weight heparin (LMWH) whilst the diagnosis of DVT is established and then proceed to full anticoagulation with warfarin. However a number of patients are unsuitable for warfarin due to perceived poor control or concerns regarding bleeding and will continue on LMWH. As rivaroxaban is orally active and does not require regular monitoring of blood levels it has potential advantages over both LMWH and warfarin but other factors need to be taken into consideration when deciding whether it is appropriate for an individual patient.

These factors include:

- Unknown long term safety profile of rivaroxaban
- Lack of a specific antidote for the reversal of rivaroxaban
- Expected duration of anticoagulation
- Renal impairment
- Clinically significant liver disease
- Bleeding risk
- Drug interactions
- Compliance
- Consideration of the patient's current INR control on warfarin

This guidance is provided both for patients newly diagnosed with either DVT or PE and for existing patients currently taking warfarin for treatment and long term prevention of VTE.

In Northamptonshire it is recommended that rivaroxaban should be initiated only by a secondary care consultant Haematologist with the support of their anticoagulant clinics. Prescribing can then be passed to the GP with shared care advice. This pathway for initiation will be reviewed once experience with rivaroxaban becomes more established.

Warfarin remains a suitable first line oral anticoagulant for most patients.

Introduction

Rivaroxaban is recommended as an option for treating deep vein thrombosis or pulmonary embolus and preventing recurrent venous thromboembolism in adults with a previous history of DVT or PE.

The decision about whether to start treatment with rivaroxaban should be made after an informed discussion between the clinician and the patient about the risks and benefits of rivaroxaban compared with enoxaparin and warfarin, which is currently the standard of care. For people who are currently taking warfarin, the risk benefit assessment should include a review of their time in therapeutic range (TTR).

Rivaroxaban

Rivaroxaban is an oral direct factor Xa inhibitor administered as a fixed dose that does not require laboratory monitoring and unlike warfarin has no known food and few drug interactions.

Evidence for the use of rivaroxaban in the treatment of DVT and long-term prevention of VTE after DVT

EINSTEIN-DVT was an open-label non-inferiority study that compared rivaroxaban (15mg twice daily for 3 weeks, then 20mg once daily for 3,6 or 12 months) with enoxaparin followed by a vitamin K antagonist (either warfarin or acenocoumarol) for treating patients with acute symptomatic DVT without any symptoms of pulmonary embolism, and for preventing recurrent DVT and PE. The primary efficacy outcome was defined as the cumulative incidence of symptomatic recurrent DVT and non-fatal or fatal PE in patients with acute symptomatic DVT. The primary safety outcome was a composite of major bleeding or clinically relevant non-major bleeding.

The study found that recurrent venous thromboembolism (VTE) occurred in 2.1% of patients in the rivaroxaban group compared with 3.0% in the enoxaparin and vitamin K antagonist group (HR 0.68; 95% CI 0.44 to 1.04, $p < 0.001$ for non-inferiority and $p = 0.076$ for superiority).

Rivaroxaban also demonstrated similar results compared to the standard of care for the principal safety outcome measuring a composite of major and non-major clinically relevant bleeding events. Clinically relevant non-major bleeding occurred in 8.1% of patients in both groups and the rates of major bleeding were also similar in both groups.

The EINSTEIN-EXT study looked at the efficacy and safety of using rivaroxaban (at a dose of 20mg/day) for continued prophylaxis after an initial treatment phase of 6-12 months. The extension study was a randomised, double blind, superiority trial. The primary efficacy outcome was recurrent VTE and primary safety outcome was major bleeding. For the primary efficacy analysis, the incidence of recurrent VTE and related mortality was 1.3% for the rivaroxaban group and 7.1% for the placebo group (HR 0.18; 95% CI 0.09 to 0.39, $p < 0.0001$). The numbers of clinically relevant non-major bleeding events were statistically significantly higher in the rivaroxaban arm than in the placebo arm. There were also more major bleeding events in patients taking rivaroxaban although this did not reach statistical significance.

Rivaroxaban has thus been shown to be as effective as standard therapy, with a similar safety profile for the treatment of acute DVT and when treatment is continued,

rivaroxaban is effective in preventing recurrences, as compared with placebo and has an acceptable risk of bleeding.

Evidence for the use of rivaroxaban in the treatment of PE and long-term prevention of VTE after PE

Einstein-PE was an event driven, open label, assessor blind, non-inferiority study that compared rivaroxaban (15mg twice daily for 21 days followed by 20mg once daily for 3, 6 or 12 months) with standard therapy i.e. therapeutic enoxaparin followed by a vitamin K antagonist (either warfarin or acenocoumarol at a target INR of 2.5 for 3, 6 or 12 months) for treatment of acute symptomatic pulmonary embolism with or without deep-vein thrombosis.

The primary efficacy outcome was symptomatic recurrent venous thromboembolism. The principal safety outcome was a composite of major or clinically relevant non major bleeding.

The study found that Rivaroxaban was non-inferior to standard therapy for the primary efficacy outcome, with 50 recurrent VTE events in the rivaroxaban group (2.1%) versus 44 recurrent VTE events in the standard-therapy group (1.8%) (HR 1.12; 95 CI 0.75 to 1.68). The average 'Time in Therapeutic Range' in the standard treatment group was reported as 62.7%.

The principal safety outcome occurred in 10.3% of patients in the rivaroxaban group and 11.4% of those in the standard-therapy group (HR, 0.90; 95% CI, 0.76 to 1.07; P=0.23). Major bleeding was observed in 26 patients (1.1%) in the rivaroxaban group and 52 patients (2.2%) in the standard-therapy group (hazard ratio, 0.49; 95% CI, 0.31 to 0.79; P=0.003).

Rivaroxaban has therefore been shown to be non-inferior to standard therapy for the treatment of pulmonary embolus and has similar rates of non-major bleeding and reduced rates of major bleeding compared to standard therapy.

There are a number of issues raised by these studies which need to be considered when putting the results in the context of normal clinical practice. These relate to the level of anticoagulant control in the standard of care groups, the exclusion of clinically relevant patient groups (creatinine clearance (CrCl) of <30ml/min, clinically significant liver disease, high blood pressure (sBP > 180 mmHg, dBP > 110 mmHg), haemodynamically unstable PE, non-proximal DVT and active bleeding/high risk of bleeding), the long term safety and tolerability of rivaroxaban and the use of placebo instead of warfarin in the EINSTEIN-EXT study. In EINSTEIN – PE patients were excluded if thrombectomy had been performed, a vena cava filter placed, or a fibrinolytic agent administered for treatment of the episode.

Guidance aims and use of Rivaroxaban

This guidance has been produced to help identify those patients who are most likely to benefit from rivaroxaban and to provide advice on its use in the safest possible manner. The guideline covers both newly diagnosed patients and existing patients currently taking warfarin.

The guidance does not and should not over-ride the NICE TAs

The guidance is based on the NICE TAs 261 and 287 but also takes into account the needs of the local population and advice and opinions of local clinicians.

Additional guidance is offered in order to take into account some of the following issues-

1. In EINSTEIN-DVT, rivaroxaban as a single agent replaces both low-molecular weight heparin (LMWH) and a vitamin K antagonist in the treatment of DVT. A great majority of patients in the rivaroxaban group either did not receive LMWH or only received a single dose. Despite this, efficacy during the first weeks of treatment was similar in the two study groups. A prespecified indicator of net clinical benefit (symptomatic recurrent VTE plus major bleeding) favoured rivaroxaban.
2. The summary of product characteristics for rivaroxaban states that 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.
3. The purpose of the EINSTEIN-EXT study was to explore the benefit to risk ratio when rivaroxaban is administered after 6 to 12 months of initial anticoagulation. At this time point, clinicians must often balance the long term risks of recurrent VTE if anticoagulation is stopped, against the burden and risks of on-going therapy. Rivaroxaban reduced the rate of recurrence by 82% (from 7.1% to 1.3% clinical events), regardless of the type of index event, with a small risk of major haemorrhage. (0.7% with no fatal haemorrhages). Thus 34 recurrent events were prevented at the cost of 4 major bleeding events. However, the incidence of non-major bleeding was increased from 1.2% in the placebo group to 5.3% with rivaroxaban. These bleeding events were predominantly mucosal and 81% of patients resumed or continued the study therapy. Overall this suggests an acceptable benefit to risk profile.
4. The INR was within the therapeutic range for 58% - 62.7% of time. Although this seems low, this is similar to the results of other recent thrombosis studies. The average TTR at Northampton General Hospital is 71% and at Kettering General Hospital is 68%.
5. The EINSTEIN-DVT reported a mixed treatment comparison for the subgroup of patients with cancer. This compared the relative effectiveness of rivaroxaban with dual LMWH and vitamin K antagonist, long term LMWH compared with LMWH and a vitamin K antagonist and rivaroxaban compared with long term LMWH. Results from the primary analysis indicate that for patients with active cancer, the VTE recurrence hazard ratio was 1.44 (95% CI 0.07 to 31.4). Secondary analysis showed that rivaroxaban was less effective than LMWH at preventing VTE recurrence but induced fewer major bleeding events, OR 0.24, (95% CI 0.00-9.44). In EINSTEIN-PE rivaroxaban was only compared to VKA treatment for this sub-group of patients. There is no data comparing rivaroxaban to LMWH in patients with cancer and as such NICE made no recommendations for treatment of this patient group.
6. Adverse events requiring discontinuation of treatment in EINSTEIN-DVT and EINSTEIN-EXT were experienced in 4% of either treatment group. The most common adverse events were headache, pain in the extremities, nasopharyngitis and nosebleed. The reported incidences of post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension were low in

both arms of EINSTEIN-DVT and EINSTEIN-EXT. Adverse event rates (including the need to discontinue treatment) were similar in EINSTEIN-PE.

7. The best method for reversing rivaroxaban is not known. Management of bleeding should be through cessation of treatment and general haemostatic measures. Studies in human volunteers have shown that prothrombin complex concentrate (PCC) can reverse the laboratory abnormalities caused by rivaroxaban. Rivaroxaban is associated with a non-linear relationship between prolongation of routine coagulation tests (APTT, PT) and bleeding tendency and drug levels. It remains uncertain whether PCC, activated PCC or recombinant factor VIIa (rfVIIa) are clinically effective methods of reversing this drug.
8. For rivaroxaban, the high degree of albumin binding in plasma means that it is not dialysable. All the measurable (laboratory) anticoagulant effects are reversed by PCC (Octaplex/Beriplex). Clinical data is lacking but it seems reasonable to give a dose of 25 IU/Kg of PCC in case of acute bleeding. PCC may work in this setting by provision of additional factor II, VII, and IX and X and thus the Xa inhibitor (rivaroxaban) is overcome.
9. There are currently no tests to definitively assess the level of anticoagulation, though anti factor Xa assays can provide some indication.
10. Rivaroxaban is partially cleared through the kidneys (33%). Decreased renal function increases plasma levels of rivaroxaban and should be used with caution in patients with CrCl 15-29ml/min. The dose should be reduced to 15mg daily if the CrCl is between 15-49mls/min and rivaroxaban should not be used if the CrCl is less than 15mls/min.
11. Long term safety and tolerability of rivaroxaban is not yet known.
12. The effects of non-compliance with rivaroxaban are likely to be significant because of the drug's short half-life compared to warfarin.

Selection of appropriate patients:

For patients newly diagnosed with DVT or haemodynamically stable PE and for existing patients currently taking vitamin K antagonists for treatment and long term prevention of VTE: Warfarin remains a suitable first-line oral anticoagulant for most patients.

Warfarin should be the preferred option in patients:

1. With CrCl / eGFR < 30 mls/min (Decreased renal function increases plasma levels of rivaroxaban and this may lead to an increased bleeding risk).
2. With a history of significant peptic ulcer disease.
3. In patients with prosthetic heart valves
4. In patients who also have valvular atrial fibrillation
5. Patients who have exemplary control of anticoagulation (TTR > 60%) with warfarin.

Enoxaparin should be the preferred option in patients:

1. Who have active cancer and suffered a VTE
2. Who are pregnant or of child bearing potential trying to become pregnant

Rivaroxaban may be the preferred option in patients:

1. Predicted to have variable interacting medications e.g. recurrent need for antibiotics
2. With known excess use of ethanol
3. Who would require domiciliary testing
4. Who are intolerant / allergic to VKAs
5. Who are intravenous drug users
6. With TTR < 60%
7. With distal DVTs (though not included in the EINSTEIN-DVT study)
8. Who have had provoked DVT or PE with transient risk factors and as such only require short term anticoagulation for 3-6 months
9. Who are on long term treatment with enoxaparin

In all other patients, warfarin is recommended as a first line treatment following discussion with patient explaining:

1. Lack of long term data on the safety of rivaroxaban
2. Issues concerning reversibility
3. NICE guidance and evidence base
4. Principles used in patient selection
5. Patients could be converted to rivaroxaban if there is an on-going need for anticoagulation and the TTR < 60% after 4 months (in the presence of compliance).

Pathway for initiation

GP or referring clinician to check

1. FBC, U&E, LFT and clotting screen (CS)
2. Refer to haematologist for assessment and decision whether rivaroxaban is suitable treatment.

If the patient is a suitable candidate for rivaroxaban (selection criteria above), the anticoagulant department will:

1. Deliver induction counselling
2. Supply initial 4 week prescription (15 mg twice daily for 3 weeks followed by either 20 mg or 15 mg once daily - depending on renal function)
3. Enter patient details on acute trust database
4. Refer back to primary care for on-going prescriptions and monitoring

Content of Induction Counselling

1. Effect of drug
2. Risks and benefits of drug
3. Risk / benefit of rivaroxaban vs. warfarin
4. Management of overdose and bleeding including the lack of a clinically proven antidote
5. Importance of compliance / taking and storage of medication
6. Notification of Health professionals / issue of alert card
7. Management of procedures
8. Information leaflet including list of known drug interactions and advice regarding platelet antagonists

Patient should seek urgent medical attention if they fall or injure themselves while on treatment, especially if they hit their head, as there is an increased risk of bleeding

Patients currently taking vitamin K antagonists

Anticoagulant department to screen database of existing patients for all patients:

1. Who currently require domiciliary INR testing
2. With TTR < 60%
3. With a history of major bleeding while on warfarin

These patients will then either be discussed with a haematology consultant/registrar or seen in the haematology clinic to determine whether treatment with rivaroxaban is appropriate.

If treatment is deemed appropriate the patient will then be seen in nurse led anticoagulant clinic to:

1. Establish compliance
2. Check FBC/U&E/LFT/CS
3. Explain the rationale for conversion
4. Counsel regarding rivaroxaban treatment
5. Manage conversion
 - a. Stop warfarin
 - b. Supply 4 weeks of rivaroxaban (20 mg or 15 mg once/day – depending on renal function)
 - c. Start rivaroxaban once $INR < 2.5$. It is recommended to repeat an INR in case of an INR exceeding 2.5 before initiating rivaroxaban with instructions to be written in Warfarin book.
6. Send the shared care letter to the GP explaining the outcome of above and recommendations concerning further monitoring.

Shared care Guidance

Information letter to be supplied to GP

Recommended monitoring

1. Renal function and LFTs to be checked monthly for first 3 months then every 3 months
2. Annual clinical review to assess risk/benefit, screening for any contraindication to on-going treatment
3. Referral to consultant Haematologist if advice is required regarding duration of anticoagulation or temporary discontinuation / restarting of rivaroxaban to cover upcoming surgical procedures

Patient identification sticker

Appendix 1

Letter to Primary Care following initiation of rivaroxaban for DVT or PE and secondary prevention of recurrent DVT and PE

Dear Dr. _____ Date _____

Your patient has today been started on rivaroxaban for treatment of DVT or PE and to prevent recurrent DVT or PE. (If your patient was previously taking either warfarin or LMWH it will have been stopped).

The decision to start rivaroxaban has been made on the basis of:

1. Predicted high risk on warfarin (polypharmacy, excess ethanol, high bleeding risk score, serious adverse reaction to warfarin or intolerance, IV drug user, long term LMWH or requirement for domiciliary testing of INR)
2. Previous poor INR control on warfarin
 - a. Time in treatment range < 60%
 - b. History of significant bleeding on warfarin
3. Predicted short duration of anticoagulation treatment

HASBLED _____ GFR _____

Your patient has been prescribed:

- Rivaroxaban 20 mg once/day for _____ duration
- Rivaroxaban 15 mg once/day for _____ duration

Treatment with rivaroxaban should be either

- discontinued on _____
- or continued long-term

Your patient

1. Has been counselled about the safe use of rivaroxaban
2. Supplied with the attached information leaflet
3. Supplied with an alert card

The following monitoring is recommended for patients on rivaroxaban

1. Base line FBC, renal function, LFTs and clotting
2. Renal function and LFTs to be checked monthly for first 3 months then every 3 months

Annual review

1. History of bleeding in the last year
2. Screen for any contraindication to on-going treatment
3. Recheck eGFR and if eGFR between 15-49ml/min, reduce rivaroxaban dose to 15 mg/day or refer for specialist assessment.

RIVAROXABAN KEY POINTS

Please also refer to the SPC

It does not require INR monitoring

If CrCl < 15mls/min rivaroxaban must not be initiated and if already initiated, must be stopped. Rivaroxaban should be used with caution if the CrCl is between 15-29mls/min. If CrCl between 15-49ml/min, reduce rivaroxaban dose to 15 mg/day

In patients with hepatic disease associated with coagulopathy and clinically significant bleeding risk, including cirrhotic patients, rivaroxaban should not be prescribed.

Rivaroxaban has a t_{1/2} of 5-9 hours in young patients and 11-13 hours in elderly patients, so compliance is crucial.

In the event of surgery or procedures, rivaroxaban should be stopped 24 hours prior to the intervention. If additional advice is required please refer to haematology

Rivaroxaban interacts with the following drugs:

- **Azole antifungals: ketoconazole, voriconazole, itraconazole, posaconazole**
- **HIV protease inhibitors**
- **Rifampicin**
- **Phenytoin, carbamazepine, phenobarbital**
- **St. John's Wort**
- **Dronedarone**

Care should be taken if concomitant anti-platelet agents, concomitant anti-thrombotics are contra-indicated

Rivaroxaban causes an increase principally in PT, but this is not a measure of degree of anticoagulation

There is no specific antidote for rivaroxaban. Management of bleeding should be through cessation of treatment and general haemostatic measures

In situations with on-going life-threatening bleeding, PCC, APCC and rfVIIa should be considered

Please notify the anticoagulation department if

- **stopping rivaroxaban so that our database can be updated and**
- **of any adverse drug reactions so that incidents and themes can be investigated as required**

For further information or advice, please contact the NGH anticoagulant service on 01604 525707 or the KGH anticoagulant service on 01536 492000 bleep 541