# Royal College of Physicians

Professor Carole Longson
Director, Centre for Health Technology Evaluation
By e-mail

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Dear Professor Longson

**Re: Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation - Appraisal Consultation Document (ACD)**

> The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 25,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

The RCP is grateful for the opportunity to respond to the above ACD consultation. We would like to make the following comments.

We note that the committee has requested further information from the manufacturer before a decision is made to recommend (or not recommend) the use of dabigatran etexilate for the prevention of stroke and systemic embolisation in people with atrial fibrillation. This information will include a cost effectiveness analysis comparing dabigatran with warfarin using different effectiveness data, different scenarios for reflecting the cost of warfarin monitoring, and assumptions suggested by the ERG.

**1. Has all of the relevant evidence been taken into account? Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

We believe that the ACD presents a reasonable interpretation of the evidence for the use of dabigatran etexilate as stroke prevention therapy, versus the currently available treatment, which is warfarin.

**2. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**

The provisional recommendation by the committee is suitable. Our experts would like to make the following points regarding requests made by the committee for further analysis and information:

i) European marketing authorisation has apparently restricted the use of dabigatran as a long-term anticoagulant to a dose schedule based on age, so that the higher dose of 150mg bd will only be available to patients aged <80 years and the lower dose of 110mg bd will be used in all patients aged ≥80 years. The

committee has requested a re-analysis of the cost effectiveness of dabigatran versus warfarin based on this sequential regimen using relative risks from the whole cohort, rather than those based on a post-hoc subgroup analysis of treatment effects at age <80 years and ≥80 years. However, a pre-specified subgroup analysis of patients aged <75 years and ≥75 years did reveal significant treatment by age interactions at different doses of dabigatran, and these effects would be lost if data from the whole cohort are used. The relative risks based on analyses of the pre-specified age groups should be reasonable approximations of expected outcomes in the groups aged <80 and ≥80 years, and could be used instead.

ii) The committee noted that a key uncertainty was the generalisability of the results from RE-LY to people with AF in the NHS. The committee asked for a resubmission of the cost-effectiveness analysis using a patient cohort representing people with AF in the UK (Gallagher et al 2008). The UK cohort, which was taken from the GP research database from 2000 onwards, included all patients with AF aged above 40 years. The UK cohort therefore included patients aged <65 years, and also included a significantly higher proportion of patients with lower CHADS2 scores compared to the RE-LY cohort; 43.2% of the UK cohort had a score of <2 versus 31.9% of the RE-LY cohort. Therefore the RE-LY cohort is probably more representative of the patient population who are eligible for thromboprophylaxis with anticoagulation based on current NICE guidelines.

iii) The committee asked that the cost-effectiveness model is run using a per-patient cost of £115.14 for anticoagulant monitoring. This cost of £115.14 is likely to be an underestimate - as it is not clear that it takes into account the costs of monitoring warfarin in patients who are unable to attend anticoagulation clinics and require district nurse visits for blood testing or supervision of warfarin administration.

iv) The committee asked that the cost-effectiveness model is run assuming that disability and mortality risks after stroke are treatment-independent. However, there is evidence that the severity of ischaemic stroke is reduced in patients taking warfarin compared to those taking aspirin, and reduced in patients on warfarin with therapeutic INRs versus those with subtherapeutic INRs.(Hylek et al, New England Journal of Medicine 2003) As dabigatran users are more likely to be adequately anticoagulated compared to warfarin users, given the relative lack of drug and food interactions associated with dabigatran use, it is expected that fewer ischaemic strokes occurring in dabigatran-users will be fatal or disabling compared to ischaemic strokes occurring on warfarin. Therefore a cost-effectiveness model which disregards this effect will be biased in favour of warfarin.

**3. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?**

We have not identified any aspects of the recommendations that unlawfully discriminate against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief.

**4. Are there any equality -related issues that need special consideration and are not covered in the appraisal consultation document?**

The present situation in which there is reduced access to anticoagulation monitoring and treatment among patients with limited mobility or age-related illnesses such as early dementia has not been taken into account in the present cost-effectiveness analysis.

A high proportion of patients who would benefit from anticoagulation are elderly, relatively immobile, socially isolated and/or suffering from cognitive difficulties. Such patients, who are otherwise eligible for anticoagulation, are often never offered treatment (Gallagher et al, Journal of Thrombosis and Haemostasis, 2008) or decline treatment, because warfarin is perceived as being too inconvenient or too unsafe to use if there are doubts about the patient's compliance and cooperation with treatment monitoring. Cognitive impairment in particular is recognised as an independent risk factor for bleeding complications on warfarin therapy, (Diug et al, Stroke 2011).  With adequate support and supervision from services such as district

nursing, there is no reason why patients with early dementia cannot take warfarin safely. The limiting factor is access to such support services.

Dabigatran is more likely to be acceptable to patients and clinicians when patients have difficulties travelling to anticoagulation clinics to comply with monitoring or have cognitive impairment and struggle with dose changes, as this drug does not require blood test monitoring, and dosing is fixed which means that the drug can be safely added to dosette boxes and taken alongside the patient's other medications. This in turn is likely to increase the uptake of anticoagulation in patients at risk of thromboembolic events across the community, and produce savings through the prevention of a greater number of thromboembolic events.

Such savings are not reflected in the current version of the Markov model used to evaluate the cost effectiveness of dabigatran versus warfarin. In this model, the assumption is that all patients start treatment when offered either warfarin or dabigatran. Although some allowance is made for switching from one medication to another or stopping treatment if adverse effects occur, the model does not allow for the possibility that fewer patients may decide to start anticoagulation when offered warfarin compared to dabigatran. Data on the likely difference in uptake between the two medications are probably lacking, but plausible differences in uptake could be factored into the model as part of a sensitivity analysis.