Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism [ID483]

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

Your name: [redacted]

Name of your organisation: RCPath, BSH

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)? **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.

The STA is most conveniently separated into its two parts: firstly the immediate treatment of DVT and PE and secondly the secondary prevention of DVT and PE.

1. Treatment

Standard treatment for DVT and PE comprises prompt anticoagulation with an immediate-acting anticoagulant, typically a low molecular weight heparin (LMWH) given by daily subcutaneous injection. At the same time, or shortly afterwards, the oral anticoagulant warfarin is commenced. Warfarin will take at least 5 days and frequently longer to achieve the desired level of anticoagulation, measured by frequent blood tests (INR), after which the heparin can be discontinued.
Warfarin treatment continues for 3 months with continued INR monitoring under current recommendations.
This 'standard' treatment is now being replaced in some cases and to varying extents in different regions, by the use of the (NICE approved) immediate acting oral anticoagulant rivaroxaban. This avoids the need for transition from one anticoagulant to another and avoids the need for monitoring by blood tests. Rivaroxaban is therefore considerably more convenient and is cheaper than LMWH, but; is more expensive per dose than warfarin, is not suitable in renal failure, has no ready means of reversal and interacts with some drugs (although the number is much smaller than for warfarin). At present its use is limited to those patients who match the trial population but is increasing in most areas of the UK.

2. Secondary prevention

After the initial treatment phase a decision has to be made as to whether long term anticoagulation is likely to be of benefit or not. Traditionally this has been achieved

using warfarin but rivaroxaban can now also be used as an alternative. The same limitations to rivaroxaban use for secondary prevention apply as mentioned under treatment and the EINSTEIN extension trial included only patients who had no clear indication for warfarin anticoagulation. In particular we have no, or limited, data on treating higher risk patients or patients with cancer.

Treatment and secondary prevention of DVT and PE are therefore undergoing a period of change. There is no major disagreement among treaters that both rivaroxaban and LMWH-warfarin are both effective treatments and both are appropriate. Although practice may be changing at different rates around the country, this is as likely to result from budgeting and administrative details as much as from any difference in clinical opinion. It is more difficult to be certain about equivalence for long term treatment (secondary prevention) because of the limited range of patients in the EINSTEIN extension study.

New technology

Dabigatran is similar to rivaroxaban in that it is orally active, immediate acting and does not normally require monitoring. However in the major licensing trial (RE-COVER) it was used in combination with initial LMWH. The LMWH-dabigatran combination was non-inferior for efficacy and safety compare to LMWH-warfarin. This does not imply it is less effective than rivaroxaban but will make it rather less attractive than rivaroxaban for acute treatment.

For long term secondary prevention dabigatran (RE-MEDY and RE-SONATE trials) was compared with both placebo and long term warfarin therapy. Dabigatran was non-inferior for efficacy and for safety with a near-significant reduction in bleeding compared with warfarin. As noted in other studies there was a small increase in myocardial infarction with dabigatran compared to warfarin but not compared to placebo.

Otherwise it broadly shares the same pros and cons as rivaroxaban with some minor differences including a greater dependence on renal excretion.

Subgroups

Although patients presenting with DVT and PE have a similar risk of recurrent VTE, patients presenting with PE are 3 fold more likely to have PE at recurrence compared with patients who initially present with DVT (Thromb Haemost 2010; 8: 2436-2442). A patient with an unprovoked PE may therefore be considered to be at more risk of fatal PE at recurrence and more likely to benefit from long term anticoagulation. Otherwise PE and DVT should be considered as the same disease and the two groups are similar in their response to the technology.

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Patients who develop recurrent VTE whilst on anticoagulant treatment should be considered separately. This is important as the usual treatment is to increase the intensity of treatment with a vit K antagonist or to swap to an alternative anticoagulant (e.g. LMWH or fondaparinux). There are no published trials comparing dabigatran with high intensity vit K antagonists (INR target >2.5) or extended LMWH or fondaparinux.

Patients with cancer will need to be considered as a separate group. Treatment with LMWH for 6 months is recommended in preference to VKA's because of published

evidence of improved efficacy. There were very few patients with cancer in the dabigatran (or rivaroxaban) trials and dabigatran has not been compared with LMWH in this circumstance.
Pregnant women and children will probably need to be excluded from the population until further data is available.

Setting
Dabigatran therapy may be initiated in primary or secondary care. Long term use (prevention) is likely to be almost entirely prescribed by primary care physicians. However this is unlikely to require additional resource due to the lack of monitoring.

Guidelines
It is too early for these new technologies to have a firm place in guidelines. The most recent ACCP guidelines gave a weak recommendation to continue with LMWH-warfarin due to lack of data for dabigatran. Kearon Chest. 2012;141(2_suppl):e419S-e494S

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 principal advantage of dabigatran is the absence of need for monitoring.
The continued requirement for initial LMWH in the acute treatment of VTE is a disadvantage compared to rivaroxaban but neutral compared to warfarin.

Compared to warfarin, it is likely to simplify treatment of VTE and prevention of VTE due to lack of need for monitoring.
Compared to rivaroxaban it is comparable for prevention and has the advantage that it has been studied in comparison with warfarin, but rather less convenient for treatment.
The reduction in drug interactions and absence of dietary restrictions may be attractive or beneficial for some patients.

Dependence on renal clearance will make it unsuitable for patients with renal failure.
Several studies have shown a small increase in the frequency of myocardial infarction: higher than warfarin but no higher than placebo.

It is a twice daily dose rather than once daily warfarin or rivaroxaban.

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.

All relevant evidence appears to be published, but further post-marketing data are awaited.

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.

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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)?

NICE has considered these problems before when approving this group of drugs (rivaroxaban, dabigatran and apixaban) for other indications such as stroke prevention in atrial fibrillation. Implementation of this technology would reduce the capacity required in anticoagulation clinics and would simplify the delivery of anticoagulation therapy overall. There would be a reduction in staffing in clinics and no additional education or training. This may therefore offset the higher per-dose cost of the technologies somewhat. However there are a number of indications for which warfarin remains necessary and there is no immediate prospect of closing anticoagulation clinics entirely
Although blood levels of dabigatran would not need routine or regular monitoring, this will be necessary in some circumstances and laboratory provision will need to be made for this. Annual check of renal function is recommended.

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 lack of need for monitoring may benefit patients with limited mobility whom no longer have to attend hospital/GP clinics.