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16 July 2019

Dear [redacted]

Re: Final Evaluation Document – Metreleptin for treating lipodystrophy [ID861]

Thank you for your letter of 5 July 2019, lodging Aegerion's appeal against the above Final Evaluation Document (FED).

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

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 7 August 2019.

Initial View

Ground 1: In making the assessment that preceded the recommendation, NICE has: (a) failed to act fairly or (b) exceeded its powers

1. The Evaluation Committee has provided no adequate reasons to explain its conclusion that the clinical data for metreleptin are insufficient

This point argues that paragraph 4.4 of the FED does not state that the committee rejected the company's explanations such that the basis for the committee's conclusions that "the updated systematic review may have missed relevant studies", "the new literature review lacked structure" and "its concerns had not been sufficiently addressed" is unclear. It further argues that it is incumbent upon the committee to explain the reasons for the divergence between its conclusion on the sufficiency of the evidence of relative effectiveness of metreleptin and the EMA's conclusion that metreleptin is an effective treatment option.

I have reviewed paragraph 4.4 of the FED and note that this does contain the committee's reasons. You may not agree with the reasons provided, or you may consider they could be more fully expressed, but I do not consider it arguable that no or that only plainly inadequate reasons are provided.

Nor do I consider it arguable that the committee must provide more detail than it has already provided in order to justify why its conclusion (which relates to the strength of the evidence of relative effectiveness of metreleptin in the context of its role in determining whether the treatment can be recommended as a cost effective use of public money) is not the same as the conclusion of the EMA on the different (albeit related) question of whether there is sufficient

evidence of effectiveness for that regulator to conclude that the product can be promoted under a marketing authorisation. I am willing to assume for present purposes only that if NICE reaches a different conclusion to the EMA it should give some reasons for doing so, (though I question whether this in fact goes any further than NICE's general practice of giving reasons for recommendations) but I am not persuaded that NICE has reached different conclusions (bearing in mind the different remit of the two bodies) and in any event it seems to me reasons are given.

I am therefore not presently minded to refer this appeal point. However you are entitled to reply to this letter with a further explanation of why you consider the reasons provided are not adequate and I will consider the point further.

2. The Evaluation Committee has seemingly failed to understand the serious consequences of untreated lipodystrophy

This point argues that the FED fails to mention various aspects of the disease, namely the impact on triglyceride levels and glycaemic control, the metabolic consequences of the disease and the impact of the disease on mortality.

I note that the appeal must be against the decision not to recommend the treatment and the reasoning for that decision. Section 4 of the FED details the committee's consideration of the evidence and shows the committee expressly discussed triglyceride (paragraph 4.6), acknowledged serious metabolic abnormalities and its preference for using a metabolic disease model as the basis for modelling had that been provided (paragraphs 4.1 and 4.10) and considered mortality (paragraphs 4.13-4.14). Section 2 provides a short form summary of the condition, but it seems to me it is clearly not intended to describe the condition comprehensively in five fairly short paragraphs, and instead the FED must be read as a whole. The non-appearance of a consideration in section 2 does not support an argument that the consideration was not taken into account overall.

If the FED overall demonstrated a failure to understand the impacts of the disease that your appeal point refers to (e.g. that the disease was life limiting) then I might be minded to refer the point, but upon reading the FED I see no evidence that the committee failed to understand the serious consequences of the disease. I am therefore not presently minded to refer this appeal point.

3. The advice provided to Aegerion by the NICE technical team and by the Evidence Review Group (ERG) in relation to the response to the ECD conflicted with the subsequent observations of the ERG in written and oral submissions to the Evaluation Committee and the fact and substance of the advice received by Aegerion was not recognised or considered by the Committee in preparing the FED.

This is a valid appeal point. I refer this to consideration by the panel.

4. The Committee's conclusions in relation to the cost-effectiveness of metreleptin are inadequately explained

This is a valid appeal point. I refer this to consideration by the panel.

5. The Committee has failed to take into account the benefits of metreleptin that are not reflected in the economic model

This point argues that it was unfair for the committee not to take into account and consider whether and/or how the benefits of metreleptin therapy that were not adequately reflected in the economic model could impact the overall cost-effectiveness of metreleptin and whether the impact of these elements could have reassured the committee that usage of metreleptin was likely to be cost-effective.

I am not presently minded to refer this appeal point. This is because it appears to me that, given the committee says in the FED that it was unable to arrive at a most plausible scenario based on the evidence base, it would have been impossible for the committee to go on to carry out the exercise you suggest, as the committee had arrived at no most plausible scenario or even range of scenarios which could then be adjusted in light of the benefits you refer to.

6. The Committee has failed to consider the status of children with lipodystrophy in accordance with the provisions of the Human Rights Act 1998

I am not entirely convinced of the parallel with dinutuximab that you draw. I accept the general propositions that the appeal panel put forward in that case (save that I do not think it was saying that as a general rule article 2 applies to all appraisals.) The specific issue there was life extension, and that the committee had not asked itself whether extending the life of a child by a certain amount might not have even greater value than extending the life of an adult by the same amount.

However I feel the general proposition that there is a legal requirement to consider or reflect the fact that many of these patients will be children and that that requirement was not met should be examined by an appeal panel. To guide your preparation, although it is a matter for you I would suggest you do not rely too heavily on parallels with past appraisals, which an appeal panel may consider turn it on their own facts, but to apply whatever you argue the principles are to this condition.

7. The Committee's overall conclusion in this evaluation exceeds its powers

This point argues that NICE concluded that, irrespective of clinical need and any economic modelling, price or assumptions, that clinical evidence is so uncertain that metreleptin should not be recommended for use within the NHS and in doing so extended beyond its role to assume a regulatory role that conflicts and undermines the EMA's decision to grant a marketing authorisation under exceptional circumstances.

I am not presently minded to refer this appeal point. I note the FED states that metreleptin is not considered to provide value for money (section 1) and that the evidence presented to support the relative effectiveness of metreleptin was insufficient (paragraph 4.4). I do not consider it arguable that NICE thereby assumed a regulatory role or otherwise exceeded its powers, which are to consider the cost effectiveness of the treatment taking into account the clinical effectiveness of the treatment among other factors (para 43 of the NICE HST interim methods process guide (May 2017)). It seems to me unarguable to suggest that by finding the evidence of relative effectiveness to be insufficient to support a recommendation for public funding NICE stepped into the shoes of the EMA, which carries out the very different function of determining whether the treatment can be promoted as a medicine for use in humans.

You state that, while NICE is entitled to find (subject to procedural fairness and reasonableness) that the cost effectiveness or value for money of a particular technology has not been demonstrated, it is not permitted to conclude, that the clinical evidence of benefit associated with a licensed medicine and accepted by the regulators, is so weak or uncertain that it can never be recommended for use. In my view the FED simply does not suggest that metreleptin can never be recommended for use; rather it says the evidence available to the committee was so uncertain that it could not be recommended as providing good value for money in the national health system. This is a quite different matter. I note paragraph 1.2 of the FED expressly states that the recommendation is not intended to affect treatment with metreleptin that was started in the NHS before the FED was published, and of course it is

always open to commissioners to decide to commission a service using a product outside a NICE recommendation (and I understand they do so for this product in a related condition.) Therefore I would not be minded to refer this point on at this time.

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

This point states that the FED is subject to multiple factual errors which, taken together, cast doubt on the reasonableness of the committee's conclusions.

I am not presently minded to refer this appeal point. The factual errors you list can be considered as corrections by NICE but I do not consider it arguable that taken alone or together these factual errors render the recommendation unreasonable.

Those are my initial conclusions.

In respect of the points that I am not minded to refer you are entitled to submit further clarification and/or evidence to me within the next 10 working days, no later than **Tuesday 30 July 2019**.

Yours sincerely

Tim Irish
Vice Chair
National Institute for Health and Care Excellence