NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

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

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Boehringer-Ingelheim	Yes, this is an appropriate topic for appraisal. The topic addresses an area of NHS priority (prevention of stroke) in a large population of patients who on average suffer more severe strokes. Further, there is a large unmet need with many AF patients receiving inadequate, inappropriate or no antithrombotic therapy.	Comment noted, no action required.
	British Association of Stroke Physicians	As highlighted in the remit, atrial fibrillation is increasingly prevelant in an ageing population and associated with a high risk of stroke recurrence. Anticoagulation with warfarin is a recognised therapy for the primary and secondary prevention of stroke and TIA in atrial fibrillation patients. Nonetheless there are a number of limitations to anticoagulation therapy with warfarin, and therefore the assessment of alternative agents is appropriate.	Comment noted, no action required.
Wording	British Association of Stroke Physicians	The wording is appropriate.	Comment noted, no action required.
Timing Issues	Boehringer-Ingelheim	The timing is appropriate.The review of the NICE Clinical Guideline for the management of atrial fibrillation (36) is due to be published in June 2010, coinciding with the upcoming launch of this technology. This technology will be the first new oral anticoagulant in this indication for over 50 years, therefore it is wholly appropriate that it is appraised as soon as possible.	Comment noted. The clinical guideline on the management of atrial fibrillation will be considered for review in 2011.
	British Association of Stroke Physicians	It is my understanding that the RELY Trial will not present until the European Society of Cardiology Meeting In September 2009. It therefore seems appropriate that the appraisal is not timed until after the availability of the efficacy trial results.	Comment noted, no action required.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	British Association of Stroke Physicians	Bleeding complications of anti-coagulation should be discussed within the background. The use of validated scores to predict future stroke risk may be useful e.g. CHADS.	Comment noted, no action required.
The technology/ intervention	British Association of Stroke Physicians	This is appropriate.	Comment noted, no action required.
Population	Boehringer-Ingelheim	Please redefine as: "People with non-valvular atrial fibrillation at moderate to high risk of stroke, or systemic embolism, with at least one additional risk factor."	Comment noted. Consultees at the scoping workshop agreed that the population should be defined as the following: people with atrial fibrillation at moderate to high risk of stroke or systemic embolism. The scope was amended accordingly.
	British Association of Stroke Physicians	This is appropriate. However, anticoagulation with warfarin is more likely to be associated with symptomatic intracranial haemorrhage as a complication of therapy in patients with hypertension, severe leukoareosis, and elevated INR values. It may be considered important to review these subgroups if data are available.	Comment noted. These subgroups were discussed at the scoping workshop and consultees agreed that they were not relevant. Therefore the scope has not been amended in regard to these subgroups.

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Comparators	Bayer Healthcare	Xarelto (rivaroxaban) is currently in phase III development for the prevention of stroke for atrial fibrillation and will be a comparator for Pradaxa (dabigatran).	Comment noted. Following the scoping workshop, the comparators in the scope have been updated and now include warfarin, and, in people for whom warfarin is unsuitable, antiplatelet agents (such as aspirin).
	Boehringer Ingelheim	It is important that the definition of "moderate" risk and "high" risk of stroke is clarified. The current NICE Clinical Guideline (36) provides for both warfarin and aspirin as treatment options for patients at "moderate" risk. Therefore the scope is incorrect to state that warfarin is the comparator in high risk patients only with aspirin the comparator in moderate risk patients. Warfarin is applicable for both. The guideline is currently being reviewed, with publication planned for June 2010. Should the revised guideline advocate another risk stratification method (such as CHADS2) then the "moderate" risk stratification may effectively disappear and aspirin may no longer be a receommended as a standard treatment option for such patients by the time of this appraisal. It is recognised however that aspirin may be used in patients who are unsuitable for warfarin. Aspirin is the only antiplatelet therapy licensed in this indication, other antiplatelet therapies (e.g. clopidogrel or dipyridamole) are not licensed in this indication. The "best alternative care" for patients at moderate to high risk of stroke is adjusted-dose warfarin and this should be the principle comparator in this appraisal. The large (18,000+ patients) pivotal phase-III clinical trial (RE-LY) compares dabigatran etexilate with adjusted-dose warfarin.	Comment noted. Consultees at the scoping workshop agreed that warfarin is offered to people with atrial fibrillation who are at moderate to high risk of stroke, for the prevention of stroke. Following the scoping workshop, the comparators in the scope have been updated and now include warfarin, and, in people for whom warfarin is unsuitable, antiplatelet agents (such as aspirin).

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	British Association of Stroke Physicians	The standard treatments according to NICE Guidelines are listed. Warfarin would be considered the best alternative care in those patients to whom it can safely be prescribed.	Comment noted. Following the scoping workshop the comparators in the scope have been updated and now include warfarin, and, in people for whom warfarin is unsuitable, antiplatelet agents (such as aspirin).
Outcomes	British Association of Stroke Physicians	These are appropriate, though it would be important to define haemorrhage by intracranial and extracranial groups.	Comment noted. Consultees at the scoping workshop agreed that haemorrhage should not be defined as intracranial and extracranial. Therefore no further changes to this section of scope were made.
Economic analysis	British Association of Stroke Physicians	This is an important consideration given that a significant proportion of costs associated with warfarin relate to monitoring. It would be noted that even if the results with Dabigatran etexilate are favourable for stroke prevention in atrial fibrillation, there will remain a lack of evidence in certain subgroups (e.g. those with mechanical heart valves) which would necessitate the continuation of monitoring services for those taking warfarin therapy.	Comment noted, no action required.

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Equality and Diversity	Boehringer-Ingelheim	Aspirin has been shown to be inferior to warfarin in the prevention of stroke in AF patients. Warfarin has many interactions and may require frequent INR tests and dose adjustments. The introduction of a clinically and cost-effective technology that avoids many of these problems can only improve access to treatment for patients, especially those who, for whatever reason, are receiving inadequate, inappropriate or no antithrombotic therapy.	Comment noted. Consultees thought that dabigatran, due to less therapeutic monitoring required, could potentially improve access to treatment to people for whom therapeutic monitoring is difficult. Therefore, the other considerations section of the scope was amended to include the following: 'Consideration should be given to the advantage of dabigatran in terms of its lower requirement for therapeutic monitoring.'
	British Association of Stroke Physicians	There should be no specific equality issues, as anti-coagulation where indicated (and not contra indicated) should be offered to all. There have been historical concerns about anticoagulation in an older population, though the BAFTA Trial has indicated that warfarin therapy is safe and effective in an older population for stroke prevention in patients with atrial fibrilation.	Comment noted, no action required.
Other considerations	Boehringer-Ingelheim	RE: Is the subgroup "people who have had a prior stroke/TIA" relevant to this appraisal? It is unclear why this particular subgroup of patients would be of interest here as opposed to any of the other cumulative risk factors for stroke (cf. CHADS2). This comparison would suggest a comparison specifically for secondary prevention of stroke which, in our opinion, is outside the remit of this proposed appraisal. A potential subgroup for investigation is those patients naïve to warfarin.	Comment noted. Consultees at the scoping workshop agreed that the suggested subgroups were not relevant and the scope has been amended accordingly. The subgroup of people who are naïve to warfarin has been added to scope.

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	British Association of Stroke Physicians	It is important that the following comments on the subgroups identified are considered: people who have had a prior ischaemic stroke/TIA episode:-there will remain patients in whom anticoagulation therapy would be inappropriate (for example those who abuse alcohol, those at significant risk of intra-cranial and extra cranial haemorrhage) and Dabigatran etexilate as with warfarin would not resolve these issues. Nonetheless, if compliance with monitoring was considered to be a contra-indication to warfarin therapy, then this may be overcome by the use of Dabigatran etexilate given the suggested lack of need for monitoring. Dabigatran etexilate remains an anticoagulant, and as with warfarin there would remain concerns about prescribing it ot patients at increased risk of intra-cranial or extracranial haemorrhage.	Comment noted. Consultees at the scoping workshop agreed that the suggested subgroups were not relevant and the scope has been amended accordingly.

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Questions for consultation	Boehringer-Ingelheim	RE: Clopidogrel plus aspirin. This combination is not yet licensed for this indication, therefore can it be considered as a comparator at all? If so, we would like to place this comparison in context. The ACTIVE-W study was halted early given the clear superiority of warfarin over clopidogrel plus aspirin in the prevention of stroke in AF patients. The ACTIVE-A trial examined only patients who were unable or unwilling to take warfarin. It has demonstrated that clopidogrel plus aspirin is superior in terms of stroke prevention compared to aspirin alone, although major bleeding was also significantly higher. Clearly then, this combination could only be considered as a potentially appropriate comparator for dabigatran etexilate in the subgroup of patients for whom aspirin is the correct current comparator. That is, patients at sufficient stroke risk to be eligible for oral anticoagulation, but unsuitable for warfarin. The relative size of this subgroup is unknown and will depend on how "unsuitability" for warfarin is defined. It is not sufficient to suggest that patients who simply prefer not to receive warfarin are therefore unsuitable for warfarin when there is no clinical reason why they should not receive it. We would suggest that only patients geuninely unsuitable for warfarin should be considered for this comparison. Even then, some patients unsuitable for warfarin will also be unsuitable for dabigatran etexilate (contra-indicated to any anticoagulant). That is, only those patients eligible for anticoagulation AND unsuitable for warfarin AND suitable for dabigatran etexilate could be considered for this comparison. For any other patient within this remit, clopidogrel plus aspirin will not be appropriate (cf: ACTIVE-W). The likely size of this subgroup should be identified to inform the comparator decision.	Comment noted. Consultees at the scoping workshop agreed that clopidogrel plus aspirin was not an appropriate comparator.
	British Association of Stroke Physicians	Clopidogrel + aspirin as an appropriate comparator. I presume this is on the basis of the ACTIVE trial, and I note that this is the subject of another draft scope. 2 - Other subgroups. Please see my comments in the other consideratiions section 3. Equality - please see comments in appropriate section	Comment noted. Consultees at the scoping workshop agreed that clopidogrel plus aspirin was not an appropriate comparator.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

- NHS Quality Improvement Scotland
- Research Institute for the Care of Older People
- Welsh Assembly Government
- National Public Health Service for Wales
- Royal College of Nursing
- Department of Health
- Teva UK