Appendix G -Professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Apixaban for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation

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

[redacted]

Name of your organisation: Heart Rhythm UK

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)
- ***I am an NHS consultant cardiologist specializing exclusively in the management of heart rhythm disturbances (arrhythmias) for 12 years, and director of the arrhythmia service at King's College Hospital. I have a >20 year research interest in atrial fibrillation.***
- ***I represent Heart Rhythm UK, the body affiliated to the British Cardiovascular Society that specifically represents medical professionals (physicians, physiologists, nurses) caring for patients with arrhythmias. Our council also has (non-voting) representation from Patients' Groups via the Arrhythmia Alliance, the MHRA, and the ABHI.***

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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?

- There is a very strong evidence base that atrial fibrillation is an important cause of stroke and systemic embolism (SSE). Oral anticoagulation can reduce this risk by at least 60%.
- There is little difference between professionals in their recommendation of anticoagulation in moderate and high risk patients, though opinion differs somewhat about the threshold for treating those in lower risk groups, those in whom there is a perceived risk from anticoagulants themselves, and those in whom compliance with the therapeutic monitoring required for warfarin may be problematic.
- Numerous studies and tools, such as the GRASP AF developed by NHS improvement, have demonstrated that the use of anticoagulants for stroke prevention in AF (SPAF) is inadequate and highly variable between GP practices.
- Traditionally, vitamin K antagonists (chiefly warfarin in the UK) have been used for oral anticoagulation. Warfarin has many shortcomings including the need for frequent blood tests for therapeutic monitoring, and numerous interactions with drugs and foods. For this reason, new oral anticoagulants have been developed.
Large scale, randomized clincal trials have been conducted >50,000 patients, comparing dabigatran (a direct thrombin inhibitor - ReLY), rivaroxaban (a factor Xa inhibitor - ROCKET-AF) and apixaban (a factor Xa inhibitor - ARISTOTLE) to warfarin. In each trial, the new drug has been found to be superior (with borderline or clear statistical significance) to warfarin in presenting stroke and systemic embolism, similar to or better than warfarin in avoiding bleeding complications, and far better than warfarin in avoiding intracranial bleeding. With apixaban, overall mortality was significantly lower than warfarin - a similar but nonsignificant effect was seen with the other drugs. Head to head comparisons have not been conducted between the new drugs and are never likely to be feasible in view of the numbers needed.
- Dabigatran and rivaroxaban have recently been licenced by the EMA and the FDA, and approved by NICE for SPAF. APIXABAN, like rivaroxaban, is a factor Xa antagonist. All the new oral anticoagulants have predictable pharmacokinetics with few interactions, so fixed dosing is possible without therapeutic monitoring.

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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?
Scoring systems based on clinical factors have been devised and validated that can stratify individual patients' annual risk of SSE which varies from <1% to >20%. Worldwide, the CHADS2 score is well-established for estimating stroke risk in AF patients. The European Society of Cardiology has suggested the use of the more complex CHA_2DS_2-VASc tool to refine the stratification of patients at the low-risk end of the spectrum.
The greatest individual benefit from oral anticoagulation including with apixaban comes in those patients at highest risk, but those at intermediate and lower risk are very numerous and should also be considered if a significant impact on stroke incidence is desired. Dose adjustment of the new oral anticoagulants should be considered in patients with significant renal or hepatic impairment. Patients with a perceived risk of intracranial haemorrhage (e.g. because of falls) may be more suitable for new oral anticoagulants such as apixaban as the incidence of this complication is uniformly far lower than with warfarin.

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)?

In common with the other new oral anticoagulant drugs, this drug should be primarily targeted for use in primary care. This is where the largest gap in anticoagulant prescribing resides, and thus the greatest opportunity for public health improvement. It may be that at first, support from secondary care (cardiac and especially anticoagulant services) will be helpful in decision-making for difficult cases. Various models of shared care have been developed by trusts and networks with primary care for dabigatran and rivaroxaban, and apixaban should be no different. However, with familiarity there is no reason why in the medium to long term most patients should not be both initiated and maintained on this drug in primary care.

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?
Apixaban is not currently licensed for stroke prevention in AF.

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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.

No clinical guidelines exist specifically for apixaban or other new oral anticoagulants (other than the recent NICE STAs for dabigatran and rivaroxaban).
The American Heart Association/American College of Cardiology/Heart Rhythm Society Guidelines 2006 and the European Society of Cardiology AF guidelines 2010 recommend "oral anticoagulation" for patients stratified according to the $CHADS_2$ and CHA_2DS_2-VASc scoring respectively. Both guidelines were written before the licensing of new anticoagulants but both the 2010 ESC guidelines and the 2011 focused update of the AHA/ACC/HRS guidelines recognize the advent of the new oral anticoagulants.

The NICE STA appraisal of apixaban, and its forthcoming revisions of AF management guideline 36 will provide clinical guidelines for these drugs.

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?

Advantages: the chief reasons for under-utilization of anticoagulation in SPAF lie in the inconvenience of regular therapeutic monitoring, the unpredictability of its therapeutic effect due to numerous interactions, and the perceived risk of life-threatening bleeding, especially in the elderly, e.g. due to falls.
Apixaban has highly predictable pharmacokinetics, with has very few drug or food interactions and does not require regular therapeutic monitoring. The majority of patients requiring oral anticoagulation can be prescribed a fixed dose regime of apixaban (as with aspirin, for example). Data from the AVERROES and ARISTOTLE trials indicate both slightly superior efficacy and greatly superior safety compared to warfarin (in respect of mortality, major and intracranial bleeding) so this drug should be more acceptable to general practitioners for stroke prevention in AF

Disadvantages: in common with dabigatran and rivaroxaban, there is no specific antidote to apixaban, though it is thought likely that commercially available coagulation products may reverse its action (research is underway). The lack of therapeutic monitoring means that compliance with therapy is difficult to assess.

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.

It is likely that the drug will need to be avoided in severe renal or hepatic insufficiency and that reduced dosing will be recommended in elderly patients with low body weight or reduced eGFR.
Guidance will be necessary regarding discontinuation of apixaban prior to elective surgery (probably 24-48h), conversion to and from other anticoagulants (warfarin, heparin products), and concomitant use of antiplatelet agents.

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 patients included in the AVERROES and ARISTOTLE trials broadly reflect the patient groups indicated for stroke prevention in the UK (those considered ineligible, and eligible for warfarin, respectively). Only 25% of patients randomized in ARISTOTLE were aged >76 but this nevertheless includes 4500 patients. Both studies recruited from both genders and within a wide range of races internationally.

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?

In ARISTOTLE, the incidence of serious bleeding was lower than that with warfarin in all subgroups and the incidence of liver dysfunction was similarly low. In AVERROES (again, double-blind) discontinuation of apixaban was slightly less frequent than that of aspirin indicating good tolerability.
I am not aware of side-effects or adverse effects other than those reported in these studies.

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.

I am not aware of any additional sources of evidence.

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)?

Administration of apixaban, in common with the other new oral anticoagulants (dabigatran, rivaroxaban) is considerably simpler than that of warfarin. Current guidance as to which patients with AF should receive oral anticoagulation is fairly clear and unambiguous. Other than for simple guidelines requiring dose reduction or avoidance in elderly patients with low body weight or renal failure, administration is simple.
However, early experience in the Far East with dabigatran emphasizes the importance of GP and patient education in avoiding over-dosage and consequent risk of bleeding. Patients should carry some sort of document identifying that they are taking an oral anticoagulant, and which one, to assist medical practitioners in the event of an emergency; emergency and haematology departments will need local or national guidance on the management of bleeding in patients taking these drugs.

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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.

The evidence base for the effectiveness and safety of apixaban is very inclusive in terms of race, gender, and socio-economic group.

The simplicity of administration of apixaban in comparison to warfarin should improve its availability and suitability for the disadvantaged, housebound, etc.