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:

Name of your organisation: UK Clinical Pharmacy Association (UKCPA)

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)

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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?

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?

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)?

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?

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 Treatments for VTE:

Treatment of Venous Thromboembolism (VTE) is usually initiated with anticoagulant drugs such as Unfractionated Heparin (UFH) or Low Molecular Weight Heparin (LMWH) (enoxaparin, bemiparin, dalteparin or tinzaparin). Treatment is continued orally with the vitamin K antagonist warfarin or, rarely, with either acenocoumarol or phenindione. For people in whom vitamin K antagonists are not considered appropriate, UFH or LMWH may be continued instead.

This appears to be standard practice for the management of VTE throughout the UK with little or negligible geographical variation.

Warfarin:

Warfarin has always been the mainstay of treatment for VTE. It is administered via the oral route and is inexpensive. However, due to its unpredictable pharmacokinetics and variation in patient response there is often difficulty with achieving stable therapeutic levels therefore its low acquisition cost is often offset by the long-term monitoring costs associated with its use. Warfarin is associated with numerous drug and food interactions. It is often not suitable for use in cancer patients on chemotherapy due to a difficulty in achieving therapeutic levels. It is also unsuitable in pregnant women.

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LMWHs:
LMWHs are favoured due to their predictable anticoagulant effect. There is ~~no~~ little need for routine anticoagulant monitoring, they are safe in pregnancy and present few significant drug interactions. However, they can be associated with Heparin Induced Thrombocytopenia (HIT) and the need for administration via the subcutaneous route makes them less appealing to patients. District nurse referral and individual patient training to facilitate self-administration pose a significant cost and time pressure within secondary care organisations.

Commentary on trials:
1. EINSTEIN–DVT (Acute) Study:
- Rivaroxaban demonstrated non-inferiority compared to enoxaparin/oral vitamin K antagonist for the prevention of recurrent VTE in patients with acute symptomatic Deep Vein Thrombosis (DVT)
- The principal safety outcome (a composite of major and non-major clinically relevant bleeding events) occurred in 8.1% of patients in both treatment groups and there was no sign of serious liver injury in either group
-Discontinuation rates related to adverse events were low and similar in both treatment groups
-It should, however, be noted that that dose of enoxaparin (1mg/kg twice daily) used in this study reflects the US dose, which differs from that used in the UK. Whether there are any significant implications of this are uncertain.

2. EINSTEIN-Extension Study:
-Rivaroxaban was shown to be an effective anticoagulant for the long-term secondary prevention of VTE in moderate to high-risk patients, without safety concerns in terms of non-bleeding adverse events
-With regard to bleeding complications, it should be noted that major bleeding events were uncommon, although, as expected the composite of major bleeding and clinically relevant non-major bleeding was significantly higher than in the placebo group
- Since international guidelines on the treatment of VTE (ACCP 2008) now recommend that a substantial proportion of patients with VTE should receive indefinite treatment with a VKA, the EINSTEIN-Extension Study may contribute to improving long-term secondary prevention strategies.

Setting & additional professional input:
This technology would be used predominantly in a secondary care setting where VTE is predominantly diagnosed. However, ongoing long-term management and ongoing supply would take place in a primary care setting.

It is essential that the implications of introducing rivaroxaban for the treatment of VTE is considered across the whole patient pathway and therefore must ensure the involvement of both primary and secondary care stakeholders in the decision-making process.

Even though rivaroxaban does not require routine monitoring of coagulation parameters it will be essential that periodic clinical visits are provided to ensure measurement of alternative blood tests in case of signs and symptoms of recurrence, bleeding or other clinical problems. This could take place in a primary or secondary setting and may require specialist nursing input.

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Clinical Guidelines:

Currently there are no clinical guidelines relating to the use of rivaroxaban for this indication stated in the technology.

Patient Groups:

Due to the cost implications of initiating rivaroxaban therapy in the entire VTE population, we believe that this technology will be most beneficial in the following groups of patients:

1. Those unable to take warfarin due to allergy or side effects/intolerances
2. Those unable to adhere to the monitoring requirements associated with warfarin therapy i.e elderly patients, patients with learning difficulties or disabilities
3. Those unable to achieve an INR within the target therapeutic range for a satisfactory period of time after a suitable trial of warfarin

Subgroups of Patients:

1. Cancer Patients

In cancer patients on chemotherapy LMWHs have been found to cause fewer adverse events when compared with warfarin. In addition, achieving therapeutic INR is difficult in cancer patients due to their increased risk of drug interactions, malnutrition, vomiting, and liver dysfunction. In contrast, LMWHs are associated with a lower risk of adverse events compared with warfarin in patients with cancer. These agents also offer practical advantages including more predictable anticoagulation. Several LMWHs have also demonstrated superior efficacy to warfarin in the secondary prevention of VTE.

As rivaroxaban is not licensed for the treatment of VTE in cancer patients this patient group may not be suitable for inclusion in this technology.

2. Patients with Inherited Thrombophilias:

Evidence shows that the risk of recurrence after a first episode of VTE is slightly increased in patients with inherited thrombophilias. Traditionally anticoagulant management in this group of patients has been challenging due to unpredictability with INR monitoring.

There is no need for routine monitoring of coagulation parameters with rivaroxaban therefore it may be a useful alternative in this group of patients. However, the trials included in this technology appraisal did not include patients with inherited or acquired thrombophilias. Hence, the use of rivaroxaban in this population would be outside its product licence.

3. Patients with Mechanical Heart Valves:

Warfarin will remain the mainstay of treatment for patients with mechanical heart valves since studies using rivaroxaban in this population have not been carried out.

4. Use in Pregnancy:

Rivaroxaban is contra-indicated in pregnancy hence is not a treatment option in this high-risk patient group.

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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?

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.

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?

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?

Advantages of rivaroxaban over traditional anticoagulants:

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-Effective anticoagulant for the treatment and long-term secondary prevention of VTE in moderate to high-risk patients with minimal safety concerns in terms of non-bleeding adverse events
-Single, fixed, daily oral dose with a rapid onset of action
-Applies to all patients irrespective of body weight or age
-More convenient for the patient
-Predictable therapeutic effect
-No requirement for routine laboratory testing
-Eliminates the need for two anticoagulant regimens (i.e. heparin and warfarin)
-No need for anticoagulant bridging for invasive procedures
-Limited or no food or drug interactions

Disadvantages of rivaroxaban over traditional anticoagulants:
-Due to lack of routine coagulation monitoring doses cannot be titrated
-Short half-life: anticoagulant effect declines quickly if compliance is poor
-Unable to determine a failure of therapy versus poor compliance
-No monitoring laboratory marker available to measure drug activity if needed
-Cost. Unless the cost is low this drug may be reserved for specific patient groups as those detailed above
-No specific antidote for direct reversal of rivaroxaban (although due to its short half life the clinical implications for this are unclear)

Important Considerations:
-Currently, when a diagnosis of VTE has been confirmed patients are initiated on treatment with LMWHs followed by a warfarin loading regimen. Patients are often held in an inpatient setting until their INR reaches a therapeutic level. Rivaroxaban does not have specific loading requirements. Patients are initiated on a standard once daily dose and can be discharged from an inpatient setting immediately. This may have a positive impact on inpatient length of stay (LOS).

-Reported sub-analyses, which are based on a limited number of patients, suggested that rivaroxaban does not require dose adjustments according to age, sex, weight or renal function. However, more information is needed on its efficacy to safety profile in special populations, such as patients with cancer, elderly patients, renally impaired patients and morbidly obese patients.

-Factor Xa inhibitors have shorter half-lives than warfarin. This may result in less protection if doses are missed. Generally, trials of these agents have not included older patients, patients at high risk of bleeding, those with complex medical illnesses or on concomitant antiplatelet treatments. Therefore, experience using the newer oral anticoagulant agents in clinical practice may be different from the trial setting.

-Along with the risk of recurrent DVT, bleeding risk also needs to be carefully considered for every patient when administering any anticoagulant drug, including rivaroxaban, for long-term treatment.

-When patients treated with conventional anticoagulants exhibit haemorrhagic complications there is a defined and evidence-based strategy for the reversal of their anticoagulant activity. Rivaroxaban lacks a specific antedote. Also, treatment of haemorrhagic complications caused by the novel agents is more complicated, due to the fact that there is no simple and effective way to monitor their activity. As a result there is little clarity on the appropriate management of

major bleeding events and on the management of patients requiring urgent invasive procedures.

-Before concluding that the new oral anticoagulants are appropriate for life-long therapy for most patients thanks to their practical advantages, additional data are necessary, in particular with regard to long-term safety and, last, but certainly not least, cost-related issues.

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.

SIMS Project:
The SIMS-anticoagulation project, was a multi-site observational evaluation of inpatient satisfaction with information about anticoagulation medicines (warfarin, rivaroxaban, dabigatran and LMWH) designed by the Kings College London research group. Although as yet unpublished, preliminary data analysis indicates that patients were less satisfied with information they were given about rivaroxaban and dabigatran compared with warfarin. This may be a consequence of a less structured/detailed approach to counselling for the newer oral anticoagulants compared to warfarin. These preliminary results are highly relevant as it is acknowledged that low patient satisfaction with information about medicines is linked to poor adherence. As such, supporting patients' adherence is likely to be a key issue for rivaroxaban and the other newer oral anticoagulants that do not require routine anticoagulation monitoring.

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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.

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)?

Reduced requirement for LMWH bridging and routine anticoagulation clinic appointments:
Currently patients are initiated on warfarin coupled with LMWH for at least five days and until the INR is therapeutic for at least 24 hours, whichever is longer. Administration of LMWH outside of the inpatient setting may require patient/carer training on administration or sometimes requires utilisation of district nurses to support administration. In addition, warfarin therapy requires INR monitoring generally in an anticoagulation clinic. At the start of warfarin therapy frequent monitoring may be required to ensure the patient is not under- or over-anticoagulated, maintaining a therapeutic INR may be complicated by the narrow therapeutic window and wide range of food and drug interactions of warfarin. Rivaroxaban alleviates the

need for concomitant use of LMWH as unlike warfarin, it has a rapid onset of action. In addition, the predictable pharmacokinetics of rivaroxaban mean that routine anticoagulation monitoring is not required.

Potential changes to patient counselling
Due to the high profile of the risks associated with warfarin therapy, patients on warfarin receive comprehensive counselling (verbal and written information) on the rationale and associated risks and benefits of treatment. In addition, for many patients regular monitoring appointments within anticoagulation clinics create frequent opportunities to reinforce counselling messages. The introduction of rivaroxaban which does not require monitoring may reduce the comprehensiveness of counselling and frequency of contact between the anticoagulated patient and healthcare professional this could adversely affect patients' understanding of the rationale, risks and benefits of treatment, resulting in reduced adherence.

Currently all pharmaceutical companies involved in the production and marketing of any new oral anticoagulants are required to produce an anticoagulation alert card. Presently the colour and content of these cards are different depending on the agent being used. It may be beneficial for a standard anticoagulation card to be used for all oral anticoagulants similar to the yellow oral anticoagulant alert card issued by the NPSA.

Simplified discharge arrangements
In some areas, newly initiated warfarin inpatients may have their discharge delayed until their INR is stabilised or until a clinic appointment in a suitable anticoagulation clinic is confirmed. The lack of a requirement for LMWH and anticoagulation clinic appointment should simplify the transfer of care / patient pathway for patients on rivaroxaban.

Changes to management of over-anticoagulation / haemorrhage
The monitoring of warfarin with the international normalised ration (INR) is well established and provides a reliable indication of the degree of anticoagulation. Currently there is no widely available coagulation monitoring test to assess levels of anticoagulation with FXa inhibitors such as rivaroxaban. Measuring thrombin time may provide qualitative evidence of rivaroxaban over-anticoagulation but it is not sufficiently sensitive to serve as an adequate quantitative measure. A chromogenic Factor Xa assay may be required to assess levels of FXa activity. In addition, unlike warfarin, there is currently no specific antidote available for rivaroxaban. The requirement for a specific antidote for rivaroxaban may be partially off-set because of its relatively short half-life. Current options for non-specific reversal of rivaroxaban include prothrombin complex concentrate and recombinant FVIIa which is expensive.

Annual review of patients on anticoagulation
Patients on rivaroxaban for over a year should be reviewed for continued appropriateness at least annually. Currently there is variation in which healthcare professionals undertake the annual review for patients on warfarin, in some cases it is the anticoagulation clinic with the support of the GP (for additional notes / information). With changes to the model of anticoagulation care for patients on rivaroxaban, the patient's GP may be the most appropriate healthcare professional to undertake annual review for the majority of patients, with referral to specialists (e.g. haematologists) for more complex patients.

Would NHS staff need extra education and training?
Healthcare professionals should be made aware of options for monitoring rivaroxaban and the management of rivaroxaban related over-anticoagulation and haemorrhage.

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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?

Not currently aware of any.