

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

HEALTH TECHNOLOGY APRAISAL

Appeal Panel HEARING

Advice on the Single Technology Appraisal of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation

Decision of the Panel

Introduction

1. An appeal panel was convened on 7th February 2012 to consider an appeal against the Institute's Final Appraisal Determination, to the NHS, on the Single Technology Appraisal of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation.
2. The Appeal Panel consisted of:
 - Professor Sir Michael Rawlins, Chair
 - Professor Rona McCandlish, Board Member
 - Dr Catriona McMahon, Industry Representative
 - Mr Bob Osborne, Lay Member
 - Professor R E Ferner. NHS Member
3. None of the members of the Appeal Panel had any competing interest to declare.
4. The panel considered an appeal submitted by NHS Salford PCT.
5. The Appellants were represented by:
 - Dr Peter Budden, General Practitioner and Prescribing Advisor
 - Claire Cheong-Leen, Commissioning Support Advisory Service
 - Dr Joyce Craig, York Health Economics Consortium
 - Dr Peter Elton, Director of Public Health, NHS Bury
 - Claire Vaughan, Deputy Head of Medicines Management, NHS Salford
6. In addition the following individuals involved in the appraisal were present and available to answer questions from the Appeal Panel:
 - Dr Christian Griffiths
 - Janet Robertson
 - Dr Jane Adam
 - Professor Iain Squire
 - Meindert Boysen
7. The Panel's legal adviser, Mr Stephen Hocking, was also present.
8. Under the Institute's appeal procedures members of the public are

admitted to appeal hearings and several members of the public were present at this appeal.

9. There are three grounds under which an appeal can be lodged:
 - The Institute has failed to act fairly
 - NICE has formulated guidance which cannot reasonably be justified in the light of the evidence submitted
 - The Institute has exceeded its powers
10. The Vice-Chair of the Appeal Committee (Mr Jonathan Tross) in preliminary correspondence had confirmed that:
 - The Appellants had potentially valid grounds of appeal as follows: Grounds 1 and 2
11. Dabigatran etexilate (Pradaxa[®], Boehringer Ingelheim; 'dabigatran') is an orally administered anticoagulant that inhibits the thrombin enzyme. Dabigatran has a UK marketing authorisation for the 'prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more of the following risk factors:
 - previous stroke,
 - transient ischaemic attack, or systemic embolism
 - left ventricular ejection fraction below 40% symptomatic heart failure of New York Heart Association (NYHA) class 2 or above age 75 years or over age 65 years or over with one of the following:
 - diabetes mellitus, coronary artery disease, or hypertension.
12. The appraisal that is the subject of the current appeal provided advice to the NHS on the use of dabigatran for the prevention of stroke and systemic embolism in atrial fibrillation.
13. Before the Appeal Panel inquired into the detailed complaints the following made preliminary statements: Dr Peter Elton for the Appellant, and Dr Jane Adam on behalf of the Appraisal Committee.

Appeal by Appellant

Appeal Ground 1: The Institute has failed to act fairly

Appeal Ground 1.1: The PCT is concerned that by not having access to primary care professionals on the Technology Appraisal Committee, or via the professional/specialist groups or selected clinical experts, the Committee has failed to act fairly.

14. Claire Cheong-Leen, for the Appellant, stated that the Appraisal Committee contained no general practitioner. While several specialist

groups were represented, the Royal College of General Practitioners was not. The Institute's own Guidance (Single Technology Appraisal paragraph 3.4.15) states that the Chair and NICE's project team base their choice of clinical specialists and patient experts on the nominees' experience of the technology and the condition(s) that the technology is designed to treat. If possible, the clinical specialists and patient experts will have complementary rather than similar backgrounds and experiences. While diagnosis and the management of complex atrial fibrillation were usually dealt with in secondary care, most patients with atrial fibrillation were cared for by their own GPs.

15. Dr Budden, for the Appellant, stated that GPs were responsible for the day-to-day management of most patients with atrial fibrillation. He believed that the Evidence Review Group had done a good job and had identified a population in whom dabigatran was not cost effective. He, as a general practitioner, did not see that warfarin was as high-risk as suggested. He would prescribe it without hesitation. The guidance gave no assistance to clinicians having to discuss the choice of dabigatran or warfarin with patients.
16. Dr Adam, for the Appraisal Committee, accepted that there had in practice been no GP present at the appraisal committee meetings. Two had been invited to attend, but were unable to do so. The Appraisal Committee was keen to have a Commissioner attend its second meeting, and had contacted NHS Salford Primary Care Trust to arrange that Dr Andrew Sutton, a GP and Commissioner, attended to provide an expert perspective, which he did.
17. Dr Elton confirmed that NHS Salford PCT could, and did, call on GPs in providing a response as Consultees.
18. Dr Cheong-Leen stated that the roles of Commissioner and of General Practitioner were at present separate. The Methods Guide (paragraph 4.5.2) stated that clinical specialists and patient experts are encouraged to interact fully in the debate with the Committee, including responding to and posing questions. In fact, Dr Sutton had only appeared briefly.
19. Dr Adam confirmed that Dr Sutton had been treated no differently than other experts.
20. In response to questions from the Appeal Panel, Dr Budden stated that a general practitioner might have been able to add his or her opinion to those expressed in the Final Appraisal Determination; for example, that the prescribing of warfarin does not represent an insurmountable problem.
21. The Appeal Panel considered that GPs had contributed to the NHS Salford response. The Panel also noted that there were comments from general practice among the published comments on the Appraisal Consultation Document. The Appraisal Committee had heard oral

evidence from a Commissioner who was a GP. The Appellant could not point to necessary evidence that was missing but which could have been supplied by a GP; and did not consider that the evidence in front of the Appraisal Committee could not be understood without the further input of a GP. It therefore concluded that the Appraisal Committee had considered all relevant material and had acted fairly.

22. The Appeal Panel therefore dismissed this appeal point.

Appeal Ground 1.2: The PCT considers that by significantly changing the recommendation in the guidance following the initial Appraisal Consultation Document, it is unfair to proceed straight to the Final Appraisal Determination. This is because had PCTs or other health care professionals identified that such a recommendation was likely, they might have responded to NICE via the Appraisal Consultation Document procedure. This is selectively unfair to commissioning stakeholders.

23. Ms Cheong-Leen stated that the Appraisal Committee's view as expressed in the Appraisal Consultation Document was that the committee was 'minded to say no.' It was therefore a surprise to the PCT that, in the Final Appraisal Determination, the Appraisal Committee reached a positive decision. NHS Salford made its comments on the Appraisal Consultation Document in the light of the implied decision not to recommend dabigatran.
24. The PCT had argued for the use of dabigatran, but in a way that targeted its use to those patients most likely to benefit: the Manchester Cardiac Consortium algorithm. NHS Salford does not support the use of dabigatran for all patients with atrial fibrillation and, had it considered that that was to be the likely recommendation, it would have opposed it.
25. NICE procedures allow for a second Appraisal Consultation Document, especially if there is a major change in recommendations. The Appellant considered that the failure to organize a second Appraisal Consultation Document did not allow it to present a case arguing against the general use of dabigatran in atrial fibrillation.
26. A further difficulty was that the opportunity to consult on the Appraisal Consultation Document was cut short by a technical problem with the website. It was not clear whether any potential commentator had found it difficult to submit a comment as a result of the website failure.
27. Dr Adam put forward the view that a 'minded no' implied that the Appraisal Committee might in fact decide in favour of recommending a drug for use in the NHS; and in fourteen of eighteen cases where the Appraisal Consultation Document had been expressed in this way, the Final Appraisal Determination had recommended the drug. The Appraisal Consultation Document had set out a series of issues where further information might have caused the Appraisal Committee to

reconsider its "minded no" position, signalling that the question was open.

28. The Appraisal Committee had received a range of detailed and helpful responses to the Appraisal Consultation Document. None of these responses advanced evidence that would have led the Appraisal Committee to a conclusion different from the one it had in fact reached.
29. Mr Boysen accepted the language in which the Appraisal Consultation Document decision was couched to be difficult for some stakeholders, although it was generally understood by those in the pharmaceutical industry.
30. Ms Robertson explained that the early closure of the website had been an error. It was rectified, prior to the close of the consultation period, although technical staff had not announced that the website was working again.
31. Ms Cheong-Leen was not herself able to provide additional evidence which might have been submitted by PCTs but for the website closure and which might have contradicted the Appraisal Committee's view as expressed in the Final Appraisal Determination.
32. Dr Elton explained that if the Appraisal Consultation Document had advocated wide use of dabigatran, then NHS Salford would have argued that the drug should only be used in those not well controlled on warfarin.
33. Dr Budden pointed out that there was residual uncertainty regarding the 'sequential' model in which dabigatran 150 milligrams twice daily was given until the age of 80 years, when the dose was reduced to 110 mg twice daily.
34. The Appeal Panel considered that the phrase '*The Committee is minded not to recommend the use of dabigatran*' as used in the Appraisal Consultation Document might reasonably have been interpreted to mean that the Appraisal Committee was likely to decide that the drug would not be recommended. If the wording had been understood in that way, the wording might have led a consultee to omit relevant evidence.
35. Whether or not the failure to issue a second consultation document in these circumstances might generate a valid appeal point would depend on the facts of the appraisal. The Appeal Panel's view is that all consultees must be taken to know that any consultation document is by definition provisional. Any consultee who does not respond or respond fully to a consultation exercise because they agree with the Appraisal Committee's preliminary conclusion, however that conclusion is expressed, does so at their peril. However, in general terms, there is a potential risk to fairness when a preliminary conclusion is reversed without further consultation. In particular, if a "minded no" is understood as Mr Boysen suggested, and the document and its associated reports

did not contain or draw attention to the main factors which might lead a committee to issue a positive recommendation, then there would be a real risk of unfairness in not re-consulting. An Appraisal Committee needs to proceed with care. However in this case the Appraisal Consultation Document had indeed specifically indicated the areas of particular interest to the Appraisal Committee, so that consultees could address them.

36. The Appeal Panel also noted that in this case, the evidence to support the use of the Manchester Cardiac Consortium's approach had been presented in response to the Appraisal Consultation Document; and that this had been considered by the Appraisal Committee in its discussions. It appeared to the Appeal Panel that the evidence NHS Salford would have presented, if a second Appraisal Consultation Document had been issued, would only have re-iterated this. It may be that there would have been a change of emphasis or expression, but the substance of the relevant issues had been fairly consulted on.
37. The Appeal Panel therefore dismissed this appeal point.

Appeal Ground 2: NICE has formulated guidance which cannot be reasonably justified in the light of the evidence submitted.

**Appeal Point Ground 2.1:A. Generalisability of RE-LY trial to UK population
The event rate reported in RELY is likely to be lower than in UK practice.**

38. Dr Adam explained that dabigatran was cost-effective for all treated patients, without any consideration of subgroups. The Appraisal Committee recognized the differences between the population studied in RE-LY and both the UK population with atrial fibrillation actually treated to prevent stroke and the population who would benefit.
39. Dr Elton accepted that the RE-LY population of patients with atrial fibrillation was probably at lower risk of stroke than the UK treated population. Dabigatran was clearly superior to warfarin in patients whose anticoagulation was poorly controlled, but approximately the same in patients whose anticoagulation was well controlled.
40. The level of control should become apparent after about three months' treatment with warfarin.
41. The Chair reminded the Appellants that the guidance permitted the use of dabigatran as an option, but did not insist on its use.
42. Dr Budden stated that there were many uncertainties. While dabigatran was substantially easier to use, there were only modest benefits in outcome, more obvious in those at high risk; and the adverse effects were uncertain.

43. Dr Adam explained that the Appraisal Committee had discussed in detail the adverse effects of dabigatran, notably the dyspepsia and gastrointestinal haemorrhage, and had been aware that slightly more dabigatran-treated patients than warfarin-treated patients had withdrawn from the RE-LY trial. The Appraisal Committee had not removed the option of using warfarin if dabigatran was unsuitable. If anything, the benefits of dabigatran would tend to be under- rather than over-stated in RE-LY, and the Committee had also seen UK data from the GP database.

Appeal Point Ground 2.1: B. Safety

The RELY study did show a significant reduction in stroke. However, it also highlighted safety concerns. The additional monitoring cost and resources do not appear to be within the cost effectiveness modelling used in the Final Appraisal Determination.

44. Dr Vaughan told the Appeal Panel that there had been a number of safety alerts regarding the prescription of dabigatran in patients with or who developed renal failure. Japanese and New Zealand regulatory authorities had issued guidance, and the manufacturer had sent a letter to UK healthcare professionals regarding this issue. Furthermore, as discussed in articles in the *New England Journal of Medicine* and the *Lancet*, there was no antidote to dabigatran. It was not generally possible to check the degree of anticoagulation with dabigatran. The risk of gastrointestinal haemorrhage, and the possible increase in myocardial infarction, were reasons for caution. A subgroup analysis of trial data specific to UK patients did not show a benefit. It is possible that patients whose anticoagulation is well controlled on warfarin might be harmed.
45. Dr Adam, while explaining that the data on myocardial infarction were not robust, assured the Appeal Panel that this potential adverse effect had been included in the model, as had the increased risk of dyspepsia. Inevitably, effective anticoagulants increased the risk of haemorrhage, but with dabigatran the risk of intracranial haemorrhage, which was often devastating, was reduced when compared to warfarin.
46. Dr Elton fully agreed that randomized controlled trials were not usually powered to detect adverse drug reactions.

Appeal Point Ground 2.1:C. Cost Effectiveness

NHS Salford stated that the Final Appraisal Determination quoted average times spent in TTR from one clinical trial (72%), plus a UK study published six years ago (67.9%), as an indication of the 'average' atrial fibrillation patient's TTR on warfarin today.

NHS Salford claimed that it was therefore irrational for the Appraisal Committee to then conclude that *'the evidence for stratifying by INR control was insufficient to exclude the minority of patients with very good control from the recommendation of dabigatran as a potential treatment option, and*

that the Incremental Cost-Effectiveness Ratio for the whole population should be the basis of the recommendation. The proportion of patients for whom dabigatran is not cost effective is significant and given the prevalence of the condition, it is unreasonable to pool the patient population and commit NHS resources to funding dabigatran for these patients when this will incur opportunity costs for other patient groups.

47. Ms Craig, for the Appellants, described weaknesses in the process by which the costs per quality-adjusted life-year were calculated. In particular, there had been a failure to consider the extent to which the time a patient's anticoagulation was maintained in the therapeutic range (TTR) might influence cost-effectiveness.
48. Dr Adam pointed out to the Appeal Panel that data on TTR derived from the RE-Ly trial was necessarily retrospective and from the patients randomized to warfarin only. The TTR was expressed as the average by centre, not as the value in individual patients. In any event, it represented an unplanned subgroup exploration of the data. It could therefore be relied on only with great caution. Even in the dataset representing patients in the upper quartile of TTR, put forward by Dr Craig, the rate of intracranial haemorrhage was twice as high as in the dabigatran group.
49. Dr Elton accepted that the comparisons among patients in different ranges of TTR were not pre-specified, but noted that they were biologically plausible.
50. Dr Adam noted that the Final Appraisal Determination allowed doctors and patients to decide whether to use dabigatran on the basis of TTR if they wished to do so.

Appeal Point Ground 2.1:D. Budget impact

NHS Salford considered that discrepancies in the cost template, released after the Final Appraisal Determination, should be considered. As a consultee the appellant assumed this was what the committee had considered in deciding whether this guidance should be referred to the Department of Health to highlight a significant financial burden to the NHS associated with implementation.

51. Ms Cheong-Leen stated that NHS Salford understood that cost-impact and affordability were not the Institute's concern. However, the costing template estimated that the uptake of dabigatran would be 10% in the first year and 20% in the second year. This seemed likely to underestimate the impact, as judged by experience in the United States and Canada. The guidance therefore had a substantial impact on the opportunity costs of introducing dabigatran. The Institute should have adopted a planned approach to implementing the guidance in the Final Appraisal Determination.

52. Dr Adam stated that the costing template was inevitably completed by the Institute after the Final Appraisal Determination had been agreed, and was not a matter for the Appraisal Committee. The Appraisal Committee was sure that the cost per quality adjusted life year was below £20,000 for dabigatran used in the entire population.
53. The Chair re-iterated that the Institute's Statutory Instruments required NICE to take into account cost effectiveness rather than affordability or budgetary impact. The only occasions when the Institute might consider affordability was after an appraisal if it proposed that the Funding Direction should be lifted when, for practical reasons, it would be impossible for the NHS to put its guidance into effect in the usual timescale.
54. The Committee had allowed for the known concerns about the safety of dabigatran. In any case, the Institute does not have a role in policing safety, which is a regulatory issue. If the costs and disbenefits associated with any safety issue were included in the Appraisal Committee's deliberations, then the Institute has taken account of safety issues in so far as they are relevant to it.
55. The Committee had discussed plausible cost-effectiveness, and reached the reasonable conclusion that dabigatran was cost-effective across the whole population of patients with atrial fibrillation eligible for treatment. The fact that alternative treatment strategies might also be cost-effective did not render this approach unjustifiable, and in any event, the Committee had merely recommended dabigatran as a treatment option. It had explicitly stated that the decision on whether to treat with dabigatran in any individual case was to be taken only after an informed discussion between clinician and patient about the comparative risks and benefits of dabigatran and warfarin. It would be wrong to read the FAD as requiring dabigatran to be prescribed in all cases.
56. The budgetary impact was not a matter with which the Appraisal Committee was or could be concerned, and the Institute had never requested the Department to phase the introduction of a treatment that was found to be cost-effective.
57. The Appeal Panel therefore dismissed the appeal on this ground.

Appeal Ground 3: The Institute has exceeded its powers

58. There was no appeal under this ground.

Conclusion and effect of the Appeal Panel's decision Conclusion and effect of the Appeal Panel's decision

59. The Appeal Panel dismissed all the grounds for appeal in this appraisal.
60. There is no possibility of further appeal against this decision of the Appeal Panel. However, this decision and NICE's decision to issue the final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of publishing the final guidance.