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Sent by email: [redacted]

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18 October 2019

Dear [redacted]

Re: Final Appraisal Document – erenumab for preventing migraine [ID1188]

Thank you for your letter of 10 October 2019, lodging British Association for the Study of Headache (BASH) and the Association of British Neurologists' joint appeal against the above Final Appraisal Document (FAD).

Introduction

The Institute's appeal procedures provide for an initial scrutiny of points that an appellant wishes to raise, to confirm that they are at least arguably within the permitted grounds of appeal ("valid"). The permitted grounds of appeal are:

- 1(a) NICE has failed to act fairly, or
- 1(b) NICE has exceeded powers;
- (2) the recommendation is unreasonable in the light of the evidence submitted to NICE

This letter sets out my initial view of the points of appeal you have raised: principally whether they fall within any of the grounds of appeal, or whether further clarification is required of any point. Only if I am satisfied that your points contain the necessary information and arguably fall within any one of the grounds will your appeal be referred to the Appeal Panel.

You have the opportunity to comment on this letter in order to elaborate on or clarify any of the points raised before I will make my final decision as to whether each appeal point should be referred on to the Appeal Panel.

Initial View

I assess each of your points in turn and then summarise the appeal points that I am presently minded to refer at the end of this letter.

You make 6 appeal points, as follows.

Ground 1(a): In making the assessment that preceded the recommendation, NICE has failed to act fairly

1. **The Committee failed to ensure that a sufficient number of clinical experts were consulted about the decision**

   This point notes the Committee sought input from 8 experts (and from the appellants) and argues that this was a "relatively small number" of experts, given that migraine is one of the most prevalent neurological conditions in the UK, and that this was a technology appraisal of the first drug in an entirely novel class. You also say that by the time of the final appraisal meeting only 3 of the 8 experts responded on the issues raised. You contend that this small number could not, and did not provide sufficient breadth or depth of expert opinion, and that this prejudiced a fair appraisal process. Finally you suggest that this also contributed to failure to properly take into account the evidence of the clinical experts and professional bodies

   I interpret your first point to be that it was unfair for the Committee to approach only 8 experts. You do not say how many experts should have been approached. As an expert body a committee may decide for itself how many expert views are required, provided that it acts in accordance with NICE's procedures and methods, is acceptably transparent, and adopts an approach that a reasonable expert body could adopt. There is no requirement to approach a given number of experts and I do not think that 8 is arguably an unusual number. I am therefore not presently minded to refer this point to the appeal panel.

   I understand your second point to be that it was unfair for the Committee to proceed with the final appraisal meeting having received responses from only 3 of the 8 experts approached. You say this number "could not" as a matter of principle be enough to provide sufficient breadth or depth of expert opinion. I am afraid I disagree, for the reasons above, and additionally because NICE cannot require experts to respond within the timeframe given to them (or at all). I would not presently be minded to refer this point to the appeal panel.

   You also say the 3 responses provided "did not" in fact provide sufficient breadth or depth of expert opinion. I do not consider this arguably falls within ground 1(a) (fairness) for the same reason, namely that NICE cannot require experts to respond to an invitation to comment.

   I am not presently minded to refer this point to the appeal panel.

2. The Committee failed to properly take into account the evidence of the clinical experts and professional bodies

I think the essential point here is that the Committee "ignored" the expert and professional body advice that it received. In particular, or alternatively, you say the Committee "failed to engage properly" with opinions on positive stopping rules and the assessment of appropriate patient pathways.

I do not see how this could fall within ground 1(a). A genuine failure to consider expert or professional body evidence at all would fall within ground 1(a), but a failure to be persuaded by it or to agree with it can only be challenged under ground 2. I note you also raise the same 2 specific examples as points below as points of reasonableness and I discuss them below under that heading.

3. The Committee failed to present a properly balanced assessment of the arguments of a commentator who had a clear conflict of interest

You make a number of points.

First, you say Allergen (the manufacturer of the comparator drug, botulinum toxin A) had a conflict of interest as they also manufacture a drug (atogepant) which is in Phase III clinical trials for chronic migraine. You appear to raise this as a fairness point in itself. In passing I do not think that the concern of a "conflict of interest" is quite right, because as a consultee with a commercial interest in competing products it is only to be expected that Allergen should be positive about those products, and you rightly accept it was quite proper to invite Allergen to comment as the manufacturer of the comparator drug.

Your complaint is that the Committee were too positive about Allergan's data. This would not be a fairness point unless the Committee were in some way biased in favour or (or against) the data rather than assessing it honestly, and I can see no evidence that they were arguably biased. You complain specifically:

- In section 3.13 of the FAD the Committee describe long-term real world data about botulinum toxin A as "promising". You argue the word "promising" is "subjective". I disagree. The Committee are required to take a view on the evidence before them and "promising" does not seem to me to imply a judgement that is not evidence based.

- In section 3.19 of the FAD the Committee concluded that applying a mode of administration utility decrement to botulinum toxin type A was not appropriate. Your appeal letter argues that this was "because of the 'long-term real-world data on QOL improvement with this treatment, but this data is not relevant to the question of treatment costs". This seems to be a non sequitur. The Committee do not claim that real world QOL data are relevant to treatment costs, they imply that those data cast doubt on the validity of a mode of treatment related utility decrement

- You argue that in section 3.22 of the FAD, the Committee wrongly concluded that the existence of long-term data for Botox and not erenumab makes it less

plausible that erenumab is more clinically effective than Botox. I have difficulty following your argument here, because FAD 3.22 deals with cost effectiveness rather than clinical effectiveness, but I think the point is the uncertainty in the ICER based on the odds ratio from the indirect treatment comparison. My reading of FAD 3.22 is only that the committee are saying that as there is real world long term data in one of the treatments compared and not the other, then the odds ratio is more uncertain (than if there was long term data in both arms) and so the ICER is uncertain. I do not see any claim that uncertainty over the long term effects of erenumab is increased by the long term data available for Botox, (which would indeed be counterintuitive), but rather a statement that the odds ratio between the two treatments is uncertain because of the lack of long term data on erenumab, which does not seem surprising.

You also say that that it would be unfair to assess erenumab and other novel treatments for migraine on anything other than their own merits, but all of NICE's appraisals proceed by comparing a new treatment to existing care, and are evidence based, and it cannot be a valid appeal ground either that erenumab was compared with other treatments or that the lack of long term data created uncertainty.

I would not be minded to refer this point to an appeal panel at present.

Ground 2: the recommendation is unreasonable in the light of the evidence submitted to NICE

4. **the Committee unreasonably failed to consider the impact of positive stopping rules on the cost-effectiveness of erenumab for patients with chronic migraine**

   A valid appeal point.

5. **The Committee unreasonably ignored the opinions of clinical experts and professional bodies on the clinical effectiveness of erenumab and its burden versus its comparator in judging its cost-effectiveness for patients with chronic migraine**

   The weight to be given to evidence before a decision maker such as the committee is very much a matter for its expert judgement, and can be challenged, if at all, only on the basis that the weight given was so extreme (or so minimal) that no reasonable decision maker could have treated the evidence in that way. I am not yet persuaded that it is arguable that the committee's approach to clinical effectiveness can be said to be outside the reasonable range of responses open to it. The Committee's discussion of the topic appears reasonably full and I cannot at present see arguable unreasonableness in it. A conclusion that it is highly uncertain whether erenumab is more clinically effective than Botox is not of its nature an unreasonable conclusion: that would depend on the underlying evidence. Contrary to your appeal letter it seems to me that the committee do address placebo and treatment response rates, in FAD 3.10.

I would agree that the issue of an administration utility decrement could be considered under ground 2, but I would not be minded to refer the remainder of this point to an appeal panel at present.

6. **The Committee unreasonably failed to consider the cost-effectiveness of erenumab versus best supportive care in those who had failed to benefit from the comparator drug in patients with chronic migraine**

In the STA process the evidence base and primary analyses are assembled by the product sponsor. In this case that submission was directed at erenumab as a fourth line treatment, positioned alongside rather than after Botox. That was a reasonable approach as that is where erenumab sits in the treatment pathway. I do not agree that there was a failure to compare alternative treatment sequences since the sponsor did not suggest that fifth line treatment was an alternative, and I am not aware that such a sequence is recommended. Whether or not it might have been open to the sponsor to prepare such an analysis, I do not think the Committee's failure to call for such an analysis itself can be argued to be unreasonable.

I would not be minded to refer this point to an appeal panel at this time.

In respect of the points that I am not minded to refer you are entitled to submit further clarification and/or evidence to me within the next 10 working days, **no later than Friday 1 November 2019,** and I will then give a final decision on the points to put before an appeal panel. For the points I am already content to refer on, an oral appeal will be held.

Many thanks

Yours sincerely

Tim Irish

Vice-Chair

National Institute for Health and Care Excellence