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:

Name of your organisation:Royal College of Pathologists
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)?No

- 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)?No

- 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.

NICE CG 180 (the management of atrial fibrillation), published in 2014, gave clear updated guidance as to the treatment of AF. Similar guidance has been published by the European Society of Cardiology. Individuals with AF should have an assessment of stroke (by CHADS-VASc score) and bleeding risks performed. Men with a CHADS-VASc score of 1 or more, and women with a CHADS-VASc score of 2 or more should be offered anticoagulation (taking the bleeding risk factors into account). This is universally accepted.
Current anticoagulant therapies available are warfarin, and now apixaban, dabigatran etexilate, and rivaroxaban. At the time that studies with edoxaban tosylate were initiated, warfarin was the only licensed anticoagulant drug available. Whilst aspirin historically was offered as an option, evidence has demonstrated that reduction in stroke risk associated with AF is significantly greater in patients taking anticoagulant therapy when compared to patients taking antiplatelet agents (eg aspirin or clopidogrel).

Apixaban, Dabigatran etexilate and Rivaroxaban are now all licensed and have been approved by NICE for this indication.

Following their introduction, over the last couple of years, there has been a significant uptake of the direct oral anticoagulants (DOACs; apixaban, dabigatran etexilate, rivaroxaban) within the UK, yet the majority of patients receiving anticoagulation to prevent stroke or systemic embolisation in AF are prescribed warfarin. There is considerable geographical variability in the use of the DOACs in the UK; the reasons

for this are multifactorial (reasons include unfamiliarity in the technology, the maturity of local cardiac and anticoagulation networks, developing consensus in their introduction in primary and secondary care, clinician enthusiasm, and clinicians awaiting the now published updated NICE guidance).

The DOACs (including edoxaban tosylate) offer significant advantages to warfarin in that there is no requirement for regular monitoring. Two of the DOACs (dabigatran and apixaban) require to be taken twice daily (bd), whereas Rivaroxaban is a once daily (od) medication, as is edoxaban tosylate. The introduction of edoxaban would offer clinicians and patients the choice of a second once daily DOAC for the prevention of stroke or systemic embolism associated with AF.

The Edoxaban study randomised patients to one of two different doses of edoxaban tosylate (high dose, 60mg once daily, or low dose, 30mg once daily) or warfarin (double blind, double dummy study using an encrypted warfarin monitoring). There are concerns that patients with impaired renal function (creatinine clearance <50mL/min), those with low body weight (<60kg), or who were taking P-glycoprotein inhibitor drugs (eg verapamil) are at increased risk of bleeding whilst taking DOACs due to an increase in anticoagulant effect. The edoxaban study incorporated a reduction in edoxaban dose in such patients. The edoxaban study demonstrated a significant reduction in haemorrhagic stroke when compared to warfarin, and a significant reduction in life-threatening and major bleeding in patients taking edoxaban when compared to warfarin. Edoxaban was non-inferior to warfarin in the study at both doses, but there was a trend towards inferiority in the prevention of stroke in patients randomised to the lower edoxaban dose (30mg od).

This technology would be used in both primary and secondary care settings. The introduction of the 3 licensed DOACs in primary care has taken some time- many GPs and anticoagulant nurses lacked the confidence, and some the competence, in the use of anticoagulant therapies. These barriers are now fading away; GPs, practice nurses and pharmacists in primary care are becoming more familiar with their use. Some areas have introduced specialist anticoagulation clinics to start patients on DOACs and to switch patients from warfarin to DOACs as appropriate. Many hospital laboratories have introduced tests (assays) to investigate patients taking DOACs who are admitted with a thrombosis or a bleeding episode; an assay for edoxaban has been developed, and will be available. Much of the work associated with the implementation of the DOACs has therefore been undertaken and it is unlikely that additional specialist input will be required for the introduction of this technology.

As yet the technology is not available- it is not yet licensed in the UK for this or any other indication. There are other DOACs (as above) licensed for other indications (prevention and treatment of venous thromboembolism) in addition to prevent stroke and systemic embolization in AF, and these are increasingly used within the UK. It is unlikely that edoxaban would be significantly used outside its licensed indication, therefore, as these alternatives are available.

The advantages and disadvantages of the technology

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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?

This technology compares favourably to warfarin for the proposed indication (stroke and systemic embolization prevention in atrial fibrillation (SPAF)). It is non inferior to warfarin for this indication, although at the lower dose (30mg od) there was a trend towards inferiority. Three other DOACs have completed trials, have been licensed and are now NICE approved for this indication. These three DOACs (apixaban, dabigatran etexilate and rivaroxaban) are widely used for this indication. There are no head-to-head studies comparing the DOACs.

There was a reduction in the risk of intracranial bleeding and major bleeding in patients taking edoxaban tosylate when compared with warfarin. There was an increase in gastrointestinal bleeding with edoxaban tosylate compared to warfarin (however major bleeding was reduced overall). Otherwise, to my knowledge, there were no other side-effects of significance or concerns recorded.

The patient population within the study had a median age of 72; many patients with atrial fibrillation are older (prevalence increases with age). It is challenging to undertake studies in the older patient population, and all the studies of the DOACs had patients of a similar age range to this study (in the apixaban ARISOTLE study the median age was 70 years). Patients at high risk of stroke were included in the edoxaban tosylate study (23% had a CHADS2 stroke risk of 4-6) as one would see in the 'general AF population'. 30% of patients in this study were taking asprin, again as one tends to see in the general AF population. The outcomes measured in this study were appropriate to the indication of the technology.

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.

On 8th January 2015 the FDA approved edoxaban for this indication, but have included a 'Boxed Warning' with additional dosing and safety warnings. In this the FDA warn that edoxaban tosylate is less effective for SPAF in AF patients (when compared with warfarin) where the patient's creatinine clearance is greater than 95mL/minute (ie patients with good renal function). It is recommended by the FDA that patients with creatinine clearance >95mL/min are offered another anticoagulant.

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)?

Possible NICE guidance would not affect the delivery of care for patients with this condition. Regions have anticoagulation services in place delivering such care. There

would be a need to educate health professionals in this new technology but there are many professionals available with skills in anticoagulant treatment therefore there would be no considerable impact.

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.

To my knowledge, this appraisal will not exclude people protected by equality legislation within the patient population for which the treatment may be licensed.
It will not lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population. It will not lead to recommendations that have an adverse impact on people with a particular disability.
I do not think the committee will require additional evidence.

The majority of patients with atrial fibrillation are elderly. The traditional requirements for monitoring of warfarin anticoagulation proves challenging to the elderly patient population. The provision of a technology that provides protection from stroke in atrial fibrillation without the need for regular monitoring is to the great advantage of, in particular, this patient group.