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14 June 2018

Dear Dr Jasmin Barman-Aksözen

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

Thank you for your letter of 6 June, lodging IPPN'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.

Initial View

Ground 1 (a)

1a.1 The Committee failed to act fairly by not acknowledging the evidence provided in patient testimonies and by expert physicians on the overwhelming clinical benefit [of treatment]

As your appeal letter quotes, the committee did take this material into account. Your complaint is that the material did not carry the day and (I infer) that the recommendation is unreasonable as a result. I am minded to refer that to an appeal panel, but under appeal ground 2.

1a.2 The committee failed to act fairly by omitting to discuss the evidence and the arguments provided by the consultees in a scientific and transparent way

The FED cannot record every aspect of a committee's considerations or deliberations verbatim. As a general complaint I am not minded to refer this to an appeal panel, although your more specific points are considered below.

1a.3 The committee failed to act fairly by choosing an approach for its assessment which knowingly underestimates the benefit of the treatment and therefore actively discriminates against EPP patients

So far as an appeal on fairness grounds is concerned, the committee has made clear what it is doing and has allowed consultation on it, so I cannot see arguable unfairness. But I think that you have misunderstood what the committee have done in any event. The committee's statement to which you take exception seems to me to be an acknowledgement that the ERG modelling would tend to underestimate benefits, and therefore a warning from the committee

to itself to take that into account when using the outputs of the modelling to inform decision making. The intent is to ensure that while the model may underestimate benefits, the committee will not.

I will return to the point about patient evidence under your appeal points on ground 2.

1a.4 The committee failed to act fairly by denying a managed access agreement based on the same arguments put forward on why it had already rejected a recommendation [to use]

I cannot see procedural unfairness here. The committee appears to have come to the view that there were difficulties inherent in the condition/treatment in collecting data on clinical benefit, and therefore that those difficulties would apply to an MAA as they would to the original clinical trials. I don't think you are arguing that the committee is not correct to perceive those difficulties ("an accurate quantification of the treatment effects is therefore not possible"), and it seems to me that their approach is transparent and consistent.

This may be a convenient point for me to explain that the nature of the appeal process is to review the work of the committee for unfairness or unreasonable error, and that neither I nor an appeal panel would ordinarily read references appended to an appeal letter, or consider evidence that was not before the committee.

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

1a.5 The committee failed to act fairly by not ensuring full representation of the patients voice at the committee meetings

NICE's processes allow for the nomination and appointment of patient experts to take part in an evaluation. Unless those processes were not followed (which I do not think you are alleging) it cannot be a ground of appeal that one patient expert was preferred to another. It is unfortunate that one of the patient experts then did not attend but again, unless there was a breach of process such as not notifying the expert of the date and time of the meeting this does not amount to a ground of appeal.

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

1a.6 The Committee failed to act fairly by demonstrating a consistent discrimination against IPPN as a stakeholder group

A valid appeal ground.

1a.7 The Committee failed to act fairly by not declaring a conflict of interest of a lead committee member

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.

I do not think there is a possibility that interest could be said to amount to bias. That interest is employment by a company some of those products are or may be marketed for indications for which afamelanotide is under investigation. Those indications are quite different to EPP. No fair observer would consider that (still less the committee) would be influenced by that fact. It is far too remote from the facts of this evaluation.

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

Ground 1b

1b.1 The Committee exceeded its powers by basing its decision on opinion rather than on evidence

As you argue under ground 2 that the committee should have based its decision on opinion, albeit that of patients and clinicians, I take this point to be that the committee's decision is its own arbitrarily formed decision rather than evidence based. That amounts to a general appeal under ground 2, although I would accept that such conduct would also be a dereliction of NICE's statutory remit.

However the FED seems to me to be clear evidence that the committee in fact sought to come to a decision based on its assessment of the evidence before it. That decision may or may not

have been reasonable (that is for ground 2) but I think it is impossible to argue that it is mere opinion or speculation by the committee uninformed by the evidence.

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

1b.2 The committee exceeded its powers by arbitrarily deciding on the validity of arguments put forward

The committee's power is precisely to decide on the validity of arguments put forward. The question is therefore whether they did so arbitrarily. The argument that you advanced was that a failure to provide treatment for these patients was discriminatory (because this is the only effective treatment available). Sadly there are other circumstances in which patients are left without effective treatments, and it may be that under any healthcare system with finite resources that will always be the case. This is generally accepted, if it is not welcomed. Therefore a bare argument that an effective treatment must always be funded, or a patient group must always have at least one effective treatment available, simply does not reflect how the NHS works. Therefore the committee's response that no potential equality issue was identified does not seem arbitrary.

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

1b.3 The committee exceeded its powers by reassessing the regulatory conclusions of the [EMA]

The regulatory conclusion of the EMA is that the clinical benefits and safety profile of the product are sufficiently positive that it may be marketed for use in EPP. I do not think the committee can be said to have reassessed that conclusion.

The EMA has no remit at all (still less "overriding authority") in decisions as to what products should be reimbursed in a national health system, indeed, that decision rests with member states and not at the EU level. I am afraid this appeal point fails to deal at all with the respective roles of the EMA and NICE.

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

Ground 2

2.1 The evidence provided shows that the benefit is significant and not small, as assessed by the committee

A valid appeal point.

2.2 The evidence provided of the measured trial outcome shows that the treatment is highly effective

A valid appeal point.

2.3 The evidence provided shows that quality of life before treatment is low and under treatment...increases dramatically and sustainably

A valid appeal point.

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