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National Institute for Health and Clinical Excellence
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Re: Dabigatran etexilate for the prevention of stroke and systemic embolism in people with atrial fibrillation ACD

On behalf of NHS Salford I would like to submit our comments on the above appraisal consultation document for which NHS Salford is a consultee.

Comments from Public Health Manager

- From the evidence presented we are in agreement with the Committees view not to recommend dabigatran etexilate for the prevention of stroke and systemic embolism and would view this as suitable guidance for the NHS.

- The ACD highlights areas of uncertainty regarding cost effectiveness and we would agree with the Committees request for further analysis. In particular the agreement of the suitable time horizon for this patient group, number of monitoring appointments and the investigation of cost effectiveness for those who have poorly controlled INR versus those with stable INR. Greater Manchester cardiac network have recommended this definition of poorly controlled as

Indicators for instability of anticoagulation include:

- Low time in therapeutic range (TTR) once stabilised on warfarin (usually 5 months.) The INR % of time in the therapeutic range of 2-3 should be 60% or greater. (TTR should be measured for individual patients using the Rosendaal Method)

- Clinic visit frequency greater than 50% above the clinic schedule of visits for patients who stay consistently within the target INR after stabilisation.

- Increases in visits that are predictable e.g. due to co-prescription of antibiotics, inter current illness, vomiting providingthese are infrequent should be excluded from this calculation.

- Initial stabilisation cannot be achieved within three months

- INR >5 more than 5 times per year

- We would also be interested in the quantification of the impact of an increased gastrointestinal bleed on NHS resources compared to lower incidence of haemorrhagic stroke and intracranial haemorrhage. Equally consideration of the higher discontinuation rates considering the advantages outlined of less inconvenience for patients. It is also not clear what the affect of dabigatran would be for NHS anticoagulation services in terms of overall societal costs.

Medicines management team comments

NHS Salford agrees with many of the statements noted in the CSAS review as detailed below

- 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. We feel further review should be on those patients with poor INR control where dabigatran might offer a cost effective treatment. This is where GM cardiac network have positioned this drug (see attached algorithms)

- 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.

- Also, PCTs might currently be in block contracts for anticoagulation services which are not able to respond quickly to changes in demand for attendances that dabigatran patients would produce. The savings in clinic attendances may not materialize in practice and if it does so it will not be immediate.

- 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. This is where GM cardiac network has positioned this drug (see attached algorithym)

- 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. Recent restrictions to the drugs license in Japan need examined (we have not yet received the data surrounding this from the company despite asking for it).

- 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.

- We feel the issue of patient choice needs to be clarified and that just because patients want dabigatran (who have stable INRs on warfarin) this is not enough reason to switch therapy.

- A clear positioning statement that this is a second line treatment in those who cannot be managed on current accepted UK treatment (warfarin) would allow PCTs to use this new drug in patients that will benefit from it and in an affordable way to the NHS.

Comments received from the Greater Manchester Cardiac Network

- We agree with the comments in the CSAS document in that the focus on the further review, specifically looking at cost effectiveness should be on the group of patients with poor INR control on warfarin and who also have a CHADSVASC score of 3+

- Warfarin should remain the 1st line treatment and in accordance with the attached algorithms and guidance which have been developed with clinicians across Greater Manchester

- An economic model has been developed in Greater Manchester, which is currently being validated by Manchester University which will support PCTs in planning their services by gaining a better understanding of the impact of the introduction of *any* new anticoagulation therapies for the treatment of patients with AF. The model aims to use local population data combined with the attached treatment algorithm to identify potential eligible patients for the new treatments and compare this with alternative scenarios. The data to populate the model will be obtained by running the GRASP-AF tool

- We believe that the drug should only be prescribed in primary care and then only after communication is received from the anti-coagulation clinic/GPwSIs or locally agreed 'gatekeeper' has confirmed all reasonable attempts to maintain stable INRs of 2-3 have been exhausted or that patients have been stopped due to contra-indications or adverse drug reactions

- The number of attendances for monitoring warfarin is largely irrelevant in cost effectiveness terms for those commissioners who have block contracts

- Further work is needed to define what is classed as 'poor control' as estimated visits per year per patient may not be a good enough marker

- As Rivaroxaban is hot on the heels of Dabigatran should NICE consider a multi-technology appraisal not two single appraisals