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: British Cardiovascular Society

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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Single Technology Appraisal (STA)

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

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

Treatment within the NHS of deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively known as venous thromboembolism (VTE), is essentially as recommended in NICE clinical guideline 144. Parenteral heparin (or fondaparinux) therapy is started along with an oral vitamin K antagonist (mainly warfarin) and the heparin is discontinued after several days when the international normalised ratio (INR) in the blood (reflecting warfarin's activity) is within the therapeutic range, allowing warfarin to be continued as monotherapy. Warfarin is highly effective in preventing extension and recurrence of VTE and the duration of therapy is reviewed at three months; warfarin is then either stopped or continued longer term (potentially life-long) for secondary prevention purposes depending on the assessment of risks, benefits and individual patient views. The initial period in particular, though often managed as an outpatient or in the community (especially in the case of DVT), requires regular blood tests to decide when heparin can stop. Even when warfarin continues as a single agent it is necessary to test the blood, either in hospital clinics or in the community, to check the INR and adjust as necessary the dose of warfarin. The frequency of testing varies between individuals and over time.

The new oral anticoagulant, rivaroxaban, is an alternative to the heparin-warfarin combination and can be used as a single agent from the outset in the treatment and secondary prevention of DVT and PE (NICE Technology Appraisals 261 and 287). From the patient angle the big advantage is convenience because there is no need for regular monitoring of the blood and the treatment can be given in fixed dose (in a twice daily regimen for the first 3 weeks and once daily subsequently).

Potentially dabigatran might be judged to have similar benefits. There are some differences in the regimens used in the clinical trials – for example, dabigatran was commenced after several days of heparin therapy rather than as a single agent from the outset.

There is no real dispute between experts on the initial treatment of VTE (apart from eg, some cases of PE where there is uncertainty over the role, for example, of thrombolytic therapy). However, there is uncertainty over the appropriate duration of anticoagulant therapy, since continuing beyond 3 months is essentially for secondary prevention purposes and the decision to continue or stop requires an assessment of risks and benefits, which is imprecise at the level of the individual patient. The individual patient's views are important in this and one aspect of care that might affect the acceptability of long-term treatment is the need for regular INR monitoring in the case of vitamin K antagonists. Lack of a need for monitoring with the new technology might be particularly attractive for some patients.

There are some important groups that would need separate evaluation as they were excluded from or not adequately represented in the clinical trials. These would include patients with active cancer, pregnant (and breastfeeding) women, patients with impaired renal function or with disturbances of liver function, intravenous drug users and children. In some of these dabigatran would not be advisable, indeed would be contra-indicated. Additionally there are some situations, eg, venous

thrombosis in unusual sites, where the technology was not tested but might nevertheless be used in clinical practice.

Implementation of the technology would require significant training because VTE is treated right across the spectrum of primary and secondary care, so there are large numbers of health care professionals involved. However, outside certain specialties, treatment of VTE is a relatively infrequent event for a given health care professional, so support would need to be ongoing. And although the new technology is in many ways simpler than standard care, there are significant risks (bleeding and thromboembolism) if not introduced with appropriate training.

A further impact of the technology would be to enable it to be delivered more easily in primary care, a significant advantage overall. However, the advantages and disadvantages of extending anticoagulation need to be reviewed at 3 months and health care professionals involved in such discussions need adequate training. If such discussions/decisions take place in primary care because the new technology enables such a shift, there is a need to train the health care professionals or to make alternative arrangements such as referral to secondary care.

The advantages and disadvantages of the technology

Patients in the trials of dabigatran in treatment of VTE were relatively young (mean age mid-50s) and had fairly normal renal function. Dabigatran is 80% excreted by the kidneys. Organisations such as acute Trusts wish, for reasons of simplicity, governance and cost, to minimise the number of agents used in the treatment of conditions, in this case VTE. There are questions to consider about the generalizability of the data on dabigatran to the general population, in particular to take account of age and impaired renal function. In the clinical trials renal function was estimated using the Cockcroft-Gault formula. In routine clinical practice, where weight is not available to laboratories, renal function is estimated by the MDRD formula. In older patients or those at extremes of body weight there are significant differences between these two estimates of renal function. It is not clear what the impact on drug handling, and therefore risks and benefits, will be if clinicians use the readily available MDRD-based result compared to the method used in the clinical trials.

From the dabigatran trials overall, including those for atrial fibrillation, there is some evidence suggesting that the risks of coronary disease may be higher with this treatment than with vitamin K antagonists. This would need careful review, particularly in view of the recognised association between VTE and subsequent myocardial infarction.

In the clinical trials of dabigatran in atrial fibrillation, two doses were used and are now licensed, the lower dose being used for elderly patients and those with an increased bleeding risk. In VTE treatment only the higher dose was used. This raises concerns about dosing in clinical practice and the potential for confusion by prescribers who may think the lower dose should be used in the same groups as for atrial fibrillation.

Additionally, rivaroxaban (the current sole new oral anticoagulant approved for VTE treatment) is given as monotherapy from the outset, a difference from dabigatran where heparin was used for the initial week or so of treatment in the trials – this creates the potential for confusion (2 different new oral anticoagulant care models, one with and one without initial heparin) and may make rivaroxaban a more attractive option, particularly in primary care.

Any additional sources of evidence

Recent data from the RELY trial of dabigatran in atrial fibrillation have been published showing that there are associations of dabigatran concentrations and frequency of stroke and major bleeding (Reilly PA et al. J Am Coll Cardiol 2014;63:321-8). This raises concerns about how to manage dosing of dabigatran within certain populations. Should there be similar concerns when dabigatran is used for treatment and secondary prevention of VTE? Does Boehringer Ingelheim have such data on file for VTE?

Implementation issues

As alluded to above, significant extra training would be required for health care professionals. Care pathways, which vary in detail locally, are in place across the NHS and implementation of this new technology is not a simple question of using dabigatran in place of warfarin but requires skilling up staff and enabling them to counsel patients about the relative merits of different interventions. Acute Trusts and commissioners will need to review the evidence and come to local views and agreements about how to re-organise care pathways and so on. This will take longer than 3 months.

At the time of writing dabigatran has not been licensed by the EMA for treatment and secondary prevention of DVT and PE.

Equality

There are no obvious concerns of the technology for groups who are protected by equality legislation. The impact, as referred to above, is that certain groups are not suitable for use of this technology on medical grounds.