NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

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

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: Mark Crowther

Name of your organisation: British Society of Haemostasis and Thrombosis

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **YES**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **YES**
- 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)? **NOT AN EMPLOYEE BUT A MEMBER OF THE SOCIETY**
- 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.

Patients are initially treated with a rapid acting, usually parenteral, anticoagulant usually low molecular weight heparin (others include unfractionated heparin and fondaparinux). Most patients are then converted to an oral vitamin K antagonist (usually warfarin). A proportion of patients remain on heparins because vitamin K antagonists are either contra-indicated (e.g. pregnancy), less effective (e.g. in cancer patients) or technically difficult (patients with poor venous access for blood sampling).

The advantage of the current treatments is they are effective, have a relatively low side-effect profile (other than bleeding) and are well known to the majority of health practitioners. The advantages specifically of vitamin K antagonists is their effect can beeasily measured in routine laboratories, they can be rapidly reversed in the event of bleeding, the dose increased in the event of treatment failure and they can be used in renal failure. They are also very cheap – the major cost is in monitoring and dosing.

The disadvantages of the current treatments is that the parenteral anticoagulants may require a continuous intravenous infusion, which in turn requires inpatient care or sub-cutaneous injections which may require administration by community health team if the patient is unwilling or unable to administer the drug themselves. Injections can also be a problem for needle-phobic patients.

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The major problem with the vitamin K antagonists is the highly variable pharmacodynamics and pharmacogenetics, and multiple drug interactions which require the regular monitoring of the drug effect and dose changing. Poor control leads to an increased risk of treatment failure, i.e further thrombosis, or bleeding.

The major side-effect of all anticoagulants is bleeding. Certain patient groups are at a higher risk of bleeding, e.g. the elderly, cancer patients.

Patients with massive life-threatening pulmonary emboli may require thrombolysis.

Pulmonary emboli require hospital attendance for diagnosis. Less severely affected patients are treated entirely as out-patients while others are admitted for investigation and initial treatment. The rate of out-patient management and the decision when to discharge is very variable between hospitals and clinicians. It would be expected that the new technology would be initiated by the hospital but treatment would be carried on by primary care.

Certain sub-groups of patients are at higher risk of recurrence of their pulmonary emboli, these include men, those who have an unprovoked event, patients with cancer and patients with antiphospholipid syndrome.
Injecting intravenous drug users who sustain VTE are currently treated with LMWH because of the issues around being able to satisfactorily monitor coumarin therapy in these patients. This group would probably benefit from the new technology which would also make a cost saving compared with LMWH
The only current guidelines which discuss in detail the use of the technology is the American College of Chest Physicians 2012 Guidelines. These guidelines follow standard guideline methodology.

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?

The evidence from the clinical trials suggest that rivaroxaban is similar in efficacy and safety to the current standard of care (heparin then a vitamin K antagonist). The major advantage it gives is it does not require drug monitoring and dose adjustment, this will significantly reduce the number of times a patient needs to interact with health professionals. Also in the initial stages rivaroxaban does not require the initial treatment with heparin injections which may speed up hospital discharge and reduce the need for the administration of heparin in the community. Therefore the technology will be much easier to use than the current standard of care.

There are several disadvantages to the new drug:

- ***There is no specific antidote to the drug. This may effect clinical care in patients admitted with bleeding or requiring emergency surgery.***
- ***For most routine laboratories there is no method of accurately measuring the anticoagulant effect, this may be required if operative procedures are to be undertaken.***
- ***Apart from bleeding vitamin K antagonists have no other major side-effects, rivaroxaban has several other side-effects e.g. nausea, diarrhoea, dizziness***
- ***The half-life is quite short meaning a missed dose will leave the patient with less than optimum anticoagulation***
- ***The vitamin K antagonists can be used in renal failure, rivaroxaban is only licensed to a GFR>15mls/min.***
- ***As rivaroxaban is a new drug the long-term safety has not be assessed.***

Rivaroxaban also cannot be used in pregnancy and there is little experience in children. The current standard of care for malignancy associated thrombosis is low molecular weight heparin alone, this has been shown to be superior to vitamin K antagonists. Rivaroxaban has not been compared to low molecular weight heparin alone in this setting and should therefore not be used. There is also no evidence of its effectiveness in antiphospholipid syndrome.

The evidence for the use of rivaroxaban in the treatment of pulmonary embolism comes from the Einstein-PE trial published in the New England Journal of Medicine. This is a large multinational trial. The comparator is the standard of care in the UK. The patient population is quite young and therefore lacks the elderly. It has relatively few UK patients but most come from western countries. It has a proportion of patients who have active malignancy, where vitamin K antagonists are not an appropriate comparator. The important outcomes are measured in this trial – death, recurrence risk and bleeding.

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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.

The only quality data I am aware of is the published 'ENSTEIN-PE' trial. I believe several other trials looking at other indications for rivaroxaban are being conducted. There are also phase IV databases of patients taking this drug recruiting.

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)?

If approved this technology will be easier to implement than the current standard of care, and requires fewer health care professional/patient interactions and resources. If approved I foresee no problems with its implementation within the 3 month timescale, especially given that the drug has been approved for a very similar indication (treatment of deep vein thrombosis).

The main problem that requires education and training is ensuring that all healthcare staff are aware of how to manage patients on this drug. This is especially important if a patient presents bleeding or requires an invasive procedure.

Equality

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NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

I am not aware of any equality issues with regard to this technology.