NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

APPEAL HEARING

Advice on erenumab for preventing migraine [ID1188]

Decision of the panel

Introduction

1. An appeal panel was convened on 4 December 2019 to consider an appeal against the final appraisal determination, to the NHS, on erenumab for preventing migraine [ID1188].

2. The appeal panel consisted of:

Prof Jonathan Cohen	Chair
Dr Rima Makarem	Non-executive director of NICE
Mr Christopher Rao	Health service representative
Dr Mercia Page	Industry representative
Mr Alan M Thomas	Lay member

3. None of the members of the appeal panel had any competing interests to declare.

4. The panel considered an appeal submitted jointly by the British Association for the Study of Headache (BASH) and the Association of British Neurologists (ABN).

5. BASH and ABN were represented by:

Dr Mark Weatherall	Chair of BASH, Consultant Neurologist
Prof Peter Goadsby	Consultant Neurologist, BASH
Prof Alexandra Sinclair	Consultant Neurologist, ABN

6. In addition, the following individuals involved in the appraisal were present and available to answer questions from the appeal panel:

Prof Gary McVeigh	Technology Appraisal (TA) Committee D Chair
Helen Knight	Programme Director, TA & HST, NICE
Nicola Hay	Technical Advisor, NICE
Jasdeep Hayre	Associate Director, NICE
Dr Andrew Hitchings	TA Committee D member
Dr Rob Hodgson	TA Committee D member

7. None of the individuals involved in the appraisal had any competing interests to declare.

8. NICE's legal adviser Miss Amy Smith, DAC Beachcroft LLP, was also present.

9. Under NICE's appeal procedures, members of the public are admitted to observe appeal hearings and several members of the public were present at this appeal.

10. There are two grounds under which an appeal can be lodged:

Ground One: In making the assessment that preceded the recommendation, NICE has:

(a) Failed to act fairly; and/or

(b) Exceeded its powers.

Ground Two: The recommendation is unreasonable in light of the evidence submitted to NICE.

11. The Vice Chair of NICE (Mr Tim Irish), in preliminary correspondence had confirmed that the appellants had potentially valid grounds of appeal as follows:

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

12. The appraisal that is the subject of the current appeal provided advice to the NHS on erenumab for preventing migraine. Erenumab is a fully human monoclonal antibody which targets the calcitonin gene-related peptide receptor for the prevention of migraine.

13. Before the appeal panel inquired into the detailed complaints the following made a preliminary statement: Dr Mark Weatherall on behalf of the appellants and Prof Gary McVeigh on behalf of the appraisal committee.

14. Migraine is characterised by headache with symptoms such as intense pain, nausea, vomiting and photophobia. Chronic migraine has a significant effect on health-related quality of life, negatively affecting physical, emotional and social aspects of daily life. The appeal panel took careful note of the statements of expert patients during the appraisal and of the many patient comments received during the consultation. The appeal panel recognised the important work of the appellants as advocates for this patient group.

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

Appeal point Ground 2.1 (panel numbering) – Appellants' appeal point 4: The Committee unreasonably failed to consider the impact of positive stopping rules on the cost-effectiveness of erenumab for patients with chronic migraine

15. Dr Mark Weatherall, for the appellants, stated that the committee had chosen to use botulinum toxin as the comparator for treatment for chronic migraine. He stated that the use of botulinum toxin for preventing headaches in adults with chronic migraine in the NHS is regulated by NICE guidelines (TA260), which contains both

starting and stopping rules for this treatment. He stated that in the FAD the committee applied the same negative stopping rule to erenumab as for botulinum toxin therapy. They had not, however, chosen to apply the same positive stopping rules (NICE recommends that treatment with botulinum toxin is stopped if the patient has reverted to episodic migraine for three consecutive months).

16. Dr Weatherall stated that the failure to apply positive stopping rules was contrary to the recommendations of the European Headache Federation (which suggest that treatment should be given for 6-12 months in the first instance), the ABN Advisory Group on Headache and Pain (who stated migraine treatment is re-evaluated after 6-12 months and often withdrawn usually without immediate return to former state) and BASH (who stated that prophylactic agents are required for 6-18 months with only a small proportion of patients continuing treatment for longer duration, and that duration of treatment of two years would be reasonable for modelling purposes and treatment could be stopped earlier if the patient was successfully converted to a low frequency episodic migraine). He stated that the failure to apply positive stopping rules therefore did not reflect how erenumab would be used in clinical practice. He stated that this was supported by expert evidence given to the committee.

17. Dr Weatherall stated that the above recommendations were all based on the natural history of the condition and that applying no stopping rules was contrary to what was known about the natural history of migraine.

18. Dr Weatherall stated that the failure to apply positive stopping rules was also contrary to relevant experience from UK clinical practice. He cited the experience from the Hull Migraine Clinic where 508 patients were treated with botulinum toxin. 177 of 294 responders had stopped treatment at 2 years, of whom 95 had done so because they had reverted to episodic migraine. This meant about a third of responders did not require treatment after 2 years. Dr Weatherall suggested that the prolonged response to erenumab therapy seen in the long-term extension study suggested that it was likely that the experience from botulinum toxin is relevant to or would be the same for erenumab.

19. Furthermore, Dr Weatherall said that he was confident that neurologists would apply positive stopping rules in clinical practice and would set patient expectations from the beginning of treatment so that there was no question whether patients would be willing to stop.

20. Prof Gary McVeigh, for the appraisal committee, accepted that a period of re-evaluation would take place (and noted this was recognised in the FAD), however he stated that there was no long-term evidence of the efficacy of erenumab, and no evidence that experience from the use of botulinum toxin could be applied to erenumab. Prof McVeigh stated the committee had to respond to the evidence and it would be unreasonable to take a position (on the application of positive stopping rules) given the lack of evidence.

21. Specifically addressing the evidence from clinical experts and consultees, Prof McVeigh stated that there was uncertainty about whether patients would accept positive stopping rules. He stated there was uncertainty in the clinical guidelines

and evidence from experts about the threshold that should be applied for positive stopping rules. Prof McVeigh highlighted the discrepancy in the marketing authorisation for erenumab which authorises its use for adults who have at least 4 migraine days per month, the agreement from BASH that it could be used in this context (i.e. continued until the patient experienced less than 4 migraine days per month), and the indications for botulinum toxin therapy which is for over 8 headache days per month. Prof McVeigh stated that erenumab was not a disease-modifying agent and therefore the committee did not know what proportion of patients would retain a response from erenumab or for how long. Prof McVeigh said that the lack of consensus about the precise positive stopping rules that would be appropriate, uncertainty about how they would be accepted by patients in clinical practice and uncertainty about the long-term efficacy of erenumab (after treatment is withdrawn) would make it difficult to apply positive stopping rules in clinical practice in a consistent way.

22. Specifically addressing the economic modelling, Prof McVeigh stated that positive stopping rules were not included by Novartis (the company) in their base case analysis (in which treatment would be continued and effect maintained long-term) but were presented subsequently in two scenario analyses. Prof McVeigh argued that these analyses were flawed. With respect to the first scenario, this required all responders to be forced into a re-evaluation stage at which it was estimated (on the basis of clinical opinion rather than evidence) that 20% would stop taking erenumab permanently. The remaining 80% would remain on treatment until, following a recycling, another 20% would stop taking erenumab permanently, and so on. Prof McVeigh said that the committee did not accept this scenario as there was no evidence to support it. The committee found the company's second scenario analysis was also inappropriate because this also assumed patients would be able to stop without re-starting therapy. The appraisal committee did not feel that the alternative analyses performed were plausible or reflect what was likely to happen in clinical practice.

23. Prof McVeigh concluded by stating careful consideration had been given to the application of positive stopping rules, however there was a paucity of long-term data on the efficacy of erenumab and the analyses supplied by Novartis incorporating positive stopping rules were not plausible. Consequently, positive stopping rules were not applied in the assessment of the cost-effectiveness of erenumab.

24. Dr Andrew Hitchings, for the appraisal committee, said that the committee acknowledged that it would be clinically appropriate to periodically reassess and potentially stop treatment, with reference to the expert opinion given to NICE during the appraisal process and in his experience as a clinician. He explained the appraisal committee was required to make a judgment on modelling and to decide which of the options available to it was most informative for decision-making. Dr Hitchings stated that there were fundamental problems with the economic modelling incorporating positive stopping scenarios presented to the appraisal committee. The appraisal committee were therefore in the position where it was more reasonable not to apply positive stopping rules rather than to adopt implausible clinical scenarios.

25. In response Dr Weatherall stated that it was not known whether erenumab is a disease-modifying agent or not. He stated that, given the natural history of the disease and its complex aetiology, it was unreasonable for the committee to assume everyone would use erenumab for life just because some patients would.

26. Dr Weatherall felt that experience in clinical practice, particularly relating to the use of botulinum toxin for chronic migraine, suggested that positive stopping rules could be operationalised in real world practice. He stated that patients would accept positive stopping rules.

27. Dr Weatherall suggested the appropriate threshold that should be applied for positive stopping rules would be reversion of chronic migraine to episodic migraine. He accepted that it was possible that a patient who reverted to episodic migraine and stopped treatment might later increase to chronic migraine and need to re-start treatment.

28. Prof Peter Goadsby, for the appellants, stated that the assertion that stopping rules could not be operationalised was contrary to experience in NHS practice.

29. Asked by the panel if there were real world data that positive stopping rules could be operationalised, Dr Weatherall again cited the Hull experience with botulinum toxin. Asked by the panel if experience from botulinum toxin could be translated to the application of erenumab, Dr Weatherall stated that clinical experience of migraine (whether as experience from oral agents or botulinum toxin) suggests that this is the type of response clinicians would expect to see and there is nothing to suggest that the same would not be true of erenumab.

30. Prof Alexandra Sinclair, for the appellants, added that in her experience she felt that patients did not want to take medications unnecessarily.

31. Asked by the panel how the evidence of clinical experts was weighed, Prof McVeigh stated that the committee had considered it. He again stated that the long-term benefits were unclear and there was no evidence that positive stopping rules could be operationalised. It was unclear how long treatment benefit might last and whether or when patients might restart treatment. Prof McVeigh suggested that whilst submissions from BASH advocated a period of re-evaluation there were no defined positive stopping rules. He said comments from professional bodies and experts were conflicting. Finally, he stated that there was no evidence that experience from botulinum toxin could be applied to erenumab.

32. Dr Weatherall drew attention to NICE guidance on technology appraisal which state that the natural history of a disease should be considered in the evaluation of a technology. In response Dr Hitchings, for the appraisal committee, stated that the committee understood the natural history of migraine, but it was not included in the economic model and it was not the role of the committee to build the model. He noted that the model ascribed an accumulation of benefit over time to erenumab rather than to the condition itself, and the committee had to grasp that when considering a positive stopping rule. He said the question for the committee was which model introduces the least bias. The positive stopping rule presented by the company introduced a lot of bias by ascribing benefit to the treatment rather than

the natural history of the condition. The committee felt that no positive stopping rule, albeit not necessarily reflecting clinical practice, better balanced the costs and benefits.

33. Helen Knight, for NICE, said that data are needed to populate the model, and if this is not available the modelling could not be performed. Asked if there was scope for the appraisal committee to ask Novartis or the Evidence Review Group (ERG) to perform further analysis if there were concerns about the plausibility of the modelling during the process of technology appraisal. Ms Knight replied that there was scope for the company (Novartis) to perform further analysis following evaluation of the plausibility of the model by the committee, however the committee were not prescriptive about how this should be done. Ms Knight stated that the committee had to be careful not to ask for modelling that would be impossible in the absence of data to populate the model. Dr Hitchings stated that the committee does not hold either the data or the model and cannot give specific directions to the company, however the company could respond to feedback on the model in the ACD.

34. Asked if the cure rate used in the company's model was feasible despite being inconsistent with data on botulinum toxin, Dr Weatherall stated that it was difficult to comment or scrutinise the model. He stated that it is not known if erenumab is a disease modifying agent or not, but application of a similar positive stopping rule to botulinum toxin would be appropriate. He suggested that, owing to the nature of the condition, if a treatment causes a patient to revert from chronic to episodic migraine this may be a lasting change.

35. Asked if he agreed that there was a lack of evidence on long term use of erenumab, Dr Weatherall agreed that long-term data were limited and came from open label long-term extension studies. He stated that clinicians advocating for the use of erenumab were in a difficult position as it would not be approved while there were no long-term data, but this would not be available until it was approved. He stated that the assumptions used in the model were not reasonable and it would have been more reasonable to model positive stopping rules for both erenumab and botulinum toxin.

36. Asked if the committee might be said to have "made the perfect the enemy of the good" (in not applying positive stopping rules in the economic modelling), Prof McVeigh replied that there was no long-term evidence. Prof McVeigh stated that in open-label extension studies the committee had no information as to why patients requested to stop treatment as they were not asked. He stated that the European guidelines were not specific or prescriptive enough to be applied in clinical practice. Finally, Prof McVeigh stated that the company modelling was based on clinical expert opinion. In response, Dr Weatherall stated that no expert had said that patients should be on erenumab treatment for life. Ms Knight stated that comparison between botulinum toxin and erenumab was problematic as they have different marketing authorisations and botulinum toxin was evaluated over a much shorter time frame.

37. The appeal panel concluded as follows:

38. The appraisal committee had recognised the potential importance of positive stopping rules. They were aware of the natural history of chronic migraine and of the way in which the comparator drug, botulinum toxin, was currently used in NHS clinical practice. The appraisal committee had given reasonable consideration to the statements from clinical experts and professional bodies on how positive stopping rules could be applied to the use of erenumab.

39. The appraisal committee had judged that the lack of long-term outcome data on the efficacy of erenumab made the practicality of applying positive stopping rules in clinical practice problematic, and difficult to model. The appraisal committee judged that scenario analyses supplied by the company were not plausible.

40. The appeal panel concluded that the appraisal committee had considered all available expert opinion and that the FAD was not unreasonable in deciding that positive stopping rules should not be included in the economic modelling.

41. The appeal panel therefore dismissed the appeal on this point.

Appeal Point Ground 2.2 (panel numbering) – Appellants' 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

42. Prof McVeigh, for the appraisal committee, asked if he was correct in understanding that the panel would consider only that part of this appeal point dealing with the application of a utility decrement. Prof Cohen, appeal panel chair, stated that that the panel had taken legal advice and confirmed that that was correct.

43. Dr Weatherall, for the appellants, stated that it was unreasonable for the appraisal committee to suggest that a utility decrement should not be applied to the use of botulinum toxin when two of the clinical experts that gave evidence to the committee clearly stated that patients treated with erenumab would have a reduced burden compared with botulinum toxin. Dr Weatherall stated that whilst in the FAD it stated that a mode of administration utility decrement to botulinum toxin is not appropriate because of long-term data showing improvement in quality of life with botulinum toxin compared with best supportive care, this does not address the disutility that botulinum toxin therapy may have in comparison to erenumab. In particular: the utility decrement of clinic visits required to administer botulinum toxin, time spent on long waiting lists for botulinum toxin treatment, travel time and lack of access as all centres do not offer botulinum toxin.

44. Prof McVeigh, for the appraisal committee, stated that in 5-year follow-up data from the population of interest taking botulinum toxin in a UK centre, over 80% of the initial responders were still on treatment after five years or had successfully withdrawn and maintained the treatment effect, suggesting that there was not a significant utility decrement associated with botulinum toxin therapy. Prof McVeigh stated that the company did not include a mode of utility decrement in its base case but provided an analysis modelling the utility decrement associated with botulinum

toxin administration. The committee felt this was not plausible as the utility decrement was applied on every day that the patient had a migraine, resulting in worse quality-of-life than best supportive care. Prof McVeigh stated that this was not the case according to either real-world quality-of-life data or expert opinion.

45. Prof Sinclair, for the appellants, described the clinical pathway associated with the administration of both botulinum toxin and erenumab, suggesting that the disutility and cost associated with botulinum toxin administration was significantly greater. Dr Rob Hodgson, for the appraisal committee, stated that the costs described by Prof Sinclair were considered in the base-case of the economic model. Prof Goadsby, for the appellants, suggested that they may have been underestimated.

46. Ms Knight, for NICE, raised concerns that discussion should be focused specifically on the utility decrement associated with the administration of botulinum toxin as the appellants had the opportunity for wider scrutiny of the validity of economic model earlier in the appraisal process. While it was confirmed that the appeal point referred to the panel was limited to consideration of a utility decrement, discussion of broader costs was permitted. On behalf of the appraisal committee, Dr Hitchings described briefly how monetary treatment related costs were taken into account, with reference to the company submission, and Prof McVeigh and Dr Hodgson confirmed that these costs were included.

47. The appeal panel concluded as follows:

48. The appraisal committee had given due consideration to the expert opinions on the quality-of life burden associated with the mode of administration of botulinum toxin administration.

49. The appraisal committee had considered an analysis provided by the company in which a utility decrement associated with botulinum toxin administration was included. The panel concluded that this was reasonably judged not to be plausible by the appraisal committee.

50. The appeal panel therefore dismissed the appeal on this point.

Appeal Point Ground 2.3 (panel numbering) – Appellants' appeal point 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.

51. Dr Weatherall, for the appellants, stated that the NICE Guide to the methods of technology appraisal, section 2.2.6, indicates that, *"Sometimes both the technology and comparator form part of a treatment sequence in the pathway of care. In these cases, the appraisal may compare alternative treatment sequences."* Dr Weatherall stated that BASH had advised the appraisal committee that erenumab may have a role in the treatment pathway following botulinum toxin. Dr Weatherall argued, based on expert opinion and the NICE guide to the methods of technology appraisal, the committee should have considered the efficacy of erenumab following botulinum toxin in the treatment pathway.

52. Prof McVeigh, for the appraisal committee, stated that this treatment scenario was not put forward by the company for consideration by the committee. He stated that in the single technology appraisal process the company hold the data, and the committee can only consider evidence that is brought before it. Prof McVeigh stated that the committee had three meetings and the company did not advance an economic model for fifth line treatment. Representatives from the appellants attended these meetings and were part of the consultation process and at no time said that this was an important subgroup, that, if the data were sufficient, should be put to the committee to consider.

53. Dr Weatherall stated that some patients who respond to one treatment such as erenumab may not respond to other therapies such as botulinum toxin. He stated that patients who do not respond to fourth line therapy have significant clinical need and limited therapies available, and whose interests were pointed out to the committee but not followed up. Dr Weatherall stated that erenumab had been found to be cost-effective compared to best supportive care. Consequently, Dr Weatherall argued that it would be unreasonable to deny erenumab to this patient population.

54. Asked whether he agreed that erenumab 140mg was cost-effective compared to best supportive care, Prof McVeigh confirmed that it was when limited to a pairwise comparison.

55. Asked to what extent the committee felt it was their role to consider other treatment pathways, for example use as fifth-line therapy or for patients contraindicated to botulinum toxin, Prof McVeigh stated that the NICE Guide to the methods of technology appraisal indicate committees *may* consider (his emphasis) alternative treatment pathways. Prof McVeigh stated if data had permitted an analysis of whether erenumab was effective in this context the committee would have considered it. He stated that in the consultation process no evidence was brought before the committee. He stated that the committee were aware of the comments and that they were made early enough in the technology appraisal process that the company could have performed modelling of the efficacy of erenumab at this place in the pathway if they had chosen to do so. He did not feel this was the committee's responsibility. These are small uncertain subgroups.

56. Prof McVeigh stated that data from the European Public Assessment Report (EPAR) for erenumab, published by the European Medicines Agency (EMA), suggested that erenumab had diminished efficacy in this sub-group of patients for whom botulinum toxin had been ineffective.

57. Asked whether the committee asked the company for data on this sub-group, Prof McVeigh stated that neither the experts from the professional bodies nor patients had suggested that this was an important sub-group and so information had not been requested from the company.

58. Dr Hitchings stated that the committee would have "loved" to have approved erenumab but the appraisal was difficult because there was so much uncertainty in the data: the target patient population was different from the trial population so the committee was already considering a biased population, which was a post hoc

sub-group, and data were from a short time frame of 12 weeks. He said it would have been illogical and incongruous for the committee to ask for more information about a smaller sub-group, which would require a post-hoc analysis of a sub-group of a sub-group. This would have introduced more uncertainty where the uncertainty was already considerable.

59. Prof Sinclair, for the appellants, stated that she understood the limitations of the data, however the clinical consensus is that erenumab may be effective in this patient sub-group. She stated that although this sub-group is small, the monetary costs and impact on health-related quality of life in this group are significant. Prof Sinclair stated that this group of patients are frequently admitted to accident and emergency and are treated with unlicensed therapies with significant side-effects and invasive therapies. Dr Hitchings, for the appraisal committee, said he was sympathetic to the sentiment. Dr Hitchings stated that if the data were available, the committee would have considered them. He stated that NICE is a body that evaluates cost-effectiveness and if the data are not available then they cannot evaluate this. Prof Goadsby, for the appellants, suggested that in the context of the clinical burden on this patient group it would have been reasonable for the committee to have considered the efficacy in this patient group.

60. The appeal panel concluded as follows:

61. The panel did not accept that the appraisal committee were unaware of the potential importance of this subgroup. The panel noted that on several occasions during the appraisal expert evidence suggested that erenumab may have a role following botulinum toxin therapy (e.g. the consultee submission by Dr Fayyaz Ahmed, on behalf of BASH (Page 17), the consultee submission by Dr Andrew Dowson on behalf of Primary Care Neurology Society (Page 12), and the expert statement by Dr Nicola Griffin on behalf of ABN (Page 12)). Dr Ahmed again suggested that erenumab has a role following botulinum toxin therapy in his response to the ACD on behalf of BASH. In his response to the ACD Dr Ahmed writes:

> *"The draft recommendation will deprive a potentially effective treatment to a highly disabled population with chronic migraine who have failed three first line treatments (or four, including onabotulinumtoxinA) or have not been able to tolerate some or all of these treatments. A 3-month trial of Erenumab in such patients would be highly appropriate before considering more invasive and expensive treatment options…"*

In response the appraisal committee do not address this issue, writing:

> *"Comment noted. The committee recognised that migraine significantly affects health-related quality of life and that well-tolerated treatments are needed."*

62. The appeal panel noted that the NICE Guide to the methods of technology appraisal 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, and that Prof McVeigh had acknowledged this option existed.

63. The appeal panel noted Prof McVeigh's observation concerning the EMA data (para 56 above) suggesting that the committee were or should have been aware of the clinical relevance of this subgroup. However, the panel were not persuaded that there was any evidence in the appraisal documents or the oral hearing that the effectiveness of treatment with erenumab after botulinum toxin therapy had been formally considered by the appraisal committee.

64. The appeal panel accepts the potential limitations of the available evidence, highlighted by Dr Andrew Hitchings in the appeal hearing. The panel concluded however, that in the light of the clear evidence from experts that this was a plausible clinical use of the drug it was unreasonable for the appraisal committee not to have considered any relevant data regarding the effectiveness of erenumab following botulinum toxin therapy.

65. The appeal panel therefore upheld the appeal on this point.

Conclusion and effect of the appeal panel's decision

66. The appeal panel therefore upholds the appeal on ground 2.3 (panel numbering) – Appellants' appeal point 6. The appeal is dismissed on all other grounds.

67. The appraisal is remitted to the appraisal committee who must now take all reasonable steps to address the failure to request any available data to enable it to consider the role of erenumab in alternative parts of the treatment pathway for chronic migraine, specifically, following the failure of treatment with botulinum toxin or when botulinum toxin is contra-indicated. Whether in the light of such data (if any) the recommendation should be amended will be a matter for the committee to consider.

68. 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 NICE publishing the final guidance.