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

Thank you for agreeing to give us a statement on your 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: University Hospital Birmingham, Queen Elizabeth (for this statement representing the Royal College of Pathologists and British Society of Haematology)

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 treatment in the NHS is predominantly with low molecular weight heparin (LMWH) when a diagnosis of venous thromboembolism (VTE) is suspected followed by introduction of warfarin (a VKA) if the diagnosis is confirmed, overlapping with LMWH until the INR is therapeutic. The VKA is then continued for a minimum of 3 months and in cases where there is a high risk of recurrence, continued long term. The non-VKA oral anticoagulant (NOAC) Rivaroxaban is an alternative (NICE TA261). In some primary and secondary care institutions, Rivaroxaban is now used as a default treatment in preference to LMWH/VKA. The most up to date clinical guideline for treatment of VTE (NICE CG144) does not include the use of NOACs as it predates the relevant NICE TA approvals.
Patients who struggle with a VKA (eg. brittle INR control, housebound, reliant on dosette boxes) potentially benefit from the fixed dose regime of a NOAC. A NOAC may be preferred by some patients because of convenience (avoiding the need for INR monitoring and dietary/alcohol restrictions).
The use of NOACs for treatment of VTE also increases the opportunity for developing diagnostic/treatment pathways within primary care as the role of secondary care in initiation of VKAs and administration of LMWH is not required.
A key subgroup of patients who require alternative therapy for VTE are those with active cancer. The current standard of care is 6 months of LMWH. The trial which assessed Apixaban for treatment of VTE (AMPLIFY) used warfarin as a comparator and excluded patients with cancer.

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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?

The innovation is similar to that of Rivaroxaban in that it avoids the need to use LMWH while loading with a VKA at diagnosis and the need for INR monitoring and is favourable in terms of dietary/alcohol and drug interactions. It is taken twiice daily and there is some debate about whether this is a disadvantage or advantage in comparison to a once daily regime (eg. Rivaroxaban).

The trial data for Apixaban (AMPLIFY) suggests that major bleeding risk is lower than with a VKA and the lower dose of Apixaban used for prevention of VTE recurrence after 6 months of treatment (AMPLIFY-EXT) showed a similar bleeding risk to placebo but appeared similarly effective to the treatment dose of Apixaban in terms of VTE prevention. This could result in a different approach to management of VTE with an initial 6 month treatment phase dose followed by a lower dose for longer term prevention in appropriate cases (eg. unprokoved or recurrent VTE).

NOACs which can be initiated at diagnosis of VTE without the need for LMWH (currently Rivaroxban and Apixaban) can be cost effective in comparison to standard therapy with LMWH and a VKA over a short period of time (3 months).

Disadvantages of Apixaban include contraindication in severe renal failure and the current lack of an effective antidote. There are several drugs which contraindicate use of Apixaban (eg. antiretroviral and systemic anti-mycotic drugs) and others which may affect Apixaban levels and compromise safety/efficacy (eg. phenytoin,

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rifampicin). Apixaban has minimal effect on basic clotting tests (INR/APTT) at therapeutic levels. There is a commercially available assay (anti-Xa) although this is difficult to perform rapidly (especially out of hours) and is currently not available in most laboratories)

Equality and Diversity

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

Patients who have limited mobility or require medicines to be given in dosette box may benefit from this technology in comparison to use of a VKA.

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.

Additional sub-analysis of data from Apixaban trials is likely to be published.
Data on relative efficacy and adverse events of apixaban in comparison to a VKA according to time in therapeutic range was presented at the American Society of Haematology meeting in December 2014 (Abstract 1543).
Data on subanalysis of vunerable patients from the AMPLIFY trial (elderly, underweight, renal disease) should be requested if available.
Although laboratory monitoring of Apixaban is not routinely recommended within current licensed indications, any data on drug levels within the treated trial population and any relationship with efficacy and bleeding woiuld be relevant.

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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)?

A NICE recommendation for Apixaban would not be materially different from the existing approval of Rivaroxaban and Dabigatran for treatment and prevention of VTE.