

Dear Bijal

Please see below our comments on the ACD for dabigatran in atrial fibrillation.

Question: Has all of the relevant evidence been taken into account?

Anticoagulant monitoring cost – ACD 1.2, 3.16, 3.28, 3.30, 3.34, 4.11, 4.15

To estimate the cost of anticoagulant monitoring, the manufacturer derived the value used in the base-case modelling from the NICE costing report that accompanied NICE clinical guideline 36 for atrial fibrillation. The cost of INR monitoring was then inflated to 2010 prices (£414.90). Such costing tools are produced by NICE to allow individual NHS organisations and local health economies to assess the impact guidance will have on local budgets. Therefore, this seems to be a reasonable source for the costs.

The ERG stated that it was likely that the average cost of monitoring had been overestimated in the model, which may bias the results in favour of dabigatran due to the inclusion of fixed costs of monitoring. In their view, fixed costs will only be offset if warfarin is no longer used in the UK and should not therefore be included. The alternative costs used by the ERG were £279.45, £241.54 and £115.14 instead of £414.90 assumed by the manufacturer.

Bayer has a number of comments regarding the issue of the cost of anticoagulant monitoring:

1. We do not agree that the cost of anticoagulant monitoring has been overestimated in the manufacturer's model.
2. It would seem that a costing report produced by NICE is a reasonable reference source for the cost of anticoagulant monitoring in the UK. If it is not considered appropriate, then it could be questioned what purpose it currently serves.
3. We do not agree with the ERG that fixed costs of anticoagulation should be excluded. The monitoring costs proposed by the ERG of £279.36 and £241.54 are therefore not appropriate:
 - According to the Drummond checklist [Drummond et al. Methods for the Economic Evaluation of Health Care Programmes. 3rd Edition. 2005] “.....*Were all the important and relevant costs and consequences for each alternative identified? Were the capital costs, as well as operating costs, included?*”
 - NHS reference costs are a recommended source according to the methods guide [5.5.4 Guide to the methods of technology appraisal 2008]. According to the NHS Reference Costs 2010/2011 Collection Guidance, 2010, “*when undertaking costing of outpatient attendances at procedure level.....All relevant overheads should be included; this covers clinic/location/ treatment function overheads in addition to an element of NHS provider wide overheads.*” Further, “*the fundamental principle is that reference costs should be produced using full absorption costing. This means that each reported unit cost will include the direct, indirect and overhead costs associated with providing that treatment / care*”. Reference Costs data is used for a variety of purposes - including to calculate the PbR tariff. As Reference Costs and Tariff costs are recommended as a source of costs for appraisals [5.5.4 Guide to the methods of technology appraisal 2008] this suggests that costs which include fixed elements are appropriate.
 - Under the resource impact section of the methods guide [5.13. 7 Guide to the methods of technology appraisal 2008] “*If implementation of the technology could have substantial resource implications for other services, the effects on the submitted cost-effectiveness evidence for the technology should be explored.*” Again, this supports the use of the overall cost of the service displaced.

- *“If introduction of the technology requires additional infrastructure to be put in place, consideration should be given to including such costs in the analysis”* [5.5.7 Guide to the methods of technology appraisal 2008]. If such costs are considered worthy of inclusion when additional infrastructure is needed, then the impact of disinvesting in the infrastructure of anticoagulation clinics over time should be modelled. This therefore mandates the inclusion of the fixed costs.
- We strongly believe that fixed costs should be included in estimates of resource use. However, even if this is not accepted to be the case in the short-term, the ERG’s approach of removing all of the fixed costs from the estimate does not seem realistic; fewer patients attending clinics will invariably lead to rationalisation and consolidation of services over time, which will indeed therefore release such fixed costs. Furthermore, without the introduction of the new oral anticoagulants, increasing demand for these services in the future associated with the ageing population may lead to further pressure on existing services or the need to invest in additional clinics.

4. The use of the 2005 Birmingham SMART trial by the ERG which reported an average annual cost of anticoagulation control of £98.47 (inflated to 2009/10; £115.14), seems contradictory to their comment that the manufacturer could have used more current published costs. This study was a randomised controlled trial and therefore could be argued is not representative of routine clinical practice. Patients in the trial had taken warfarin for at least 6 months, with a target INR of 2.5-3.5. Not all of the patients had AF and the mean age of those recruited was 65. GPs were asked to remove patients from computer lists they believed should be excluded from the trial on clinical or social grounds. All of these factors reduce the applicability to the appraisal in question.

5. Bayer agrees with the clinical advisers to the ERG that there is high variability of monitoring costs in practice - variability will be driven by the local arrangements for anticoagulant monitoring. In addition, Bayer agrees that people with well-controlled INR will have lower costs than people with uncontrolled INR.

Dyspepsia associated with dabigatran etexilate treatment – ACD 1.2, 3.32, 3.34, 4.15

Bayer share the concern about whether appropriate costs have been applied with respect to discontinuations (and the implications in terms of stroke risk) due to dyspepsia and the symptomatic treatment of dyspepsia. If the patient does not discontinue due to this side effect of treatment, they are likely to receive symptomatic therapy for longer than the first three months of therapy. In addition, the manufacturer’s submission uses an antacid as first line treatment for dyspepsia – if long term symptomatic treatment is required, the cost of introducing H₂-receptor antagonists or proton pump inhibitors should also be considered.

Long term costs and disutility associated with myocardial infarction – ACD 3.12, 3.26

Bayer agrees with the ERG that long term costs and disutility associated with myocardial infarction should be modelled. Since the Manufacturer’s Submission, further data has been presented that reports acute coronary syndrome events associated with dabigatran and this is therefore an important point - acute coronary syndromes were observed in 13 patients (0.9%) on treatment with dabigatran and in 3 patients (0.2%) on warfarin (P=0.02). [Schulman, S et al. Dabigatran or warfarin for Extended Maintenance Therapy of Venous Thromboembolism, Abstract O-TH-033. Special Issue: Abstracts of the XXIII Congress of the International Society on Thrombosis and Haemostasis 57th Annual SSC Meeting, July 23-28 2011, ICC Kyoto, Japan Volume 9, Issue Supplement s2, p731, July 2011]. The RE-DEEM study has also been published since the submission and this also reports on cardiovascular ischaemic events.[Oldgren, J et al. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. European Heart Journal 2011. doi: 10.1093/eurheartj/ehr113] [Please note - the attached references are subject to copyright and are for your use only.](#)

List of the compressed files:
[j.1538-7836.2011.04380_4.x.pdf](#)
[eurheartj.ehr113.full.pdf](#)

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No comment further to those made above.

Question: Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

No comment further to those made above.

Question: 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?

No comment

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

No comment