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14 June 2018

Dear Lachlan Hay

Final Evaluation Determination: Afamelanotide for treating erythropoietic protoporphyria (EPP)

Thank you for your letter of 6 June, lodging Clinuvel's appeal against the above Final Evaluation Determination.

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 make my final decision as to whether each appeal point should be referred on to the Appeal Panel.

I can confirm that there will be an oral hearing of the appeal.

I have retained the numbering of appeal points used in your appeal letter, but taken them in order of NICE's appeal grounds.

Initial View

Ground 1 (a)

Ground one NICE acted unfairly in that (i) one influential panel member of the HST committee was not impartial and (ii) NICE failed to take action in respect of his partiality upon notification by the company

It will be common ground between us that the test here is whether a properly informed fair minded observer, neither unduly suspicious nor unduly trusting, would consider there was a real possibility that the decision maker (in this case the committee) was biased. For present purposes I take bias to mean that there is an extraneous and improper factor acting on the committee's decision making, but that that factor does not need to be exclusive or dominant. Nor does it need to be shown that the extraneous factor in fact made a difference to the decision: it is enough that that is a possibility.

In this case the factor said to establish a real possibility of bias is an interaction between one of its members and your company. That interaction is said to have two consequences:

- The committee member had received confidential information from your company. This creates a risk of unfairness if he contributed to the committee's work.
- Your company's rejection of the member's financial proposal to work with you may mean he is not impartial.

As to the first point, it assumes that the information received by the committee member in commercial discussions with your company is different to the confidential information he will have received from your company as a committee member. I will assume for now that there

would be a legitimate explanation for any such difference, but this might need to be proved were this point to go further.

The first point also assumes that there is a real possibility that the committee member will both recall the earlier confidential information, and will not honour whatever undertaking of confidentiality he gave in respect of it. I do not think that the fair minded observer would think there was a real danger of this. The fair minded observer would know that professional people frequently receive confidential information in connection with business discussions that ultimately do not go anywhere, and that they understand the importance of not using that information for any purpose other than that for which it was disclosed to them. The observer would see no reason to suppose there was a risk that the committee member had not been able to respect that restriction, and would not detect apparent bias.

As to the second point, Howell v Lees Millais does not establish a general rule that rejection of a commercial proposal necessarily means that the person rejected will be biased against the rejecting party. The facts of Howell must not be mistaken for an authority. It is always necessary to apply the general test to the facts of the actual case. In any event the differences between that case and this are that the rejection of the commercial proposal was some two and a half to three years before the decisions (contrast one month), there is no evidence of any animus on the committee member's part (contrast the judge's email and his conduct in court) and the committee member is one member of a collective decision maker (contrast the judge as the sole decision maker). I do not think a fair minded observer would see a possibility of apparent bias here.

On that basis your sub-ground (ii) does not arise.

I am therefore not minded to refer this point to an appeal panel.

Ground four: NICE acted unfairly by failing to give the Company an opportunity to discuss and negotiate its proposed MAA to NHS England before presenting it

I begin from the position that it is the primary responsibility of the Company to prepare and submit its value proposition to the committee, and the committee's duty to assess a product fairly does not extend to seeking a "better" case than the case your company chose to make.

The possibility of an MAA is allowed in the HST process. It is clear that MAA are intended to allow data collection to address uncertainty. Therefore it seems to me fairness requires a

committee to identify where they are concerned about uncertainty, but this seems to have happened in this case. You imply that NICE is under a duty to facilitate discussions between your company and NHS England, but I am not sure how that duty is said to arise.

I am not sure whether your complaint goes beyond that your company began work too late on any MAA, (and I note from the FED that the idea of an MAA does not seem to have originated with your Company, and your Company seems to have seen major difficulties with any MAA) with the result that the MAA you submitted was not discussed with NHS England in advance. It would be helpful to have more information about the discussions referred to in your paragraph 29 and how they led your Company to an understanding that NICE had undertaken that you would have a discussion with NHS England.

Given the timing of your MAA and the conclusions expressed at FED 4.22 it would also be helpful to know why it was unfair for NICE to have consulted with NHS England on the content of the MAA submitted. If the FED is accurate it might seem fair to say that your company's desire to submit an MAA came very late indeed in the day, and was apparently rather less than enthusiastic, with the result that I currently doubt whether there is any real unfairness or unreasonableness here.

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

Ground 1(b)

Ground five NICE unlawfully discriminated against EPP patients and/or failed to have due regard to the need to eliminate discrimination and advance equal opportunities

A valid appeal point.

Ground 2

Ground two NICE acted unreasonably and/or irrationally in light of the evidence in treating the ICER expressed as a cost per QALY as effectively determinative of its decision not to recommend the product

I cannot see any part of the FED which suggests that the committee were unaware that a technology that falls outside the usual ICER range cannot be recommended. Indeed the discussion at FED 4.19 makes clear that the committee were aware that they could make such

a recommendation. I also note that the committee does discuss wider impact beyond direct health benefits. Additionally, if the committee's range of possible ICERs at FED 4.20 is reasonable, and noting that they are 13-17 times higher than the £100,000 guide referenced in the interim process, and provided uncertainty and wider benefits are considered as they appear to have been, I cannot see that it could be said to be unreasonable to base the decision on the ICERs.

I also think it is relevant to ask what the alternative would be. It is clear that calculating a reliable ICER in this case was challenging, to put it no more highly. But it is not sufficient to point that out to establish unreasonableness. There needs to be some alternative approach which would have been so clearly superior that no reasonable committee would have relied on ICERs. I am not sure what that approach would have been.

I am not minded to refer this point to an appeal panel.

Ground three NICE acted unreasonably and/or irrationally in departing from the conclusions of the EMA in its assessment of the Product without proper justification and without transparency

It is common ground that the EMA and NICE ask different questions, and that the EMA does not bind NICE. In the *Servier* case, the Court of Appeal addressed the case where the EMA had relied on a specific ex post facto subgroup analysis to establish clinical efficacy, and NICE (as the Court of Appeal thought) refused to place any weight at all on that same analysis when considering the same question. Those facts, according to the Court, called for explanation.

Could you elaborate for me on specifically what conclusion of the EMA NICE has departed from? The existence and possible relevance of conditioned behaviour does not seem to be in dispute. I do not think that the willingness of the EMA to base a conclusion in part on expert and patient testimony (I assume for present purposes that is a correct description of how they proceeded) can call for an explanation from NICE in the same way as a difference of opinion on exactly the same analysis did. Further I do not think NICE can be said not to have taken account of patient and expert testimony (though I agree it has not been given decisive weight). Finally if explanation is needed is it not provided in the FED and in the process guides?

I am not minded to refer this point to an appeal panel.

Please let me have any further observations you may have on the points that I am not minded to consider valid within the next ten working days, **no later than Thursday 28 June**, and I will then finalise my decision on initial scrutiny.

Yours sincerely

Dr Rosie Benneyworth
Vice Chair
National Institute for Health and Care Excellence