Response to:

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Appraisal consultation document

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

Prepared by:

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Response to the Appraisal Consultation Document: Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation

Approved Name of Medicinal Product:	Dabigatran
Brand Name:	Pradaxa
Company:	Boehringer Ingelheim

Bristol-Myers Squibb Pharmaceuticals Ltd. and Pfizer Ltd. welcome the opportunity to review and comment on the Appraisal Consultation Document (ACD) relating to the ongoing appraisal of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation (AF).

BMS/Pfizer believe that AF patients should have access to all efficacious medicines in the UK. However, we have some concerns about the basis of the Appraisal Committee's (AC) conclusions relating to the appraisal of dabigatran. In summary:

- We believe that any recommendation for dabigatran should be specifically for patients suitable for warfarin, as there is no robust evidence in patients unsuitable for warfarin. Furthermore, the clinical data suggest that this recommendation should be further restricted to patients who are not at high risk of bleeding.
- Robust warfarin monitoring costs are not available for this appraisal. Those previously developed by NICE should be used as a basis for decision-making, rather than the alternative estimates preferred by the ERG, which are less representative of UK clinical practice and more opaque in their methodology. It should be noted, however, that even the costs developed by NICE require further refinement as they may underestimate the monitoring costs in the UK.
- Cost effectiveness analyses of medicines in AF should assume that the risk of disability and mortality post stroke are treatment dependent. They should also examine the impact of time in therapeutic international normalised ratio (INR) range (TTR) rather than INR ranges alone.

We therefore ask the AC to take these comments into account in its reconsideration of its preliminary recommendation..

Detailed Comments in ACD

Our detailed comments on the ACD and Evaluation Report are structured under the four questions posed by NICE in the consultation:

1. Has all of the relevant evidence been taken into account?
2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

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

1. Has all of the relevant evidence been taken into account?

BMS/Pfizer consider that all relevant clinical evidence has been taken into account, and we are not aware of any additional cost effectiveness evidence that should be taken into account

2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

BMS/Pfizer disagree with some of the summaries of clinical and cost effectiveness and believe they are not reasonable interpretations of the evidence.

Clinical evidence

Results of the RE-LY study indicate that dabigatran 150mg is superior to warfarin in preventing stroke and systemic embolism, however, we note the high rates of bleeding in patients taking the 150mg dose. Both doses of dabigatran were associated with a higher rate of gastrointestinal (GI) bleeds (dabigatran 150 mg: RR 1.50, 95% CI 1.19 to 1.89 p<0.001; dabigatran 110 mg: RR 1.10, 95% CI 0.86 to 1.41 p 0.43).[1] Consideration should therefore be given to NOT recommending dabigatran in patients who have a high risk of bleeding.

Whilst the RE-LY study shows superiority for dabigatran 150mg compared with warfarin in preventing stroke and systemic embolism, we do not agree with the ERG's view that the open label design of this trial is free from bias. Patients who had previously failed with warfarin, and who were then subsequently randomised to the warfarin treatment arm, would be aware of the treatment they were receiving and would be more likely to discontinue from the study.

Furthermore, whilst the adjudication of events in the study was blinded, there could still be a reporting bias because patients or clinicians might be more likely to report an event where they are aware of the treatment assigned.

An illustration of the potential impact of open label vs double blind double dummy trials is given by comparing the SPORTIF III [2] and V trials [3]. SPORTIF III and V were trials with identical protocols but SPORTIF III uses a PROBE design whereas SPORTIF V was a double-blind RCT. The incidence of stroke events was found to be lower in the ximelagatran arm compared with the warfarin arm in the open label study, wheras in SPORTIF V the opposite result was observed. Apart from the countries involved, there were few differences between these trials, including TTR, which was similar (66% in SPORTIF III and 68% in SPORTIF V). Although it is impossible to establish the exact reason for this discrepancy in the results, the possibility that knowledge about novel therapy or warfarin treatment assignment on the part of those collecting outcome measurements could have contributed to the observed results cannot be excluded. Therefore a similar possibility exists and cannot be excluded with regard to the RE-LY study.

Both of these potential effects may over-estimate the benefit of dabigatran in the trial. Clinical evidence should therefore ideally be derived using a double-blind, double dummy, randomised, controlled trial.

Finally, the majority of patients within the RE-LY study were those who would be suitable for warfarin. This means that the efficacy and safety of dabigatran has not been studied in patients who are unsuitable for warfarin – which is likely to be a significant proportion of AF patients in the UK. Consideration should therefore be given to recommending dabigatran in warfarin suitable patients only, rather than all non-valvular AF patients, as per the licensed indication.

Cost effectiveness evidence – monitoring costs

According to the ERG, a key weakness in the manufacturer's model is the choice of anticoagulation monitoring cost. They believe the manufacturer's preferred cost is an over-estimate, so as a consequence have introduced a much lower monitoring cost into the appraisal compared with that preferred by the manufacturer. BMS/Pfizer believe that the manufacturer has systematically reviewed the cost literature and appropriately chosen the most generalisable cost to the UK population – which is that derived by NICE in the costing template for their AF clinical guideline [4]. This cost is partly based on NHS reference costs (which are routinely used in economic evaluations) and are more nationally representative compared with costs derived from local studies. However, this cost is still limited because the resource use in primary care is based on crude and unsubstantiated assumptions, and so in the longer term, more robust estimates will be required.

The cost preferred by the ERG is derived from a cost effectiveness analysis undertaken by Connock et al. [5], which estimated the cost of warfarin monitoring to be £98.47 (£73.86 - £123.09) (2005 prices) using the SMART trial [6] and the economic methods of Jowett et al. [7]. As there is very limited information in these publications regarding the quantities of each type of resource use, it is unclear how robust and nationally representative these costs actually are. This study bases the resource use on what was observed in the SMART trial; however, this may not be representative of clinics nationally as clinical trials do not often represent routine clinical practice, and the study was undertaken at a specific geographical locality in the UK. On this basis the ERG's monitoring cost of £115 should not be relied upon for decision-making purposes.

BMS/Pfizer also recommend that monitoring costs higher than those being used should be considered by the Committee. For example, the CG36 costs assume that 25% of monitoring will occur in secondary care and 75% in primary care, based on a 2006 survey conducted by the National Patient Safety Agency [8]. However, with the introduction of new oral anticoagulants in the UK, consideration should be given to a potential shift of use to centralised clinics concentrated within secondary care, in order to achieve economies of scale. This is very likely to occur if the use of warfarin reduces the need for the majority of monitoring to be carried out in primary care. As such, we recommend that alternative estimates be considered based on a higher percentage of monitoring being undertaken in secondary care. Increasing the ratio for secondary care

monitoring from 25% to 75% significantly increases the CG36 cost (**from £382.9 to £504.9 at 2006 prices**), which implies that the current costs being considered by the AC are potential under-estimates.

In addition, the ERG (see table 51 pp116 of ERG report) consider two scenarios: (1) the possibility of the variable costs of primary care being savings (ERG alternative 1) and (2) only the variable costs of primary and secondary care being savings (ERG alternative 2). However, the calculations made to deduct fixed secondary care costs from the NHS references are arbitrary and crude. Furthermore, BMS/Pfizer do not agree with the ERG's assumption that primary care fixed costs would not be saved as a result of the introduction of new oral anticoagulants not requiring routine monitoring. Indeed, we would expect a reduction in the number of clinics in primary care and at least some fixed cost savings to be made by the NHS. In addition, with a rescaling of clinics in secondary care, due to a reduction in the demand for monitoring, we would expect a reduction in fixed costs too. BMS/Pfizer therefore suggest that fixed costs are included in the savings attributed to new oral therapies.

Cost effectiveness evidence – modelling assumptions

In their economic model the manufacturer assumed that disability and mortality risks after stroke are treatment-dependent, an assumption that the ERG argue is not appropriate. BMS/Pfizer consider that these risks would be treatment independent for chronic or long-term risk of disability and mortality, but not so for acute phases of stroke, where avoidance of severe stroke may impact on both disability and mortality in a treatment dependent manner. For example, the RE-LY [1] study shows that, compared with warfarin, dabigatran 150mg bd significantly reduced the incidence of disabling and fatal stroke (modified Rankin score 3 to 6) with a relative risk of 0.66 (95% CI 0.50, 0.88). Similarly, the AVERROES trial [9] shows that, compared with aspirin, apixaban results in a significantly lower incidence of disabling and fatal strokes (modified Rankin score 3 to 6) of 2.3% vs 1% respectively (0.43 HR (95% CI= 0.28, 0.65). BMS/Pfizer would request that the Committee consider our alternative assumption.

Lastly, we note that the ERG have undertaken an analysis of the cost effectiveness of dabigatran based on those patients who were able to maintain their INR values within particular ranges. We believe this approach is not appropriate because INR is highly variable over time, meaning a significant proportion of patients would be excluded from this analysis if their INR varied across these ranges. Time in therapeutic INR range (TTR) is a more robust approach to capturing the cost effectiveness of dabigatran according to the extent of INR control.

3. The provisional recommendations are a sound and suitable basis for guidance to the NHS

BMS/Pfizer consider the provisional recommendations set out in the ACD are NOT a sound basis for guidance to the NHS.

BMS/Pfizer advocate that AF patients should have access to all efficacious medicines and note that the RE-LY trial suggests that dabigatran 150mg is superior to warfarin in the prevention of stroke and systemic embolism.

BMS/Pfizer would therefore request that any NICE recommendation for dabigatran be restricted to those patients for whom there is sufficient clinical evidence.

Notwithstanding the bias inherent in an open-label trial design, the RE-LY study was undertaken in a predominately warfarin suitable patient population. However, there is an important and significant patient population with AF who are unsuitable for warfarin because of intolerance, poor response or personal preference (factors such as; impact on quality of life, work absence for monitoring, strict monitoring of diet, and other medications). No clinical trial has demonstrated the efficacy and safety of dabigatran in this warfarin unsuitable patient population and so dabigatran should not be recommended for all AF patients in the absence of such evidence.

As mentioned above, BMS/Pfizer also note the higher rates of major and life-threatening bleeding with dabigatran 150mg and would therefore suggest that these patients are specifically excluded from any recommendation by NICE.

In summary, any recommendation for dabigatran should be restricted to non-valvular AF patients who are **suitable** for warfarin and have a low risk of bleeding.

4. 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?

BMS/Pfizer do not consider there are any aspects of the recommendations that need particular consideration regarding unlawful discrimination against any group.

References

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