NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

APPEAL HEARING

# Advice on fenfluramine for treating seizures associated with Lennox–Gastaut syndrome in people 2 years and over [ID1651]

# Decision of the panel

## Introduction

1. An appeal panel was convened on 6 September 2024 to consider an appeal against NICE’s final draft guidance, to the NHS, on fenfluramine for treating seizures associated with Lennox–Gastaut syndrome in people 2 years and over.
2. The appeal panel consisted of:

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| * Professor Jon Cohen
 | Chair |
| * Dr Justin Whatling
 | Non-Executive Director of NICE |
| * Professor Peter Groves
 | Health service representative |
| * Rachel Russell
 | Industry representative |
| * Rosemary Harris
 | Lay representative |

1. None of the members of the appeal panel had any competing interest to declare.
2. The panel considered appeals submitted by – UCB Pharma ("The company" or "UCB"), the Royal College of Physicians ("The Royal College" or "RCP") and the Tuberous Sclerosis Association ("TSA").
3. The company was represented by:

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| * Matthew Binns
 | Area Access and Pricing Lead, UCB |
| * Adela Williams
 | Partner, Arnold Porter |
| * Zhen Tan
 | Epilepsy Medical Head, UCB |
| * Dr Micheal Taylor
 | Consultant paediatric neurologist, Leeds Teaching Hospitals NHS Trust |
| * Florence Bianic
 | Managing Director, Syneos Consulting |

1. The Royal College was represented by:

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| * Dr Shanika Samarasekera
 | Consultant Neurologist, RCP |
| * Dr Rhys Thomas
 | Consultant Neurologist, RCP |
| * Dr Johann Te Water Naude
 | Paediatric Neurologist, RCP |
| * Dr Archana Desurka
 | Paediatric Neurologist, RCP |

1. TSA was represented by:

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| * Dr Suresh Pujar
 | Paediatric Neurologist, TSA |
| * Dr Stephanie Prince
 | Oncologist and rare epilepsy parent representative, TSA |
| * Jane Hanna
 | Director of Policy and Influencing, SUDEP Action |
| * Allison Watson
 | Chair, UKRET |

1. In addition, the following individuals involved in the evaluation were present and available to answer questions from the appeal panel:

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| * Dr Raju Reddy
 | Chair, Technology Appraisal Committee D |
| * Dr Jacoline Bouvy
 | Programme Director, Medicines Evaluation, NICE |
| * Dr Will Sullivan
 | Member, Technology Appraisal Committee D |
| * Lizzie Walker
 | Technical Advisor, NICE |
| * Robert Woolf
 | External Assessment Group representative, NICE |

1. The appeal panel’s legal adviser – Amy Smith, Senior Associate at DAC Beachcroft LLP –was also present.
2. The following members of the appeal panel for technology appraisals and highly specialised technologies were present as silent observers throughout the hearing and panel discussions.

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| * Dr Malcolm Oswald
 | * Appeal panel lay member
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| * Sheba Joseph
 | * Appeal panel lay member
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| * Dr Stephen Hoole
 | * Appeal panel health service representative
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1. Under NICE’s appeal procedures, members of the public are admitted to observe appeal hearings and several members of the public and NICE staff observed the proceedings which were held via Zoom.
2. There are two grounds under which an appeal can be lodged:

Ground One: In making the assessment that preceded the recommendation, NICE has:

(a) Failed to act fairly; and/or

(b) Exceeded its powers.

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

1. Dr Mark Chakravarty, NICE Lead non-executive director for appeals, in preliminary correspondence had confirmed that:
* The company had potentially valid grounds of appeal as follows: Grounds 1(a) and 2.
* The Royal College had potentially valid grounds of appeal as follows: Ground 2
* TSA had potentially valid grounds of appeal as follows: Grounds 1(a) and 2
1. The evaluation that is the subject of the current appeal provided advice to the NHS on fenfluramine for treating seizures associated with Lennox–Gastaut syndrome (LGS) in people 2 years and over.
2. Before the appeal panel inquired into the detailed complaints the following made a preliminary statement: Alison Watson for TSA, Dr Shanika Samarasekera for the RCP, Matthews Binns for the company and Dr Raju Reddy on behalf of the appraisal committee.

## Appeal by the company

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

### Appeal Ground 1a.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

1. Adela Williams, for UCB, stated that the committee's decision arose from a conclusion that clinical and cost effectiveness were uncertain, and the company considered this was inevitable from the outset of the evaluation due to the rarity and heterogeneity of the condition and the wide range of treatments used. The purpose of technical engagement was set out in NICE's previous Guide to the Processes of Technology Appraisal as being to seek views on the judgements made by the technical team and to allow the company to consider how it could mitigate the remaining uncertainties in the case for clinical and cost effectiveness in the evidence base. It was therefore particularly pertinent to this evaluation and the company considered the need for technical engagement was particularly strong in this evaluation. NICE's current Manual provides for technical engagement when appropriate, helpful and proportionate, taking into account whether the technical engagement process is likely to resolve key issues before the committee meeting. In a complex evaluation, key issues need to be discussed before the first committee meeting, and it is inefficient and unfair if inadequate time is afforded to issues during the committee meetings. Further, the company's request for technical engagement was refused by NICE on the same day, and the initial response from NICE suggested the key reason not to go to technical engagement was that NICE did not want to delay the committee meeting. Time ought not to be a driver if fairness requires technical engagement. NICE explained its reasons by email 17 days later, saying that the decision was because the areas of uncertainty identified by the company would be dealt with at the committee meeting. But it gave apparently no consideration to whether these areas could be resolved *before* that meeting, as set out in the Manual. The issues identified by the company remain outstanding in the Final Draft Guidance (FDG). The company consider this inconsistent with NICE's procedures and, while technical engagement is not mandatory, NICE is required to exercise its discretion in a reasonable and fair way.
2. Matthew Binns, for UCB, reiterated that section 5.7.2 of NICE's Manual requires NICE to take into account if technical engagement is likely to resolve key issues "before" the committee meeting and submitted that NICE had applied an incorrect test of whether key issues could be resolved "at" that meeting.
3. Dr Jacoline Bouvy, for NICE, said that NICE would have considered whether technical engagement was needed before the company's request. She said that the key reason NICE decided technical engagement was not required was that, having seen the External Assessment Group (EAG) report and clarification questions and the company's response, NICE saw the committee's judgement as being crucial to resolve the key issues where there was disagreement between the EAG and the company (as set out in NICE's explanation to the company). NICE did not think there was no value whatsoever of technical engagement but decided against it because it would have delayed the process and a number of issues needed the committee's judgement to resolve them.
4. Adela Williams accepted there were points where committee judgement was required, but stated that this did not answer the fact there was and remained uncertainty as to the correct modelling approach and how fenfluramine was to be compared with cannabidiol plus clobazam (C+C) plus standard of care (SoC). A lot of the issues the company had identified at the beginning of November were not for committee judgement and would have been assisted by technical engagement to consider issues with the EAG. That was demonstrated, she said, by issues remaining outstanding at FDG stage that were not questions of committee judgement, and by the fact that further analyses were required immediately before the second meeting. If there had been technical engagement the company could have resolved some issues and provided data earlier and would not be where it is now.
5. Adela Williams noted criticism of the company for failing to submit data. She said that the company always wished to cooperate fully with the committee but there was substantial uncertainty as to what was required and the appropriate approach. Those issues might have been resolved by technical engagement. Many issues raised by the company did not require committee judgement and remained outstanding, such as the appropriate comparator, model structure, how to extrapolate treatment effect and waning. All of these could have been discussed in technical engagement and the company considered that would have been an efficient and constructive way to manage uncertainties.
6. Matthew Binns said that as soon as the company saw the EAG report it believed technical engagement would be useful as an opportunity for more discussion with patients and clinical experts outside the company. LGS is complex and technical engagement was undertaken for the same disease area in NICE's evaluation of cannabidiol with clobazam for treating seizures associated with LGS.
7. Dr Raju Reddy, for NICE, confirmed that the decision on technical engagement is taken by NICE without involvement of the committee.
8. Dr Jacoline Bouvy explained that the question of whether technical engagement might be required is considered by NICE's technical team from the start of an evaluation, based on its understanding of the decision problem and likely challenges. This is considered first when NICE receives the company submission, then when it receives the draft EAG report and subsequently the final EAG report. So there is some time in NICE's process for the NICE team to consider if technical engagement is appropriate.
9. Lizzie Walker, for NICE, confirmed that the technical team consider this throughout and a final decision is taken after receipt of the final EAG report, in this case about a week before UCB requested technical engagement and NICE replied refusing that request. The NICE technical team had had a week to consider if technical engagement was appropriate and would have considered it; they have a meeting in that period to discuss. Asked by the Panel why it took NICE 17 days to provide the company with a written explanation, Lizzie Walker replied that for most evaluations NICE do not tell the company why the decision was made but, given UCB had requested further information, it had put together full information for UCB. The team did not spend 17 days justifying its decision but rather drafting the explanation.
10. Dr Jacoline Bouvy asked by the Panel if NICE has key performance indicators (KPIs) or target timelines in evaluations, said that NICE does have KPIs around timely guidance. It intends to publish final guidance within 90 days of a marketing authorisation being granted by the regulator. This is achieved in less than 20% of technology appraisals, and where it is feasible NICE strives to publish final guidance within another certain number of days of the marketing authorisation. NICE's key objective is to publish timely and high quality guidance. Timeliness is important to NICE but high quality will essentially always trump timeliness as NICE wants to make sure it gets things right. She said it was not the case that NICE refused technical engagement because it wanted to rush to committee; NICE will do technical engagement where it considers it appropriate, even if this delays the committee meeting. The company and EAG base cases often have key differences in approach and there is a role for technical engagement if NICE think it is feasible to align on more of those key differences before the first committee meeting. In those circumstances technical engagement is a good use of time. In this evaluation there were a number of differences, but the company response to the EAG clarification questions had already drawn out where there were disagreements and NICE felt, given the difference of positions between them and EAG, the only real way to resolve this was through the committee's judgement and steer on its preferred approach.
11. Lizzie Walker, when asked whether NICE's usual process is to reconsider its decision following challenge by a company, said that whether to go to technical engagement is a decision for NICE and that challenge by companies is rare. Her understanding was that NICE does not or rarely changes its decision once made.
12. Dr Jacoline Bouvy, when asked by the panel what NICE considers to be "key issues", explained that these are key drivers for the decision-making and potentially influential assumptions for cost effectiveness where there is a difference between EAG and company. For example, whether SoC was an appropriate comparator and how it should be modelled was key to the decision problem and clinical effectiveness.
13. Robert Woolf, for NICE, noted that the EAG has been an EAG for ten years. Key issues are normally identified as part of the EAG report and it tries to find impactful points that could influence effectiveness or cost effectiveness. He said he was surprised by Adela Williams' examples of points that the company considered suitable for technical engagement as in his experience these examples are typically resolved in appraisal committee meetings.
14. The appeal panel concluded as follows:
15. The Appeal Panel were satisfied that NICE had given due consideration to the question of technical engagement in the week after receipt of the final EAG report and before communicating its decision to the company. It was persuaded that the decision not to undertake technical engagement prior to the first committee meeting was made on the basis of the need for the committee to independently provide guidance on the resolution of some key differences and disagreements between the company and the EAG on the approach to economic modelling, such that NICE did not consider technical engagement likely to resolve key issues before the committee meeting. The panel accepted the explanation provided by NICE, that resolution of these differences without committee involvement would have been unlikely even with technical engagement prior to the first committee meeting; that the evaulation process would have been delayed; and that NICE processes indicate that whether or not they undertake technical engagement is a judgement for NICE to make alone and is not regarded as a matter for negotiation with the company. The appeal panel also took into account, however, the context of this evaluation in regard to its complexity, the uncertainty of the evidence base and the rarity of the underlying disease and in this regard considered it may have been unwise and potentially a missed opportunity to resolve some of the uncertainties at an early stage, for NICE not to have undertaken technical engagement. Nonetheless, the appeal panel were satisfied that it was consistent with NICE methods and processes and that it was neither unprecedented nor procedurally unfair for NICE to have decided not to undertake technical engagement in this evaluation.
16. The appeal panel therefore dismissed the appeal on this point.

### Appeal Ground 1a.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

1. Adela Williams, for UCB, stated that this point follows on from the previous appeal point: in all the circumstances, including lack of technical engagement, a third committee meeting should have been scheduled before the FDG was issued. This was a complex evaluation. A number of central issues remained unresolved including the appropriate comparator and assessment of clinical effectiveness. In the absence of technical engagement there was inadequate time to consider such matters at two meetings. For example, at the first meeting the company understood that the committee preferred an intention-to-treat (ITT) analysis so it submitted that at consultation on draft guidance. But at the second meeting the committee wanted to consider other options. This apparent shift gave the company inadequate time to prepare a new analysis. There was also inadequate time for the committee and EAG to review the requested material. There should have been a third meeting to give the company time to prepare materials and others the opportunity to review them, as when such information is disclosed it is a requirement of procedural fairness that sufficient time is given for consideration. The company requested a third meeting for consideration of new analyses and remaining uncertainty. NICE refused. The only explanation given was that this would deviate from NICE's procedures. That was incorrect. NICE's Manual envisages up to two meetings but multiple evaluations have more and two is not a maximum, certainly not where fairness requires a third. The company considered a third meeting was particularly important in view of unresolved issues that could have been resolved earlier through technical engagement.
2. Dr Raju Reddy, for NICE, explained that a third meeting is held only if new key issues are identified. He said that the company describe some of the issues identified by the company for technical engagement as 'not resolved', but the company does not accept an issue as resolved unless it has been resolved to the company's satisfaction.
3. Dr Jacoline Bouvy, for NICE, reiterated that the issues the company describes as 'unresolved' were not unresolved in the view of the committee or NICE: the committee had landed on preferred assumptions and felt comfortable it had done so in a fair and reasonable way. The company disagreed with the committee's conclusions.
4. Dr Jacoline Bouvy explained that although the majority of evaluations have two meetings, it is not standard to have a second. The Manual requires that only if, after the first meeting, the committee cannot make a recommendation so must consult on a negative recommendation and after consultation a further meeting is required to move to FDG. That happened here. When it comes to whether a third meeting is required, the Manual at 5.8.59 envisages this when, in response to consultation, there are “comments that lead to a substantial revision of the committee's previous decision, involving a significant change in the recommendations, discussions or the evidence base”.
5. In this case NICE considered the company's request but thought on balance a third meeting was not required as, while the committee felt there were still uncertainties in the evidence base, it was confident that it had reached its preferred assumptions on the available evidence. Dr Bouvy explained that even where there are uncertainties in the evidence base there is a question about the decision risk associated with a recommendation, which relates to where the Incremental Cost Effectiveness Ratios (ICERs) are. In this case the decision risk, i.e. the risk associated with not recommending fenfluramine, was not very high as most of the ICERs using the committee's preferred assumptions suggested fenfluramine was not a cost-effective use of NHS resource.
6. Dr Will Sullivan, for NICE, stated that there is an important difference between an issue being uncertain and unresolved. The committee were aware this is an extremely severe disease and that the evidence was extremely uncertain. Given the evidence submitted it was clear to the committee what the decision should be.
7. Dr Jacoline Bouvy, when asked if NICE's position was that the ICERs were so unacceptably high that it was a moot issue whether the committee's request for analyses and disclosure of material very shortly before the second meeting permitted a reasonable opportunity for response (company appeal point 1a.3), disagreed. She explained the committee had requested the same analyses in its draft guidance.
8. Lizzie Walker, for NICE, said that the additional analyses requested before the second meeting were not in fact "additional" but rather the request was reiterating a statement that had been made in the draft guidance, that the committee wanted to see results of a comparison against SoC alone. She added that the company's original model and its model in response to draft guidance included SoC alone as comparator, so the NICE technical team could have run analyses to extract the requested results, but given the format of the model it would not have been possible to include this in the papers transparently. NICE did not consider this to be new analysis. As for the additional material provided before the second meeting, she acknowledged this was provided within a short time frame before the second meeting and explained this was because the EAG was originally unable to develop an updated base case because of a lack of transparency in the company submission which meant the EAG could not reproduce the company's original base case. The committee shared as much as it could as soon as it could. She stated that it is not unusual to share documents close to a second meeting given tight timelines.
9. Dr Jacoline Bouvy stated that there were 4 pages of additional analyses that were shared shortly before the second meeting containing a number of tables reporting cost effectiveness results. Given everyone at the second meeting had an understanding of the evaluation and previous analyses, NICE felt on balance that the timing of disclosure was reasonable for someone familiar with the data to interpret and digest those additional results.
10. Adela Williams stated that the company considered it was asked to submit new data and disagreed that it had been required to submit the additional analyses at an earlier stage. That is because the company understood it was accepted by the committee that the appropriate comparator was C+C plus SoC, not SoC alone, hence SoC comparator data was not submitted earlier. In those circumstances, asking the company to submit an analysis without full transparency on assumptions is not acceptable on any view of process (see UCB’s next appeal point 1a.6). Regarding NICE's late disclosure of new material, that was unfair because the company did not have time to consider the EAG's critique of the analyses. She stated that if NICE doesn’t routinely afford time for consideration of material before committee meetings, it ought to.
11. Matthew Binns, for UCB, stated that the reason the company believed a third meeting was so important was that it had been asked at the last moment before the second meeting to perform additional analyses regarding SoC. At draft guidance stage the company thought the committee preferred the use of ITT populations in both groups using the same imputation methodology and assumptions so other analyses were not needed; it was only at the second meeting that it became clear to the company that the committee wanted to consider an alternative analytic approach. A third meeting would have allowed time to consider those additional analyses.
12. Dr Raju Reddy stated that the committee was very surprised by the company's comments in its appeal on the draft guidance.
13. Dr Jacoline Bouvy stated that NICE was surprised to hear the company did not understand that the committee considered SoC to be an appropriate comparator from the draft guidance as section 3.3 of the draft guidance concluded that both C+C plus SoC and SoC alone were appropriate comparators. NICE felt this was fairly clear. The NICE team also met with the company at its request to help it understand the draft guidance and prepare its consultation response. NICE went to considerable effort to help the company understand the draft guidance and what additional analyses were requested by the committee.
14. Lizzie Walker stated that NICE do not consider it appropriate for the company to still have ambiguity after that meeting.
15. Asked if the committee (despite requesting and disclosing material shortly before the second meeting) decided there was little point in a third meeting because there was nothing the company could do to alter the committee's view, Dr Raju Reddy stated that this was a misinterpretation. He stated the same information was requested in draft guidance and the company had the opportunity to price the drug between the two meetings.
16. Dr Jacoline Bouvy stated that it was not the case that the committee decided there was no value in a third meeting because the drug was not cost effective. Rather, this was because the committee felt it had landed on preferred assumptions in a fair and reasonable way and did not consider there were unresolved issues.
17. Dr Jacoline Bouvy confirmed that about 11% of appraisals have gone to a third meeting in recent years. Asked when this happens, she stated NICE cannot be too specific but this tends to be if there is new evidence that significantly shifts the clinical or cost effectiveness estimates and stakeholders need to be able to respond to new set of assumptions that are potentially decision-changing. For example this might happen when substantial new evidence is presented in response to consultation and discussed at the second meeting that means there are fundamental changes to the modelling or evidence, or if it turns out there are errors in the modelling presented to Committee, or if in response to consultation the Committee develops a different view or realises further evidence or analyses are required.
18. Lizzie Walker when asked if the additional analyses requested by NICE (comparing fenfluramine against SoC) were considered material to the cost effectiveness decision, stated that these were indeed material as the committee considered SoC to be an appropriate comparator.
19. Dr Jacoline Bouvy added that these analyses, while material, were not new because they were already in the company's submission.
20. Matthew Binns concluded the discussion by stating that a full list of assumptions was not provided after draft guidance and that, while this is not unusual, it was difficult for the company to determine cost effectiveness. He said the company had always objected to SoC being an appropriate comparator, and that the company could have provided additional analyses before a third meeting that may have helped decision-making.
21. The appeal panel concluded as follows:
22. The panel understood that while the Manual does not preclude holding a third committee meeting (ACM3) such meetings are held relatively infrequently, and that exceptionality is important: there needs to be a clear justification to hold a further committee meeting, given that this will inevitably delay a final decision. The panel noted that the Manual (para 5.8.59) refers to circumstances in which there had been “a substantial revision of the committee’s previous decision, involving a significant change in the recommendations, discussions or evidence base” as grounds for considering the need for further consultation. In this case, a key relevant issue was the committee’s decision not to use the ITT analysis but rather to use a naïve comparison based on the Open Label Extension (OLE) data. The panel were aware that the consideration here was not whether this was a reasonable decision, or the circumstances that caused the committee to make the decision, but simply whether this constituted a “significant change……in the evidence base”. In forming their view, the panel were aware of the broader context of the evaluation, in which earlier opportunities to resolve some of the uncertainties, such as technical engagement, had been declined by NICE, and also the very complex nature of this evaluation of a treatment for a rare disease in which inevitably there was a relative paucity of evidence and a high degree of uncertainty. On balance, therefore, the panel felt that the committee’s decision to change its mind at the second committee about its preferred methodology for the comparative data analysis was sufficiently important, in the context of this particular evaluation, as to require a third meeting, such that the committee’s decision not to proceed to ACM3 was unfair.
23. The appeal panel therefore upheld the appeal on this point.

### Appeal Ground 1a.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.

1. Adela Williams, for UCB, noted that this appeal point overlaps with the above appeal points. She summarised that this point argues that NICE afforded inadequate time for the company to produce new analyses and consider important material from the EAG that was disclosed to the company before the second meeting. First, as to the requested analyses, if it was right that the committee already had access to the information requested from the company then the additional analyses should not have been requested at the last moment. Fairness requires that the company is given adequate time to prepare new information. If the information was needed, then half a day was clearly inconsistent with a fair process. Secondly, as to the late disclosure, that information related in part to the committee's view of the company's response to consultation. The company needed to consider if it agreed with the committee and if it wanted to make submissions in relation to this at the second meeting. Two days for that consideration was not consistent with fair process, even if that is NICE's standard approach. As a matter of basic procedural fairness, where material is disclosed for the purposes of a meeting there must be adequate time to consider it.
2. Matthew Binns, for UCB, reiterated that the company had said SoC was not an appropriate comparator so NICE asking the company for the analysis comparing fenfluramine against SoC involved the company not just extracting those results but considering the thought behind the request. He stated that this involved a lot of work and was not trivial.
3. Dr Raju Reddy, for NICE, repeated that section 3.3 of the draft guidance clearly said the committee considered SoC an appropriate comparator so the request should not have been a surprise for the company.
4. Lizzie Walker, for NICE, stated that her understanding was that it would not be time consuming to extract the SoC results from the company's model. She explained that the timing was due to NICE's desire for transparency. The request was made before the weekend and gave half a working day for the company to provide the analyses so that the committee could review before the meeting; the request was not half a day before the meeting. She noted the company provided a document titled 'factual inaccuracies in the committee meeting slides' before the second meeting suggesting it did have time to review materials.
5. Dr Jacoline Bouvy, for NICE, when asked about the meeting between the company and NICE between the two committee meetings, pointed to an email from the company summarising that meeting and indicating it was of use to the company. Lizzie Walker added that she did not recall discussion of SoC. NICE's technical team thought the draft guidance was clear that it was an appropriate comparator so it was surprised the company did not submit results against SoC.
6. Matthew Binns confirmed the company was thankful for the meeting and discussed some of the issues there, but it did not clear up issues around SoC and the company did not accept it was an appropriate comparator. He noted NICE's advice at that meeting was not binding.
7. Florence Bianic, for UCB, stated that the main technical point was about how to integrate the data from the OLE study into the model. That took a lot of the time and the company's focus was on that and presenting results from the comparison of fenfluramine and C+C.
8. Dr Will Sullivan, for NICE, noted the final scope included SoC as a comparator, so the company coming back without a comparison against SoC was a surprise. The committee was asking for information that was contained in the company's previous submission so it would have been strange if the company had removed that information.
9. Adela Williams concluded by noting that the company's summary of its meeting with NICE between committee meetings stated the company would provide a comparison with C+C and did not mention SoC alone, and irrespective of NICE's expectations there was a request at the last moment with inadequate time for the company to do the work requested. Finally, she stated it does not answer the point that the company was able to put in a response before the meeting, as it still had inadequate time to do that.
10. The appeal panel concluded as follows:
11. In considering this appeal point, the panel were aware of the claim by the company that NICE had provided the company with newly disclosed material a short time before the second committee meeting (ACM2) giving them inadequate time to consider this, and also that the company had been asked to provide additional analyses within a very short timeframe before ACM2. In particular, the panel had sight of an email from NICE sent at 5pm on a Friday afternoon, requesting additional analyses be sent to them by 1pm the following Monday. The panel understood clearly from NICE that, in their view, this was information that had been requested earlier from the company and that the company either already had it readily available, or else that it would have been easy to retrieve. However, the panel were persuaded by the company's argument that it was unfair of NICE to make this assumption, and that it was not a trivial matter for the company to consider the request and then provide the information requested in such a short timeframe.
12. The panel considered that if NICE felt that these data were of sufficient importance to request them, fairness required that the company were given sufficient time to provide them, and that did not happen in this case.
13. The appeal panel concluded, therefore, that there was evidence of procedural unfairness on this issue and upheld the appeal point.

### Appeal Ground 1a.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)

1. Adela Williams, for UCB, submitted that the approach followed by the committee was procedurally unfair in the context of the available information. She stated that there was no direct comparison data for fenfluramine against C+C from clinical trials. The company compared treatment effects using data from an OLE study. There were two possible approaches: either to use data from patients undergoing treatment in the OLE or to use data from the full intention to treat population. At paragraph 3.10 of the draft guidance the committee stated a preference for using the ITT data as using only the treated population could result in bias (as people lost to follow up may impact the effectiveness of treatment). In response the company obtained the only available ITT data, which used the 'last observation carried forward' (LOCF) methodology to impute data for patients who had dropped out or were lost to follow up. The company did the same for fenfluramine to ensure fair comparison. However, after the second meeting the committee decided to use the treated population data for decision making. The FDG indicated that the committee rejected the company's ITT LOCF method on the basis of potential bias due to a difference in drop-out rates between studies. The FDG also criticised the company for not performing different analysis requested in the draft guidance using state occupancy data from the treated population assuming drop outs had less than a 25% reduction in drop seizure frequency. That was inconsistent with the committee's earlier preference for ITT analysis and this alternative method of imputation was inconsistent with the company's model structure (which modelled discontinued patients separately). The committee's shifting position prejudiced the company as it resulted in confusion about its requirements; the company would have wished to comply with the committee's requirements but was unable to do so.
2. Dr Will Sullivan, for NICE, explained that paragraph 3.10 of the draft guidance was clear that the committee's key requirement was to avoid an assumption that people left the study at random (i.e. were "missing at random") as this would introduce bias. What the company did was contrary to the committee's request in draft guidance, so the committee decided to rely on the company's original submission. This was explained at paragraph 3.6 of the FDG.
3. Adela Williams stated that the company was pleased that it had found the ITT data the committee wanted and, had the company appreciated the committee would require additional analysis even if the company could find the ITT data, then the company would have provided this. The company's point is that the draft guidance was unclear and ambiguous to the company's detriment, as the company understood that the other analysis described there was required only if the company could not find the ITT data.
4. Florence Bianic, for UCB, stated that the company understood the potential bias involved in using an LOCF approach but pointed out that the model structure meant that other methods also carried with them potential disadvantages.
5. Dr Raju Reddy and Dr Will Sullivan, for NICE, when asked about the different methodological approach taken in TA615 (which used LOCF), confirmed that this was because a different set of data informed the decision on methodology.
6. Florence Bianic accepted that the data available in TA615 was different and the methodology was dependent on the data. She confirmed the company's argument was about the lack of clarity in the committee's requirements and inconsistency of those with the company's model.
7. The appeal panel concluded as follows:
8. The panel noted that the committee's preferred methodology to indirectly compare the treatment effects of fenfluramine with standard care and C+C with standard care was stated in the draft guidance and would have required the use of ITT populations in both groups using the same imputation methodology and assumptions. In particular, it noted that the preferred approach to account for missing data points and patient drop outs was considered important and the committee's preferred approach in this regard was also specified in the draft guidance. The panel noted, however, that the company had chosen to adopt a different approach to accounting for patient drop outs (last observation carried forward; LOCF) in their response to the draft guidance and that this led to concerns in the minds of the committee about the potential introduction of significant levels of bias in regard to the missing data points. The panel were satisfied that the judgement of the committee in regard to its preferred methodology was based on a desire to minimise bias in the assumptions that informed the economic modelling and that the committee's concerns about the level of bias introduced by the methodology applied by the company in its response to the draft guidance were clearly described in section 3.12 of the final draft guidance. The panel concluded that it was not procedurally unfair for NICE to change its mind at the second committee meeting about its considered preference for the use of the OLE treated population data to compare the treatment effects of fenfluramine with C+C, since the company had been informed of the committee's preferred approach in the draft guidance and had had the opportunity to undertake this preferred analysis but had chosen to do differently. The panel further noted that the company had acknowledged in the hearing, that while the imputation methodology in TA615 also used LOCF data, the models used and the data sources in that and the present evaluation were quite different. On the relatively narrow basis of this ground 1a4, the panel was satisfied it was fair for the committee to change its mind (albeit that the panel do think it was unfair, having done so, not to go to an ACM3). The appeal panel concluded, therefore, that the preference of a different imputation methodology by the committees in the two evaluations was understandable and not procedurally unfair.
9. The appeal panel therefore dismissed the appeal on this point.

## Appeal by TSA

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

**Appeal Ground 1a.2: The committee compares Fenfluramine versus not having Fenfluramine – usual standard of care and refusal to base its recommendations on a comparison with cannabidiol plus clobazam (feedback received from SUDEP Action)**

1. This point was discussed along with TSA's appeal point 2.2: see summary of the discussion and the panel's decision below.

## Appeal by the company

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

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

1. Adela Williams, for UCB, stated that in response to the draft guidance the company carried out an indirect treatment comparison (ITC) using OLE data, and that this was criticised by the committee on three grounds (at FDG paragraph 3.7), namely that the data did not include clobazam, potential changes in placebo response were not accounted for and heterogeneity between the populations was not properly investigated. Instead the committee decided to rely on a naïve comparison comparing raw data from two trials, inconsistent with NICE's preference for using adjusted data and seemingly for no reason. The company considered the above criticisms were applicable with greater force to the naïve comparison, and there was no indication in the FDG that the committee recognised or took this into account. The company had inadequate time to engage with this, as explained at appeal point 1a.6.
2. Dr Will Sullivan, for NICE, explained the committee's reasons were at sections 3.5, 2.6, 2.7 and 3.12 of the FDG. The committee's preference was what it considered the 'least worst' option, rather than an endorsement of a naïve comparison as better than an ITC. The committee made clear it was unhappy with the naïve approach in the first meeting so asked the company for the ITC. It was a shame the company did not provide what the committee requested. NICE's Manual says alternative methods like meta-analysis and ITC may be considered when a Randomised Controlled Trial (RCT) is not possible, but those methods must be rigorous and transparent. The committee did not find the company's handling of missing data rigorous or balanced. The committee's position in and after ACM2 was the same as the company's submitted position.
3. Adela Williams stated that the issue is not whether the ITC was as good as the committee wanted, but that the committee preferred the naïve comparison over the ITC, which the company say is less reliable and less robust, and the committee do not seem to have recognised that by simply criticising the ITC then accepting the naïve comparison which had all the same flaws and worse. She stated that the reasoning needs to be in the FDG, absent which there must be no or no adequate reasons.
4. Matthew Binns, for UCB, said the company put its case in response to the draft guidance, when it noted uncertainty associated with a naïve comparison. The committee stated its preference for a naïve comparison at the second meeting and there was no chance for UCB to respond as there was no third meeting.
5. Florence Bianic, for UCB, when asked why the company's original submission used a naïve comparison, stated that there was a lot of discussion on how to integrate the data from the OLE study and the company adjusted its approach based on EAG comments. Comments the company received led to the company using a state occupancy method and it appeared relevant to run an ITC. There was no opportunity to discuss this after the second meeting. The company acknowledges biases in the ITC method but considers those biases stronger in a naïve comparison.
6. Dr Raju Reddy, for NICE, when asked if the committee considered these concerns, reiterated that the committee felt it had to pick the least worst option presented to it. Dr Will Sullivan, for NICE, added that the committee deliberated this at the second meeting, which the company attended. He stated that the original submission is the company's best opportunity to inform the deliberation and choose its method. The company chose the naïve comparison for its original submission. He also confirmed that the committee rely on the EAG to interpret the company's evidence and provide a perspective.
7. Dr Will Sullivan when asked what the company could have done differently for the committee to accept its ITC analysis, stated that an ITC not based on the assumption that patients who leave the study do so at random would have been informative.
8. Robert Woolf, for NICE, stated that the chosen method impacted the ICER and that both methods were biased in favour of the company.
9. Lizzie Walker, for NICE, stated that regardless of the chosen method the ICERs were not within NICE's usual cost effectiveness threshold. She stated that the FDG does give reasons and it was clear why the committee did not use the ITC: the committee did not know where the bias was in an ITC that it considered inappropriate, whereas at least with the naïve comparison the committee knew where the uncertainty was.
10. The appeal panel concluded as follows:
11. The appeal panel noted the concerns in the minds of the committee in regard to the bias introduced by the company's use of an imputation method with LOCF data to account for patient drop outs, when modelling the treatment effects of fenfluramine as compared with C+C for cycles 2 to 5 in the economic modelling. The panel considered that the reasons for these concerns were clearly described in sections 3.6, 3.7 and 3.12 of the final draft guidance. The appeal panel was also satisfied that the committee was aware of, and had given due consideration to, the bias that was introduced by using state occupancy trial data to inform the modelling of the treatment effects of fenfluramine as compared with C+C for cycles 2 to 5 in the economic modelling, and that this was also clearly stated in 3.6 and 3.7 of the final draft guidance. The panel were satisfied that the combination of the perceived limitations associated with the imputation method chosen by the company for the ITT analysis, as well as with the OLE network meta-analysis methodology presented by the company, led to high levels of bias in the results, and that it was difficult for the committee to be certain as to the specific nature of these. Under these circumstances, the panel considered that it was not unreasonable for the committee to conclude that the results were not sufficiently robust for decision-making. The appeal panel were persuaded that the committee recognised that while the use of state occupancy trial data was also associated with uncertainty and bias the specific nature of the bias introduced with this methodology was clearer to them. The appeal panel concluded, therefore, that in the face of uncertainty on both counts, it was not unreasonable for the committee to conclude that the use of state occupancy trial data for indirect treatment comparisons was their preferred methodology in the absence of any direct comparative trial data.
12. The appeal panel therefore dismissed the appeal on this point.

### Appeal point 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

1. Adela Williams, for UCB, referred to paragraph 3.14 of the FDG and stated there was no data to support the company's decision to calculate treatment waning transition probabilities by assuming that 100% of people (rather than 5.2%) who experienced treatment waning in the last 3 months of the Study 1601 OLE, would experience treatment waning from cycle 10 onwards. The company's revised base case analysis used 5.2% as a conservative figure for waning, supported by expert clinical opinion and a US observational study. In contrast the EAG proposed a waning figure of 80% with no transparency as to the evidence if any on which this was based, and the committee adopted a 100% waning figure, rejecting the observational study simply on the basis it was a US study with no analysis of why it should not be taken into account and not recognising other NICE evaluations.
2. Dr Micheal Taylor, for UCB, said that lack of efficacy in some patients is managed through a stopping rule. In LGS clinical opinion is that waning is not routinely seen especially after two years. Indeed, in his and colleagues' experience nationally, if there is a persistent effect after a honeymoon period of 6 months there is no proof of declining efficacy. Everyday clinical practice suggests waning is not being seen after that point. Dr Taylor stated he had never been to a scientific epilepsy meeting or seen a paper about waning and there is good data saying that at 6 months a response to the drug predicts long term response. So the committee saying the results using 5.2% were unreasonable and correcting for that was probably an over adjustment. He stated he has a Dravet-specific clinic and about 15 patients on fenfluramine, of whom two stopped for lack of efficacy within the first 6 months and the others have sustained effect.
3. Dr Suresh Pujar, for the Royal College, agreed waning is not seen in clinical practice.
4. Lizzie Walker, for NICE, explained how waning is applied in the model. This is from cycle 10 onwards, when patients stay in the same state unless they move based on waning, discontinuation or death. Waning has 2 elements:
	1. the proportion of people stopping because of lack of efficacy – company base case used 5.2% here, based on the last 3 months of the Study 1601 OLE; in the committee's preference it is 100%; and
	2. transition probabilities, which explain how people move between health states. After the first meeting this was aligned between the company, committee and EAG and mean the vast majority of patients stay in the same state.

The committee wanted to apply the transition probabilities across all (100%) of patients still on treatment in the model to identify a small proportion who experience waning. If it applied the probabilities instead to a very small number of people only, then fewer than 1% would move to a worse state, which the committee considered to be implausibly low. The clinical experts said it was reasonable to use the last 3 months of the OLE so the committee considers its preference was supported by expert opinion.

1. Dr Will Sullivan, for NICE, explained that preferring the 100% figure meant using all of the data from the last 3 months of the OLE study.
2. Florence Bianic, for UCB, stated that the deterioration of treatment effect is accounted for in models through different mechanisms, as in TA615, with discontinuation and a stopping rule to reflect clinical practice. In the fenfluramine model the company included a waning function after cycle 10. When waning starts to apply at cycle 10, over 65% of patients have already ceased treatment mostly due to the stopping rule. This illustrates the model really accounted for a possible deterioration of treatment effect through a different mechanism.
3. Lizzie Walker said the committee expected treatment would be monitored closely and stopped for fenfluramine too.
4. Dr Will Sullivan stated waning is a low evidence area but in general NICE considers waning important for cost effectiveness estimates. The committee invited experts and asked Dr Rhys Thomas at the meeting, who said it was reasonable to use the last 3 months of the OLE, so the committee used what happened in the company's trial to inform the assumptions in the model, which, he said, was an evidence-driven approach.
5. Dr Raju Reddy, for NICE, stated that societies and the Royal College also had the opportunity to comment in consultation, the EAG speaks to clinical experts, and Dr Thomas and a doctor from Great Ormond Street Children’s Hospital were at the committee meeting. He confirmed the committee discussed the EAG position. The evidence came from the company's OLE study. The US study was a Dravet syndrome-only study with fewer patient numbers than the OLE study.
6. Lizzie Walker when asked if the committee did not accept 5.2% because it considered the numbers implausibly low, denied this. She stated that 5.2% resulted in a number that was much lower than seen in the OLE, an observational study (Polega et al 2022) and another study. That was why the committee thought it was not reflective of clinical practice to use 5.2% together with the transition probabilities in the model. She argued that the committee's concern about using 5.2% was not because 5.2% was not reflective of clinical practice; their concern was the way that figure was incorporated in the model.
7. Dr Rhys Thomas, for the Royal College, when asked if he agreed with the committee's approach, stated that he had found waning challenging as it was a new area for him and he does not deal with waning in clinical practice. He stated that waning will reduce over time, but he appreciates there was no data. He stated he probably misled the committee by accepting 5% carry over as there was no better figure to work with. He stated the committee's justification for remodelling seemed to be that the figure was implausibly low, and he felt there was a believability issue as well as a data issue.
8. The appeal panel concluded as follows:
9. The appeal panel noted that the estimates of treatment waning effect with fenfluramine and comparators were uncertain in the minds of the committee in the absence of robust and long-term clinical trial data. It also understood, therefore, that the committee judgements around whether or not treatment waning should be included as a consideration in the economic modelling for fenfluramine and comparators, as well as its relative magnitude, were significantly influenced by expert opinion. The panel were satisfied that clinical and patient expert input had been sought on this issue during the course of the evaluation, as described in section 3.14 of the final draft guidance, and that due consideration and discussion of treatment waning had been undertaken in the committee meetings. Nonetheless, the panel recalled that the expert who had been consulted on this issue during the second committee meeting had said during the appeal hearing that, on reflection, he had probably misled the committee by indicating that he accepted that a figure of 5.2% (representing the number of patients stopping treatment during the last 3 months of the study 1601 OLE) should reasonably be applied recurrently from cycles 10 onwards in both treatment arms of the model, to account for treatment waning. The panel were persuaded, having heard the opinions of other clinical experts that spoke in the hearing, that treatment waning is not seen in their clinical practice in patients receiving anti-epileptic treatment at this stage in the care pathway. Furthermore, the appeal panel considered the reasonableness of the conclusion of the committee, as stated in section 3.14 of the final draft guidance, that an assumption of treatment waning should be assumed for 100% (rather than 5.2%) of people from cycle 10 onwards. The panel considered that it had neither seen nor heard of any evidence to be able to substantiate this assumption on behalf of the committee, and indeed was persuaded by the evidence and by comments provided by clinical experts for the appellants during the hearing to the contrary. Consequently, the appeal panel concluded that the assumptions arrived at by the committee in regard to treatment waning and its application to the economic modelling were unreasonable.
10. The appeal panel therefore upheld the appeal on this point.

### Appeal point 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

1. Adela Williams, for UCB, stated the FDG said there was insufficient evidence to support differences in wastage so the committee preferred to assume no wastage for either treatment. However, cannabidiol (CBD) is oily and contained in glass bottles, while fenfluramine is not oily and contained in plastic bottles. So it is plausible that breakage and wastage are higher with CBD than fenfluramine. This was consistently confirmed by clinicians at both committee meetings. She stated that the only evidence to the contrary was the manufacturer of CBD, who stated in consultation that both are supplied in similar containers. That was noted in ACM2 slides without comment but was factually incorrect as one is supplied in glass and the other in plastic bottles. Therefore the company say the committee's conclusion was unreasonable on the evidence.
2. Lizzie Walker, for NICE, stated the slide was clear this was the opinion of one organisation and the committee did discuss the plausibility of the CBD manufacturer's comments. *(In fact, there was no dispute that cannabidiol is supplied in glass bottles and fenfluramine in plastic bottles, and this was identified clearly in the consultation comments provided by the CBD manufacturer.)*  The committee also discussed the absence of evidence on wastage and the company's scenarios.
3. Dr Raju Reddy, for NICE, noted the company base case did not include wastage. The response to consultation was that wastage was not a significant issue and was a maximum of a bottle per year across 45 patients using a bottle each per week. He confirmed the patient expert at the meeting had not used fenfluramine.
4. Dr Rhys Thomas, for the Royal College, confirmed that he had provided the comment that in his experience a bottle was lost per year across 45 patients.
5. Matthew Binns, for the company, said the company added wastage to the model as it became apparent as an issue during the process.
6. Dr Will Sullivan, for NICE, stated the committee heard anecdotal evidence on wastage from patient and clinical experts at the first meeting and the key reasons for wastage were common to both CBD and fenfluramine, recognising they come in different packages. The committee sought data on wastage beyond anecdotal evidence, but the company provided scenario analyses not informed by data. So the committee assumed no wastage in the absence of evidence in the data.
7. Dr Micheal Taylor, for UCB, said that obtaining data will be difficult, but clinicians have emails about someone smashing a CBD bottle and its manufacturer's easy guide mentioned in Q&A 'what to do if I break or lose a bottle', recognising wastage is a potential issue for CBD. He added that an oily substance will also accumulate at the end of the bottle for CBD, in addition to wastage through breakage.
8. The appeal panel concluded as follows:
9. The panel were satisfied that the question of differential wastage with fenfluramine and CBD had been considered by the committee in its deliberations over its preferred assumption for economic modelling. It noted that in the absence of published evidence, a determination of the significance of drug wastage and its differential relative importance to fenfluramine and CBD was significantly influenced by clinical expert input as well as plausibility. The appeal panel were satisfied that expert advice had indicated that drug wastage is, in practice, relatively small for both drugs but that it does nonetheless occur. It was persuaded that, given the fact that CBD is an oily substance that is provided in glass bottles and fenfluramine is a liquid that is provided in plastic bottles, the consequences of accidents or an inability to aspirate all of the contents of the vial are likely to be greater for CBD than for fenfluramine. Although the panel accepted that this is likely to be a relatively small consideration in regard to the economic modelling and its outcomes, it considered that it was unreasonable for the committee to conclude that drug wastage does not occur at all (0%) and that this is equally the case for fenfluramine and CBD.
10. The appeal panel therefore upheld the appeal on this point.

### Appeal point Ground 2.4: (originally appeal point 1a.3) Standard of Care (SoC) alone does not reflect NHS clinical practice and is not an appropriate comparator for fenfluramine

1. This point was discussed alongside the Royal College's appeal point 2.1, below.

## Appeal by the Royal College

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

### Appeal point Ground 2.1: It was unreasonable for the committee to consider standard of care alone as a comparator for fenfluramine

1. Dr Shanika Samarasekera, for the Royal College, stated that the appropriate comparator is C+C plus SoC not SoC alone. Other treatments are not appropriate, would have been tried much earlier in the pathway and do not make an impact. She confirmed the Royal College found it difficult to understand how clinical input could have resulted in the conclusion that SoC is an appropriate comparator.
2. Adela Williams, for UCB, said the company was aware of no evidence supporting SoC at the point where fenfluramine would be considered. The clinical studies were from over 20 years ago so do not reflect clinical practice. Use of SoC was inconsistent with NICE procedures, misrepresented the company's submissions, was unsupported by evidence and was therefore unreasonable.
3. Dr Micheal Taylor, for UCB, explained that children come to a paediatric neurologist having failed 2 or 3 therapies already, often without diagnosis, and they will have tried 4 to 6 drugs often in combination before they reach the point of C+C. By the time they try C+C the risk of sudden, unexpected death of someone with epilepsy (SUDEP) is high. SoC reflects drugs clinicians try but does not capture true real-world information, which is that if a child cannot go on C+C or fail C+C they will not revert back to SoC but rather try research trials or other things like invasive surgeries. Fenfluramine should therefore be considered as a comparator to C+C.
4. Dr Raju Reddy, for NICE, explained that fenfluramine's marketing authorisation positioning is third line and the committee accepted C+C is third line, but other drugs are also used third line and it would be unreasonable to disregard them in comparisons. Further, some people may not be able to have C+C so other third line options cannot be excluded as comparator; in response to the draft guidance clinical experts said there are people for whom fenfluramine may be an option and C+C not. The committee requested the company provide additional information on the proportion of people who cannot have C+C, but it was unable to do so. It is very difficult to determine but the committee understand this is not a small number, and if such a group exists then in a world without fenfluramine third line treatment for them would be SoC. The committee have to compare with any third line drugs even where there is a dearth of evidence. The company also included analysis against SoC in its submission and clarification response. The committee considered both C+C plus SoC and SoC alone were appropriate comparators, and the committee's decision was based on comparisons against both.
5. Matthew Binns, for UCB, when asked about the company's statements at various points that SoC both is and is not a comparator, emphasised that the company said C+C was the appropriate comparator and its response to draft guidance was clear it did not consider SoC alone an appropriate comparator, even if it had submitted that previously.
6. Dr Rhys Thomas, for the Royal College, stated that the terms first, second and third line are unusual in this disease area and third line might be better thought of as "late stage”. Asked if the notion that a patient in a world without fenfluramine who could not have C+C would have SoC is an oversimplification, he agreed.
7. Dr Archana Desurka, for the Royal College, stated that by the time they start C+C the patient will have already explored more than half of available options. The majority will have gone through epilepsy surgery evaluation and/or neurostimulator. Once it is apparent they are not responding to C+C (not all can tolerate it, not all respond) they will have already tried many options.
8. Dr Micheal Taylor stated that patients being ineligible for C+C did not mean C+C should be ruled out and SoC used as comparator; C+C should still be the comparator as those who are ineligible for it are truly pharmaco-resistant. Children and young people will have had all these drugs generally before C+C so to say they will then have another third line drug is not realistic. He stated that all clinicians are saying C+C is the only comparator that NICE need to consider. SoC was offered by the company for transparency and completeness, more as a complementary analysis and not as a true comparator. C+C and fenfluramine are the direct comparators.
9. Dr Jacoline Bouvy, for NICE, stated that NICE found C+C a relevant treatment option but the committee heard there was a part of the patient population not eligible for C+C and in a world without fenfluramine, those patients would have a basket of treatments we call SoC.
10. Dr Will Sullivan, for NICE, added that SoC is shorthand for a range of options for different, heterogenous patients and that the comparator in the RCT was proxy evidence for SoC, so the committee had better evidence for that.
11. Adela Williams stated that her understanding is that where a patient is not eligible for C+C, SoC alone would essentially amount to no treatment as all such patients will have already received SoC. It is very unusual for a NICE committee to consider no treatment as a comparator when a treatment is available; an approach where we have to look at "no treatment" as well as C+C is inconsistent with how NICE typically carries out evaluations and with the clinical reality in this situation.
12. Dr Micheal Taylor, when asked if the company's argument is that while it can see the theoretical case for using SoC as a comparator it considered this was not a meaningful comparison because patients have been through so many treatments already, agreed. He added that the last patients enrolled in CBD studies (comparing CBD with SoC) were enrolled in 2019, which is a different era.
13. Dr Johann Te Waerr Naude, for the Royal College, stated that Dravet syndrome is more homogeneous and has more clearcut management strategies (certain drugs in a certain order) than LGS. The majority of children he has treated with LGS have gone through all drugs, have been re-exposed to previous drugs after a few years and have found C+C helpful in some cases. He stated it was invidious to think about a logical comparator when the condition is so heterogenous and difficult to manage and patients will take anything. In his experience getting a child on fenfluramine changed their outcome.
14. Dr Shanika Samarasekera stated that the drive for this appeal was the need to reduce intensive care admissions and this has an impact not just on the patient and family but much wider: if a patient is in intensive care weekly or monthly there is a real concern resources are not being used properly.
15. Allison Watson, for the TSA, said that as the mother of a young man with LGS who has tried over 12 treatments they live in fear of regular nighttime seizures. It is a case of trial and error and neither the family nor the clinicians know what may work. She said she was intrigued to understand what comparators could be used in this population when nothing works.
16. Dr Archana Desurka said that when you make any treatment changes for individuals with refractory epilepsy you take clinically driven decisions. The question of what fenfluramine will replace does not come into play as it’s a complex clinical decision.
17. Adela Williams, when asked why there is an objection to the committee basing its recommendation on comparisons of fenfluramine against both SoC alone as well as C+C plus SoC, stated that the company has to know what it is shooting for. If unsuccessful in the evaluation, it has to understand NICE's parameters for approaching a future evaluation. Also there are other issues raised in this appeal that, if successfully appealed and changed in future guidance, might result in a favourable outcome.
18. Dr Raju Reddy, when asked if a comparison with C+C was intellectually understandable but not meaningful due to the nature of the patient population, explained that this goes back to NICE's methods, which require the committee to compare against whatever fenfluramine would displace from the treatment pathway. For patients on C+C it would displace that. For others, the committee considered it would displace SoC.
19. Dr Will Sullivan noted the costs associated with C+C and fenfluramine and various alternatives are different. He stated that NICE may compare against only one treatment, even when there are other options for patients, if the group that receive that treatment can be identified. In this case NICE asked the company if it were possible to identify the group that would receive C+C but it was not possible to do so.
20. Lizzie Walker, for NICE, stated that the committee asks clinical experts whether the clinical trial is reflective of clinical practice, and in this evaluation the experts and company thought the clinical trial, which used SoC as the comparator arm, was reasonable for decision-making, so the committee considered it must assume SoC is reflective of clinical practice.
21. The appeal panel concluded as follows:
22. The appeal panel understood that the issue of whether SoC alone would be an important comparator was discussed at various times during the evaluation, and indeed that the company’s position had apparently changed several times. It also noted that in the original index randomised controlled trial, carried out some years ago, fenfluramine and SoC had been compared to placebo and SoC. However, the issue here was whether SoC was a relevant comparator in terms of current clinical practice. The panel heard clearly that there was no disagreement that the most appropriate comparator was C+C. However, the committee were concerned that in those cases in which C+C was unsuitable or ineffective, patients would revert to some other combination of treatments, hence the need to additionally compare fenfluramine and SoC with SoC alone.
23. At the hearing, the panel heard from a number of adult and paediatric neurologists representing the Royal College who acknowledged that there were instances when C+C was unsuitable, but given the highly heterogenous nature of the disease and current clinical practice in managing patients with LGS, felt that comparing fenfluramine and SoC with SoC alone had no clinical relevance.
24. The panel understood the committee’s view and agreed that a comparison of fenfluramine with SoC would be informative, although that would only be the case if the data to support such a comparison could be evidence-based. However in this regard, the panel noted the committee’s view (at paragraph 3.3 of the FDG) that “most of the studies for these treatments [i.e. the alternative treatments that would constitute SoC] were conducted over 20 years ago and so do not reflect current clinical practice” and that “any comparisons with these treatments may not be robust and clinically meaningful”. In the light of this and the consistent perspectives provided by the clinical experts who attended the hearing as appellants and explained their positions during the evaluation, the panel agreed that it was unreasonable of the committee to insist that fenfluramine should additionally be compared to SoC alone.
25. The appeal panel therefore upheld the appeal on this point and UCB appeal point 2.4.

## Appeal by TSA

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

### Appeal point Ground 2.2: The Appraisal Committee’s refusal to consider the use of fenfluramine was based on an error and therefore cannot reasonably be justified in the light of the evidence submitted (feedback received from SUDEP Action)

1. This point was discussed alongside TSA's appeal point 1a.2. The panel understood from the appeal correspondence that these points both related to the change in position between paragraph 1 of the draft guidance (which stated "an indirect comparison suggested that fenfluramine may be more effective than C+C in reducing the number of drop seizures") and the FDG (which stated "The results of an indirect comparison comparing fenfluramine with C+C are uncertain").
2. Jane Hanna, for TSA, stated the TSA was concerned the committee had refused to recommend fenfluramine based on a comparison with standard of care. Fenfluramine could be a lifeline for individuals with LGS resulting in a considerable reduction in debilitating seizures and sudden unexpected death, giving families a lifeline when older anti-seizure medicines are no longer effective. She expressed concern for a future absence of options for people with epilepsy and a NICE decision that could represent a barrier. She stated the comparator was unfair as was the change of position by the committee from draft guidance to FDG. She stated the committee had not listened adequately to clinical opinion.
3. Jane Hanna went on to say that it is important that NICE's determination is very clear for patients and families in a desperate situation. The reason for this appeal point was because there was no clarity on the face of the decision explaining the change from draft guidance to FDG and what clinical opinion justified this radical change. It was concerning that there were other matters in the FDG where clinical representation appeared to be missing, and it was unclear what had informed the committee's assessment and conclusion on uncertainties. For example, the committee wanted to factor in waning and it was not clear where that was supported by evidence from clinicians. All these points interact: the lack of clarity of the committee's reasoning is in the context of what looks like a rushed consideration of evidence and an assessment without proper regard to clinical opinion. The fundamental point is that LGS is as severe as Dravet syndrome and the committee needed to consider what is available to this community of patients and why their needs and those of local systems are so urgent as well as the opportunity for a significant reduction in seizures and avoidance of intensive care or sudden death. In that context it was critical that NICE was clear on what justified its change of opinion. It is important that NICE procedures are not rushed so there is real clarity of decision-making and how all the evidence and clinical and patient voices have been brought to bear on the decision.
4. Dr Raju Reddy, for NICE, stated the rationale for the committee's updated statement in the FDG is provided at section 3.3.
5. Lizzie Walker for NICE, explained that the draft guidance acknowledges the indirect comparison suggested fenfluramine "may" be more effective than C+C, and consultation comments on that sentence prompted the committee to reconsider that wording. The manufacturer of CBD requested that the phrase "not statistically significant" be added, and an expert suggested NICE reexamine this. Given the consultation response, NICE considered it appropriate to update the FDG. It was mindful that the credible intervals for the efficacy of fenfluramine and CBD overlapped (that is, a measure of the statistical confidence that there is a real difference between two treatments), as explained at paragraph 3.5 of the FDG, suggesting there was no meaningful difference between them. The phrase "not statistically significant" was not appropriate, but NICE agreed that the wording of the draft guidance did not reflect the uncertainty. It therefore updated this sentence in the FDG. This was not because the manufacturer of CBD asked them to but rather because the committee agreed it could be misleading to say "may be more effective", given the uncertainty. Materially the two sentences are not hugely different, as "may be more effective" and "is uncertain" both reflect uncertainty, but after the consultation comments the committee wanted to make clear this was very uncertain. The relevant sentence is in paragraph 1 of the FDG, which is the brief introductory section that aims to be accessible to public. A full explanation of the committee's reasoning is in the body of the FDG: paragraph 3.5 explains the uncertainty and the overlapping credible intervals and why that change was made.
6. The appeal panel concluded as follows:
7. The appeal panel were persuaded that the change of the wording of section 1.2 of the final draft guidance, as compared with the wording of the same section of the draft guidance, was a consequence of re-consideration by the committee following the receipt of comments during the consultation process, as well as the results of new analyses undertaken by the company after the publication of the draft guidance. The panel were satisfied that this change in wording reflected the high levels of uncertainty that remained in the minds of the committee in regard to the methodology and results of the OLE network meta-analyses that were submitted by the company after the first committee meeting and considered by the committee in the second meeting. The panel also noted that this high level of uncertainly was clearly discussed in sections 3.5 and 3.7 of the final draft guidance. The appeal panel accepted that the consultation period is an important opportunity, during NICE evaluations, for stakeholders to challenge the committee's conclusions and for the company to submit new analyses and data for committee consideration. It also accepted that this may result in changes to the committee's conclusions and therefore changes in the wording of the final draft guidance. In this evaluation, the appeal panel concluded that the change in wording of section 1.2, following the consultation period, was both procedurally fair and reasonable in the light of the evidence submitted to NICE.
8. The appeal panel therefore dismissed the appeal on both points TSA 1a2 and TSA 2.2.

## Conclusion and effect of the appeal panel’s decision

1. The appeal panel therefore upholds the appeal on the grounds UCB 1a2, 1a6, 2.2, 2.3, 2.4 and RCP 2.1. The appeal is dismissed on all other grounds.
2. The evaluation is remitted to the appraisal committee who must now take all reasonable steps to address the concerns identified by the panel. In particular, the panel identified a number of occasions where it felt that the company did not have an adequate opportunity to respond to, or to challenge the committee’s views (UCB 1a2, 1a6), and further, instances where the panel felt that the committee’s decisions were unreasonable (in respect to wastage, waning and appropriate comparators, UCB 2.2, 2.3, 2.4/RCP 2.1). In the light of this, and specifically the finding in relation to UCB point 1a2, the committee may feel that the most appropriate way to address these concerns would be to hold a further meeting at which it could consider whether to amend any of its preferred assumptions, paying particular attention to waning, wastage and comparators and affording the company an opportunity to respond to the committee's preference for a naïve comparison over the ITT analysis, and (if so) whether this altered the economic case.
3. There is no possibility of further appeal against this decision of the appeal panel. However, this decision and NICE’s decision to issue the final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of NICE publishing the final guidance.