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Place

London E20 1JQ 24 May 2024

Dear Dr Chakravarty,

# Re: Final draft guidance (‘FDG’) for ID1651: Fenfluramine for treating seizures associated with Lennox–Gastaut syndrome (‘LGS’) in people 2 years and over

Thank you for your letter dated 10 May 2024, in which you set out your preliminary views on the admissibility of the points of appeal advanced by UCB and set out in our appeal document of 2 May 2024. This letter provides our response to your preliminary views before you make your final decision on those points of appeal which will be permitted to proceed to an oral hearing.

# Ground 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

In your letter of 10 May 2024, you say that you are minded to refer this appeal point to the Appeal Panel. However, before making a final decision, you request further detail from UCB on the consequences which flow from the absence of technical engagement in this case.

The purpose of technical engagement, as set out in NICE’s Guide to the Processes of Technology Appraisal, is to consider the judgments made by the technical team and to provide an opportunity for any remaining uncertainties in the case for clinical effectiveness and cost effectiveness to be mitigated before the technology is considered by the Appraisal Committee. The fact that technical judgments have

been considered and uncertainties mitigated means that fewer Appraisal Committee meetings are likely to be needed in order to conclude the appraisal.

In this case, as explained in our appeal document of 2 May 2024, the specific issues identified by UCB for technical engagement remained unresolved at ACM1 and even in some instances at ACM2. If there had been technical engagement before ACM1, as UCB contends there should have been, there would have been substantial progress in resolving these issues before any meeting of the Committee and it is likely that some of them would have been resolved. The main result would have been that two meetings of the Appraisal Committee would have been sufficient to bring the appraisal to a satisfactory conclusion, rather than the current situation where important issues remain unresolved after ACM2. The prejudice to the appraisal resulting from this situation is demonstrated, for example by the following:

* + Technical engagement would have permitted adequate consideration of the relevant comparators for this appraisal. Right up to ACM2 the EAG maintained that the issue of comparators had not been resolved and criticised the network meta-analysis submitted by UCB on the basis that this did not include a number of treatments considered by the EAG to be relevant. UCB was ultimately asked, a mere two days before ACM2 to provide a comparison between fenfluramine and standard of care alone, despite its position that such a comparison is inappropriate.
	+ The efficacy assumptions are complex in this appraisal in view of the absence of head to head trials and the heterogeneous nature of the patient population. It was therefore inevitable that, without technical engagement, it would be challenging to agree the appropriate method to compare the efficacy of fenfluramine and cannabidiol and to resolve the issues in a timely manner within the scope of two Appraisal Committee meetings. Ultimately the first discussions regarding these matters took place during ACM1, with the result that UCB was asked to explore a range of options following the draft guidance, in circumstances where there was inadequate time for consideration at ACM2

Overall, in the context of a complex appraisal of a treatment, such as fenfluramine, for a rare disease with a heterogeneous patient population and no direct treatment comparison, technical engagement is almost certainly necessary in order to resolve uncertainties before ACM1. The experience with the current appraisal clearly

illustrates that, in the absence of technical engagement, two meetings of the Appraisal Committee is insufficient for consideration of the issues.

Our appeal document of 2 May explained that NICE had applied an incorrect test in deciding not to include a technical engagement step in this case and why it should, in accordance with the Manual and as a matter of procedural fairness, have included this part of the process in the current case. We understood from your letter that you accepted that this argument should proceed to appeal and required only further details of the prejudice resulting from technical engagement. We have therefore limited the information in this letter to the prejudice element of this point of appeal and why the lack of technical engagement has resulted in an appraisal where key issues have not been resolved following two meetings of the Appraisal Committee.

# Ground 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

You suggest in your letter of 10 May 2024 that you are not minded to refer this appeal point to the Appeal Panel on the basis that, you say, outstanding uncertainty is not a basis on its own for a conclusion that it was procedurally unfair not to hold a third meeting of the Committee.

However, the point of appeal advanced by UCB is not based solely on residual uncertainty, but on the following matters which cumulatively mean that a third meeting of the Appraisal Committee was required as a matter of procedural fairness.

* + The lack of technical engagement in the context of a complex appraisal for a rare disease with a heterogeneous patient population, which meant there were unresolved issues following ACM2.
	+ The fact that additional analyses were requested from UCB immediately before ACM2 with inadequate time for fair preparation (in one case a mere half a working day) and inadequate time for consideration by NICE or the Committee before the date of the meeting. If additional analyses are required by the Committee it is clearly necessary that sufficient time is permitted for these to be prepared and then considered and the fact that this

was not the position in relation to the material requested before ACM2 means that a further meeting should have been scheduled to address the unfairness.

* + Key material was disclosed to UCB by NICE only the day before ACM2, with inadequate time for appropriate consideration in advance of the meeting. If material is disclosed it is clearly necessary as a matter of fairness that sufficient time is provided for this to be reviewed; that did not happen in the current appraisal. A third meeting of the Appraisal Committee would have allowed adequate time for consideration of this material and any responses made before FDG was issued.
	+ UCB’s response to the draft guidance reflected the acceptance of the Committee at ACM1 for an indirect treatment comparison for the registrational trial (cycle 1 within the model), as an indirect treatment comparison was also conducted for the OLE period (cycles 2-5). Only for UCB to be informed that the Committee selectively prefers the naïve comparison in some areas of the analysis instead of a more robust method to inform the analysis, an indirect treatment comparison. While it is UCB’s position that the Committee’s preference for a naïve comparison is unreasonable, it is also the case that the inconsistent, unreasonable approach to evaluating and considering the comparison of efficacy between ACM1 and ACM2 amounted to a substantial back and forth in the evaluation process. An example of a key unresolved issue with regards to the indirect treatment comparison mentioned within the FDG in section 3.7 was that

“potential changes in the placebo response during the trials, for example because of changes in the participants’ beliefs or the natural history of the disease, were not accounted for”. The continued issues should have resulted in a second consultation and third meeting of the Committee so that UCB had an opportunity to resolve this.

The cumulative effect of each of the above elements is that it was plainly necessary for a third meeting of the Committee in order to ensure procedural fairness in this appraisal.

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

You express the preliminary view that this point of appeal should be advanced under Ground 2, rather than Ground 1 on the basis that, you say, the Committee did not fail to seek relevant information before reaching its view and that you construe UCB’s point of appeal to be that having collected such information the conclusion of the Committee was unreasonable.

Paragraph 2.2.12 of the Manual describes “potentially relevant comparators” as those that are “established practice in the NHS”. The evidence from all clinical experts was that cannabidiol is the appropriate comparator (as reflected in the Committee slides at ACM1) and this was the positioning advanced by UCB. There was no evidence given to the Committee suggesting that standard of care alone should be considered.

In these circumstances, the view of the Committee at paragraph 3.3 of the FDG that standard of care alone is an appropriate comparator, conflicts with the test at paragraph 2.2.12 of the Manual, the views of clinical experts and UCB. The conflict with the procedural test under the Manual was the basis for the inclusion of this point of appeal under Ground 1, however to the extent that the point raises questions of interpretation of the evidence of clinical experts, we agree that it also raises issues under Ground 2.

# Ground 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)

We note your view that this point of appeal should proceed to an oral hearing.

# Ground 1(a).5: The absence of indications 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

You suggest, in your letter of 10 May 2024 that this point of appeal should not proceed to an oral hearing. Your reason is that it is open to the Committee to develop its preferred assumptions throughout the appraisal, until finalisation in the FDG and therefore, you say, the fact that the Committee did not make its preferred assumptions clear at the draft guidance stage was not unfair.

However if consultation is to be effective, it is essential that the Committee’s proposals are clear and that the basis for these is explained, failing which it is impossible for stakeholders to understand whether the preliminary guidance is fair and reasonable. Transparency is a fundamental part of a fair procedure and, while UCB agrees that the Committee’s views (including its preferred assumptions) may develop during the appraisal, this does not relieve the Committee of the obligation to provide reasons for its conclusions at both the draft guidance stage and in the FDG. This is a requirement as a matter of good administration and to ensure that decisions are soundly based and also so that stakeholders are able to participate in consultation.

The consequence of the lack of transparency in this appraisal at the consultation stage, in terms of each of the matters, central to any consideration of fenfluramine, set out at paragraph 25.3 of our appeal document, was to preclude effective consultation and, as explained, to prevent UCB considering any financial offer to improve cost effectiveness. This is procedurally unfair and inconsistent with high standards of rigorous decision making.

# Ground 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

We note your view that this point of appeal should proceed to an oral hearing.

# Ground 2.1: The Committee’s preference for a naïve comparison between the trials instead of an indirect treatment comparison of ITT data was unreasonable

We note your view that this point of appeal should proceed to an oral hearing.

# Ground 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

We note your view that this point of appeal should proceed to an oral hearing.

# Ground 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

Your letter expresses the preliminary view that this point of appeal should not proceed to an oral hearing on the basis that the Committee’s consideration of the issue is explained at paragraph 3.19 of the FDG and you suggest, in light of the evidence discussed in that paragraph, the Committee’s conclusion cannot be said to be unreasonable.

Paragraph 3.19 of the FDG refers to: the evidence of clinical experts at the first Appraisal Committee meeting (ACM1) “that there may be treatment wastage caused by bottle breakages or leftover liquid medicine in the bottle”; and the evidence of a patient carer expert that wastage of liquid treatments for LGS is often caused by the person having the treatment knocking it out of a carer’s hand which, the Committee concluded, was not specific to the treatment used. The Committee then stated that it had not seen “sufficient” evidence to support differences in treatment wastage between fenfluramine and cannabidiol. The Committee’s conclusion is unreasonable including for the following reasons:

* + All three clinical experts stated at ACM1 that there could be wastage of cannabidiol due to the fact that this is an oily substance and is provided in a glass bottle; these factors may result in cannabidiol being leftover in the bottle and bottle breakage. This possibility was reflected in the Draft Guidance at paragraph 3.16. However in preparing the FDG, the Committee has omitted to state that the evidence of the clinical experts related to wastage of cannabidiol not to potential wastage of fenfluramine.
	+ During ACM2, the clinical experts stated (i) that they expect at least one 100ml bottle of cannabidiol to be dropped per year and (ii) there is generally cannabidiol liquid left in bottles; this level of wastage is consistent with one of the scenarios submitted to NICE by UCB in response to the Draft Guidance.

The evidence of the clinical experts at ACM2 has however been disregarded during preparation of the FDG.

* + The FDG characterises the evidence of the patient carer expert as “not specific to the treatment used”. This is incorrect, as cannabidiol is presented an oily liquid resulting on increased bottle droppage. It is obvious that, if a glass bottle is dropped this may result in breakage, consistent with the evidence of the clinical experts and resulting in the loss of the entire contents, whereas if fenfluramine (Fintepla is presented in a High Density Polyethylene (HDPE) with a child resistant cap, tamper evident cap and press in bottle adaptor) is dropped there will be no breakage, but only the possibility of some minor spillage. In any event, UCB’s understanding from the Committee meeting is that the patient carer expert had not used fenfluramine and therefore it is unclear how they can provide evidence on something they have not experienced, and their comments may have been taken out of context.
	+ The slides shown to the Committee by the lead team at ACM2 referred to comments from the manufacturer of cannabidiol, which asserted that the containers for fenfluramine and cannabidiol were “similar” and stated that “bottle breakage an isolated incident → unlikely any difference in wastage”. It is clearly incorrect to state that the containers for the two products are “similar” (one is glass and one is plastic) and the evidence of the manufacturer of cannabidiol is unsupported by evidence and conflicts with the experience of the clinical experts. The evidence from the manufacturer of cannabidiol is not referenced explicitly in paragraph 3.19 of the FDG, however such evidence was presented as fact in the slides presented by the lead team at ACM2 and UCB was given no opportunity to refute it. In these circumstances the incorrect statements by the manufacturer of cannabidiol must be assumed to have influenced the Committee’s view that it had not seen “sufficient” evidence to support differences in treatment wastage.

In summary, with the exception of the comments from the manufacturer of cannabidiol (which are incorrect, as demonstrated by the summaries of product characteristics for the respective products) the evidence available to the Committee indicates consistently that wastage is more likely to occur with cannabidiol than with fenfluramine. In these circumstances, the analysis of the data at paragraph 3.19 of the FDG is inaccurate and the conclusion of the Committee that it had not seen sufficient evidence to support differences in treatment wastage is unreasonable.

Thank you for considering the further elaboration and clarification of our appeal provided in this response to your letter of 10 May 2024. On the basis of this, we hope you agree that all the points of appeal set out in our appeal document submitted on 2 May 2024 should proceed to an oral hearing.

Yours sincerely

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