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8th December 2011

For the Appeals Committee Chair
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)

Thank you for your letter regarding your initial scrutiny of points of our appeal. We have considered your advice and further clarified some of the points in our initial submission. We hope this will be helpful.

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 (60% of the 56% of AF patients with a CHADS2 score > 1).¹

The NICE costing template² (released for consultation after the FAD) models a 10% uptake of dabigatran amongst the eligible population in the first year, rising to only 20% at year 5. 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).

¹NICE: atrial fibrillation Guidance 2006

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

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. Dabigatran's 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 on the 27th October 2011 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 cost impact is likely to be large. The CSAS/PCT response to the consultation on the NICE Costing Template estimates that a realistic cost is in excess of £300m (rather than £29.5million suggested in the template sent out for consultation) 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

³Boehringer Ingelheim communication on importance of assessing renal function in patients treated with Pradaxa®

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 Committee⁴, nor via the professional/specialist groups or selected clinical experts, the Committee has failed to act fairly.

The NICE Social Value Judgment Principles state that professional and stakeholder involvement and inclusiveness are important features of the NICE framework of procedural principles⁵.

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

(dabigatran etexilate). <http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con134763.pdf>

⁴NICE FAD, Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation, October 2011. Appendices A and B <http://guidance.nice.org.uk/TA/Wave21/10/FAD/FinalAppraisalDetermination/pdf/English>.

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

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

*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. Although centre time in therapeutic range (cTTR) in the RE-LY trial suggest UK centres achieved 72% mean cTTR the proportion of patients with adequate individual control (>65% TTR) is not reported. Other studies suggest the numbers of patients with adequate control could be substantial. One Welsh study from 2005 reports that the quartile (bottom 25%) with worst control spent 71.6% of their time out of target range compared with 16.3% out of range in the best controlled quartile (top 25%).

Suggesting that at least 25% of patients can achieve a TTR of 84%.⁸ GPRD data suggests a mean % TTR of 63% amongst all 18113 patients on the registry with AF.⁹

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

⁸ Jones M et al., Heart 2005;91:472-477

⁹ Gallagher AM et al., Thromb Haemost 2001;106:968-977

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...'

And in section 1.2

'The decision about whether to start treatment with dabigatran etexilate should be made after an informed discussion between the clinician and the person about the risks and benefits of dabigatran etexilate compared with warfarin. For people who are taking warfarin, the potential risks and benefits

of switching to dabigatran etexilate should be considered in light of their level of international normalized ratio (INR) control.'

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, particularly in light of the lack of GP expertise available to the Appraisal Committee (Ground 1.1 above).

The Guide to the Single Technology Appraisal Process allows the possibility of a second appraisal (section 3.5.35)¹⁰

'When consultees and commentators submit comments and/or new evidence that lead to a substantial revision of the ACD, involving a major change in the recommendations, considerations and/or evidence base, the Centre Director and the Chair of the Appraisal Committee will decide whether it is necessary to prepare another ACD. If so, the consultation process will be repeated. The decision to produce another ACD will extend the timelines for the appraisal. NICE will distribute the evaluation report with the second ACD, together with any new evidence not circulated with the previous ACD and consultation comments on the first ACD.'

¹⁰NICE Guide to the single technology appraisal process. October 2009. 3.5.35

And the possibility of this taking place in the circumstance of an unrestricted recommendation is seems allowable (Section 3.5.24) as it should be considered that this circumstance is 'not normal'.

*'Normally, formal consultation (when an ACD is produced) takes place only if the recommendations from the Appraisal Committee are restrictive or if the manufacturer or sponsor is requested to provide further clarification on their evidence submission. Restrictive recommendations limit the use of the product further than the licence for the indication being appraised. In the absence of a regulatory approval process (for example, for a device), a restrictive recommendation will be one that is more limited than the instructions for use that accompany the technology. Otherwise, formal consultation does not take place and a FAD is agreed.'*¹¹

The first formal indication of this complete U-turn was the publication of the FAD. This has not allowed the basis of the change of recommendation to be commented upon. It denies stakeholders such as PCTs and GPs the opportunity to fully consider the basis of the very different recommendations now being made by the Appraisal Committee. It also denies the Appraisal Committee access to potentially important relevant information.

Had the preliminary recommendations in the ACD given an indication that NICE would be likely to recommend the prescribing of dabigatran to all high

¹¹NICE Guide to the single technology appraisal process. October 2009. 3.5.24

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.

It is a matter of concern that recommendations with restriction are required to be consulted upon, but that recommendations with no restriction are 'normally' directed straight to FAD. This inherently introduces bias in favour of those stakeholders who support an intervention.

NHS Salford 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.¹² 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.

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

2.1. The PCT considers that it is unreasonable that the Appraisal

¹²Email correspondence from CSAS dated 8th September 2011

Committee did not differentiate 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 Appraisal Committee *'concluded that the most plausible ICERS for the whole population eligible for dabigatran were within the range normally considered a cost-effective use of resources, being less than £20,000 per QALY gained.'*

And that the 'RELY trial was appropriate and broadly relevant to UK clinical practice'.

NHS Salford considers that this is unreasonable because:

A. Generalisability of RELY trial to UK population.

There are important differences in the study group in the RELY trial: it is younger and had significantly fewer women than seen in AF patients in England. The major difference was that over 30% patients in the RELY study had a CHAD2 score of 0 or 1 whereas in UK clinical practice the treated population with a CHADS2=0/1 is 8.6%.¹³ The event rate reported in RELY is, therefore, likely to be lower than in UK practice and existing patients with a CHADS2=0/1 are not treated with warfarin as their stroke risk is low.

¹³ Economic Appraisal of Dabigatran Etexilate 110mg compared to Warfarin or Aspirin in Patients with Atrial Fibrillation. Report for West Yorkshire Cardiac Network. September 2011

Consequently there are not exposed to risks associated with taking warfarin. Additionally the majority of UK patients are managed in primary care and the Committee had no access to clinical expertise and experience from primary care physicians.

B. Safety

Dabigatran is a new oral anticoagulant which offers some important advantages to patients over warfarin. The RELY study did show a significant reduction in stroke. However, it also highlighted safety concerns. In older patients these may be higher than reported in RELY – in particular bleeds and all cause mortality. 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 information was available before the final FAD was issued but does not appear to been considered.

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, released after this change to SPC, nor do the serious renal consequences emerging in countries which have wider experience of dabigatran prescribing, available at the time of issue of the FAD.

C. Cost Effectiveness

The NICE FAD states that for patients whose INR remains 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.

It is 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 ICER 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.

The Institute is asked to *take account of the overall resources available to the NHS*¹⁴ and so given the uncertainties, it is unreasonable to use the RELY pooled population ICER only and advocate funding an intervention in a

¹⁴NICE Guide to the single technology appraisal process. October 2009.6.2.13

patient group in whom the intervention is unnecessary, not cost effective and may have additional clinical risks does not appear reasonable.

D. Budget impact

Discrepancies in the cost template, released after the FAD, should be considered. As a consultee we have to assume this is what the committee has evaluated to consider whether this guidance should be referred to the Department of Health to highlight a significant financial burden to the NHS associated with implementation. The modeling for 1,000 fewer MIs and very limited uptake (10% uptake in year 1 rising to a 20%) by year 5, seem unrealistic especially with the new GP contract QOF AF indicators which will lead to more patients being identified and treated. Several of the estimates of costs avoided (stroke care, aspirin and warfarin acquisition, INR monitoring) do not correlate with the actual costs to NHS.

Although the potential budget impact of the adoption of a new technology does not determine the Appraisal Committee's decision, the Committee may require more robust evidence on the effectiveness and cost effectiveness of technologies that are expected to have a large impact on NHS resources¹⁵. If the Appraisal Committee did assume that the implementation of the FAD would cause only a relatively modest impact on NHS resources, then it might have been more reasonable for the Committee to allow dabigatran to be an option for all patients regardless of the ICER.

¹⁵NICE Guide to the single technology appraisal process. October 2009.6.2.14

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 judgments 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...”

Together these points lead NHS Salford to consider that the conclusion to include in the recommendation patients who are or could be well managed on warfarin is unreasonable.

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. In addition, we hoped that the guidance would provide clinicians a clear rationale to allow frank discussions of the risks and benefits of treatment to facilitate an informed discussion with patients in whom dabigatran treatment was an option.

Ground 3: The Institute has exceeded its powers

3.1 The PCT is concerned that the Appraisal Committee was unable to consider adequately 'the effective use of available resources within the health service' or 'the broad balance of clinical benefits and cost' in the development of the guidance stated in the FAD and therefore has exceeded its powers under the Institute's Establishment Order.

The NICE Social Value Judgements document describes in Section 3¹⁶:

'legal obligations and fundamental principles underlying the processes by which the Institute produces its guidance and NICE must always adhere to them.'

The Legal Obligations in 3.1 state that:

'The Institute's Establishment Order states that:

Subject to and in accordance with such Directions as the Secretary of State may give, the Institute shall perform

*a. such functions in the promotion of clinical excellence, **and the effective use of available resources within the health service**'.*

¹⁶NICE Social value judgments: principles for the development of NICE guidance. Second edition.3.1

The Secretary of State's Directions to the Institute require that... in the appraisal of the clinical benefits and the cost of interventions, NICE should consider the following factors.

a. the broad balance of clinical benefits and costs

Given the

- Lack of any GP involvement in the development of the FAD
- The apparent ten-fold variation of opinion about the estimated cost impact
- The recommendation in the FAD to allow those patients for whom dabigatran is not cost effective to choose dabigatran
- And the lack of a 2nd ACD where commissioners and prescribers could have provided the Appraisal Committee with relevant important information,

it is unclear how NICE could have adequately considered **'the effective use of available resources within the health service'** or **'the broad balance of clinical benefits and cost'** in the development of the guidance stated in the FAD and therefore has exceeded its powers under the Institute's Establishment Order.

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 even though the treatment choice is beyond the established NICE criteria for the cost effective use of NHS resources, there is no clinical advantage and indeed there may be an additional risk of harm.

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 accept your view that this appeal should go forward to an oral hearing.

Yours Sincerely

Chief Executive
NHS Greater Manchester
(Includes NHS Salford)

Deputy Head of Medicines Management
NHS Salford

GP Prescribing Lead
NHS Salford

