NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

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

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: DR ROOPEN ARYA

Name of your organisation KING'S THROMBOSIS CENTRE, KING'S COLLEGE HOSPITAL NHS FOUNDATION TRUST

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? √
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? √
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

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

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

DVT is usually treated in outpatient or inpatient settings, with considerable geographical variation in the configuration of care and follow-up. The standard treatment of DVT involves treatment initiation with low molecular weight heparin (LMWH) and vitamin K antagonists (VKA). Patients receive at least 5 days of LMWH and are subsequently on VKA alone for at least 3 months duration. The majority of patients are treated at home from the outset and encouraged to be ambulant. In addition to anticoagulant therapy, graduated compression stockings are recommended to help prevent post-thrombotic syndrome (PTS).

Areas of differences of opinion between professionals with regard to current practice include:

1. Optimal management of below-knee DVT
2. Determining appropriate duration of treatment for proximal DVT depending on the clinical presentation , risk factors and laboratory testing.
3. Role of systemic thrombolysis and catheter-directed thrombolysis in treatment of proximal DVT.

The current alternatives to rivaroxaban are the parenteral anticoagulants unfractionated heparin (now rarely used), LMWH and fondaparinux and the oral VKA. The parenteral anticoagulants are usually employed in a bridging role until the VKA are within therapeutic range.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

The subgroups of patients with DVT with might have a different prognosis include:

1. Those with cancer-related DVT who are conventionally treated with LMWH alone. LMWH is preferred to VKA for reasons of efficacy and safety in this population. The role of rivaroxaban in management of such patients remains to be determined, since the number of patients with cancer in the trials were small and there was not a head to head comparison with the standard therapy LMWH.
2. Patients with ilio-femoral DVT have a higher incidence of post-thrombotic syndrome (PTS). Current standard of care remains medical therapy but

debate remains around the possible role of thrombolysis, whether systemic or catheter- directed, in such patients.
3. There is insufficient evidence comparing the natural history of upper extremity DVT to leg vein DVT and uncertainty regarding the optimal therapy particularly in those with catheter-related upper extremity DVT who have had the catheter removed.
4. Patients at high risk of recurrence such as those with antiphospholipid syndrome or combined genetic thrombophilic defects. Unable to comment on role of rivaroxaban in these patients due to a lack of data.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?
Initially, rivaroxaban would be likely to be initiated in secondary care, whether in specialist DVT Clinics, emergency departments or in inpatients. In primary care there are currently a small number of practices that diagnose and treat DVT. The ease of treatment with rivaroxaban might facilitate growth of primary care DVT management. Continued prescription of the drug is likely to be in primary care.

There would be requirements for additional professional input whether it is around monitoring adherence and patient safety, aftercare for thrombophilia testing or post-thrombotic syndrome, and deciding about the appropriate duration of anticoagulation therapy. This might involve a multi-disciplinary approach including specialist physicians, nurses and pharmacists and orthotic practitioners. Care of DVT has progressed from a formulaic provision of 3 or 6 months of VKAs to a more individualised approach tailoring investigations, choice and duration of anticoagulant as well as appropriate aftercare, to the individual's clinical scenario and ongoing needs.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?
Rivaroxaban is currently being used primarily in the orthopaedic setting for extended thromboprophylaxis after hip and knee arthroplasties. In the real-world setting there has been some variation in usage with some using rivaroxaban as a single agent started post-operatively as indicated in the licence and other electing to initiate prophylaxis with LMWH as per their previous practice and discharging the patients with the oral agent for extended prophylaxis.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.
Current UK clinical guidelines on treatment of DVT do not include rivaroxaban.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

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

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

The advantages of rivaroxaban in this setting are that it provides a single agent approach to treatment, has an oral route of administration in a fixed dose, no dietary and few drug interactions, and no requirement for routine monitoring. These advantages suggest it should be easier to use and more convenient for patients and also ensure the patients, if compliant, are consistently therapeutic for the period of anticoagulation.

Rivaroxaban will make it less burdensome for patients to be anticoagulated and would facilitate reconfiguration of the DVT pathway. Currently, once the diagnosis of DVT is made, the emphasis during the early follow-up visits is on ensuring the patient is adequately anticoagulated and the INR is therapeutic. The DVT Clinic has many functions, including :

1. Investigating the aetiology of the DVT, whether it is screening for cancer at presentation or testing for thrombophilia after completion of treatment.
2. Ensuring patient adherence and addressing patients' concerns about safety and response to therapy.
3. Deciding on duration of therapy which is tailored to the individual's requirement.This requires consideration of whether the DVT was provoked or unprovoked and might also incorporate the results of laboratory testing.
4. Aftercare of patients including detection, prevention and treatment of post-thrombotic syndrome.

These functions will need to be retained in DVT Clinics and it is possible that a more convenient anticoagulation process may release time and resource for the holistic care of the patient.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

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

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The conventional efficacy and safety outcomes of recurrent VTE, major bleeding and all-cause mortality were measured in these trials. In common with other similar anticoagulation trials, the trial design and duration is not designed to adequately predict and detect longterm outcomes such as PTS.
The clinical trials do generally reflect current UK practice except the time in therapeutic range at 58% was lower than many UK anticoagulation clinics; this in part probably reflects the initiation phase INRs which will all be subtherapeutic.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The main adverse effect of concern is bleeding – the relative significance of this is that rivaroxaban does not have an antidote and since it will not be routinely monitored, there might be a lack of knowledge and experience regarding monitoring and management if a patient were to present with bleeding.

Use of rivaroxaban in the orthopaedic setting has not revealed any unexpected adverse effects.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

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

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

None

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

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

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Implementation of rivaroxaban as a single agent treatment for DVT would make it easier to anticoagulate patients as it is oral, given as a fixed dose and does not require monitoring. It could be introduced into current treatment settings, whether in the DVT or anticoagulation clinic, emergency department or hospital ward. NHS staff would require education about rivaroxaban.
No additional resources would routinely be required. Users would need to establish a protocol for the use of rivaroxaban for treatment of VTE, including a section on the management of bleeding associated with rivaroxaban. Coagulation laboratories might wish to establish tests for monitoring rivaroxaban in high risk situations.

Equality

Are there any issues that require special attention in light of the NICE's duties to have due regard to the need to eliminate unlawful discrimination and promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others?

None