xxxxxxxxxxxxxxx

Director of Global Operations

Clinuvel Group

Sent by e-mail only: xxxxxxxxxxxxxxx

31 March 2023

Dear xxxxxxxxx,

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

Thank you for your letter of 24 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.

As a preliminary point, I note that CLINUVEL’s appeal letter is marked ‘PRIVILEGED & CONFIDENTIAL’. Please could you confirm the basis on which any legal privilege is asserted over the contents of the letter, and which, if any, parts of the letter you consider to be confidential, and the reasons for that view? NICE’s usual practice is to publish appeal letters alongside the remaining appeal documents.

Initial View

I assess each of your points in turn. I have considered the ground 1a points first, then the 1b point, then finally the ground 2 points.

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

**Appeal point 1(a).1; The procedure followed by the Committee was not sufficiently transparent**

I am minded to refer this appeal point to the Appeal Panel. I agree that it is arguable that the Committee was insufficiently clear about:

1. the criteria on which it accepted or rejected evidence;
2. its approach to evaluating different types of evidence under consideration.

**Appeal point 1(a).2;** **The requirement of ‘conscientious consideration’ was not met**

I am not minded to refer this appeal point to the Appeal Panel. I do not consider that the point is arguable and note that CLINUVEL has not provided any justification for the assertion that the Committee would never have been prepared to change course in the light of the evidence presented to it, save that the Committee was not prepared to accept certain evidence that was presented to it.

**Appeal point 1(a).3;** **NICE acted unfairly by reason of delay**

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 CLINUVEL on any impact of the ‘pause and further delays’ on the outcome of the appraisal.

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

**Appeal point 1(b). NICE breached its duties under the Equality Act 2010**

I am minded to refer this appeal point to the Appeal Panel, so far as it relates to the duty to make reasonable adjustments.

In reaching this view I note that as a body exercising a public function, the relevant obligation on NICE is:

*Where a provision, criterion or practice puts disabled people at a substantial disadvantage compared with those who are not disabled, to take reasonable steps to avoid that disadvantage*

CLINUVEL argues that NICE has failed to meet that duty. CLINUVEL makes extensive submissions in support of this argument, which it seems to me can be summarised as follows:

1. The Committee did recognise that:
	1. people with EPP are disabled;
	2. the normal operation of the HST Process Guide would put people with EPP at a substantial disadvantage, in particular because of the specific challenge in measuring the effect of the condition and its treatment on quality of life (see e.g. paragraphs 4.8, 4.17-4.20 and 4.57-4.59 of the FED). The Committee identified particular features of EPP that put people with EPP at a disadvantage including the ‘important lack of robust scientific instruments to measure such effects’ and ‘conditioned light avoidance behaviours’ and
	3. accordingly the duty to take reasonable steps to avoid that disadvantage applied.

1. In CLINUVEL’s view, however, the Committee did not interrogate the nature of the disadvantage suffered by people with EPP sufficiently rigorously. CLINUVEL provides a list of 13 disadvantages that it says should have been taken into account[[1]](#footnote-1). It seems to me that the Appeal Panel will wish to consider whether these are substantial disadvantages arising as a result of the normal operation of the HST Process Guide. This will enable the Appeal Panel to consider whether or not reasonable steps were taken to avoid the identified disadvantage(s).
2. In CLINUVEL’s view, the sole adjustment made by the Committee was to derive ICERs from QoL evidence submitted by the IPPN. CLINUVEL acknowledges that in doing so, the Committee used that QoL evidence to capture benefits of afamelanotide that would ordinarily go uncaptured. However, CLINUVEL criticises the Committee for not considering whether other reasonable adjustments were required, and in particular whether disadvantages faced by people with EPP required “a more holistic approach to the appraisal of afamelanotide”. I anticipate that the Appeal Panel will wish to consider what adjustment(s) were made by the Committee to its approach.
3. By contrast with the ‘holistic approach’ it favoured, CLINUVEL argues that ICERs were determinative (notwithstanding the Committee’s statement to the contrary in section 4.42) and that the Committee placed too much weight upon (or alternatively misunderstood) the extent to which the NICE Principles and/or HST Process Guide ‘mandate a central role for ICERs in the assessment of value for money’.
4. CLINUVEL argues that in the absence of ‘a more holistic approach to the appraisal of afamelanotide’, the only reasonable adjustment in this case would have been to accept a plausible ICER above £100,000 per QALY gained, for either routine use or managed access.
5. In support of this position, CLINUVEL cites what it characterises as the Committee’s unreasonable rejection or failure to give ‘material weight’ to unstructured qualitative data, including treatment adherence data, and quantitative data from post-authorisation and observational studies. Having done so, CLINUVEL submits that the only reasonable adjustment available to the Committee would have been to accept a higher plausible ICER.
6. In light of the above, I anticipate that the Appeal Panel will wish to consider whether the statutory test is met: i.e. whether the Committee has taken reasonable steps to avoid the disadvantage(s) at which people with EPP are placed as a result of the normal operation of the HST Process.

I note that CLINUVEL makes a related argument that the Committee did not expressly address the need to promote equality of opportunity and its implications for adjustments to the Committee’s approach. I am not minded to refer this point to the Appeal Panel. I cannot see what, if anything, it adds to the substance of the argument summarised above.

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

**Appeal point 2.1: The Committee’s decision-making did not follow the relevant NICE Principles**

CLINUVEL makes three discrete arguments within this appeal point. I am minded to refer the point made in paragraph 9.7 of CLINUVEL’s letter, namely that it is arguable that the Committee focused unreasonably narrowly upon ICERS to the exclusion of other relevant factors.

I am not minded to refer the points made in paragraphs 9.8 and 9.9. These are respectively that the Committee paid insufficient attention to the need for best value for taxpayers, and that the Committee did not expressly consider ‘overall population need’. Neither seems to me to add anything substantive to the point argued in paragraph 9.7, and CLINUVEL has not provided evidence to support either, independently of the point argued in paragraph 9.7.

**Appeal point 2.2; It was unreasonable for the Committee to conclude that afamelanotide could not be recommended for funding on the basis of the ICERs falling outside the normal range in the HST Process Guide**

I am minded to refer this appeal point to the Appeal Panel. I anticipate that the Appeal Panel will wish to consider first, whether the Committee’s decision not to recommend was made on the basis that the ICERs fell outside the normal range (i.e. by considering the extent of the weight the Committee put onto the ICER in its decision-making), second, if so, the Committee’s reasons for basing its decision on that factor, and third, whether those reasons fall within the reasonable range.

**Appeal point 2.3; The reasons in the FED for refusing to recommend an MAA were illogical**

I am minded to refer this appeal point to the Appeal Panel. I anticipate that the Appeal Panel will wish to examine the Committee’s reasons for refusing to recommend an MAA, and whether or not those reasons were unreasonable – i.e. so unreasonable that no reasonable Committee acting reasonably could have reached them.

**Appeal point 2.4; The emphasis placed by the Committee and NICE on the importance and usefulness of a vignette study to inform the QALY was irrational**

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 2.5;** **The failure to place any (or any adequate) weight on treatment adherence data was irrational**

I am not minded to refer this appeal point to the Appeal Panel. I note that the Committee did take account of the fact that the adherence rate was high, whilst properly also acknowledging that adherence rates are not a direct marker of effectiveness and do not quantify the size of the treatment benefit. I cannot presently see how it could arguably be said that this was an irrational approach for it to take.

**Appeal point 2.6;** **The failure to place any (or any adequate) weight on data from post-authorisation and observational studies was irrational**

I am not minded to refer this appeal point to the Appeal Panel as a freestanding appeal point. I note that appeal point 2.4 argues that it was irrational for the Committee to place the weight that it did on the importance of a vignette study, at the expense of other kinds of unstructured evidence. I do not presently see that this proposed appeal point adds anything of substance to the consideration required to resolve appeal point 2.4.

**Appeal point 2.7; The decision to disregard the EPP-QoL tool reflected a factual error**

I am not minded to refer this appeal point to the Appeal Panel. The argument made appears to be that the statement that the EPP-QoL “was developed by the company” is erroneous, because in fact it was developed by the company “alongside and in conjunction with independent EPP experts”. I cannot see any arguable basis for unreasonableness arising from this clarification. CLINUVEL is entitled to seek a factual correction to the FED, should it wish to do so.

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

1. 1. *the extent to which clinical trial data may underestimate the impact of the disorder;*
	2. *the lifelong conditioned behaviour of EPP patients to avoid light exposure and phototoxicity;*
	3. *the impact of prodromal symptoms;*
	4. *the impact of cumulative exposure;*
	5. *EPP patients’ anxiety towards light exposure;*
	6. *the impact of the disorder on employment, study or family life;*
	7. *the impact of the disorder on interpretation of clinical and/or observational trial results;*
	8. *the rarity of the condition, even by the standard of HST appraisals;*
	9. *the impact of EPP patients’ diagnostic odyssey;*
	10. *the challenges of conducting clinical trials and developing clinical assessment tools for a previously unaddressed disorder;*
	11. *the proposed use of a preventative therapy in the disorder, rather than one which focused on symptomatic relief;*
	12. *the lack of alternative therapy;*
	13. *the unique nature of the findings of the EMA in its review and approval of SCENESSE® under exceptional circumstances.* [↑](#footnote-ref-1)