



NHS Salford
St James's House
Pendleton Way
Salford
M6 5FW

15th November 2011

Chair, Appeal Committee
National Institute for Health and Clinical Excellence
Mid City Place
71 High Holborn
London
WC1V 6NA

Dear

**Re: Final Appraisal Determination – Dabigatran etexilate for the
prevention of stroke or systemic embolism in people with atrial
fibrillation (AF)**

The Primary Care Trust would like to appeal against the Final Appraisal Determination for the above mentioned technology appraisal on the following grounds:

- Ground one:** The Institute has failed to act fairly.
- Ground two:** The Institute has formulated guidance which cannot reasonably be justified in the light of the evidence submitted.
- Ground three:** The Institute has exceeded its powers.

As a possible alternative to warfarin, dabigatran represents the first of a new group of oral anticoagulants for the above indication. The potential population that could benefit from dabigatran for patients with nonvalvular AF with one or more risk factors is large, i.e. more than 200,000 people across England ¹ (60% of the 56% of AF patients with a CHADS2 score > 1). The NICE costing template² (released for consultation after the FAD) models a 20% uptake of dabigatran amongst the eligible population at 5 years. We and other PCTs consider this to be unrealistic and local networks estimate a higher and more rapid uptake, with more than 300,000 patients opting for dabigatran (based on 50% of untreated and aspirin only treated patients commencing treatment with dabigatran and 50% of patients treated with warfarin switching to dabigatran).

The vast majority of these patients are managed by GPs in a primary care setting. Recent changes to the GP contract quality and outcomes framework (QOF) which are welcomed include the new AF indicator. This will increase further the number of new patients being identified and treated with anticoagulation therapy.

¹ NICE: atrial fibrillation Guidance 2006

² NICE Costing Template, Dabigatran etexilate for the prevention of stroke or systemic embolism in people with atrial fibrillation. Consultation 8th November-22nd November 2011

Dabigatrans widespread use for this indication in the NHS would involve a significant anticoagulant service redesign which cannot be implemented quickly. Patient safety data supporting the potential wide scale and long term use of dabigatran in AF in clinical practice is currently limited and recent changes to the products summary of product characteristics (SPC)³ as a result of wider exposure to dabigatran out with the clinical trial setting highlight this. This has also changed the monitoring requirements for this drug and the associated costs and potential harms. The potential increased cost impact is likely to be large (i.e. will be more than £100 million pa across England) reinforced by the statutory requirement for NHS organisations to fund Technology Appraisal Guidance recommendations.

Taking all the above factors into account, the recommendations made in the above Technology Appraisal (TA) for this drug will potentially have one of the largest impacts on the NHS of any NICE FAD published to date. Therefore, it is in the context of ensuring that these recommendations can be justified in terms of their development and content, that the concerns outlined in this appeal are being made.

Ground 1: The Institute has failed to act fairly

1.1. The PCT is concerned that by not having access to primary care

professionals neither on the Technology Appraisal Committee, nor

³ Boehringer Ingelheim communication on importance of assessing renal function in patients treated with Pradaxa® (dabigatran etexilate). <http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con134763.pdf>

**via the professional/specialist groups or selected clinical experts,
the Committee has failed to act fairly.⁴**

The NICE Equality Scheme⁵ states that professional and stakeholder involvement and inclusiveness are important features of the NICE framework of procedural principles. Furthermore, the NICE Guide to the Single Technology Appraisal Process states that:

2.2.1 Identifying interested parties is an important stage of the process⁶.

3.4.15 It is important that sufficient expertise feeds into the technology appraisal.⁷

The majority of the prescribing and monitoring of anticoagulants and ongoing care for people with AF is undertaken in primary care by GPs. Therefore, GPs are the clinicians with the most experience and expertise in the long term, ongoing prescribing of oral anticoagulants for AF patients. The Appraisal Committee members included clinical specialists with high levels of expertise and experience in the diagnosis of AF and management of complicated or unstable AF. However, at any one time these subgroups of AF patients will not constitute the majority of people with AF needing anticoagulation being managed in the NHS.

⁴ NICE FAD, Dabigatran exelate for the prevention of stroke and systemic embolism in atrial fibrillation, October 2011. Appendices A and B.

⁵ National Institute for Health and Clinical Excellence Social value judgments: principles for the development of NICE guidance. Second edition.

⁶ NICE Guide to the single technology appraisal process. October 2009. 2.2.1

1.2. The PCT considers that by significantly changing the recommendation in the guidance following the initial ACD, it is unfair to proceed straight to the FAD. 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 ACD procedure. This is selectively unfair to commissioning stakeholders.

The Appraisal Committee's main preliminary recommendation stated in the ACD was that

'The Committee is minded not to recommend the use of dabigatran etexilate for the prevention of stroke and systemic embolism in people with atrial fibrillation'.

The main recommendation made by NICE in the FAD is that

'Dabigatran etexilate is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication'.

The key recommendations stated in the FAD therefore represents a complete U-turn on the key recommendation in the Appraisal Document i.e. a change from not recommending any NHS prescribing of dabigatran for this indication to recommending prescribing for almost all AF patients at high risk of stroke. Such a clearly significant difference in these two key recommendations should be considered for further ACD.

⁷ NICE Guide to the single technology appraisal process. October 2009. 3.4.15

The first formal indication of this complete U-turn was the publication of the FAD. This has not allowed enough time or opportunity for stakeholders such as PCTs and GP commissioners to fully consider the basis of the very different recommendations now being made by NICE and be allowed to submit comments accordingly. Nor is there an opportunity for them to do so, as the NICE process dictates that the only option now available is that of a formal appeal. Had the preliminary recommendations in the ACD given an indication that NICE would be likely to recommend the prescribing of dabigatran to all high stroke risk AF patients, this would have made a significant difference in terms of the ACD comments and their focus and content that NICE would have received for consideration by the Appraisal Committee. E.g. More information on the proportion of AF patients on warfarin controlled within the target therapeutic range in current clinical practice in England.

Salford PCT has also been advised by CSAS that at 10.30am on the final day of the ACD consultation (8th September), the NICE ACD webpage has already closed in advance of 5pm. There is a real possibility that PCTs wished to respond to the ACD in the only way that they are allowed (i.e. via the web) but were unable to do so. If this were the case, then the Appraisal Committee may not have considered all the comments that they would have received otherwise.⁸

⁸ Email correspondence from CSAS dated 8th September 2011

1.3. The PCT considers that NICE has acted unfairly by not differentiating in its recommendation in this FAD between those people for whom it has been shown that dabigatran is a cost effective use of NHS resources for this indication compared to those subgroup patients for whom the ERG has shown that the use of dabigatran is not a cost effective use of NHS resources. The implementation of this guidance is likely to adversely impact on the resources available to commission services and treatments available for the rest of population.

It has also failed to acknowledge that anticoagulation services vary significantly in costs and models of delivery and so this guidance will have inequitable net health benefit and net cost impact across England when implemented. NHS Salford pay significantly less than the £241 used in the costing models for dabigatran, as do many other PCTs. The PCTs currently paying significantly less than the figure used will, therefore, be unfairly penalised as they will not be recouping the savings NICE assume can be offset against the cost of dabigatran acquisition.

This approach does not support the equitable use of limited NHS resources in obtaining the optimum benefit for patients. Additionally, this absence of patient subgroup differentiation in the FAD's recommendations does not support prescribers in helping patients and clinicians to make fully informed choices concerning the different potential risks and benefits of dabigatran to AF patients currently well controlled in target therapeutic range on warfarin. This implementation of this guidance is likely to adversely impact on the resources

available to commission services and treatments available for the rest of population.

Ground 2: The Institute has formulated guidance which cannot reasonably be justified in the light of the evidence submitted

2.1. The PCT is concerned that it seems unreasonable to use a lack of evidence as the main basis for adding a subgroup of patients to a larger, significantly more cost effective patient group, to allow an averaging effect to enable the patient subgroup for which the intervention is not supported by evidence as being cost effective (QALY > £30K).

The NICE FAD states that for patients whose INR is within the target therapeutic range (TTR) 83.7% of the time, the ICER for dabigatran compared with warfarin was £46,989 per QALY gained. Also that, the ICER per QALY gained compared to warfarin would be above £30,000 for patients whose INR was within the target range for an average of 75-76% or more. The FAD quotes 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' AF patient's TTR on warfarin today. The FAD then states the conclusion 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 ICER for the whole population should be the basis of the recommendation.

This conclusion cannot be reasonably justified from an evidence based or cost effectiveness perspective. The application of such an approach in Technology Appraisal Guidance obliges us, the PCT, to fund interventions in identifiable patient subgroups that are not a cost effective use of NHS resources, primarily because of the presence of a larger, significantly more cost effective patient group being considered in the same appraisal, allowing smaller subgroups to appear significantly more cost effective as a result of data aggregation and the effect of averaging. As a PCT we had hoped that NICE guidance on dabigatran would allow us to prioritise the patients most likely to gain from dabigatran treatment and allow us to focus our resources there.

2.2. The PCT is concerned that patient safety considerations were not adequately considered by the Appraisal Committee in the development of the recommendations stated in the FAD.

Minimal weighting appears to have been given to the lack of long term safety data on the use of dabigatran, especially in the elderly with declining renal function. This is especially important given that AF prevalence increases with age. Additionally, the single clinical trial which formed the main basis of this appraisal, raised questions on the possible increased risk of myocardial infarction on dabigatran compared to warfarin, but was not powered to be able to answer these. Recent changes to Dabigatran SPC (27/10/11)³ regarding renal function monitoring shows that the licensing authorities regard the emerging picture of safety of dabigatran in this group as significant. This

additional monitoring cost and resources does not appear to be within the cost effectiveness modelling used in the FAD, or in the cost model, nor do the serious renal consequences emerging in countries which have wider experience of dabigatran prescribing.

2.3 The PCT is concerned that the comments received from NHS Salford and other PCTs regarding cost impact were not adequately considered.

It is not clear that the committee considered these points using anything other than the most optimistic (and implausible) estimates of net cost. Given the uncertainty regarding cost impact (in part due to the lack of primary care professional involvement in the process of developing the guidance) it is possible that the modeled uptake of dabigatran is extremely conservative (20% at 5 years but only 10% take up in year 1), and therefore the Committee could have underestimated the net cost impact. NHS Salford would like to suggest that it would be reasonable for the Appraisal Committee to reconsider the issues for implementation as suggested in the Guide to Methods of technology appraisal (6.2.28). This would include considering resource availability to support implementation and the need to suggest that the Institute should consider recommending varying their advice to the Department of Health.

Ground 3: The Institute has exceeded its powers

3.1 For AF patients currently being prescribed warfarin and well

controlled within target therapeutic range, as referred to in section 2

above, this FAD does not adequately justify the basis of recommending dabigatran as an alternative to warfarin as there is evidence that this is not a cost effective intervention. Therefore, the Institute has not complied with its own 'Guide to the methods of technology appraisals' in making the recommendations in this FAD.

The NICE Guide to the Methods of Technology Appraisal 6.2.23-25 state that:
"above a most plausible ICER of £20,000 per QALY gained judgements about the acceptability of the technology as an effective use of NHS resources will specifically take account of the following factors:

Degree of certainty about the ICER. In particular, the Committee will be more cautious about recommending a technology when they are less certain about the ICERs presented.

Whether there are strong reasons to indicate that the assessment of the change in the HRQoL has been inadequately captured, and may therefore misrepresent, the health utility gained..."

...Above a most plausible ICER of £30,000 per QALY gained, the Committee will need to make an increasingly stronger case for supporting the intervention as an effective use of NHS resources with respect to the factors considered above.

Conclusion

This appeal has highlighted issues within all three grounds for appeal. If not addressed, the effect of these weaknesses in the development of this NICE guidance will be that this FAD's recommendations will oblige the NHS to

prioritise funding for this treatment beyond the established NICE criteria for the cost effective use of NHS resources, at the expense of the provision of competing healthcare benefits for patients.

NHS Salford welcomes the introduction of dabigatran and feels it will offer a significant and beneficial change in the management for a defined patient group who are currently under treated. Fairer and more reasonable guidance on dabigatran for the prevention of stroke or systemic embolism in people with atrial fibrillation would consist of recommendations that included some differentiation between those people for whom the appraisal has shown dabigatran to provide QALYs compared to warfarin of less than £30K, compared to the subgroup of people, identified in the appraisal, for which the evidence does not show a benefit at this level of cost effectiveness.

We wish this appeal to go forward as a written appeal.

Yours Sincerely

Chief Executive
NHS Greater Manchester
(Includes NHS Salford)

Deputy Head of Medicines Management
NHS Salford

GP Prescribing Lead
NHS Salford