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10th October 2019

Professor Tim Irish, Vice Chair
National Institute for Health and Care Excellence
10 Spring Gardens
London
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Re: Final Appraisal Document: erenumab for preventing migraine [ID1188], published Thursday 26th September 2019

Dear Professor Irish

I am writing to you on behalf of the British Association for the Study of Headache (BASH), the national professional headache society for the United Kingdom, and the Association of British Neurologists (ABN). Both organisations were consultees in the appraisal process for erenumab and wish to lodge a joint appeal against the conclusion of the technology appraisal committee in this case.

In making this appeal, BASH and the ABN would remind NICE that the World Health Organisation equates severe migraine to quadriplegia in terms of the disability caused, and there are numerous studies that indicate this neurological condition causes a heavy burden of functional impairment, both in terms of work, social activities and general activities of daily living, particularly in patients with chronic migraine (that is, headaches on more days than not). NICE will be aware of the desperate state that many migraine patients find themselves in, both from the huge amount of patient feedback received after the interim decision announced in January 2019, and from the public outcry following the publication of the FAD on 26th September 2019.

BASH and the ABN recognise the importance to the UK economy of ensuring that only treatments that can be demonstrated to be cost-effective should be approved for use in the NHS. We have also taken into account the guidance provided for appeals of this nature. Specifically, we recognise that appeals can only be made on the grounds that NICE has failed to act fairly in making its recommendation (1 (a)), has exceeded its powers (1 (b)), or has produced a recommendation that is unreasonable in light of the evidence submitted to NICE (2) – and that in the latter case the recommendations in the final draft guidance is obviously and unarguably wrong, illogical, or so absurd that a reasonable advisory committee could not have reached such conclusions.

We believe that there are issues to be considered in both Ground 1 (a), and Ground 2, which we will consider in turn.

We note that we cannot comment on the actual ICER values reached by the Committee's technical advisors, as all bar one of those figures (the ICER for episodic migraine versus best supportive care) are redacted in the committee papers.

Grounds for Appeal

1. Ground 1 (a): the Committee failed to ensure that a sufficient number of clinical experts were consulted about the decision

In communications dated 6th and 25th February 2019, NICE announced that the final appraisal of erenumab would be delayed in order to allow time for the Committee to canvass expert opinion to "make the most informed and robust decision".

According to the public committee slides, NICE approached 8 clinical experts to provide input following the release of their preliminary guidance on erenumab for preventing migraine. Even allowing for the fact that information was also sought from BASH and the ABN, this would appear to be a relatively small number, 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 of treatment.

Moreover, by the time of the final appraisal meeting, only 3 of the 8 experts had responded on the issues raised. We contend that this small number could not, and did not provide sufficient breadth or depth of expert opinion, that this prejudiced a fair appraisal process, and in turn contributed to a further issue under Ground 1 (a) - a failure to properly taken into account the evidence of the clinical experts and professional bodies.

2. Ground 1 (a): the Committee failed to properly take into account the evidence of the clinical experts and professional bodies

Throughout the Committee Papers and the FAD, there are multiple examples of where the Committee ignored the advice of the clinical experts and professional bodies. Some of the most relevant of these examples occurred where the Committee dealt with issues around positive stopping rules and the assessment of the appropriate patient pathways, addressed in more detail below in Paragraphs 4-6.

We stress that we are not complaining about areas where the Committee disagreed with expert opinion, and gave reasons for this, but about areas where it acted unfairly by failing properly to engage with the professional opinions it had sought.

3. Ground 1 (a): the Committee failed to present a properly balanced assessment of the arguments of a commentator who had a clear conflict of interest

As the manufacturer of the comparator drug for the appraisal of erenumab for the treatment of chronic migraine, Allergan plc were quite properly invited to comment on the Appraisal Consultation Document produced in January 2019. There was however a clear conflict of interest, in that Allergan are not only manufacturers of the direct comparator for chronic migraine (botulinum toxin A), but also another drug (atogepant) which is currently in Phase III clinical trials for chronic migraine

prevention. It was therefore incumbent on the Committee to treat the information provided by Allergan in a fair and balanced manner, and to present it accordingly in the FAD. It is noteworthy that the major revisions and additions to the appraisal documents between the consultation in January 2019 and the final meeting in August 2019 relate to comparisons between Botox and erenumab (particularly in sections 3:13, 3:14, 3:17, 3:19, and 3:22 of the FAD).

We are concerned about the way in which the data presented by Allergan about studies done since the approval of Botox for use in the NHS is framed and utilized in the FAD:

> In section 3:13 of the FAD the Committee state that the reason for considering the relative long-term effectiveness of erenumab to be uncertain when compared with botulinum toxin type A is the "long-term and *promising* real-world data" for the latter (our italics – this is the only instance of such subjective language being used in the document).
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> In section 3:19 of the FAD, it is stated that a mode of administration utility decrement for botulinum toxin type A is not appropriate 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.
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> In section 3:22 of the FAD, it is stated that the existence of long-term data for Botox and not erenumab makes it less plausible that erenumab is more clinically effective than Botox. We agree that there is uncertainty over the long term effects of erenumab, but this uncertainty is *not* increased by the data now available for Botox.

Long-term treatment data was not available for botulinum toxin type A when it was assessed and approved for use in the NHS in 2012. We contend that it would be unfair to assess erenumab and other novel treatments for migraine on anything other their own merits, acknowledging the uncertainties of long term treatment, and attempting to mitigate them with sensible starting and stopping rules.

4. Ground 2: the Committee unreasonably failed to consider the impact of positive stopping rules on the cost-effectiveness of erenumab for patients with chronic migraine

The Committee chose to use botulinum toxin type A as the comparator for treatment for chronic migraine, having presumably taken into account the natural history of migraine in doing so (as recommended in the *Guidance to the methods of technology appraisal 2013*, section 6.2.2). The use of botulinum toxin type A in the NHS is regulated by TA260, issued in 2012, which contains both starting and stopping rules for this treatment. In assessing erenumab, the Committee decided to apply the same starting criteria, and the same negative stopping rule (failure to reduce migraine days by 30% after 3 months). However, they chose not to apply the same (or indeed any) positive stopping rules.

In this they went against the recommendations of the European Headache Federation guidelines, which suggest treatment should be given for 6-12 months in the first instance, and also of UK professional bodies:

> The ABN Advisory Group on Headache and Pain (Committee Papers p 59)* stated that the 'general standard of care with migraine preventives is that if migraine is well controlled on a given preventive agent for 6-12 months then treatment is re-evaluated and often withdrawn usually without immediate return to former state". The Committee's response to this

comment (Committee Papers pp 22-23) did not address this point, but discussed treatment waning, which is a completely different issue.

BASH (Committee Papers p 63) stated that most "prophylactic agents are required for 6-18 months, with only a small proportion of patients continuing treatment for longer duration. Duration of treatment of two years would be reasonable for modelling purposes, and the treatment could be stopped earlier if the patient is successfully converted to a low frequency episodic migraine". The Committee (Committee Papers p 26) ignored this suggestion.

The Committee seem instead to have based their opinion that a lifetime horizon should be assumed, with only a very minor annual discontinuation rate, on clinical expert comments that *some* patients might stay on treatment indefinitely (our italics – note the experts specifically did *not* state that all patients would be expected to stay on treatment indefinitely; this response has very clearly been taken out of context, see Committee Papers pp 296-297) and on an anecdotal report from a patient expert whose migraines had recurred shortly after discontinuing treatment with erenumab. The Committee's opinion runs contrary to what is known about the natural history of migraine, and the data available from the long-term real-world studies of botulinum toxin A, on which the Committee put so much store throughout:

> The 'Long term outcome for Onabotulinum Toxin A therapy in Chronic Migraine; a two Year follow up of 508 Patients from the Hull Migraine Clinic' poster cited by Allergan in their evidence (their reference number 10) shows that of these patients, 294 had responded to treatment after 2 cycles (i.e. at 6 months). At 2 years, 177 of those patients had stopped treatment, of whom 95 had done so because they had reverted to episodic migraine, and remained so. This equates to 32.3% of the responders not requiring treatment at 2 years because of a positive response to treatment (Committee Papers p 81).

Given the prolonged positive response to erenumab treatment seen in the long term extension studies presented by Novartis, there can be little doubt that similar figures would pertain if positive stopping rules were applied to the use of erenumab for chronic migraine. All three clinical experts clearly stated that clinicians would apply positive stopping rules (one expert pointing out that only 25% of Botox patients are still on treatment at 5 years).

5. Ground 2: 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

There are no head-to-head trials of any preventive medications for migraine. Even where comparative trials have been undertaken (with amitriptyline and topiramate, for example), the trials have only been designed to show non-inferiority. It is not reasonable, therefore, to expect direct comparative data comparing the effectiveness of a novel therapeutic agent with an established treatment. Indirect comparison data is the best that can be provided, and this data should be interpreted in the light of clinical expert opinion. Whilst it is the case that only one of the three clinical experts clearly states that erenumab is more effective than Botox (Committee Papers p 295), the submission from BASH points out (Committee Papers pp 23-24) that the 50% responder rate for erenumab 140 mg in the chronic migraine trials was 38.5% vs placebo 15.3%, a significantly better therapeutic gain than in the comparable Botox trials (48% vs 36%). The Committee's response did not directly address this question, simply pointing out issues of uncertainty (especially the use of placebo as comparator).

Two of clinical experts clearly stated that patients treated with erenumab would have a reduced burden compared with Botox (Committee Papers p 296) but in the FAD it is stated that a mode of administration utility decrement to Botox is not appropriate because of "long-term real-world evidence" showing improvements in quality of life with botulinum toxin A compared with best supportive care; but this response does not actually address the issue of what effect erenumab might have in comparison.

We note that there are precedents for approving drugs where clinical uncertainty remains, e.g. the interferons for MS, with the proviso that real world registry data is accumulated over a set period to address the specific clinical questions that arise.

6. Ground 2: 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

The NICE *Guidance to methods of technology appraisal*, section 2.2.6, indicates that where both the technology being assessed and the comparator form part of a treatment sequence in the pathway of care, the appraisal may compare alternative treatment sequences. This guidance was not followed by the Committee.

In its reply to the question "Are the provisional recommendations sound and a suitable basis for guidance to the NHS?", BASH noted that the draft recommendation made in January 2019 would deprive a potentially effective treatment to a highly disabled population with chronic migraine who have failed three first line treatments. BASH also mentioned the existence of a population who had also failed botulinum toxin type A. BASH stated that a "trial of erenumab in such patients would be highly appropriate before considering more invasive and expensive treatment options such as intravenous dihydroergotamine, occipital nerve stimulation or even some of the non-invasive neuromodulation therapies that have limited NICE recommendations without mandatory funding" (Committee Papers, p 64). In reply to this the Committee failed to address the existence or needs of this population, simply stating that they recognised "that migraine significantly affects health-related quality of life and that well-tolerated treatments are needed" (Committee Papers, p 23).

There is no evidence that the Committee properly considered the potential positioning of erenumab in a treatment pathway after botulinum toxin A. BASH stated that erenumab should be assessed versus best supportive care for chronic migraine (Committee Papers, p 24), which would be appropriate for this population as erenumab 140 mg was noted to be clinically effective.

Conclusion

The contents of this appeal were discussed and approved by the Council of BASH, and by the ABN Advisory Group on Headache and Pain. The decision to appeal was ratified by the Council of BASH, and by the President of the ABN on behalf of the Council of that body. In addition, the appeal has been endorsed by the National Migraine Centre, the leading UK migraine charity involved in the direct care of patients, which urges a reconsideration of the decision in the interests of people living with this debilitating chronic neurological disorder.

BASH and the ABN believe that we have demonstrated there are several grounds for appealing the decision of the Committee not to recommend the use of erenumab for preventing migraine in the

NHS. We would value the opportunity to discuss our case in an oral hearing, and look forward to receiving your response to this letter within the stipulated timescale.

Yours sincerely

[redacted]

Chair, British Association for the Study of Headache,
on behalf of BASH and the Association of British Neurologists

* All references to the Committee Papers refer to the page number in the pdf available on the NICE website.