NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

sent by email: [redacted]

Dr Rebecca Sanders
Chair and Co-founder
Lipodystrophy UK
29 Collington Way
Abingdon OX13 5GP

16 July 2019

Dear Dr Sanders

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

Thank you for your letter of 5 July, lodging Lipodystrophy UK'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

I assess each of your points in turn and then summarise the appeal points that I am presently minded to refer at the end of this letter.

You make 14 separate points relating to 14 passages of the FAD, as follows.

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

1a.1 Page 1-2, Section 1.2 "these studies do not include any objective measure of hyperphagia or any comparison of metreleptin with other treatments. Therefore, the relative treatment benefit of metreleptin is unclear"

This point argues that 'objective measures of hyperphagia' and 'comparative treatments' do not exist, and that it is procedurally unfair to seek to compare the relative treatment benefit of metreleptin against a dataset that does not exist. You say patients should not be punished for the failure of the company and clinicians to produce a suitable comparative dataset.

I see no evidence that NICE sought to compare the relative treatment benefit of metreleptin against a non-existent dataset. Rather NICE found the relative treatment benefit was unclear owing to lack of evidence.

I will therefore interpret your point to be that it was unfair for NICE to take account of the lack of evidence of relative treatment benefit in circumstances where no comparative data exists. I am afraid I do not agree. As an expert body a committee must decide for itself what approach it will take to judging treatment benefit, provided that it acts in accordance with NICE's procedures and methods, is acceptably transparent, and adopts an approach that a reasonable expert body could adopt. Provided it acts in that way if it concludes that a particular

form of evidence would be necessary to make a robust judgement on a particular topic, the fact that that evidence has not been generated does not make the conclusion unfair.

I would not presently be minded to refer this point to the appeal panel.

1a.2 Page 2, Section 1.2 ***"There is a lack of real-world data outlining how lipodystrophy progresses in people who have not had metreleptin, so underlying progression of the condition is unclear****"*

I think the essential point here is that the evaluation's expectations should have been adjusted to take account of the fact that in an ultra-rare disease evidence may be sparse. However I cannot refer that to an appeal panel as a general point. The HST process is itself an adjustment to reflect the nature of very rare diseases. While a specific allegation that this or that specific adjustment should have been made for a particular treatment (for example, if a committee criticised the lack of long term data in a condition that had hitherto always caused death in infancy, that would be a valid point), an appeal panel would not be able to consider a general complaint, as this is too vague to work with.

I would not be minded to refer this point to an appeal panel.

1a.3 Page 2, Section 1.2 "*even with an appropriate model, any benefits attributed to metreleptin would be highly uncertain because of the substantial uncertainties in the clinical evidence*."

I think this essentially repeats or is a conclusion drawn from the points above, and for the same reasons I would not presently be minded to refer it to an appeal panel.

1a.4 Page 3. Section 3.1 "*Metreleptin has a UK marketing authorisation under 'exceptional circumstances' as 'an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients*"

This point again builds on the points above, and adds that as the EMA has accepted the present evidence base for the grant of an MA, it was unfair of NICE not to be persuaded by the evidence, and also that it would not now be possible to perform comparator studies for ethical reasons. For present purposes I will assume that last point is correct, although there may be a view that it begs the question.

I am not minded to find that this is a valid appeal point. As far as the EMA is concerned, this is a different body assessing evidence for a different purpose, it does not bind NICE and it is not necessarily unfair (or unreasonable) to reach different conclusions from what is admitted on all sides to be a limited evidence base. As to the impossibility of performing comparator studies, unless (which I do not understand to be the case) the committee is saying that it could only be persuaded by evidence that it is now impossible to generate, I do not think it can be said to be unfair if the committee has noted that the absence of past comparator studies has resulted in an uncertain evidence base. That seems to me to be a judgement that they can fairly reach.

I would not be minded to refer this point to an appeal panel at present.

1a.5 Page 5. Section 4.1 "*The committee acknowledged that lipodystrophy is a debilitating condition, and that hyperphagia is associated with very poor quality of life which affects patients, parents and carers. It recognised that there is a significant unmet need for an effective treatment option*."

This point argues that NICE's decision not to recommend metreleptin is in "complete contradiction" to its statement that there is a significant unmet need.

I fully understand your frustration and disappointment. However you will know that sadly the NHS operates in a world where there is a great deal of unmet need for healthcare of all kinds, and its role is to help the NHS prioritise. Provided a committee is aware of need, it does not necessarily act unfairly in making a recommendation that does not then address that need.

I would not be minded to refer this point to an appeal panel at present.

1a.6 Page 6-7. Section 4.3 "*The ERG highlighted that estimates of treatment effects were based on changes from baseline in single-arm metreleptin treatment studies, and no data for the comparator arm were presented within the clinical evidence. It stated that the submission did not include any search term for comparators, and that there was no attempt to do indirect comparisons to study the effects of established clinical management*."

I think this point repeats the points above and for the same reasons I would not be minded to refer this point to an appeal panel at present.

1a.7 Page 9. Section 4.6 ***"without understanding the experience of people whose disease is managed without metreleptin, any estimates of relative effectiveness would be highly uncertain"***

Again I think this repeats your underlying point and I would not be minded to refer this point to an appeal panel at present.

1a.8 Page 10. Section 4.7 "*The clinical experts also explained that hyperphagia is caused by a deficiency in the hormone leptin (see section 2.1), so any improvements in hyperphagia signal improvements in underlying lipodystrophy"…"Results from the NIH follow-up study showed that 99% of people who had metreleptin reported improvements in hyperphagia. The ERG highlighted that improvements were assessed in a review of medical notes and, although results suggested metreleptin improved hyperphagia, these judgements were not made using an objective measure.*"

This point argues that there is clear evidence of the impact of metreleptin on hyperphagia such that the burden of evidence applied by NICE was too high given the rarity of the disease, that 99% leaves no room for doubt and that patients should not be penalised for poor study designs.

As a matter of fairness I think this essentially repeats your points above and I would not be minded to refer this point to an appeal panel at present. I do note you also raise the same point below as a point of reasonableness.

1a.9 Page 15. Section 4.10 "It recalled concerns about the lack of comparator evidence (see sections 4.3, 4.5 and 4.6), and the uncertainty surrounding metreleptin's effect on improving hyperphagia (see section 4.7)."

I think this essentially repeats your points above and I would not be minded to refer this point to an appeal panel at present.

1a.10 Page 16. Section 4.11 ***"The committee had concerns about the generalisability of the GL/PL natural history study population to the population of people with lipodystrophy in England" … "The committee concluded that it had not been presented with adequate comparator data to allow a sufficiently robust comparison of metreleptin with standard of care."***

This point argues that too much weight is given to the need for comparator data and that any available data should be considered, due to the ultra-rare nature of the condition.

The weight to be given to evidence before a decision maker such as the committee is very much a matter for its expert judgement, and can be challenged, if at all, only on the basis that the weight given was so extreme (or so minimal) that no reasonable decision maker could have treated the evidence in that way. I would not be minded to refer this point to an appeal panel at present.

1a.11 Page 18. Section 4.13 "*The committee agreed that the matching exercise did not address its overall concerns relating to the lack of relative effectiveness evidence for metreleptin*."

This point argues (again) that too much weight is given to the need for comparator data.
For the reasons already given I would not be minded to refer this point to an appeal panel at present.

1a.12 Page 21. Section 4.16 "The ERG highlighted that the small sample size was a concern."

This point argues (again) that the ultra-rare nature of the condition precludes large patient cohorts.

For the reasons already given I would not be minded to refer this point to an appeal panel at present.

1a.13 Page 27. Section 6.1 ***"The committee discussed whether its concerns about the clinical and economic uncertainties in the evidence could be addressed by an 'only in research' recommendation or in the context of a managed access agreement. It recalled not only the lack of evidence in the submission but more importantly that there was no reliable framework on which to base an opinion on metreleptin's cost effectiveness. The committee did not believe this was an issue that could be addressed by further interventional research. Therefore, neither data collection as part of a managed access agreement nor an 'only in research' recommendation were considered appropriate."***

You ask for an opportunity to collect the relevant data for reassessment. I think this is a request that the treatment be recommended rather than an appeal point?

1a.14 This point argues that it is unfair that Metreleptin funding has been approved for congenital leptin deficiency, despite being unlicensed for this condition, and not for people with lipodystrophy when they often have similarly undetectable leptin levels.

This refers to an NHSE commissioning policy rather than a decision of NICE. NHSE does not bind NICE, and it will take its own decisions on its own criteria. It cannot render a NICE evaluation unfair if a commissioner commissions the same treatment for a different (albeit closely related) condition. This point might be better directed to NHSE. I would not be minded to refer it to an appeal panel at this time.

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

2.1 Page 1, A. Section 1.2 ***"This recommendation is not intended to affect treatment with metreleptin that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For a child or young person, the decision should be made jointly by them and their parents or carers, and their clinician."***

This point argues that patients currently on treatment are in fact not being funded via the NHS but rather the company, Aegerion, is providing metreleptin free of charge on compassionate grounds.

Without an agreement to fund metreleptin via the NHS, all patients will be withdrawn from treatment.

Addenbrooke's has already contacted patients receiving metreleptin to this effect. Therefore, whilst NICE's recommendation is not intended to impact current patient recipients, the reality is that all patients will lose access to metreleptin as a direct result of this decision.

NICE's recommendations can guide and affect only treatment that is funded by the NHS. It is not responsible for actions that a third party might take in response to a recommendation. This standard paragraph is intended only to ensure that if there is any existing treatment that is NHS funded, NICE is not recommending that it is stopped. It would clearly be extremely

disappointing if the company were to withdraw treatment as a result of this FED but that would be its decision. Its obligations to supply or not supply will be governed by whatever arrangements it and not the NHS have put in place.

2.2 Page 1, Section 1.2 "*Lipodystrophy is a rare and serious condition that severely affects the quality of life of people with the condition, and their families and carers*."

This point argues that the gravity of the condition has not been recognised by the committee as it cannot be described as a quality of life issue, but mortality issue (i.e., the disease not only reduces quality of life but also shortens life expectancy).

A valid appeal point. However, to guide your preparation for any hearing, I anticipate that you will need to explain what evidence was available to the committee that demonstrates your assertion that metreleptin would provide a survival benefit, and to what extent.

2.3 Page 2, Section 1.2 "*metreleptin is not considered to provide value for money within the context of a highly specialised service, and is not recommended in the NHS as an option for treating lipodystrophy*."

I think this is a general disagreement with the committee's overall conclusion and so not a valid appeal point?

2.4 Page 2. Section 2.1 "*Lipodystrophy is often diagnosed late in the disease course or remains undiagnosed*."

This point argues that the committee made a factual error here as generalised lipodystrophy is often picked up at a very young age. I do not think this is an appeal point, but it can be considered by NICE as a possible factual correction.

2.5 Page 3. Section 2.3 "*It is estimated that there are around 200 people with lipodystrophy in England; a proportion of these people will be eligible for metreleptin treatment*"

This point argues that 140 people with lipodystrophy is a more accurate estimate.

I do not think this will have been relevant to the evaluation, as population size might go to affordability, but that is not an issue that NICE considers. I do not think it will have been

relevant to an assessment of cost effectiveness. I would not be minded to refer this point to an appeal panel at this time.

2.6 Page 4. Section 3.3 "*The most common treatment-emergent adverse events in metreleptin studies included weight loss, hypoglycaemia, fatigue, injection site reactions, neutralising antibodies, decreased appetite, nausea, headache, abdominal pain, menorrhagia and alopecia*"

This part of the FED appears to be a close paraphrase of section 3.4 of the EPAR, (https://www.ema.europa.eu/en/documents/assessment-report/myalepta-epar-public-assessmentreport_en.pdf) including the words you object to, and so I do not think it could be argued to be unreasonable. I am not currently minded to refer this point on to an appeal panel.

2.7 Page 10. Section 4.7 *"The clinical experts also explained that hyperphagia is caused by a deficiency in the hormone leptin (see section 2.1), so any improvements in hyperphagia signal improvements in underlying lipodystrophy"…"Results from the NIH follow-up study showed that 99% of people who had metreleptin reported improvements in hyperphagia. The ERG highlighted that improvements were assessed in a review of medical notes and, although results suggested metreleptin improved hyperphagia, these judgements were not made using an objective measure."*

This point argues that there is clear evidence of the impact of metreleptin on hyperphagia (NIH follow-up study and Brown, et al. (2016)) and the burden of evidence is too high for such an ultra-rare disease. An improvement in 99% of patients is compelling evidence.

This is a valid appeal point.

2.8 Page 17-18. Section 4.13 "The model showed that metreleptin was associated with a 71.9% reduced mortality risk (hazard ratio 0.281; p=0.017)."

This point argues that, with such a marked reduction in mortality risk, NICE's recommendation cannot reasonably be justified from the evidence presented to the committee.

However the passage you cite simply reports a feature of the company's model. It seems to me from the last paragraph of FED 4.14 that the committee did not accept that feature. Whether that was reasonable or not might be a different point, (and indeed you make that point below) but I cannot see that it can be said that they have failed to make a

recommendation knowing that there was a 71.9% reduction in mortality risk. Therefore I would not be minded to refer this point on.

2.9 Page 19. Section 4.14 ***"In its preferred analysis, the ERG assumed that the survival of people with partial lipodystrophy who had and had not had metreleptin were equivalent … It concluded that, because of the limitations associated with the structure of the model, any modelled survival benefits needed to be plausible. Therefore, it agreed that the adjustments made by the ERG were appropriate."***

This point argues that assumption by the ERG is fundamentally flawed and the reasons for making survival between treated and untreated partial patients equivalent are not outlined in this report.

This is a valid appeal point.

2.10 Page 20. Section 4.16 "[The ERG] also noted that asking clinicians to score people who had not had treatment could have caused confusion, implying that they had nothing rather than standard of care."

This point argues that the ERG is assuming that the standard of care without metreleptin improves utility values. A valid appeal point, although you may need to explore how it could have impacted on the 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,** and I will then give a final decision on the points to put before an appeal panel.

Many thanks

Yours sincerely

Tim Irish
Vice Chair
National Institute for Health and Care Excellence