Sent by e-mail only: XXXXXXXXXX

FAO XXXXXXXXXX

Interim Head of Access and Pricing Bll

UCB Pharma Limited

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10 May 2024

Dear XXXXXXXXXX

**Re: Final Draft Guidance – Fenfluramine for treating seizures associated with Lennox-Gastaut Syndrome in people 2 years and over (ID1651)**

Thank you for your letter of 2 May 2024, lodging an appeal against the above Final Draft Guidance (FDG).

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.

Initial View

I assess each of your points in turn.

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

**Appeal point 1(a).1: NICE’s refusal of UCB’s request for technical engagement before the first meeting of the Appraisal Committee was procedurally unfair and has prejudiced the conduct of the appraisal.**

I am currently minded to refer this appeal point to the Appeal Panel on the basis that it was arguably procedurally unfair for the Committee to decline UCB's request for technical engagement and that doing so arguably prejudiced the conduct of the appraisal.

I note that NICE's Manual for health technology evaluations is clear (at 5.7.8) that technical engagement is not a mandatory stage of the evaluation process. That being the case, I should be grateful, before reaching my final view on referral for further detail from UCB about what, if any, consequences you say flow from the absence of technical engagement, and in particular, how UCB considers that the conduct of the appraisal and/or the recommendation reached was negatively impacted.

**Appeal point 1(a).2: In the circumstances of this appraisal, including the lack of technical engagement, the multiple unresolved issues and the change in approach between ACM1 and ACM2, a third meeting of the Appraisal Committee should have been scheduled prior to issue of Final Draft Guidance.**

I am not minded to refer this appeal point to the Appeal Panel.

I understand that UCB's argument is that it was procedurally unfair for the Committee not to meet for a third time before issuing the FDG. In reaching my initial view that this point does not raise arguable unfairness, I note that your appeal point relies on areas of uncertainty that you say remained unresolved after the second committee meeting. I do not consider outstanding uncertainty to be a basis on its own for an arguable conclusion that it was procedurally unfair not to hold a third committee meeting. The Manual is clear that in reaching any decision, a committee will need to base its recommendations on the evidence presented, and in doing so, consider and highlight areas of contention and uncertainty that have arisen during the committee's discussions of the evidence. Uncertainty is inherent in any NICE evaluation.

I have also reviewed paragraph 5.8.59 of the Manual, which states as follows:

*When stakeholders submit comments that lead to a substantive revision of the committee's previous decision, involving a significant change in the recommendations, discussions or the evidence base, NICE and the chair of the committee will decide whether it is necessary to repeat the draft guidance consultation. The decision to hold another consultation will extend the timelines for the evaluation.*

I note that the Manual does not here envisage a further consultation (and thus, a third committee meeting) being required solely on the basis of outstanding uncertainty.

**Appeal point 1(a).3: Standard of Care (SoC) alone does not reflect NHS clinical practice and is not an appropriate comparator for fenfluramine.**

I do not regard this as a valid appeal point under ground 1 but am minded to refer this appeal point to the Appeal Panel under ground 2.

That is because I can see that it is arguable that the Committee's conclusion that SoC was an appropriate comparator was unreasonable. I cannot see an arguable basis for determining that conclusion to have been procedurally unfair. The Committee plainly fulfilled its role of gathering information and data, forming a view on preferred assumptions including as to the appropriate comparator. I do not understand your argument to be that the Committee failed to seek relevant information before reaching its view; it appears to me that your argument is that having done so, the view that the Committee reached was unreasonable on the basis of the evidence it had.

Separately, the points made in paragraphs 16.4 and 18.1 of your letter both appear to highlight potential factual errors in the FDG. If that is your intention, these should be raised separately with NICE (see paragraph 5.8.66 of the Manual).

**Appeal point 1(a).4: NICE’s approach to the use of ITT LOCF data versus clinical trial state occupancy data in order to compare fenfluramine + SoC with CBD + CLB + SoC, is procedurally unfair and inconsistent with the approach followed in the appraisal of CBD for the same indication (TA615).**

I am minded to refer this appeal point to the Appeal Panel.

In considering this appeal point, I anticipate that the Appeal Panel may wish to consider two related arguments made in your appeal letter:

1. that it was procedurally unfair for the Committee to adopt a different methodology in the current evaluation from that adopted in TA615, without sufficient explanation, in circumstances where the "patient population is the same and the appraisal faces the same challenges in terms of a rare disease with a heterogeneous patient population" (paragraph 23 of UCB's appeal letter); and
2. that it was procedurally unfair for the Committee to rely upon and criticise UCB's focus on the ITT population, in circumstances where the Draft Guidance had stated explicitly that an ITT methodology was preferred (paragraph 22 of UCB's appeal letter).

**Appeal point 1(a).5: The absence of any indication of the Committee’s preferred assumptions at the Draft Guidance stage and the lack of clear explanation of how the Committee had taken into account the status of LGS as a rare disease, substantially prejudiced UCB’s ability to offer a discount that would meet the Committee’s expectations of cost-effectiveness.**

I am not minded to refer this appeal point to the Appeal Panel.

I understand UCB's argument to be, in summary, that the Committee should have set out its preferred assumptions sooner, either as part of technical engagement (which did not take place) or in draft guidance, and that the Committee's failure to do so inhibited UCB's ability to propose a patient access scheme because UCB did not know what level of discount (or other commercial arrangement) would be required to bring the ICER within acceptable range.

I am not persuaded that the absence of preferred assumptions at an earlier stage can be said to be procedurally unfair. The Manual is clear that a committee's preferred assumptions may develop over the life of the evaluation, until finalisation in the FDG (see for example, 5.8.64).

**Appeal point 1(a).6: The requirement for UCB to produce new analyses and for substantive disclosure of important material from the EAG immediately before ACM2 did not allow adequate time for consideration and was inconsistent with a fair procedure.**

I am minded to refer this appeal point to the Appeal Panel.

In considering this appeal point, the Appeal Panel may wish to consider separately whether it was procedurally unfair to:

1. request additional analyses from UCB within a short timeframe, and/or
2. provide UCB with a short timeframe within which to consider newly disclosed material before the second committee meeting.

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

**Appeal point 2.1: The Committee’s preference for a naïve comparison between the trials instead of an indirect treatment comparison of ITT data was unreasonable.**

I am minded to refer this appeal point to the Appeal Panel.

**Appeal point 2.2: The Committee’s conclusions in relation to the waning of the treatment effects associated with fenfluramine and cannabidiol are inconsistent with the available evidence and with the approach followed in previous appraisals.**

I am minded to refer this appeal point to the Appeal Panel.

**Appeal point 2.3: NICE’s conclusion that it should assume no treatment wastage between fenfluramine and cannabidiol is inconsistent with the available evidence and therefore unreasonable**

I am not minded to refer this appeal point to the Appeal Panel.

I understand UCB's argument to be that the Committee's conclusion that it should assume equivalent (zero) levels of wastage for fenfluramine and cannabidiol, was unreasonable because cannabidiol is oily and so residue remains in the bottle, and because cannabidiol is provided in glass bottles which are more likely to break if dropped than the plastic containers used for fenfluramine.

This point is well discussed in paragraph 3.19 of the FDG, which explains the Committee's consideration of evidence received from UCB, the EAG, patient experts, and clinical experts. In the light of the evidence discussed in that paragraph, I cannot see that the Committee's conclusion could arguably be said to be unreasonable, i.e. that it cannot reasonably be justified from the evidence presented to the committee, is obviously and unarguably wrong, illogical, or 'does not add up'.

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 within the next 10 working days, 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 is likely to be held remotely.

1. 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 3 June 2024.
2. 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 28 May 2024. 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

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Dr Mark Chakravarty

Lead Non-Executive Director for Appeals & Vice Chairman

National Institute for Health and Care Excellence