NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism [ID726]

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: [redacted]

Name of your organisation: British Thoracic Society

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.

Given the Society's specialty (thoracic medicine), this response is focussed on pulmonary embolism (PE) in the following:

Standard management of patients with non-massive (ie non-acutely life threatening) PE is initial therapeutic low molecular weight heparin while warfarin is commenced. Warfarin is then continued for at least 3 months. Patients with cancer-related PE are treated with low molecular weight heparin rather than warfarin due to superior efficacy and lower interaction with chemotherapeutic agents.

Over recent years 3 main developments have challenged this traditional approach.

1. Although patients with clearly provoked PE are at low risk of recurrence, patients with unprovoked events have a risk of ≈20-25% recurrence in the first 3 years following a PE on stopping anticoagulation. Increasingly risks and benefits of longer-term anticoagulation are assessed in these patients.

2. The safety of out-patient anticoagulation has been demonstrated in patients with low clinical risk scores for mortality (eg PESI, simplified PESI or HESTIA) +/- negative markers for right ventricular dysfunction and ischemia.

3. The NICE approval of the direct Xa inhibitor, rivaroxaban, for the treatment and prevention of recurrence of PE has provided an alternative oral therapy for the initial and longer-term management of PE. Rivaroxaban has several benefits when compared with warfarin including rapid onset of access, lack of requirement to monitor levels, and lower risk of intracerebral bleeding. The rapid onset of rivaroxaban and the trial design with no requirement for heparin following study randomisation means that rivaroxaban may be especially useful in patients treated in an ambulatory/early discharge pathway.

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?

Apixaban is a bd direct Xa inhibitor which has been demonstrated in a large RCT of 5295 patients with acute venous thromboembolic embolism (VTE) to be non-inferior to warfarin in preventing recurrent VTE or fatal PE ,while having significantly lower incidence of intra-cranial or gastrointestinal haemorrhages. No heparin was required during commencement of apixaban once patients had been randomised into the study. In common with other trials of novel oral anticoagulants (NOACs) the study population differed somewhat from that seen in clinical practice in that few patients >80yrs, at the extremes of body weight or with creatinine clearance <30 ml/min were enrolled. The AMPLIFY-extension study of 2486 patients also demonstrated an 80% reduction in recurrent VTE following initial 6-12 months of anticoagulation compared with

placebo, while the 2.5mg bd dose was not associated with any significant increase in major or clinically relevant non-major bleeding risk compared with placebo.

Conclusion: When compared with other oral Xa inhibitors, Apixaban is associated with a lower risk of gastrointestinal haemorrhage, and importantly the 2.5mg bd longer-term dose appears not to be associated with an increased risk of major or clinically relevant non-major bleeding. As in rivaroxban (and unlike in edoxaban and dabigatran, an oral direct thrombin inhibitor) a period of anticoagulation with heparin is not required making it a potential agent for ambulatory care/early discharge. Apixaban is therefore a clinically useful agent with several advantages over other anticoagulants and the British Thoracic Society specialist advisory group for pulmonary vascular disease would support its approval by NICE.

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.

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)?

Equality

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.