

## Appendix D – Clinical specialist statement template

### Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation

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:** Professor Gregory Y H Lip

#### Name of your organisation

University of Birmingham, UK – nominated by the 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? 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)

I was the clinical adviser to the NICE guidelines on atrial fibrillation (2006), as well as the stroke prevention section lead for the 2010 European Society of Cardiology guidelines on atrial fibrillation and Deputy Editor ('content expert') for the 9<sup>th</sup> American College of Cardiology guidelines on antithrombotic therapy for atrial fibrillation (due Jan 2012).

I have chaired position documents or consensus statements from the European Society of Cardiology Working Group on Thrombosis and the European Heart Rhythm Association, in relation to antithrombotic therapy and atrial fibrillation.

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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.*

Stroke prevention is central to our everyday management of atrial fibrillation (AF). AF is the commonest cardiac rhythm disorder. Strokes in AF are associated with a greater mortality, greater disability, longer hospital stays and lower rates of discharge to own homes.

When compared to control/placebo, oral anticoagulation (OAC) significantly reduces stroke and all cause mortality.

Until recently, the only available OAC agent was warfarin, which has significant limitations and disadvantages, including the need for monitoring, drug/food/alcohol interactions etc. It is pretty well accepted that the best way to prevent strokes in AF is by use of OAC.

In the NHS, most AF is managed by general practitioners and cardiologists, although very common in geriatric practice. OAC use varies, usually due to physician *and* patient concerns over the safety and difficulties with managing warfarin.

There is a misconception that aspirin is a useful alternative to warfarin, but the available evidence shows a nonsignificant small impact on stroke, with no difference in major bleeding with aspirin compared to warfarin, esp in the elderly.

As alternatives to warfarin, new OACs have been in development for stroke prevention in AF, broadly in 2 classes – the oral direct thrombin inhibitors (eg dabigatran – part of this appraisal) and oral Factor Xa inhibitors (eg, rivaroxaban, apixaban). These drugs are given in a fixed dose, and do not need monitoring, and have few drug/food/alcohol interactions.

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The main disadvantage is the moderate half life, so if patient compliance is poor and a few doses are missed, the patient may have limited protection against thrombosis. Also, there is no specific antidote in cases of overdose or bleeding.

Dabigatran can be used in most settings where AF patients present – including primary and secondary care. In 2006, the NICE AF guidelines stated that ‘OAC should be started without delay, after the diagnosis is confirmed. The risk of stroke can largely be assessed on the basis of clinical stroke risk factors.

Dabigatran is already available in UK for short term use as prophylaxis against venous thromboembolism. It is awaiting licence for stroke prevention in UK (at time of writing – June 2011).

The European Society of Cardiology guideline (2010) mention that dabigatran is an alternative to warfarin, for stroke prevention in AF. The focussed update from the American College of Cardiology/American Heart Association/Heart Rhythm Society (2011) say the same. Both guidelines are largely based on expert consensus.

The Canadian Cardiovascular Society guidelines (2011) state that dabigatran should be used in preference to warfare, for stroke prevention in AF. These guidelines are based on GRADE methodology.

The UK NICE guidelines from 2006 are outdated, and a new revision is anticipated in 2012.

### **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?*

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Dabigatran was tested in the large RELY trial – the 110mg BID dose had noninferior efficacy for preventing stroke/systemic embolism and 20% less major bleeds compared to warfarin; the 150mg BID dose had approx 35% superior efficacy and similar rates of major bleeds to warfarin. Both dabigatran dose arms has significantly less intracranial bleeds or haemorrhagic strokes, compared to warfarin – even in the subset with well controlled warfarin (as reflected by high time in therapeutic range, >72.6%). Both dose arms also had less life threatening bleeds. There was a significant reduction in vascular mortality ( $p=0.04$ ) and borderline reduction in all cause mortality ( $p=0.05$ ) with dabigatran 150mg BID compared to warfarin. An indirect network analysis shows that dabigatran 150mg BID resulted in a significant reduction in all cause mortality vs placebo.

Dabigatran will be easier to use than warfarin – no monitoring, no significant drug/food interactions.

Use with a few drugs eg verapamil can increase dabigatran drug levels, but this has not translated to a material impact on bleeding etc.

Patients do NOT like attending for anticoagulation monitoring, and the lifestyle restrictions associated with warfarin (perceived to be ‘rat poison’)

Whilst there is a tendency to compare the actual cost of the drug *per se* ie. dabigatran (expensive) vs warfarin (cheap), it is important to consider the wider picture – the potential increased uptake and improved efforts at preventing stroke (a major burden on NHS costs), superior efficacy on preventing stroke/systemic embolism with dabigatran 150mg BID compared to warfarin, less intracranial bleeds (the most feared complication of OAC with high mortality and morbidity) compared to warfarin

The European Society of Cardiology guidelines (2010) provides text on how to choose between dabigatran 110mg BID and 150mg BID on the basis of a simple bleeding risk assessment score, HAS-BLED (see text of guideline for details).

The trial evidence seems applicable to clinical practice – the RELY trial was conducted in a PROBE design, so the everyday management reflects the use by clinicians of this drug. A substudy on  $n=1800$  cardioversions has been published, showing that it is generally safe to cardiovert AF patients on dabigatran. Data in secondary prevention cohort (approx 20% of the RELY population) have been published, as has an analysis by CHADS2 score showing that dabigatran works consistently across a range of stroke risk starta.

A indirect and network metaanalysis confirms consistency of RELY with the performance of warfarin in historical trials. One Markov decision analysis model comparing the relative hazard of ischaemic stroke vs the relative hazard of intracranial bleeds suggests that a new OAC such as dabigatran treatment should even be considered in AF patients with an ischaemic stroke rates of 0.9% and above.

3 cost-effectiveness studies (2 USA, 1 Canada) have already been published, and all 3 independently and consistently show that dabigatran is cost effective therapy.

In RELY there was a higher prevalence of dyspepsia compared to warfarin, and an increase numerically (but not statistically significant) in myocardial infarction events in dabigatran treated patients. No liver toxicity issues were identified.

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### **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.*

Dabigatran has been approved by the US FDA – the submitted file, available on the FDA webpage contains a lot of data, including nonpublished information.

### **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)?*

Uptake in countries where dabigatran has been approved (eg USA, Canada, Far East) has been very high.

The drug is already available in the UK and Europe for venous thromboembolism.