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International Porphyria Patient Network (IPPN)

Sent by e-mail only: xxxxxxxxxxxxxxxxxxxxxxxxx

31 March 2023

Dear xxxxxxxxxxx,

**Re: Final Evaluation Determination — Afamelanotide for erythropoietic protoporphyria (EPP) [ID927]**

Thank you for your letter of 23 March 2023, lodging an appeal against the above Final Evaluation Determination (FED).

Introduction

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

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

**Appeal point 1(a).1; Pausing the appraisal during the pandemic and further delays in the evaluation of afamelanotide were unfair to patients with EPP in England and Wales**

I am minded to refer this appeal point to the Appeal Panel. I anticipate that in considering this appeal point, the Panel will wish to hear from IPPN on any impact of the ‘pause and further delays’ on the outcome of the appraisal.

**Appeal point 1(a).2; It was unfair to not grant access to an executable version of the economic model to the IPPN**

I am not minded to refer this appeal point to the Appeal Panel. That is because I understand that the Committee was unable to grant access to an executable version of the economic model to the IPPN, because of CLINUVEL’s assertion of confidentiality over the model (see pp 13-14 of the Committee papers published [here](https://www.nice.org.uk/guidance/gid-hst10009/documents/committee-papers-2) on 22 May 2018). In those circumstances, I do not consider it arguably unfair for the Committee not to provide the executable model to IPPN.

**Appeal point 1(a).3; It was unfair to change the requirements for a managed access agreement between the first and the second FED**

I am not minded to refer this appeal point to the Appeal Panel.

I understand IPPN to be arguing that unfairness arises because, on the basis of the Committee’s conclusions in the second FED, the technology would have been eligible for an MAA under the requirements that were in place at the time of the first FED.

I understand the IPPN’s argument to be that in 2018, the cost-effectiveness requirement for entry into the MAA was defined by the need to have a ‘plausible potential to be considered cost-effective’; whereas in 2022 the IPPN considers that the Committee have replaced that more flexible target with a hard-edged requirement for an ICER of less than £100,000 per QALY gained.

On the basis of my understanding of the IPPN’s point, I am not minded to refer it to the Appeal Panel. I note in particular relevant MAA (Innovative Medicines Fund) principles, which include:

* Principle 2: “*The Innovative Medicines Fund**should target the most promising medicines for which there is significant remaining uncertainty around the level of clinical benefit and cost-effectiveness.*”
* Principle 3: “*Recommendations with managed access should be reserved for medicines that (a) demonstrate plausible potential to be cost effective; and (b) are priced responsibly during the period of managed access, reflecting their uncertain cost effectiveness.*“

I note in particular that principle 3 says “*The price should reflect both the uncertainty as well as the overall burden imposed on the NHS by any data collection arrangements. Those medicines that show greatest certainty of clinical benefit and cost-effectiveness should be valued most highly*.”

It is incorrect that if a plausible, most optimistic ICER were below £100k it automatically considered cost effective and would enter routine funding. As stated in the methods for HST, the committee’s judgements on value for money are influenced by a number of factors including the strength of the supporting clinical evidence, the robustness of the economic model, the plausibility of the inputs and the range and plausibility of the ICERs presented. As well as the likelihood of decision error and its consequences. The ICER alone is not indicative.

For those reasons, I cannot see that the appeal point is arguable, and I believe it to be based on a false premise – that the criteria for managed access have materially changed to the detriment of Afamelanotide since 2018.

***GROUND 1b: in making the assessment that preceded the recommendation, NICE has exceeded its powers***

**Appeal point 1(b).1; The Institute has exceeded its powers by retrospectively changing the narrative of the history of the appraisal, i.e., stating a different justification and timeline for pausing the appraisal of afamelanotide**

I am not minded to refer this appeal point to the Appeal Panel as a free-standing point of appeal. I anticipate that the explanation provided by the Institute for any delays will be relevant to the consideration of unfairness under ground 1a1, and a separate appeal point under Ground 1b would not add anything to that discussion.

**Appeal point 1(b)2; The Institute has exceeded its powers by pre-determining the preferred form of evidence for the generation of EQ-5D data as a vignette study**

I am not minded to refer this appeal point to the Appeal Panel. I cannot see any basis for the assertion that the Institute has exceeded its powers by expressing a preference for a vignette study. I have however noted below that I am minded to refer appeal point 2.2 to the Appeal Panel, on the basis that the Committee’s conclusion on this point was arguably unreasonable.

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

**Appeal point 2.1; Using a shorter than usual time-horizon for the economic model was unreasonable given that EPP is a lifelong chronic condition and the justification for the decision discriminates against patients aged 70 years and older**

I am not minded to refer this appeal point to the Appeal Panel. I understand IPPN’s argument to be that it was unreasonable for the Committee to adopt a 60 year time horizon for the economic model as opposed to a longer time horizon. It is said that this potentially impacts the cost-effectiveness calculation by reducing the number of QALYs associated with the technology, and discriminates against patients aged 70 years and older.

I note first that the time horizon adopted has no impact on the age or other profile of patients treated with the technology. I therefore cannot currently see any basis for an argument that the time horizon discriminates against any particular group of patients.

Secondly, I note that the Committee provides clear reasons for its adoption of a 60 year time horizon, which can be summarised as follows:

1. Average age of diagnosis is 22 years. Treatment for 60 years from that point would take the patient to approximately average life expectancy.
2. The marketing authorisation is clear that afamelanotide is not authorised in children, and that “afamelanotide should not be used in patients over 70 years of age”. The fact that the authorisation goes on to give guidance to doctors who nevertheless decide to use afamelanotide in older patients does not detract from that clear statement.
3. The application of age adjustment utility values could actually lead to a negative impact on cost effectiveness if a longer time horizon was adopted.

On the basis of the above, I cannot currently see that the Committee’s conclusions are arguably unreasonable on this point.

**Appeal point 2.2; It is unreasonable for the committee to assess the EQ-5D feasibility study as less scientifically valid than vignette studies**

I am minded to refer this appeal point to the Appeal Panel. I agree that it is arguably unreasonable for the Committee to place the relative importance that it did on the benefits of a vignette study.

**Appeal point 2.3; It was unreasonable for the committee to not apply a QALY weighting in the case of afamelanotide**

I am minded to refer this appeal point to the Appeal Panel. In reaching this view I note that the Committee has accepted that the evidence it considered (and in particular, the HRQOL data) drives a plausible ICER. Having reached that view, it appears to me that in deciding not to apply a QALY weighting, the Committee must have concluded either that the evidence it considered is not compelling enough to do so, or that the plausible number of QALYs gained over the lifetime of patients is less than or equal to 10. I anticipate that the Appeal Panel will wish to explore this point.

Conclusion

The above sets out above my initial views on all of your appeal points.

In respect of your points which I am not minded to refer on you are entitled to submit further clarification and/or evidence to me **no later than 5pm on 18 April 2023** 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 which will be held remotely.

Once I have made my final decision, and where there is more than one appellant, each appellant will receive the valid appeal points of the other appellants and their redacted appeal letter. This is to enable appellants to avoid duplication at the hearing where there are overlapping appeal points. If the appeal letter and/or responses to scrutiny contain confidential information, please ensure you have provided a version with this information redacted by **24 April 2023.**

Ordinarily appeals are conducted on the basis of the appellants’ written appeal letters, and the material generated during the appraisal process. Use of additional written material is discouraged, and the panel cannot receive any new evidence. If, exceptionally, you feel there is written material that will not be before the panel that you would wish to rely on you must let the NICE Appeal team know by return of letter, indicating what the material is, why it is desirable to submit it, and when it will be available, by no later than **19 April 2023**. Please note that the appeal panel cannot accept papers that are tabled late or ad hoc, as this affects the preparation of the panel and other parties for the appeal.

Yours sincerely

Dr Mark Chakravarty

Lead Non-Executive Director for Appeals & Vice Chairman

National Institute for Health and Care Excellence