Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Edoxaban tosylate for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation

Thank you for agreeing to make a submission 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 submission, 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: Ameet Bakhai

Name of your organisation: Royal Free London NHS Trust / Royal National Orthopaedic Hospital NHS Trust / Amore Health Ltd / Spire Bushey Hospital
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)? Yes✓

- other? (please specify) Consultant undertaking private practice. Consultant supporting clinical research and health economics via advisory functions for design of trials, economic models, registry studies, interpretation, analyses and reporting of outcomes and supporting the construction and implementation of patient care pathways, Intermittent expert invited to the NICE scientific advisory panel service, previous member of NICE horizon scanning committees, member of previous NICE guidance and NICE external reference group. Member of UCL partners task forces for improvement programmes in AF and Heart Failure. Author of various clinical papers and books related to health care, clinical research and health economics. Principal investigator of various clinical trials and registries. Lecturer and advisor to pharma and device manufacturers including Daiichi Sankyo, Bayer, Boehringer Ingelheim, BMS and Pfizer (declaration) and health care providers including the NHS, NHS England, McKinsey, Boston Consulting Group, IMS and others (declaration). Mentor and appraiser in medicine and active in

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What is the expected place of the technology in current practice?

As an oral anticoagulant to prevent stroke in non-valvular AF patients at increased risk of stroke.

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?

Considerable variation in practice with varying access to anticoagulation, anticoagulation specialists, monitoring, supervision and patient support.
Warfarin, heparin based regimes, dabigatran, rivaroxaban and apixaban and dual anti-platelet regimes are alternatives. Warfarin has considerable experience but needs monitoring and we often have poor anticoagulation effect in patients (less than 2 out of 3 results are outside range in most patients) but it has a broad indication range. It is slow to have effect and to remove effect and is cumbersome. Heparin injections are not convenient to take and expensive albeit effective. The newer agents are associated with less monitoring, higher efficacy of anticoagulation and lower intracranial haemorrhage. Dabigatran and rivaroxaban do not have as good safety profiles as apixiban and edoxaban in their higher doses. Edoxaban is a once a day agent, very well tolerated by patients, with greater safety and less interactions than warfarin, in a large very well conducted clinical study with an excellent adaptive dosing regime that proves its safety profile and non-inferiority to very well controlled warfarin. The outcome of the trial was almost superior to warfarin depending but not quite in the main design.

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?

There was a suggestion that people with very good renal function do not benefit from edoxaban presumed as cleared too efficiently. This outcome may be true for other novel agents but the issue has only come to light with this trial data immediately. Interesting people on aspirin and who had not previously been on warfarin did even better and those with high blood pressure – suggesting to me – that the main benefit is again where people are more likely to bleed are safer on edoxaban than 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)?

As customary with new anticoagulant, it is likely that people with confidence in managing warfarin will use edoxaban and these individual exist in both primary and secondary care with more in the latter. Anticoagulation clinics are the ideal starting point where GPs and consultant have less initial confidence. The drug can be continued in any setting as warfarin is.

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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?

Not yet available but similar drugs are being used and there is again considerable variation which si why NICE has issue prescribing decision aids also. Access to this additional once a day novel agent will enhance more inform practice as the previous once a day novel oral anticoagulant has not shown as good safety data against warfarin.

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.

All of the previous evaluations of novel oral anticoagulants and recent AF and medicines optimisation guidelines are relevant to the equation from NICE and then there are European society of cardiology guidelines on AF and other national groups that support the introduction of novel oral anticoagulants as options either alongside or in preference to warfarin, where affordable. The NICE guidance and single technology appraisals have robust methods of evaluation which additionally considers cost effectiveness while the cardiovascular society guidelines do not reflect a cost effectiveness approach, but focus on clinical effectiveness mainly.

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?

I have stated this above. Edoxaban will be easier to use than existing technologies because it provides better safety, both non-inferior and almost superior efficacy to warfarin, better tolerability and clinical trial confidence at a price equal to the lowest novel oral anticoagulants with an excellent dosing regime focused on safety. This will enhance our ability to reduce strokes more cost effectively.

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.

There are excellent regimes for starting, interrupting and stopping edoxaban both in the clinical trial protocols and in prescribing protocols. Daiichi-Sankyo are extremely committed to a safety and a very safe introduction of the new technology having learnt much from previous trials but also investing heavily in quality and scrutiny of use of the new drug. Having supported the use of many new technologies, I do not say this lightly. I am very impressed by their responsible attitude here.

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?

We can refer to my above answers which state how well I feel the ENGAGE-AF trial was undertaken, analysed and reported and data shared in the public domain. As a responsible company, they have even made the difficult decision early not to pursue the less effective dose of 30 mgs od, from the onset which reflects their ability to challenge their own behaviour and focus on values.

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?

There is a large evidence base of good data here to show how well the drug was tolerated and indeed less people discontinued edoxaban than warfarin. There were no major adverse effects seen in the trials.

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 main dataset are large and robust and very representative. We do have data that anticoagulation is still not offered or accepted by many people at risk in the UK but this is relevant to all oral anticoagulants and not this technology alone.

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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)?

The NICE guidance would enhance our ability to provide people with better options than currently available today if the guidance supported the introduction of this agent. We have struggled to have a well-tolerated, safer, once a day alternative to warfarin as previous promising agents have not shown such good safety data. Edoxaban for no additional cost fills that need (although not tested head to head against the other alternatives, other than warfarin) with acceptable cost effectiveness in comparison to warfarin. Educational training, development of antidotes, guidelines and registries to oversee safety are all in place to provide support for a very responsible introduction of this technology if supported by the NICE appraisal process.

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.

I see no equality or access issues other than against people with supra-normal or considerably compromised renal function who are not recommended the current doses of edoxaban for appraisal here.