

30th August 2011

National Institute for Health and Clinical Excellence

Dear [REDACTED]

RE: Dabigatran etexilate for the prevention of stroke and systemic embolism in people with atrial fibrillation as an alternative to adjusted dose warfarin

On behalf of Commissioning Support, Appraisals Service (CSAS), Solutions for Public Health, I would like to submit our comments on the appraisal consultation document for Dabigatran etexilate for the prevention of stroke and systemic embolism in people with atrial fibrillation as an alternative to adjusted dose warfarin.

We are in agreement with the recommendations in the ACD not to recommend dabigatran for this indication as on the basis of the evidence considered it is unlikely that this treatment can be considered clinically and cost effective as a replacement for warfarin.

- **Warfarin is the most cost effective treatment in patients with atrial fibrillation with INR control within the recommended range.** In this group, the ICER for dabigatran vs warfarin is £60,895 per QALY. The Committee has requested 'further comment and consideration' of cost effectiveness in this subgroup. The focus of further review should be on those patients with poor INR control where dabigatran might offer a cost effective treatment.
- **The manufacturer of dabigatran has assumed higher attendances for monitoring warfarin than is usual in clinical practice.** They estimate 20 visits per year per patient for INR monitoring where clinical practice suggests that 5-12 visits is more realistic. This makes warfarin appear more expensive and consequently makes dabigatran appear relatively cost effective.
- **Time in therapeutic range should be considered in sensitivity analysis of clinical and cost effectiveness.** In the RE-LY study, mean TTR for warfarin in the UK was 72% . The RE-LY study did not demonstrate superiority of dabigatran over warfarin above a median TTR of 67%.
- **Time horizon should be included in further assessments of cost effectiveness.** The time horizon influenced the ICER greatly with a 2-year time horizon resulting in ICERs of £75,891per QALY in people under 80yrs old and £23,403 per QALY in people over 80 yrs old for the dabigatran sequential regimen vs warfarin.
- **No information is provided regarding dabigatran as a second line treatment in patients who are inadequately treated with warfarin.** This is a potential treatment option that was not modelled in the manufacturer's submission but it should be considered in case it is a cost effective treatment in this specific patient group.
- **Safety.** There is an increased risk of gastrointestinal bleed with dabigatran 150mg and there is no specific antidote in the event of haemorrhage or overdose. The RE-LY study was conducted over a 2 year period and further safety data over a longer time period should be requested.

- **Patient Acceptability:** Discontinuation rates in the RE-LY study were higher amongst patients treated with dabigatran than with warfarin. This is not clearly explained. Warfarin, unlike dabigatran, is associated with a number of inconveniences such as food and drug interactions, regular monitoring and dose adjustments which can cause disruption and inconvenience. However a quantification of this impact was not presented in the ACD and factored into the cost effectiveness model. Proper quantification of this could affect the relative cost effectiveness of dabigatran compared to warfarin.
- **There were limitations to the quality of the research: Patients were treated in the RELY study who would not have been eligible for treatment in the UK, using the current NICE guidelines. This affects the generalisability of the RELY study to UK clinical practice.**