Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Edoxaban tosylate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism

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: [redacted]

Name of your organisation:
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?

NICE CG 144 issued in June 2102 recommends initial treatment of VTE with low molecular weight heparin (LMWH), fondaparinux or unfractionated heparin (UFH) until the patient is established on a vitamin K antagonist (VKA).

Those with transient risk factors for venous thromboembolism (VTE) should be treated for 3 months and there should be a consideration for long-term treatment (balance of thrombotic versus haemorrhagic risks) in those patients who have experienced an unprovoked VTE. The guideline recommends continuation of heparin (treating for at least 6 months) in those patients with cancer.

Since June 2012 rivaroxaban (TA 261 and 287) and dabigatran (TA 327) have both gained approval from NICE for use in the treatment of VTE. Both have been compared against LMWH and VKA for the acute treatment of VTE and found to be non-inferior. With regards to longer term secondary prevention dabigatran has been compared to long-term treatment with warfarin and found to be non-inferior whereas rivaroxaban was compared against no treatment and was, as expected, superior in regard to prevention of VTE recurrence.

It is with regard to the choice of treatment agent that there is the most variation between different centres. There is also variation in opinion as to whether distal DVT should be assessed for and, if found, treated. In addition there is increasing interest in the role of measuring the antithrombotic effects of the newer oral agents in specific circumstances i.e. at the time of recurrence, bleed, overdose or if there is a need for emergency surgery. There may also be a role in patients with renal impairment, those at the extremes of body weight and those on interacting medications.

Current alternatives to the technology
LMWH followed by VKA – this is a well-established and effective treatment. There is an effective reversal agent for VKAs available if required. However this approach requires initial parental administration of heparin and on-going blood tests to monitor the anticoagulation effects of the VKA, in addition there are many drug interactions and the need for some dietary modifications.

Rivaroxaban – has been shown to be non-inferior to LMWH and VKA in the prevention of VTE recurrence and there is no requirement for parental heparin administration. It is taken as a fixed dose with no requirements to monitor the level of anticoagulation. However there is currently no specific antidote and

there are certain contraindications including pregnancy and conditions in which use is not recommended such as severe renal impairment.

LMWH followed by dabigatran – This approach also requires initial parental administration of heparin. Dabigatran is taken as a fixed dose with no requirements for monitoring the level of anticoagulation. However there is currently no specific antidote and there are certain contraindications to use including severe renal impairment, certain concomitant medications and prosthetic heart valves.

Apixaban – licenced for use in the treatment of VTE but currently awaiting guidance from NICE. As for rivaroxaban, this approach has been shown to be non-inferior to LMWH and VKA in the prevention of VTE recurrence and there is no requirement for parental heparin administration. It is taken as a fixed dose with no requirements to monitor the level of anticoagulation. However there is currently no specific antidote and there are certain contraindications and conditions in which use is not recommended such as pregnancy and severe renal impairment.

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?

For patients with cancer the current gold standard treatment is 6 months of LMWH, however the newer oral anticoagulants have a role in certain circumstances. In this setting there is limited data from the trials involving the newer oral anticoagulants.

Patients with pulmonary hypertension – interesting results in the Hokusai VTE trial that for those patients treated with edoxaban the recurrence risk was approximately half that seen in the warfarin group.

Edoxaban provides another option for patients with higher risks of bleeding as the trial data show a significant reduction in bleeding events compared to 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)?

This technology could be used in both primary and secondary care in ambulatory clinics and for treatment of hospital inpatients. Education would be required (packages similar to those for the other available anticoagulants).

The use of at least 5 days of parental heparin in the Hokusai trial would mean that district nurse support would be required for certain patients at the start of treatment i.e. those who are ambulatory but unable to self inject.

The longer-term assessment of suitability for on-going anticoagulation should be the same as for those patients on the currently available anticoagulants.

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 currently in use.

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.

There are no specific guidelines in place for edoxaban.

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?

The new technology is a direct inhibitor of activated factor X. The indications for use, exclusions and management of overdose, bleeding and emergency surgery will be similar to the factor X inhibitors already available in the UK. However it is a once daily medication (dabigatran is taken twice daily) with no dose change (rivaroxaban is twice daily for 3 weeks then once daily). This could be associated with improved compliance and a reduction in dosing errors.

The requirement for at least 5 days of parental heparin may reduce the use of this new technology in some circumstances (i.e. if there is a need for district

nurse administration of LMWH) but potentially for those patients with extensive VTE initial heparin treatment may offer reassurance to clinicians and may be thought to be a preferable treatment.

Some of the previous trials for the newer oral anticoagulants have excluded certain relevant patient groups, this has led to concerns that the study population in these trials does not reflect the treatment population in the UK. The Hokusai investigators state that it was their intention to design the trial to broaden applicability to real world practice and allow recruitment of as many as possible. Examples include, initiating LMWH to encourage recruitment of those with extensive VTE, allowing dose reduction in those with renal impairment and low body weight and allowing the treating physician to determine treatment duration.

In the published trial the primary efficacy endpoint of VTE recurrence and principal safety outcomes of major and clinically relevant bleeding are in my view the most important outcomes. Data are also provided regarding rates of any serious adverse event and death from any cause.

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?

As with any anticoagulant the most relevant significant side effect is bleeding. There have not been head to head trials of the different newer oral anticoagulant agents but they have all been trialled against LMWH/VKA. The rivaroxaban and dabigatran trials reported similar safety profiles to warfarin. Both the edoxaban and apixaban have reported significantly fewer bleeding events compared to warfarin.

The lack of a clinically proven antidote does reduce the use of the newer oral anticoagulants in some patient groups but development of antidotes is in progress. Hospital laboratories are gradually increasing the availability of tests to measure the level of anticoagulation associated with the newer oral anticoagulants and quality assessment is being introduced. Clinician experience in the interpretation of such results is also building.

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.

Not aware of any unpublished evidence regarding this technology.

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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)?

If approved by NICE this technology would provide another treatment option for patients with VTE.

Like rivaroxaban and apixaban it is direct inhibitor of activated factor X. The required education and training regarding the use of the newer oral anticoagulants has already begun in the NHS. The education required for the use of edoxaban would add on to the existing education, (taking into account the differences outlined in the summary of product characteristics). This training and subsequent implementation should be able to take place within 3 months of the publication of guidance.

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.

N/A