Single Technology Appraisal

Fenfluramine for treating seizures associated with Lennox–Gastaut syndrome in people 2 years and over [ID1651]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Fenfluramine for treating seizures associated with Lennox–Gastaut syndrome in people 2 years and over [ID1651]

The committee papers sent with the Draft Guidance consultation 2, are the same as issued with the Final Draft Guidance in April 2024. The papers are issued for information.

Documents related to the appeal are available to view on the NICE website

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from UCB Pharma**
   a. Draft guidance response
   b. First addendum to draft guidance response
   c. Second addendum to draft guidance response

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Tuberous Sclerosis Association - *written by patient expert Dr Pooja Takhar*
   b. Jazz Pharma

3. **Comments on the Draft Guidance from experts:**
   a. Professor Helen Cross, Director of the UCL Great Ormond Street Institute of Child Health – clinical expert
   b. Lisa Suchet – patient expert
   c. Dr Rhys Thomas, Clinical Senior Lecturer, Honorary Consultant in Epilepsy – clinical expert nominated by UCB Pharma

4. **Comments on the Draft Guidance received through the NICE website**

5. **External Assessment Group critique of company response to the Draft Guidance**

6. **External Assessment Group updated base case**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Fenfluramine hydrochloride for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

UCB response to Draft Guidance

February 2024

File name	Version	Contains confidential information	Date
ID1651_Fenfluramine_LGS_ Answers to Committee's requests [CON]	1.0	Yes	21st February 2024

Executive Summary

As stated in 3.1 of the draft guidance, Lennox-Gastaut syndrome (LGS) is a rare and severe drug-resistant neurological disorder that typically emerges in childhood and is marked by a high frequency of seizures, and cognitive deterioration. NICE committee D concluded that LGS has a significant quality of life impact on patients, carers, and their families.

UCB agrees with the NICE committees' conclusions in 3.2 of the draft guidance that LGS is a heterogenous disease and there remains a significant unmet need for additional treatment options with novel mechanisms of action for patients whose condition remains uncontrolled due to failed multiple anti-seizure medicines (ASMs).

In response to the draft guidance published UCB have provided a comprehensive response within the limits of the evidence base for a rare disease such as LGS and the time available. Uncertainties remain following ACM1 and this is due to heterogeneity of LGS and the absence of long term data which is often a feature of uncertainty when undertaking health technology assessments in rare diseases. UCB has engaged with multiple stakeholders including members of the NICE team to reduce uncertainty and revised the base case accordingly.

Alignment following ACM1

UCB acknowledges that at the first meeting, there has been alignment on the following key aspects:

- Positioning of FFA + Standard of Care (SoC) as a comparator to cannabidiol (CBD) + clobazam (CLB) + SoC. (Section 3.3 of the draft guidance).
- Recognising the clinical effectiveness of FFA based on its clinical trial data and that the NMA suggests FFA + SoC demonstrates superior efficacy to CBD + CLB + SoC for the named outcomes. (Section 3.5 of the draft guidance)
- The model structure being appropriate for decision making (Section 3.8 of the draft guidance)
- The doses that should be considered for both FFA and CBD (Section 3.15 and 3.16 of the draft guidance)

Remaining areas of uncertainty

The long-term efficacy of fenfluramine (FFA), was raised as an area of uncertainty in section 3.10 of the draft guidance consultation. The committee noted that incremental QALYs in favour of FFA + SoC were mostly obtained in the unobserved period (cycle 6 onwards). UCB has diligently addressed this issue using ITT population state occupancy data for cycles 2-5 for both FFA and CBD (as per committee preferences). Given the availability of this new data for cycles 2-5, UCB has adopted a more robust method to compare FFA OLE study results with those of CBD by employing a Bayesian anchored indirect comparison. This approach ensures the most reliable comparison between treatment arms across observed cycles, supported by accepted statistical analysis methods (as described in section 3.). This aligns with the approach taken to compare the registrational trials of FFA and CBD for Cycle 1.

The Committee requested additional data and clarifications that UCB has presented in this response document. Following this, numerous scenario analysis have been undertaken which explore alternative efficacy assumptions for cycles 6-9, discontinuation and waning rates, dosing, and wastage assumptions as well as baseline carer utility assumptions.

The revised base case assumptions presented in section 4. align with committee requests, and results in a base case ICER of [redacted] with the severity modifier applied at the 1.7 level to patients only. Notably, the probabilistic mean ICER was [redacted] than the base case, [redacted] per QALY gained, and the probability of being cost-effective at the ICER threshold of £30,000 (with the severity modifier applied) is [redacted]. These results confirm that FFA is a cost-effective treatment option for the NHS. UCB is keen to continue to work with NICE committee team D to ensure patients have timely access to FFA for this rare, difficult-to-treat childhood-onset epilepsy syndrome.

1. Additional data requests

1.1. Proportion of people ineligible for cannabidiol plus clobazam in NHS clinical practice (section 3.2 of the draft guidance)

The reasons why some patients may be ineligible to use CBD is widely understood, e.g. those with moderate or severe hepatic impairment (1). Furthermore, as per CBD's

license (stating use alongside CLB), concerns with using CLB would also apply to patients being considered for CBD e.g. those with muscle weakness and personality disorders. Clinicians are unable to provide an evidence-based estimate of people ineligible for CBD + CLB. This is due to heterogeneity (in both pathophysiology and treatment), the rarity of LGS, and for multifactorial reasons why patients may be ineligible. It is therefore difficult to determine an average proportion of those ineligible.

1.2. Proportion of people with LGS using clobazam, rufinamide and topiramate in NHS clinical practice (section 3.3 of the draft guidance)

LGS patients are extremely heterogeneous in their seizure frequency and treatment history. Their disease evolves over time, and treatment needs to be individualized. Currently, due to limitations in the available data sets it is not possible to obtain an accurate estimate of the proportions of patients using CLB, rufinamide and topiramate for LGS in NHS clinical practice beyond the information that is already available for this rare disease.

UCB notes that these products are considered within the 'basket' of SoC treatment options as agreed by the committee and as seen in the three previous STAs (TA615, TA614, and TA808) for DS and LGS (2, 3). UCB has understood from an advisory board that clinicians treating LGS consider the proportions identified within the clinical trial (4) (and therefore incorporated within the economic model) are reflective of clinical practice.

1.3. Company's assumption of 5.2% of people experiencing treatment waning after cycle 9 (section 3.12 of the draft guidance)

To clarify, this was calculated as the proportion of patients discontinuing due to lack of efficacy in the last cycle of the FFA OLE study divided by total number of patients in this cycle (form Table 2.1 and 1.3 of amendment analysis) which is 6/116=5.2%. Please see Table 1 below.

Table 1 Estimated calculation for proportion of patients experiencing treatment waning after cycle 9

	Discontinued due to lack of efficacy*	Total number of patients **
Month 10-12 of FFA OLE	6	116

*From Table 2.1 of amendment analysis Last row (total number of discontinued due to lack of efficacy);**From Table 1.3, total number of patients in Month 10-12 for sum of states 0,1,2 and 3 which is 31,21,29, and 35.(5)
Abbreviations: FFA= Fenfluramine; OLE= Open-Label Extension

There is little data to support treatment waning assumptions for FFA and CBD, therefore any related analysis should be viewed with caution. One observational study found that FFA patients with LGS discontinue due to lack of efficacy at a low rate in the real-world (6.8%), thus confirming that the 5.2% assumption within the base case is reasonable.

Additionally, UK clinical experts are not able to define the proportion of patients that should be assumed to wane for either treatment arm, it is also difficult to determine this accurately within clinical trials for a rare disease such as LGS. Due to uncertainty in assumptions for waning for both FFA and CBD treatment arms, it is conservative to assume equal waning for both to reduce any bias. Different assumptions for waning (as per section 4.2.) have been explored in scenario analysis as per the committee's request (scenarios 4 and 5 within Table 11).

1.4. Average maintenance dosage of cannabidiol used in NHS clinical practice (section 3.16 of the draft guidance)

The average dose of CBD is underestimated given that, in the real-world OLE study (6), CBD was provided at a mean modal dose of 24 mg/kg/day. Feedback from clinical experts treating LGS showed that the average dose is varied. In some centres doses are maintained at slightly lower levels (such as 12 mg/kg/day or 13 mg/kg/day) to balance safety and efficacy, whilst in many others the dose is continuously increased, even beyond the doses seen within trials, making CBD a costly treatment option to the NHS.

At the first appraisal committee meeting, two of the clinical experts present (one specialist neurologist and a specialised pharmacist) stated the average dose in clinical practice for CBD is likely to be between 14-16 mg/kg/day. The third clinical expert mentioned a dose closer to 12 mg/kg/day. Noting that the clinical expert who mentioned the lower dose treats adult patients only, and that adult patients encompass a small proportion of the LGS patient population, it is likely the actual average dose for all LGS patients is close to 16mg/kg/day as per UCB's original base case assumption. However, UCB agrees with the committee that a dose between 12-16 mg/kg/day is plausible (as per section 3.16 in the draft guidance), and therefore the average dose used within the new base case has been revised to 14 mg/kg/day.

A range of CBD doses have been explored in scenario analysis (see section 4.4.) as per the committee request (scenarios 6 to 9 within Table 11).

1.5. Data on the per-arm use of non-pharmacological treatments (section 3.6 of the draft guidance)

Following further internal statistical analysis, the proportions of patients on Vagus Nerve Stimulation (VNS), Ketogenic diet and surgery, split by treatment arm, are presented in the Table 2 below.

Table 2 . Proportions of patients per arm on non-pharmacological treatments in study 1601

		Part 1 Treatment Group			All Subjects
		Placebo	FFA 0.2 mg/kg/day	FFA 0.7 mg/kg/day	
All Subjects	N per Group	[redacted]	[redacted]	[redacted]	[redacted]
VNS	N	[redacted]	[redacted]	[redacted]	[redacted]
	% of Group	[redacted]	[redacted]	[redacted]	[redacted]
Ketogenic Diet (Expanded Definition)*	N	[redacted]	[redacted]	[redacted]	[redacted]
	% of Group	[redacted]	[redacted]	[redacted]	[redacted]
Ketogenic Diet	N	[redacted]	[redacted]	[redacted]	[redacted]
	% of Group	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	N	[redacted]	[redacted]	[redacted]	[redacted]
	% of Group	[redacted]	[redacted]	[redacted]	[redacted]

*Expanded definition includes patients on a modified Atkins diet or a low glycaemic diet
Abbreviations: FFA= Fenfluramine ; VNS= Vagus Nerve Stimulation

Observing the data above, there appears to be little/minimal differences in the use of non-pharmacological treatments per treatment arm. In-line with suggestions by the committee, considering the small patient numbers and variability in the treatment of LGS (using different combinations of pharmacological and non-pharmacological treatments for each patient) it is highly unlikely any of these non-pharmacological treatments have an impact on treatment outcomes.

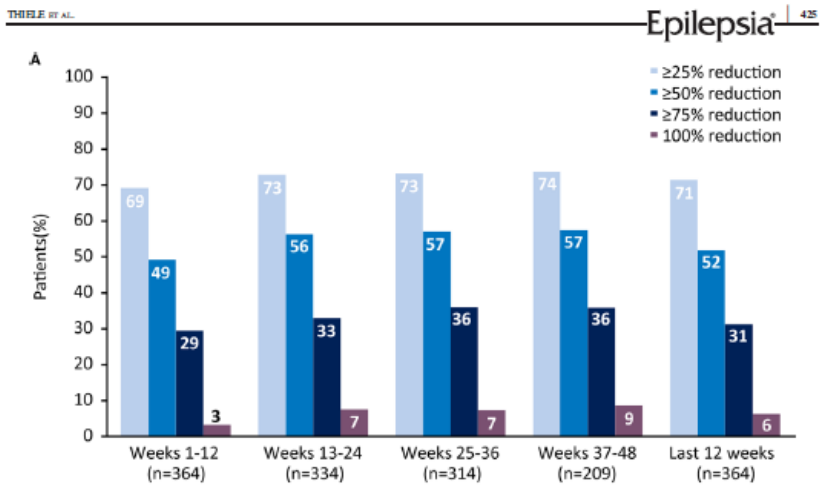
2. Clarifications

2.1. Whether the cannabidiol OLE data that was used to populate the cannabidiol plus clobazam plus SoC health states for cycles 2 to 5 was based on the treated population or the ITT population. If based on the ITT population, the committee would also like clarification on the methodology

and assumptions used to account for missing data points (section 3.10 of the draft guidance).

The CBD OLE data used to populate the CBD + CLB + SoC health states for cycles 2 to 5 was based on the treated population data available within the trial publication (6) as per **Figure 1** below.

Figure 1 OLE data for the treated population for CBD within Thiele et al. 2019



Considering committee preferred assumptions to use ITT data, UCB identified that ITT data is available for CBD within the appendix of its clinical trial publication (6), where there are reported response rates for drop seizures based on Last Observation Carried Forward (LOCF) analyses. Further explanation of the approach to integrate the OLE data into the model is provided in section 3.

2.2. How the company's original base case maintenance dosage for FFA of 0.5 mg/kg/day was calculated, how the updated maintenance dosage was calculated and the rationale for the discrepancy between the dosages (section 3.15 of the draft guidance).

Please note that when UCB asked clinical experts to comment on the average dose of FFA reflecting clinical practice in the UK. They agreed that the average dose within the OLE would be a reasonable assumption reflective of practice, and not specifically 0.5 mg/kg/day.

When UCB originally considered the average dose to use for decision making, it was noted that only ranges are reported within the clinical paper, (4) as per Table 3 below:

Table 3 Average dose ranges reported within FFA's OLE study paper Knupp et al., 2022. (4)

Characteristic	Value
N	247
Duration of exposure by age group at entry into core study, days, median (IQR)	
Pediatric: 2 to < 18 years, $n = 174$[a]	364 (191–368)
Adult: 18–36 years, $n = 73$	364 (210–373)
Mean daily dose of fenfluramine, mg/kg/day, *n* (%)	
Up to .2	6 (2.4)
>.2 to <.3	67 (27.1)
.3 to .5	113 (45.7)
>.5 to .7	60 (24.3)

Abbreviations: IQR, interquartile range; OLE, open-label extension.

[a]Six patients in the core study turned 18 years of age before the start of the OLE ($n = 168$ patients were 2 to <18 years old at the beginning of the OLE).

As illustrated in Table 3 the mean daily dose range for FFA is 0.3 – 0.5 mg/kg/day. Until UCB had further information on the exact average dose from the global statistics team, an average of 0.5mg/kg/day was conservatively assumed. In retrospect, 0.4 mg/kg/day is more appropriate as it is the value between 0.3 and 0.5 and a larger proportion of patients were taking doses <0.3 mg/kg/day compared to >0.5 mg/kg/day.

UCB reported additional data as per Table 4 below after receiving clarifications from the EAG. The calculated weighted average mean daily dose is 0.413mg/kg/day and reflects the average dose detailed within the OLE paper (please note that the [redacted] mg/kg/day dose in Table 4 below also reflects those subjects that received >0.7 mg/kg/day, these patients were removed from the average assumed within the model, as clinicians will not exceed the maximum stated dose within clinical practice).

Table 4 Mean daily doses of FFA within the OLE (unpublished post-hoc analysis)

Mean Daily Dose Category of FFA	Mean Daily Dose of FFA	
	No. of Subjects	Average Mean Daily Dose (mg/kg/day)
<= 0.2 mg/kg/day	[redacted]	[redacted]
> 0.2 - <= 0.3 mg/kg/day	[redacted]	[redacted]
> 0.3 - <= 0.4 mg/kg/day	[redacted]	[redacted]
> 0.4 - <= 0.5 mg/kg/day	[redacted]	[redacted]
> 0.5 - <= 0.6 mg/kg/day	[redacted]	[redacted]
> 0.6 - <= 0.7 mg/kg/day	[redacted]	[redacted]
> 0.7 mg/kg/day	[redacted]	[redacted]
All Subjects	[redacted]	[redacted]

Abbreviations: FFA= Fenfluramine

As the committee prefers using the mean dose from the Study 1601 OLE as it is reflective of clinical practice (section 3.15 within the draft guidance), the actual average dose of 0.413 mg/kg/day has been applied within the base case.

2.3. Evidence supporting the validity of the eDiary as a measurement device (section 3.6 of the draft guidance).

As per Gray et al., 2022, eDiaries are now the gold standard to capture data in epilepsy studies. They enable carers to record seizures quickly, accurately and improve the quality and quantity of data versus the traditional paper diary. This also reduces the risk of bias. (7)

The eDiary used in the trial was developed by Signant Health and the Epilepsy Study Consortium (ESC) validated the quality of the device, acknowledging the manufacturers "considerable experience developing complex eDiaries and conducting epilepsy trials" (8). UCB would like to emphasize that the use of this specific eDiary was validated at the regulatory approval stage via both the FDA and EMA. In the NICE appraisal of FFA for Dravet Syndrome (2) the use and validity of eDiaries was not commented on as a potential issue.

2.4. External validity of the trial being unclear (section 3.6 of the draft guidance)

UCB is not aware of any clinical expert opinion that may suggest age, gender and/or ethnicity may be treatment effect modifiers in LGS. Such concerns have not been raised as potential issues within previous HTA appraisals for DS and LGS (TA808, TA614 and TA615). Furthermore, UCB believe that the entire eligible population is relevant, and all should obtain equal access to new epilepsy products such as FFA, particularly considering that US, EU and MHRA labelling for the product indicate its use within a broad population.

3. Treatment effect assumptions

UCB has noted the committee preference to use ITT data and clinical trial state occupancies data for both FFA and CBD, where analysis using the same methodology

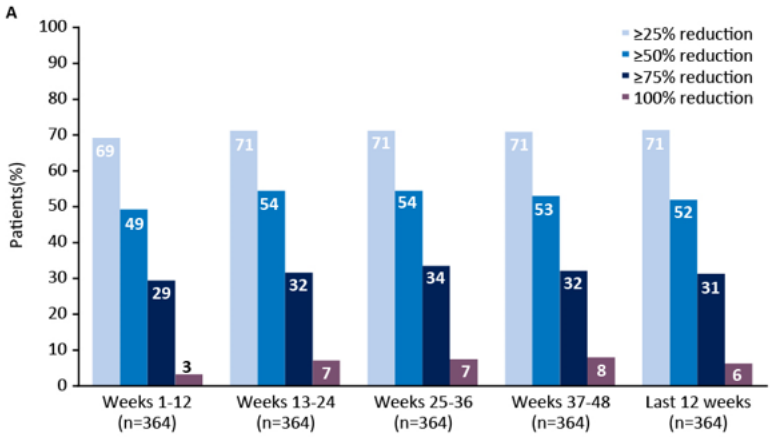
and assumptions to account for missing data points in FFA's OLE data analysis are also applied to CBD OLE data.

3.1. Modelling treatment effect during the OLE period (cycles 2-5)

Within the appendix of Thiele *et al.,* the ITT data for CBD can be found as per Figure 2 below. (6)

Figure 2 OLE data for the ITT population based on LOCF analyses for CBD within Thiele et al. 2019

Figure S2. Responder rates for (A) drop and (B) total seizures based on LOCF analyses.



To enable a like-for-like comparison with FFA patients, UCB has performed an ITT analysis using all patients who received open-label FFA, or equivalently, the Safety Population. Note that for CBD, the ITT analysis excluded 2 patients for having less than 2 weeks of seizure data. This additional analysis for FFA has been done using the committee requested time periods of Weeks 1-12, Weeks 13-24, Weeks 25-36, and Weeks 37-48, which also match the time periods used in the analysis done for CBD. UCB performed analysis with LOCF imputation to match FFA's analysis with CBD's. The CBD publication described that LOCF imputation was conducted as follows. "If a patient had valid data for ≥1 consecutive periods from and inclusive of the first period but only missing periods thereafter, then imputation of the missing period(s) was carried out using the last 12 weeks of valid data." As such in the LOCF imputed analysis of FFA, if a patient had valid data for ≥1 consecutive periods from and inclusive of the first period, the periods with any non-missing data were considered to have valid data and the seizure frequency for that period was calculated based on the

available data. For any periods with only missing data, imputation of the missing period(s) was carried out using the seizure frequency from the last 12-week period that had (any non-missing) valid data. In other terms, if a patient dropped out during a given period, the seizure rate for the period was calculated based on the available data in the period, and then was carried forward to the following periods.

These results can be found in the supplement material document. (9)

3.2. An indirect treatment comparison for cycles 2-5

UCB noted the uncertainty that is associated with directly comparing the results from FFA's OLE trial with that of CBD. UCB has therefore explored an alternative method to compare the trials accounting for the differences between the placebo response rates seen in the phase III trials of FFA and CBD.

As per the approach taken for cycle 1, a Bayesian anchored indirect comparison has been conducted using the ITT state occupancy data identified for both FFA and CBD. This approach aligns with committee preferred use of data for both treatment arms and enables a robust comparison between the treatment arms for the observed cycles, which is supported by accepted statistical analysis methods.

The indirect treatment comparison used a binomial likelihood model and a log link. A fixed effect model was selected as the network is composed of 2 studies. Analysis was done with 3 chains, 25000 burn-in iterations and 25000 simulation iteration. Analyses was done with R V4.0.1 using the package gemtc (which performs the Bayesian simulations with JAGS); based on a UCB adapted version of metaInsight V3.14 (10).

Data inputs were based on Figure S2 A of the appendix within Theile et al, 2019 for CBD (6) and Table 14.2.1.12.1.1.1_safe_imp of ZX008 generated post hoc for FFA (9). For placebo, rates were carried forward using the data in the global NMA, appendix G, table G1, using the rows Knupp 2022 for the PBO of FFA (4), and combining the rows Thiele 2018 and Devinsky 2018 for PBO of CBD (11) (12).

The most plausible assumption in the absence of efficacy data for the placebo arm within the OLE studies, was that the placebo effect continues as per the last observed period within the respective trials. There is no evidence to suggest, or any plausible

explanation to believe that a placebo drug will directly provide any improvements or decrements in efficacy, therefore a maintained effect was assumed as the most appropriate for the purposes of the ITC.

Results of the ITC can be seen in Table 5 below and have been incorporated into the model base case to provide efficacy results for FFA + SoC versus CBD + CLB + SoC in cycles 2-5.

Table 5 Summary of efficacy results comparing FFA and CBD with placebo, fixed effects, all time points

	Treatment Arm	
Health State	**RR FFA versus Placebo (95% CrI)**	**RR CBD versus Placebo (95% CrI)**
Timepoint: After 3 months in OLE study (weeks 1-12)		
>= 25% response	[redacted]	[redacted]
>= 50% response	[redacted]	[redacted]
>= 75% response	[redacted]	[redacted]
Timepoint: After 6 months in OLE study (weeks 13-24)		
>= 25% response	[redacted]	[redacted]
>= 50% response	[redacted]	[redacted]
>= 75% response	[redacted]	[redacted]
Timepoint: After 9 months in OLE study (weeks 25-36)		
>= 25% response	[redacted]	[redacted]
>= 50% response	[redacted]	[redacted]
>= 75% response	[redacted]	[redacted]
Timepoint: After 12 months in OLE study (weeks 37-48)		
>= 25% response	[redacted]	[redacted]
>= 50% response	[redacted]	[redacted]
>= 75% response	[redacted]	[redacted]

Abbreviations: CBD= Cannabidiol; CrI= Credible Interval; FFA= Fenfluramine; OLE= Open-Label Extension; RR= Risk Ratio

As per the table, we can observe that improvements in the RR values versus placebo for FFA are larger versus CBD for all timepoints for the 25% and 50% responses, however the 75% response values for CBD are larger versus FFA. This aligns with the results seen within the original ITC analysis conducted for the registrational trials and incorporated within the model for cycle 1.

Although long-term data on the use of FFA for LGS does not exist beyond 15 months within its OLE trial (apart from 2-3 patients and some patients that are currently using FFA for LGS via individual funding requests), there is evidence of its increasing long-term efficacy from other publications. A recent paper, Carbo et al., 2024, reveals the

long-term efficacy results (for patients that have been on compassionate use or post OLE) of FFA in LGS in 13 patients within Spain. (13) The paper states that analysis of real-world data (retrospectively assessed for 12 months, n=13) were consistent with those seen in randomised controlled trials. Specifically, 50% (n=6) of patients experienced >50% reduction in overall seizures, and 8.3% (n=1) experienced seizure freedom.

We have heard from clinicians within the advisory board that the use of CBD in clinical practice has been disappointing as efficacy is lower than what has been observed within late phase clinical trials data. Clinicians mention that, without the request from families, they would prescribe it less or stop it earlier. Following UCB's continued discussions with clinicians, given the experience clinicians have in DS with FFA, they do expect FFA's efficacy to also be superior to CBD in LGS. (14)

3.3. Extrapolation of FFA treatment effect (cycles 6-9) and assumptions for cycle 10 onwards

Given the limited available observed data post 15 months, the revised base case analysis assumed that treatment effect is maintained from cycles 6-9, based on the last observed efficacy from cycle 5 for both treatment arms. The same methodology is applied to FFA + SoC and CBD + CLB + SoC. Waning will be then applied from cycle 10.

Two alternative scenarios (scenarios 1 and 2 within Table 11) have been tested in order to explore the uncertainty around the treatment effect of cycles 6-9. First, a scenario assuming treatment effect would be maintained at the average effect observed in cycles 2-5. A second scenario assumed treatment effect duration would be maintained up until 15 months meaning cycle 5 (instead of 27 months in the base case which corresponds to cycle 9) and waning would start at cycle 6 (instead of cycle 10 as in the base case).

3.4. Summary of efficacy inputs within the updated model

Table 6 Summary of efficacy inputs from cycle 2 to 9

FFA + SoC					
State occupancy	State 0	State 1	State 2	State 3	Source
Cycle 2 (3-6 months)	[redacted]	[redacted]	[redacted]	[redacted]	Based on ITC on OLE studies

Cycle 3 (6-9 months)	[redacted]	[redacted]	[redacted]	[redacted]	
Cycle 4 (9-12 months)	[redacted]	[redacted]	[redacted]	[redacted]	
Cycle 5 (12-15 months)	[redacted]	[redacted]	[redacted]	[redacted]	
Cycles 6-9	Patients remain in the same health states as last observed in cycle 5				Assumption
CBD w CLB + SoC					
State occupancy	State 0	State 1	State 2	State 3	Source
Cycle 2 (3-6 months)	[redacted]	[redacted]	[redacted]	[redacted]	Based on ITC on OLE studies
Cycle 3 (6-9 months)	[redacted]	[redacted]	[redacted]	[redacted]	
Cycle 4 (9-12 months)	[redacted]	[redacted]	[redacted]	[redacted]	
Cycle 5 (12-15 months)	[redacted]	[redacted]	[redacted]	[redacted]	
Cycles 6-9	Patients remain in the same health state as last observed in cycle 5				Assumption

Abbreviations: FFA= Fenfluramine; SoC= Standard of care

4. Base case & scenario analyses

4.1. Proportion in which clobazam, rufinamide and topiramate are considered separately as comparators in the cost-effectiveness analysis

UCB does not consider this analysis to be valid. As described previously, many of the patient characteristics and outcome measures are missing within these trials e.g. baseline number of seizures, preventing comparisons to be made even if they were plausible.

UCB agrees with the committee that CBD + CLB + SoC and SoC alone are the most appropriate comparators to FFA + SoC. UCB also agrees with the committee that separate comparisons against CLB, rufinamide and topiramate may not be robust and clinically meaningful (as per section 3.3 within the draft guidance), particularly as data from these trials are approximately 20 years old and do not provide comparable patient characteristics and treatment methodologies.

4.2. Exploring different proportions of people experiencing treatment waning and a scenario with 10% of people discontinuing treatment as explored in TA615

UCB has considered two alternative scenarios assessing 19.6% and 30.0% of patients experience wanning of treatment efficacy (scenarios 4 and 5 within Table 11). The first scenario (19.6%) is based on the discontinuation of patients who reported “no effect” as the reason to end treatment with CBD (as part of a long-term real-world evidence study in Germany on various epilepsy types).(15) The second scenario is based on what UCB considers to be a high assumption for this parameter. UCB considers

neither scenario to be plausible, as there is no evidence of treatment waning being significantly more than 5.2% for FFA, therefore 5.2% should remain as the base case analysis.

Additionally, UCB has implemented a scenario where 10% of patients discontinue every cycle, starting at cycle 2, until the end of the time horizon (see scenario 3 within Table 11). In this scenario, the stopping rule is replaced by a direct discontinuation due to lack of efficacy applied every cycle. It is important to note that this scenario was manually tested and that it's not possible to implement in the model without directly changing the cells of the Markov traces.

To implement this scenario, UCB has modified cells 'Markov Trace (FFA)'!V12:V402 and 'Markov Trace (CBD)'!V12:V402 (direct discontinuation due to lack of efficacy) to be equal to 10% and the cells 'Markov Trace (FFA)'!W13:W402 and 'Markov Trace (CBD)'!W13:W402 (discontinuation due to stopping rule) to be equal to 0%. The stopping rule was deactivated in this scenario to avoid double counting discontinuation due to lack of efficacy.

4.3. In which the FFA dose in cycle 1 reflects the mean dose in the 0.7mg/kg/day arm of Study 1601

UCB considered a dose of 0.7mg/kg/day for FFA in cycle 1 as a scenario analysis (scenario 10 within Table 11). Please note that it was mentioned in the draft appraisal document (section 3.15) that efficacy continues to improve at lower average doses than used in Study 1601. If 0.7 mg/kg/day is assumed as the mean dose from the first cycle, this would not reflect true UK clinical practice.

As observed during a UCB advisory board and clinician feedback, doses are gradually increased to the maximum tolerated dose, opposed to dosing to the maximum licensed and bringing the dose down. (14) Therefore, applying this within the model for cycle 1 is not aligned to UK clinical practice. It is also not appropriate, as, in the first cycle of FFA's OLE study, all patients were re-started on 0.2mg/kg/day and titrated upwards, and therefore this dose should also be applied in cycle 2 for consistency in approach if 0.7mg/kg/day is assumed to be the dose for cycle 1.

4.4. Exploring the impact on cost-effectiveness for the range of cannabidiol maintenance dosages the committee considered plausible.

As per the committee's request, UCB has provided additional scenario analysis exploring CBD maintenance doses of 12, 13, 15 and 16 mg/kg/day (scenarios 6-9 in Table 11). However, as described earlier, given the average dose within the CBDs OLE study (24 mg/kg/day) and considering expert clinical opinion at the first committee meeting (2/3 which said the average dose is 14-16mg/kg/day), it is very likely that the true average dose of CBD within UK clinical practice is higher than the base case dose of 14 mg/kg/day and closer to 16 mg/kg/day. Regardless of this, the new base case has been amended to 14 mg/kg/day given the committee preferred assumptions (see section 1.4.)

4.5. Incorporating wastage costs associated with both CBD and FFA treatment. That is, a scenario in which greater wastage is assumed for CBD and a scenario in which equal wastage is assumed for FFA and CB

There are numerous methods to incorporate wastage for example, by using average patient body weights and expected bottle usage per age group, however this would unnecessarily complicate the calculation given the data available. To simplify the incorporation of wastage costs within the model, the following scenarios have been provided where additional usage has been applied assuming an additional percentage of dose/volume used (scenarios 11-13 within Table 11):

- An assumed 5% wastage per bottle for both FFA and CBD (equal wastage)
- An assumed 5% wastage for FFA and 10% for CBD (considering clinician feedback at the initial appraisal meeting that the CBD solution is an oily liquid, in a glass bottle and likely to have more wastage per bottle than FFA)
- An assumed 0% wastage per bottle for FFA and 10% for CBD

It is highly unlikely that FFA and CBD have equal wastage, therefore equal wastage should not be considered as appropriate. During the first committee meeting, clinicians brought to light that CBD is an oily liquid (unlike FFA) and, due to it being a slippery liquid, glass bottles do tend to break when dropped on hard kitchen floors (unlikely FFA which is presented in plastic bottles). There was no mention of wastage being an

issue for FFA, therefore, the most appropriate scenario, given clinician feedback, would be to assume 0% wastage for FFA and 10% for CBD (scenario 13 in Table 14).

4.6. Correction: Issue related to the implementation of the stopping rule at 6 months in the model

The stopping rule at 6 months in UCB's original base case model was implemented by discontinuing patients from health state 0 (and a percentage of health state 1 in the case of less than 30% and 50% reduction in drop seizure frequency) discontinued every 6 months. The EAG believed that this implementation was not optimal as there was a possibility of patients that had experienced sub-optimal response for less than 6 months to discontinue treatment as well.

This approach was selected in the model because it's not feasible to track patients, e.g., for how long patients have been in a particular health state. This is due to state transitions in the model being determined based on state occupancy data and not on transition probability data. State occupancy data represent the proportion of the cohort of patients in each heath state at a given point in time and provide no information as to the movement of patients in between states. To track the number of patients that have stayed in health states 0 and 1 for a period of 6 consecutive months, the model would have to rely on transition probabilities. However, such data is not currently available for the CBD arm.

Since tracking of patients is not possible, to address this comment from the EAG and supported by the committee, UCB estimated the proportion of patients remaining in health state 0 and health state 1 from the transition probabilities of FFA treated patients during the OLE study. On average, 61.2% of patients in health state 0 remain on health state 0, while 37.9% of patients in health state 1 remains in health state 1 the following cycle.

The updated stopping rule uses this data to discontinue the patients that remain in both health state 0 and 1 for at least 6 months. Considering cycle length in the model is 3 months, the probability of remaining in health state 0 for 6 months is 61.2%*61.2%=37.5% and in health state 1 is 37.9%*37.9%=14.3%. These probabilities are applied every cycle to both FFA and CBD arms to determine patients who discontinue due to lack of efficacy in both treatment arms.

4.7. Application of carer disutility values

UCB acknowledges the committee preferences to use carer disutility values in a manner that do not result in negative QALYs. However, it was not feasible for UCB to present results in another way.

Two methodologies for caregiver QoL are currently available in the model. The first one was used in the initial model and consists of including carer utilities for each health state by applying the same utility values used for people with LGS. That method leads to positive total QALYs. However, the EAG highlighted the limitations of that approach that may overestimate the impact of mortality (as the carers' QALYs will stop accruing when the person they care for die) and UCB agreed with this limitation.

The EAG recommended to use the disutility approach, similarly to TA615, and that was implemented in the model. Having negative QALYs is inherent to that method, considering that patients have very low QALYs and require more than 1 caregiver (1.8 in this case) resulting in high disutilities. Although negative utility values lack face validity, there is no plausible method to convert these to positive values. With the current disutility approach, the decrement in utility is applied equally for both FFA and CBD, which alleviates any concern of bias.

Negative QALYs were similarly observed in TA615, as shown below. The note under the table specifies that the QALY changes are spread across the patients and applied to an average of 2 caregivers, and that they do not represent a worse-than-death outcome for anyone in the cohort. This comment also applies for the FFA QALYs results.

A scenario was performed to test the baseline utility used to assess the disutility of caregiver (scenario 14 . The base case used the UK VAS norm (0.828), and a scenario considered the value (0.78) associated with the least severe health state (30 seizure-free days in a month and 0 drop seizures in a month from Auvin 2021).(16)

Table 7 GW's Base case after draft guidance consultation illustrating the negative QALYs (source: https://www.nice.org.uk/guidance/ta615/documents/committee-papers-2)

Table 2. Company's Base Case after ACD

Technologies	Total costs (£)	Total QALYs*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Patients still on CBD at:	
						2 years	50 years
CCM	£195,302	-5.0696	-	-	-	-	-
CCM + CBD	£243,988	-3.4250	**£48,686**	**1.6445**	**£29,605**	49.00%	3.54%

*Note: the QALY changes are spread across the patient and an average of 2 caregivers, and a time horizon of 90 years. They do not represent a worse-than-death outcome for any one individual in the cohorts.

4.8. Uncaptured benefits within the model

There are several uncaptured benefits of FFA within the economic model. These uncaptured benefits could improve the cost-effectiveness estimates of FFA as there is potentially more value in FFA than what can currently be captured in the model. Uncaptured benefits of FFA include:

- The reduction in the duration of drop seizures and non-drop seizures
- The benefits of FFA on the quality of life of siblings of children or young people and other family members of patients living with LGS.
- Improvements in a child's intellectual development due to fewer seizures resulting in extended periods between seizures which may facilitate progress in speech and other key indicators of developmental progress.
- Motor function improvements (such as walking) and executive function improvements.
- Work productivity loss for caregivers and families due to need of life-long and round-the-clock care brought on by high seizure frequency rates may be reduced with FFA, thus also providing a wider societal benefit.

5. *Revised base case and additional scenario analysis*

Considering the committee preferred assumptions and suggestions, a revised base case and scenario analysis has been conducted based on the below inputs:

Table 8 Summary of model assumptions

Input	UCB's original base case	Assumption based on committee preferences	Commentary/ rationale
Baseline inputs	Study 1601	Unchanged	N/A
FFA + SoC efficacy	**Cycle 1**: TPs based on RR derived from NMA results **Cycles 2-5**: TPs based on Study 1601 OLE **Cycles 6-9**: TPs assumed to equal TPs observed in cycle 4-5 **Cycles 10+**: Change in state occupancy based on treatment waning, discontinuation and death	**Cycle 1**: TPs based on RR derived from NMA results **Cycles 2-5**: State occupancies derived from NMA results of OLE studies **Cycles 6-9**: State occupancies assumed to equal those observed in cycle 4-5 **Cycles 10+**: Change in state occupancy based on treatment waning, discontinuation and death	Use of state occupancies during the OLE period, derived from the Indirect Treatment Comparison using the ITT data of both FFA and CBD OLE studies using LOCF in both treatment arms. Long-term effects (cycles 6-9 onwards) are now assumed to be stable opposed to increasing for FFA and only maintained for CBD
CBD + CLB + SoC efficacy	**Cycle 1:** TPs based on a RR derived from the NMA results using a weighted average of the 10 mg/kg/day and 20 mg/kg/day subgroups **Cycles 2-5:** State occupancy based on CBD + CLB + SoC trial OLE	**Cycle 1:** TPs based on a RR derived from the NMA results using a weighted average of the 10 mg/kg/day and 20 mg/kg/day subgroups **Cycles 2-5**: State occupancies derived from NMA results of OLE studies	Use of state occupancies during the OLE period, derived from the Indirect Treatment Comparison using the ITT data and LOCF of both FFA and CBD OLE studies

	Cycles 6-9: Assumed no change in state occupancy (except discontinuation and death) **Cycles 10+:** Change in state occupancy based on treatment waning, discontinuation and death	**Cycles 6-9**: State occupancies assumed to equal those observed in cycle 4-5 **Cycles 10+:** Change in state occupancy based on treatment waning, discontinuation and death	
Treatment discontinuation	Discontinuation can occur at any cycle including titration, due to AE (all cycles), lack of efficacy (cycles 1 and 2) or stopping rule (after cycle 2). Discontinued patients were assumed to go to the discontinuation state (equivalent to state 0).	Unchanged	As per the committee conclusions
Treatment waning	Calculated only using patients that stayed in health state or deteriorated from month 9 to month 12	Calculated using all patients on treatment from month 9 to 12	As per the committee conclusions
Patient utility approach	Verdian et al.	Unchanged	As per the committee conclusions
Caregiver (dis)utility approach	Utility approach using Verdian et al.	Disutility approach using utility estimates from Lo et al.	As per EAG preference
Severity modifier application	Modifier of 1.7 applied to patient and caregiver QALYs	Modifier of 1.7 applied to only patient QALYs	As per the committee conclusions in the draft guidance.
FFA maintenance dose	0.413 mg/kg/day	Unchanged	As per the committee conclusions in the draft guidance.
CBD maintenance dose	16 mg/kg/day	14 mg/kg/day	UCB acknowledges that the committee considers the appropriate CBD maintenance dosage for the model was likely between 12 and 16

			mg/kg/day. And therefore, UCB has lowered the base case assumption given the evidence available
Impact of institutionalisation on caregiver dis(utility)	Excluded	Unchanged	No available evidence and little bearing on results.
Institutionalisation costs	Excluded	Included	As per the committee conclusions in the draft guidance
Stopping rule	<25% reduction in DSF assessed every 3 months	<30% reduction in DSF assessed every 6 months	Applied as per the committee conclusions in the draft guidance. See Base case & scenario analyses paragraph 4.6. where a correction has been made to the stopping rule being applied.
Treatment for pulmonary hypertension	Not included	Unchanged	In-line with the committee preferred assumptions.
Residential care	Assume 10% of people 18+ years will need residential care, assuming the need of 0.7 carers for these patients	Unchanged	Applied as per the committee conclusions in the draft guidance

Abbreviations: AE= Adverse Events; CBD= Cannabidiol; CLB=Clobazam; DSF= Drop Seizure Frequency; FFA= Fenfluramine; ITT= Intention to Treat; LOCF= Last observation carried forward ; NMA= Network Meta-Analysis ; OLE= Open-Label Extension; SoC= Standard of care; QALYs, Quality-Adjusted Life Years; RR= Risk Ratio; TP= Transition Probabilities

Table 9, Table 10 and Table 11 provide the results of the revised base case and scenario analyses.

Table 9 Base-case results: FFA + SoC versus CBD + CLB + SoC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
CBD + CLB + SoC	[redacted]	20.30	-19.18	-	-	-	-
FFA + SoC	[redacted]	20.37	-18.84	[redacted]	0.07	0.34	[redacted]

Abbreviations: CBD w CLB, Cannabidiol with Clobazam; FFA, Fenfluramine; ICER, Incremental Cost-Effectiveness Ratio; LYG, Life Years Gained; QALYs, Quality-Adjusted Life Years; SoC, Standard of Care.

Table 10. Base-case results with severity modifier applied: FFA + SoC versus CBD + CLB + SoC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
CBD + CLB + SoC	[redacted]	20.30	-18.54	-	-	-	-
FFA + SoC	[redacted]	20.37	-18.07	[redacted]	0.07	0.48	[redacted]

Abbreviations: CBD w CLB, Cannabidiol with Clobazam; FFA, Fenfluramine; ICER, Incremental Cost-Effectiveness Ratio; LYG, Life Years Gained; QALYs, Quality-Adjusted Life Years; SoC, Standard of Care.

Table 11 Summary of the scenario analyses explored and comparison to the base case

Scenario no.	Parameter	Base case	Scenario analyses	FFA+SoC versus CBD + CLB + SoC			ICER	ICER (severity modifier applied to patients only)
				Incremental costs	Incremental QALYs	Incremental QALYs (with severity modifier)		
	Base case	**N/A**	**N/A**	[redacted]	0.34	0.48	[redacted]	[redacted]
	New scenarios (as discussed in the above of the current document)							
	Varying the efficacy for cycle 6-9							
1	Assumption for cycles 6-9	Maintained efficacy using cycle 5	Maintained efficacy using average of cycles 2-5	[redacted]	0.30	0.41	[redacted]	[redacted]
2	Assumption for cycles 6-9	Long-term efficacy 27 months	Efficacy duration = observed period (15 months)	[redacted]	0.35	0.50	[redacted]	[redacted]
	Varying the discontinuation due to lack of efficacy for FFA and CBD (cycle 2-393)							
3	Discontinuation rate	7.3% Cycle 2 Stopping rule (<30% response, 6 months)	10% Cycles 2-393 No Stopping rule	[redacted]	0.19	0.28	[redacted]	[redacted]
Varying the waning for FFA and CBD (from cycle 10)								

Scenario no.	Parameter	Base case	Scenario analyses	FFA+SoC versus CBD + CLB + SoC			ICER	ICER (severity modifier applied to patients only)
				Incremental costs	Incremental QALYs	Incremental QALYs (with severity modifier)		
	Base case	**N/A**	**N/A**	[redacted]	0.34	0.48	[redacted]	[redacted]
	New scenarios (as discussed in the above of the current document)							
4	% of patients undergoing waning	5.2%	19.6%	[redacted]	0.27	0.37	[redacted]	[redacted]
5	% of patients undergoing waning		30%	[redacted]	0.24	0.34	[redacted]	[redacted]
	Varying the drug dosage							
6	CBD maintenance dosage	14 mg/kg/day	12 mg/kg/day	[redacted]	0.34	0.48	[redacted]	[redacted]
7	CBD maintenance dosage		13 mg/kg/day	[redacted]	0.34	0.48	[redacted]	[redacted]
8	CBD maintenance dosage		15 mg/kg/day	[redacted]	0.34	0.48	[redacted]	[redacted]
9	CBD maintenance dosage		16 mg/kg/day	[redacted]	0.34	0.48	[redacted]	[redacted]
10	FFA first cycle dosage	0.413 mg/kg/day	0.7 mg/kg/day	[redacted]	0.34	0.48	[redacted]	[redacted]
	Including drug wastage							
11	Drug wastage	No wastage	FFA: 5% CBD: 5%	[redacted]	0.34	0.48	[redacted]	[redacted]
12	Drug wastage		FFA: 5% CBD: 10%	[redacted]	0.34	0.48	[redacted]	[redacted]
13	Drug wastage		FFA: 0% CBD: 10%	[redacted]	0.34	0.48	[redacted]	[redacted]
	Varying the baseline utility for caregivers							
14	Baseline utility	0.856	0.78	[redacted]	0.35	0.49	[redacted]	[redacted]

Abbreviations: CBD w CLB, Cannabidiol with Clobazam; FFA, Fenfluramine; ICER, Incremental Cost-Effectiveness Ratio; QALYs, Quality-Adjusted Life Years; SoC, Standard of Care.

6. *Exploring uncertainty*

6.1. Probabilistic sensitivity analysis

Cost-effectiveness plane

Results from the PSA are presented in Figure 3.

The cost-effectiveness plane of FFA + SoC versus CBD w CLB + SoC shows that [redacted] of the simulations are located in the North-East quadrant where FFA + SoC is associated with higher costs but also higher QALYs; [redacted] of the simulations are located in the South-East quadrant where FFA + SoC is associated with higher QALYs, and lower costs compared to CBD + SoC.

The probabilistic mean ICER was [redacted] per QALY gained (Table 12) which is lower than the base case ICER [redacted].

Table 12. Average results from the probabilistic sensitivity analysis

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
CBD w CLB + SoC	[redacted]	-18.88	-	-	-
FFA + SoC	[redacted]	-19.31	[redacted]	0.42	[redacted]

Abbreviations: CBD w CLB, Cannabidiol with Clobazam; FFA, Fenfluramine; ICER, Incremental Cost-Effectiveness Ratio; QALYs, Quality-Adjusted Life Years; SoC, Standard of Care.

Figure 3 Cost-effectiveness plane FFA + SoC versus CBD w CLB + SoC

Abbreviations: CBD w CLB, Cannabidiol with Clobazam; FFA, Fenfluramine; QALYs, Quality-Adjusted Life Years; SoC, Standard of Care.

Cost-effectiveness acceptability curves

The results from the cost-effectiveness acceptability curve are presented in Figure 4 below. The cost-effectiveness acceptability curve (CEAC) plots the probability that the intervention is cost-effective at a range of decision thresholds. The probability of being cost-effective at a threshold of £30,000 (with severity modifier) is [redacted].

Figure 4. Cost-effectiveness acceptability curve

Abbreviations: CBD, Cannabidiol; FFA, Fenfluramine.

6.2. Deterministic sensitivity analysis

Figure 5 presents a tornado diagram showing the twenty parameters with the greatest impact on the ICER, with descending ICER sensitivity.

Figure 5: Tornado plot: deterministic sensitivity analyses: FFA + SoC versus CBD w CLB + SoC

Abbreviations: CBD w CLB, Cannabidiol with Clobazam; EQ-5D, EuroQol 5 Dimension; FFA, Fenfluramine; GTC, Generalised Tonic-Clonic; HCRU, Healthcare Resource Use; SoC, Standard of Care; T+M, Titration and Maintenance.

References

1.EMA. Epidyolex : EPAR - Product information (SmPC) 2019 [Accessed July 2023]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/epidyolex#:~:text=Epidyolex%20is%20a%20medicine%20used,also%20aged%20two%20and%20above.
2.NICE. Fenfluramine for treating seizures associated with Dravet syndrome [TA808] 2022 [Accessed July 2023]. Available from: https://www.nice.org.uk/guidance/ta808.
3.NICE. Cannabidiol with clobazam for treating seizures associated with Lennox–Gastaut syndrome - Technology appraisal guidance [TA615] [ID1308] 2019 [Accessed July 2023]. Available from: https://www.nice.org.uk/guidance/ta615.
4.Knupp KG, Scheffer IE, Ceulemans B, Sullivan JE, Nickels KC, Lagae L, et al. Efficacy and Safety of Fenfluramine for the Treatment of Seizures Associated With Lennox-Gastaut Syndrome: A Randomized Clinical Trial. JAMA Neurology. 2022;79(6):554-64.
5.UCB Pharma S.A. UCB Data on File. Study statistical analysis Study 1601 and OLE [Confidential]. 2022.
6.Thiele E, Marsh E, Mazurkiewicz-Beldzinska M, Halford JJ, Gunning B, Devinsky O, et al. Cannabidiol in patients with Lennox-Gastaut syndrome: Interim analysis of an open-label extension study. Epilepsia. 2019;60(3):419-28.
7.Gray TE, Hirsch LJ, Quraishi IH. Electronic seizure diaries for clinical care and research. Epileptic Disord. 2022;24(5):803-11.
8.SignanHealth. Signant Introduces Standardized Electronic Seizure Diary 2023 [Available from: https://www.signanthealth.com/news/signant-health-debuts-standardized-electronic-seizure-diary-developed-in-collaboration-with-the-epilepsy-study-consortium/.
9.UCB Pharma S.A. UCB Data on File. ITT analysis of OLE study. . 2024.
10.Owen RK, Bradbury N, Xin Y, Cooper N, Sutton A. MetaInsight: An interactive web-based tool for analyzing, interrogating, and visualizing network meta-analyses using R-shiny and netmeta. Research synthesis methods. 2019;10(4):569-81.
11.Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2018;391(10125):1085-96.
12.Devinsky O, Patel AD, Cross JH, Villanueva V, Wirrell EC, Privitera M, et al. Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome. N Engl J Med. 2018;378(20):1888-97.
13.Valls Carbó A, Beltrán Á, Sánchez-Miranda Román I, Cabal B, Gómez-Porro P, Aledo-Serrano Á, et al. What have we learned from the real-world efficacy of FFA in DS and LGS? A post-marketing study in clinical practice. Epilepsy & Behavior. 2024;151.
14.UCB Pharma S.A. UCB Data on File. Medical & HTA Advisory board of UK experts on May 17th 2023 [Confidential]. 2023.
15.Kühne F, Becker LL, Bast T, Bertsche A, Borggraefe I, Boßelmann CM, et al. Real-world data on cannabidiol treatment of various epilepsy subtypes: A retrospective, multicenter study. Epilepsia Open. 2023;8(2):360-70.
16.Auvin S, Damera V, Martin M, Holland R, Simontacchi K, Saich A. The impact of seizure frequency on quality of life in patients with Lennox-Gastaut syndrome or Dravet syndrome. Epilepsy & Behavior. 2021;123:108239.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Fenfluramine hydrochloride for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

UCB addendum to responses to Draft Guidance

February 2024

File name	Version	Contains confidential information	Date
ID1651_Fenfluramine_LGS_ Addendum to draft guidance responses [Redacted]	1.0	Yes	29th February 2024

1. ***Additional figure: figure based on the LOCF analysis conducted for fenfluramine as part of the response to draft guidance.***

Figure 1 LOCF analysis conducted for fenfluramine OLE study

2. ***EAG clarification***

In this section, UCB provides an overview of the changes in the model since the company's base-case submission on September 21st 2023, as well as a detailed description of how individual changes were implemented in the economic model.

Table 1 List of model changes and step by step cumulative impact on ICER.

Category	Parameter	UCB's Original Base Case	UCB's New Base Case	Excel cells modified	ICER (cost per QALY)	ICER with Severity modifier
Original Base Case ICER submitted on 21/09/2023:					[redacted]	[redacted]
Severity modifier options	Severity modifier	Applied to: Patients & Caregivers	Applied to: Patients Only	Results!K11	[redacted]	[redacted]
CBD dosage	CBD dosage distribution - OLE period (proportion on 20 g/kg/d)	60% (OLE CBD dose =16mg/kg/day)	40% (OLE CBD dose =14mg/kg/day)	'Model Settings'!F54	[redacted]	[redacted]
Stopping Rule Options	Stopping rule approach and frequency	- Discontinue if <25% response - 3 months	- Discontinue if <30% response - 6 months - 20.7% patients in state 1 with <30% response	'Model Settings'!F68 'Model Settings'!F70 'Model Settings'!J68	[redacted]	[redacted]

Category	Parameter	UCB's Original Base Case	UCB's New Base Case	Excel cells modified	ICER (cost per QALY)	ICER with Severity modifier
Caregiver Utility Source Options	Caregiver Utility Source	Verdian et al. (2008) - EQ-5D	Caregiver disutility Lo et al. (2021)	'Model Settings'!F82	[redacted]	[redacted]
Caregiver Utility Inputs	Number of caregivers for institutionalised patients	1.8	0.7	'Caregiver Utility Inputs'!B69	[redacted]	[redacted]
Cost Options	Institutionalization costs	Excluded	Included	'Model Settings'!F121	[redacted]	[redacted]
Waning Options	Deteriorating transition probabilities based on:	Deteriorating patients	All patients	'Transition prob - data'!BG40	[redacted]	[redacted]

Category	Parameter	UCB's Original Base Case	UCB's New Base Case	Excel cells modified	ICER (cost per QALY)	ICER with Severity modifier
Stopping Rule Methods (detailed description can be found below)	Stopping rule: discontinuation due to lack of efficacy	6 months stopping rule leading all unresponsive patients to discontinue every other cycle	6 months stopping rule applied every cycle to the estimate number of patients that have not responded to treatment for 6 months - 61.2% patients remaining in state 0 - 37.9% patients remaining in state 1	Calculations: 'Markov Trace (SoC)'!W13:W402 'Markov Trace (FFA)'!W13:W402 'Markov Trace (CBD)'!W13:W402 Input cells: 'Model Settings'!J70 'Model Settings'!J72	[redacted]	[redacted]
Efficacy data for the OLE period (cycles 2-5) (detailed description	FFA + SoC efficacy	**Cycles 2-5:** TPs based on Study 1601 OLE **Cycles 6-9:** TPs assumed to equal TPs	**Cycles 2-5:** State occupancies derived from NMA results of OLE studies **Cycles 6-9:** State occupancies assumed to equal those observed in cycle 5	'Transition prob - data'!U23:X27 'Calc - TP - FFA'!E16:H366	[redacted]	[redacted]

Category	Parameter	UCB's Original Base Case	UCB's New Base Case	Excel cells modified	ICER (cost per QALY)	ICER with Severity modifier
can be found below)		observed in cycle 4-5				
	CBD + CLB + SoC efficacy	**Cycles 2-5:** State occupancy based on CBD + CLB + SoC trial OLE **Cycles 6-9:** Assumed no change in state occupancy (except discontinuation and death)	**Cycles 2-5:** State occupancies derived from NMA results of OLE studies **Cycles 6-9:** State occupancies assumed to equal those observed in cycle 5	'Transition prob - data'!U14:X18 'Calc - TP - CBD'!E16:H366		
New Base Case ICER submitted on 21/02/2024:					[redacted]	[redacted]

Abbreviations: CBD= Cannabidiol; CLB=Clobazam; FFA= Fenfluramine; NMA= Network Meta-Analysis ; OLE= Open-Label Extension; SoC= Standard of care; QALYs, Quality-Adjusted Life Years; TP= Transition Probabilities

2.1 Stopping Rule Methods

The stopping rule calculation method was modified to address the EAG comment supported by the committee. The rational and methods used are explained in the response document. The cells that were modified in the model were 'Markov Trace (SoC)'!W13:W402, 'Markov Trace (FFA)'!W13:W402, and 'Markov Trace (CBD)'!W13:W402. Additional input cells were created in the model settings sheet (cells 'Model Settings'!J70 and 'Model Settings'!J72, see **Figure 2**) to allow for transparency in the additional data required for this approach. The new inputs represent the proportion of patients remaining in health state 0 and health state 1 for more than 1 cycle, and data from FFA transition probabilities reported in Study 1601 OLE was used to inform these parameters. The data can be found in cells 'Transition prob - data'!K13:O35, as shown in **Figure 2** and **Figure 4**.

Figure 2 Screenshot of the Stopping rule options in the "Model Settings" sheet

Figure 3 Screenshot of the model's transition probabilities sheet

Figure 4 Screenshot of the FFA transition probabilities table in the model

The proportion of patients remaining in health state 0 was determined as the average of [redacted], [redacted], [redacted], and [redacted] (cells highlighted in yellow in the figures above). The proportion of patients remaining in health state 1 was determined as the average of [redacted], [redacted], [redacted], and [redacted] (cells highlighted in orange in the figures above).

2.2 Efficacy data for the OLE period (cycles 2-5): An indirect treatment comparison

As is described in the response document, UCB noted the uncertainty that is associated with directly comparing the results from FFA's OLE trial with that of CBD and has therefore explored a statistically robust and widely recognised method to compare the trials via an indirect treatment comparison analysis. The result of the ITC can be seen in **Table 2**.

Table 2 Summary of efficacy results comparing FFA and CBD with placebo, fixed effects, all time points

	Treatment Arm	
Health State	**RR FFA versus Placebo (95% CrI)**	**RR CBD versus Placebo (95% CrI)**
Timepoint: After 3 months in OLE study (weeks 1-12)		
>= 25% response	[redacted]	[redacted]
>= 50% response	[redacted]	[redacted]
>= 75% response	[redacted]	[redacted]
Timepoint: After 6 months in OLE study (weeks 13-24)		
>= 25% response	[redacted]	[redacted]
>= 50% response	[redacted]	[redacted]
>= 75% response	[redacted]	[redacted]
Timepoint: After 9 months in OLE study (weeks 25-36)		
>= 25% response	[redacted]	[redacted]
>= 50% response	[redacted]	[redacted]
>= 75% response	[redacted]	[redacted]
Timepoint: After 12 months in OLE study (weeks 37-48)		
>= 25% response	[redacted]	[redacted]
>= 50% response	[redacted]	[redacted]
>= 75% response	[redacted]	[redacted]

Abbreviations: CBD= Cannabidiol; CrI= Credible Interval; FFA= Fenfluramine; OLE= Open-Label Extension; RR= Risk Ratio

The data resulting from the analysis has been implemented in the model and can be found in cells 'Transition prob - data'!B94:R147 (see **Figure 5**).

Figure 5 Screenshot of the model's transition probabilities sheet focused on the OLE NMA data and calculation of state occupancies

In these cells the results of the ITC analysis are transformed into the state occupancies for both CBD and FFA required to inform treatment efficacy for the OLE period (cycles 2-5). The calculated state occupancies are then used in cells 'Transition prob - data'!U23:X27 for FFA and 'Transition prob - data'!U14:X18 for CBD which link to the "Calc – TP" sheets of each comparator arm. In the "Calc – TP" sheets modifications were made to cells 'Calc - TP - FFA'!E16:H366 and 'Calc - TP - CBD'!E16:H366 (see **Figure 6** and **Figure 7**) to allow the model to use the new data, particularly in the FFA arm where the previous version of the model used transition probabilities and not state occupancy data. FFA's transition probability data is still available in the model since it is used to determine deteriorating transition probabilities applied during the waning of efficacy period (cycles 10+) to both FFA and CBD treatment arms.

Figure 6 Screenshot of the model's 'Calc - TP - FFA' sheet

Figure 7 Screenshot of the model's 'Calc - TP - CBD' sheet

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Fenfluramine hydrochloride for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

UCB addendum to responses to Draft Guidance

March 2024

File name	Version	Contains confidential information	Date
ID1651_Fenfluramine_LGS_ Second Addendum to draft guidance responses [Redacted]	1.0	Yes	4th March 2024

1. Clarification statement

At the request of the NICE the committee D chair UCB have provided a scenario comparing against standard of care (SoC), which is not the most appropriate comparator and therefore deemed innapropriate. Using SoC as a comparator is also against the proposed positioning of Fenfluaramine in Lennox-Gastuat syndrome as a third-line add-on therapy, in line with the positioning of cannabidiol plus clobazam (TA615).

In the appraisal consultation document (ACD) section 3.3. it is stated '*The committee concluded that the positioning of fenfluramine plus SoC in the treatment pathway in line with cannabidiol plus clobazam plus SoC was appropriate'* and UCB highlight this should continue to be the core comparison against FFA + SoC.

2. Additional reasons highlighting the uncertainty of viewing SoC alone as a comparator

Long-term assumptions for the SoC treatment arm

Data for the SoC alone arm is only available for cycle 1 (0-3 months) via the registrational trial. The efficacy for the SoC in the model was extracted from the SoC + placebo arm of the fenfluramine trial. The model assumed patients would stay at their respective state at T+M for the rest of the time-horizon with potential for discontinuation or death. Therefore, all data beyond cycle 1 is based on assumptions.

Following the committees request, the treatment arm (FFA + SoC) that SoC is now being compared to is based on the ITT population state occupancies based on LOCF analysis. This is different to the assumptions being made for the SoC treatment arm, which are not based on LOCF, and are instead state occupancies as observed from the registrational trial and maintained for the remainder of the cycles, whilst assuming that all costs, the number of concomitant SoC medications and management costs remain consistent – this is highly unlikely to reflect practice, however there is no long-term data to support alternative, more likely, assumptions.

Heterogeneity in the treatment of LGS

In clinical practice, we expect patients to be much more stable in their response to maintained FFA treatment, where efficacy increases as per OLE data. However, when considering SoC, it is known that patients fluctuate in their response to treatment and therefore it is difficult to model this alongside cost without any definitive real-world data for this rare disease.

We understand from numerous consultant neurologists throughout the UK that LGS is highly heterogenous to treat, resulting in various levels of the number of SoC drugs being taken, with varying levels of cost and efficacy. The low treatment costs combined with the low QALY gains from the SoC treatment arm make cost-effectiveness analysis much more sensitive to assumptions, particularly as we do not have long-term data (beyond 3 months).

To highlight the modelling uncertainty that exists when comparing to SoC alone, UCB have provided an additional scenario, where the assumption on how many patients remain uncontrolled with SoC increases. As per scenario analysis presented (scenario 1) below, all patients on the SoC alone treatment arm are assumed to move to State 0 from cycle 2 onwards, reflecting a scenario where all patients are uncontrolled on current SoC. This is a scenario which is commonplace in clinical practice.

Combined with changes to the number of SoC regimens patients are on, varying levels of costs associated with these (both directly due to treatment and indirectly due to other management costs) comparing to SoC alone is much more uncertain versus comparing to CBD plus CLB + SoC.

The proportion of patients that are unsuitable for CBD plus CLB + SoC alone, as well as the proportions of patients who have discontinued CBD plus CLB + SoC alone is also highly variable.

3. *UCB's closing remarks for comparing to SoC alone*

Treating LGS patients with SoC alone results in patients remaining uncontrolled. As a result, clinicians consider adding a third-line treatment option to SoC, which is CBD plus CLB or FFA.

Large heterogeneity in the treatment of LGS exist, and the uncertainties raised when comparing to SoC alone were also raised within FFA's appraisal for Dravet Syndrome (DS) in TA808, where FFA is broadly "recommended as an add-on to other antiseizure medicines".

CBD + CLB + SoC is the only treatment arm providing robust data when comparing to FFA + SoC. A recommendation of FFA, in-line with CBD, would enable equality of access for all patients, the majority of which are children, that experience continued risk of further disability and death.

4. *Cost-Effectiveness Results versus SoC – complementary analysis*

Complementary results for the cost-effectiveness of fenfluramine + SoC compared with SoC are presented in **Table 1**.

Compared to SoC, fenfluramine has resulted in an incremental gain of 0.80 QALYs and incremental cost of [redacted], yielding an ICER of [redacted] (**Table 1**). However, when the x1.7 severity modifier is applied as a QALY weight (patients only), the resulting ICER is [redacted] (**Table 2**).

Table 1. Complementary results: FFA + SoC versus SoC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER incremental (£/QALY)
SoC	[redacted]	20.19	-19.64	-	-	-	-
FFA + SoC	[redacted]	20.37	-18.84	[redacted]	0.18	0.80	[redacted]

Abbreviations: FFA, Fenfluramine; ICER, Incremental Cost-Effectiveness Ratio; Incr., Incremental; LYG, Life Years Gained; QALYs, Quality-Adjusted Life Years; SoC, Standard of Care.

Table 2. Complementary results with severity modifier applied: FFA + SoC versus SoC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER incremental (£/QALY)
SoC	[redacted]	20.19	-19.20	-	-	-	-
FFA + SoC	[redacted]	20.37	-18.07	[redacted]	0.18	1.13	[redacted]

Abbreviations: FFA, Fenfluramine; ICER, Incremental Cost-Effectiveness Ratio; Incr., Incremental; LYG, Life Years Gained; QALYs, Quality-Adjusted Life Years; SoC, Standard of Care.

5. Scenario Analysis

UCB has implemented a scenario analysis exploring the uncertainty around the efficacy of SoC treatment. In the scenario it is considered that all patients will be inadequately controlled by SoC alone after a 3 months period when considered for FFA. To simulate this scenario, a discontinuation rate of 100% was include in the SoC arm in the model. The results of this scenario can be seen in **Table 3**. The resulting ICER considering the severity modifier (patients only) is [redacted] per QALY gained.

Table 3 Summary of the scenario analysis explored and comparison to the complementary analysis: FFA + SoC versus SoC

Scenario no.	Parameter	Complementary analysis	Scenario analyses	FFA+SoC versus SoC			ICER	ICER (severity modifier applied to patients only)
				Incremental costs	Incremental QALYs	Incremental QALYs (with severity modifier)		
	-	N/A	N/A	[redacted]	0.80	1.13	[redacted]	[redacted]
	New scenarios (as discussed in the above of the current document)							
1	Discontinuation rate	0.0% Cycle 2 Stopping rule (<30% response, 6 months)	100% Cycles 2-393 No Stopping rule	[redacted]	1.16	1.58	[redacted]	[redacted]

Abbreviations: FFA, Fenfluramine; ICER, Incremental Cost-Effectiveness Ratio; QALYs, Quality-Adjusted Life Years; SoC, Standard of Care.

NICE National Institute for Health and Care Excellence

Fenfluramine for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 February 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected chaTracteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Tuberous Sclerosis Association

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Fenfluramine for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 February 2024. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	None
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We believe that NICE Appraisal Committee has overlooked the following key areas that are extremely important to people living with Lennox Gastaut Syndrome (LGS) and their family and carers:

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Fenfluramine for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 February 2024. Please submit via NICE Docs.

	(1) **The massive positive impact on quality of life that seizure reduction can have on people living with LGS**. Seizures are a frightening experience for all involved but more so for children. Affected children are often too young to understand what is happening to them and young siblings won't understand either which means they often become very distressed seeing their family member having a seizure. We also know that people with epilepsy often find that over time they have to take larger and larger doses of their seizure medicine to achieve the same result or try up to 20 different antiepileptic drugs as the effectiveness of medication tends to wear off over time (often referred to as the "honeymoon period"). Those patients who gradually develop tolerance to the more standard antiepileptic drugs present a more difficult problem. This group, in particular, would benefit from a new treatment like fenfluramine as an additional option. (2) **The role of seizure reduction in care responsibilities and challenges**. Care for people with epilepsy (which is often at least two-to-one) can lead to secondary challenges in employment, financial security, social interactions and the wider family unit (such as the impact on siblings). Seizure reduction can play a major part in making these challenges easier. The occurrence of a seizure is very unpredictable therefore families often organise their lives around the possibility that their child could have a seizure at any time. Family outings and get togethers, childcare, school trips and any activities that children would usually take part in take careful planning and organisation. Often, parents feel unable to leave their child with anyone but trained professionals, meaning usual family childcare arrangements may be impossible. Finding the right type of care for a child with difficulties such as these may be extremely challenging, and expensive. The carers of those living with epilepsy also experience a significant impact on their physical and mental health due to caring for someone with the condition. Care for people with LGS that is two-to-one does not therefore demonstrate a reduced burden on the two carers compared to if it was a single carer. In a family unit, two-to-one care often leads to massive secondary care challenges in employment, financial security, social interactions and the wider family unit such as the impact on siblings as the focus of both parents becomes wholly on the person with LGS. Seizure reduction can play a major part in making these challenges easier for all carers. If seizures can be reduced in frequency and severity, carers can begin to rebuild their own lives and thereby improve the lives of entire family units. Caregivers have shared with us how reduced or controlled seizures will impact their lives as carers: *"It would quite simply improve my mental and physical well-being. Seizure control (or a lack of it) is a constant worry and something we as parents carry with us always. As our daughter can have seizures at any time of day and has them on a daily basis, it is something that is always on the back of our mind, as well as that of her younger sister who is only 7 and has been able to identify them since a young age."*

Please return to: **NICE DOCS**

Fenfluramine for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 February 2024. Please submit via NICE Docs.

	"If our son was having less seizures then I might be able to get better sleep at night and my husband and I could also have a better quality of life. I sleep with a baby monitor on my bedside table and are up at least 2 or 3 times a night with him fitting - he is 18 but I am 58. If he had less seizures in the day, he wouldn't sleep as much so he would sleep better at night." *"For me personally it would mean I could take him out on my own without feeling too afraid he was going to have a seizure out. He is a big lad now and I'm 65 so keeping him safe is difficult, less seizures means less difficulties for me (and injuries). We could take holidays abroad without the worry."* *"As a parent and carer, a reduction in seizures is everything. To watch my son have seizures every day is not only heart-breaking, it's tiring. It's as if normal family life goes on hold for periods of time when seizures decide to increase, change pattern or appearance. Sleeping with an eye open is difficult and obviously puts a stain on most things that I can think of."* *"I live in constant fear of my son having a seizure which requires hospitalisation, and also of SUDEP. Improved seizure control would he alleviate the risks. I currently work, but if his epilepsy doesn't improve, I may have to stop working. I receive ad hoc support from NHS to deal with the mental toll his epilepsy has on me - anti anxiety medication, counselling etc. It adversely affects the whole family."* *"I could work, sleep at night, not have to tap into expensive social care respite services, have less ineffective epilepsy medications, less NHS appointment and basically save the government money."* *"I have watched uncontrolled epilepsy rob my child of the life she was leading. To see improvements would bring a joy to my heart and decrease the pain and stress we live with everyday watching our daughter and the regression that is occurring due to this horrendous condition. Achieving decreased seizures would improve her cognitive ability - fewer seizures, less recovery time, less sleeping. Increase confidence. Ability to interact more with peers. Improve ability to follow academic studies-the list is endless."* *"Wouldn't be as anxious and on edge watching him waiting for another one to happen."* *"A weight off our minds. Relief for a brighter future. Normality"*
2	We would also like to draw your attention to an additional piece of evidence which supports the draft proposal to fund Fenfluramine for LGS-related epilepsy in England. Research published by Public Health England (PHE) in 2018 has found that the number of annual deaths of epilepsy patients has increased by 70 per cent between 2001 to 2014. Deaths occur on average eight years earlier than those for the rest of the population. With the right treatment, over 60% of people with epilepsy could stop having seizures altogether. Of all the neurological conditions studied by PHE only epilepsy was found to have a significant relationship with deprivation, with 13 deaths per 100,000 population in the most deprived areas compared to five deaths per 100,000 in the least deprived. (Summary from HSJ article on 19 March 2018). Access to Fenfluramine would

NICE National Institute for Health and Care Excellence

Fenfluramine for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 February 2024. Please submit via NICE Docs.

	have the potential to further reduce the number of annual deaths related to epilepsy in England

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Fenfluramine for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 February 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Jazz Pharmaceuticals

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Fenfluramine for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 February 2024. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No direct or indirect links to, or funding from, the tobacco industry.
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Section 1 - Why the committee made these recommendations:** *"People with LGS are offered a range of antiseizure medicines that collectively make up standard care. If this does not control their seizures, other treatments can be introduced, including cannabidiol plus clobazam."* The above statement is factually incorrect as it asserts that cannabidiol plus clobazam is not standard care.

Please return to: **NICE DOCS**

Fenfluramine for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 February 2024. Please submit via NICE Docs.

	For the purpose of the economic modelling, UCB made a distinction between standard care (only) and standard care plus cannabidiol plus clobazam. This does not reflect clinical practice where standard care includes cannabidiol plus clobazam, a treatment that has been reimbursed in Lennox-Gastaut Syndrome (LGS) since 2019 (TA615). Note also that this is outlined in the final scope agreed by NICE and UCB on page 17 of the company submission (Table 1. The decision problem) which refers to established clinical management as *'antiseizure medications, including but not limited to: cannabidiol with clobazam, sodium valproate, lamotrigine, rufinamide, topiramate, felbamate, clobazam, levetiracetam.'*
2	**Section 1 - Why the committee made these recommendations:** *"But, an indirect comparison suggested that fenfluramine may be more effective than cannabidiol plus clobazam in reducing the number of drop seizures"* The results generated by indirect treatment comparisons should be approached with caution as studies will be set up differently with differing protocols and inclusion criteria resulting in different enrolled patient demographics. As a result, the findings of indirect treatment comparisons cannot definitively show statistically significant differences between medicines and could introduce an element of bias. , especially if not controlling for treatment effect modifiers or prognostic factors as in this case. Furthermore, in this instance, only three studies were used to inform the network diagram which could lead to a high level of uncertainty due to the small number of studies included in the comparison. Consequently, caution should be exerted when making claims around one medicine being more effective than another, based on an indirect treatment comparison. We request that the phrase ***"(not statistically significant)"*** be added to the end of the above statement for clarity.
3	**Section 3.2:** *"The NICE guideline on epilepsies in children, young people and adults (from here referred to as NG217) recommends offering sodium valproate first."* The above statement is factually inaccurate. The recommendation in NG217 states "***Consider*** *sodium valproate as first-line treatment for people with Lennox–Gastaut syndrome."* Similarly for all other statements of this nature within Section 3.2, the recommendations are ***'to consider'*** these treatments at their respective lines of treatment. The omission of 'consider' from these statements incorrectly asserts that there is a defined order of treatment however this is not the case. Due to the highly individualised nature of LGS and patient response to treatment, combined with the new NICE initiative to ensure that STA guidance is incorporate into NICE guidelines, it is essential to ensure correct wording and we request that the guidance and guidelines reflect each other, to avoid any confusion in clinical practice that may pose a barrier to patient access.
4	**Section 3.2:** *"For example, some people cannot have cannabidiol plus clobazam because of drug–drug interactions"* We request that this sentence be removed. The majority, if not all, medicines hold the potential for drug-drug interactions, but this statement incorrectly asserts that the effect is specific to cannabidiol plus clobazam. Taken out of context, the statement holds potential to introduce bias against cannabidiol plus clobazam.
5	**Section 3.5:**

Please return to: **NICE DOCS**

Fenfluramine for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 February 2024. Please submit via NICE Docs.

	"The company's base case NMA results suggested that fenfluramine plus SC is superior to placebo plus SC and cannabidiol plus clobazam plus SC for all outcomes assessed, except the 75% or more reduction in DSF" The findings of indirect treatment comparisons (ITC) cannot definitively show statistically significant differences between medicines and could introduce an element of bias. The results generated by indirect treatment comparisons should be approached with caution as studies will be set up differently with differing protocols and inclusion criteria resulting in different enrolled patient demographics. Furthermore, in this instance, only three studies were used to inform the network diagram which could lead to a high level of uncertainty due to the small number of studies included in the comparison. Consequently, caution should be exerted when making claims around one medicine being more effective than another, based on an indirect treatment comparison. We request that the phrase ***"(not statistically significant)"*** be added to the end of the above statement for clarity.
6	**Section 3.11:** "*The company stated that the data suggested that the treatment effect of fenfluramine is sustained and increases, based on increasing percentages of people showing improvement in DSF reduction over time. Whereas cannabidiol's efficacy plateaus with state occupancy remaining fixed for almost 6 months (from month 6 to 12 of the cannabidiol OLE)."* As written, this is factually incorrect, as this statement does not clarify that this is only with respect to the economic model. We request that this is rewritten to remove the statement "*cannabidiol's efficacy plateaus" a*nd to clarify that the assumptions here are modelled and not based on clinical data about the long-term efficacy of cannabidiol plus clobazam. It is important that NICE distinguishes between modelled data and published clinical trial data.
7	**Section 3.11:** *"For fenfluramine plus SC, the company assumed that the transition probabilities for cycle 6 to cycle 9 in the model equalled the transition probabilities of cycle 4 to 5, which were based on the last 3 months of the Study 1601 OLE."* We query the appropriateness of using the final 3 months of the Study 1601 OLE given that patients within the trial were able to add additional concomitant treatments at this stage. As such, any added treatment efficacy at this timepoint may not be solely attributable to fenfluramine. Given this, we agree with the committee's request for an analysis that accounts for missing data points in the Study 1601. OLE data, as this is needed to inform the treatment effect for fenfluramine plus SC for cycle 6 to cycle 9, and an analysis on the treatment effect assumptions for cycle 6 to cycle 9 based on the conclusions of the imputation analyses requested by the committee. Further, we note that within the OLE phase of Study 1601, cannabidiol was a concomitant medication in 4.9% (n=12) of the patients at baseline, and that cannabidiol was the most common treatment addition after 6 months, with a further 10 patients starting cannabidiol during the study (Knupp et al, 2023). Has this evidence been accounted for when considering the treatment effects of fenfluramine compared with the comparators within the indirect treatment comparison and the economic model?

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Fenfluramine for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 February 2024. Please submit via NICE Docs.

8	**Section 3.15 fenfluramine maintenance dose:** We agree with the committee recommendation for a scenario in which the dose in cycle 1 of the model reflects the mean dose in the 0.7 mg/kg/day fenfluramine arm in Study 1601. The company's cost effectiveness model did not adjust for the lower dose used in cycle 1, where the indirect treatment comparison estimates are used to support the anticipated efficacy of treatment. The company assume that throughout future cycles the efficacy from the 0.4 mg/kg/day dose is equal to the 0.7 mg/kg/day dose without data to support this assumption. Therefore, we agree with the committee recommendations to provide a scenario using the 0.7 mg/kg/day dose in cycle 1 of the model, as this additional evidence is highly relevant for the decision making. It is thus important that this evidence is considered when reviewing the efficacy and safety of fenfluramine within the context of the model.
9	**Section 3.16 cannabidiol maintenance dose:** *"The SPC for cannabidiol states that the dosage can be increased from a maintenance dosage of 10 mg/kg/day to 20 mg/kg/day. In its initial model, the company implemented a base case maintenance dosage for cannabidiol of 14 mg/kg/day. This was based on real-world use of cannabidiol for Dravet syndrome (Silvennoinen 2021) and expert opinion stating that the dosage is not expected to exceed 14 mg/kg/day. But, at the clarification stage, the company increased the base case cannabidiol dosage to 16 mg/kg/day. The company considered that 16 mg/kg/day is conservative based on UK expert clinical opinion and the cannabidiol OLE study"* We agree with the EAG approach to using the dosage for cannabidiol plus clobazam in LGS as previously assessed by NICE (TA615).
10	**Section 3.16 cannabidiol maintenance dose:** *"They added that cannabidiol is an oily substance and is provided in a glass bottle. So there can be wastage due to the glass bottle breaking or some cannabidiol being leftover in the bottle. They also noted that there may be less wastage of fenfluramine in practice"* With regards the comments about wastage made by the committee, that cannabidiol plus clobazam is likely to result in more wastage than fenfluramine, we note the similarities between the two products, outlined in the SPCs, Section 6.5 Nature and contents of container: Fenfluramine https://www.medicines.org.uk/emc/product/11998/smpc#gref • presented in a white High Density Polyethylene (HDPE) bottle with a child-resistant, tamper-evident cap packaged in a carton, a Low Density Polyethylene (LDPE) press-in bottle adaptor, and Polypropylene (PP)/HDPE oral syringes. The oral syringe included in the pack should be used to administer the prescribed dose. Epidyolex https://www.medicines.org.uk/emc/product/10781/smpc#gref • Amber glass bottle (type III) with a child-resistant and tamper-evident screw cap (polypropylene). The bottle is packaged in a carton with two 5 ml and two 1 ml calibrated oral dosing syringes (plunger HDPE and barrel polypropylene) and two bottle adaptors (LDPE). The 5 ml syringes are graduated in 0.1 ml increments and the 1 ml syringes are graduated in 0.05 ml increments. Both cannabidiol and fenfluramine are oral solutions, provided in bottles and with bottle adapters, both use syringes for administration, and both use a mg/kg/day dosing, thus it is unlikely that there will be any difference in wastage between the two drugs. Glass is a strong, non-reactive material, meaning that it will not leak any matter into the liquid within any glass container. This feature is of course especially important for pharmaceuticals, as

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Fenfluramine for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 February 2024. Please submit via NICE Docs.

	medicines are comprised of delicate balances of elements to create the correct mixture that will treat the patient. We acknowledge the comments made by the clinical expert in the committee meeting about bottle breakage, however this appears to be an isolated incident. As the manufacturer of cannabidiol, we have queried this with our wholesaler, but they did not report any product complaints or issues with wastage nor breakage.
11	**Section 3.16 Cannabidiol maintenance dose:** *"The company considered that 16 mg/kg/day is conservative based on UK expert clinical opinion and the cannabidiol OLE study. The mean modal dosage within the cannabidiol OLE was 24 mg/kg/day. It acknowledged that in clinical practice some people have 10 to 12 mg/kg/day, but stated that adequate reductions in DSF are rarely seen at lower cannabidiol dosages"* This statement is factually incorrect, and we request that it is removed. Published evidence from randomised controlled trials in LGS (GWPCARE3 and GWPCARE4) demonstrated that Epidyolex provides a statistically significant reduction in the number of drop and non-drop seizures at doses at a dose of 10 mg/kg/day. This efficacy is acknowledged in NICE TA615, page 4: "*Clinical trials show that cannabidiol reduces the number of drop and non-drop seizures when compared with usual care*".

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Fenfluramine for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 February 2024. Please submit via NICE Docs.

comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Fenfluramine for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 February 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[Insert organisation name]

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Fenfluramine for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 February 2024. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	I have spoken at educational fora for Zogenix, UCB and Jazz Pharmaceuticals for which honoraria have been paid to my department All have ceased
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[Insert name]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Lennox Gastaut syndrome is complex developmental and epileptic encephalopathy; an epilepsy with many underlying causes, associated with long term ongoing seizures, severe learning difficulties and behaviour disorder. Standard treatments provide long term seizure control in about 0.7%.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Fenfluramine for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 February 2024. Please submit via NICE Docs.

2	All available data from clinical trials that I am aware of has been taken into account. This said there are many assumptions for the economic modelling without core data. For example percent in residential care is indicated as 10% by 18 years, but this percent would be presumed to increase as time goes on and carers become older with their own health problems as those with LGS proceed into later adulthood.
3	There is further analysis and data that is requested. It would be presumed for it to be important for such data to be considered if available. Interestingly there is a statement on page 10 'The committee concluded that the company's base case NMA suggests that fenfluramine plus SC demonstrates superior efficacy to cannabidiol plus clobazam plus SC and SC alone for the outcomes: • median percentage reduction in frequency of GTC seizures • reductions in DSF of: − 25% or more and − 50% or more. But, fenfluramine did not demonstrate superior efficacy for the 75% or more reduction in DSF outcome. Taking into consideration the uncertainties about the economic modelling, and the request for further data, it would seem appropriate to acquire this and re-examine prior to final decisions.
4	In the light of the degree of uncertainties, and lack of effective therapies in this group of individuals, the current recommendations would not appear sound.
5	People with LGS are a complex group. All have moderate to severe learning difficulties (contrasting with the statement 'may' have learning difficulties as stated on page 31), with ongoing seizures that put them at risk of injury and death. The majority are resistant to standard antiseizure medication. Many of those included in the fenfluramine trials will already have been trialled on standard medication, and likely many cannabidiol with clobazam prior to entry into the studies. Further, many would be excluded from trial of cannabidiol with clobazam because of previous adverse reaction (behavioural) to clobazam (not currently mentioned on page 6). Acknowledging the need for regular echocardiogram which may be difficult for some individuals, fenfluramine provides a realistic option to improvement in seizure frequency in this group. Unavailability through the NHS would be regarded as inequality in optimised care compared to other countries internationally, maybe even within the UK.
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Fenfluramine for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 February 2024. Please submit via NICE Docs.

- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Fenfluramine for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 February 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Fenfluramine for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 February 2024. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Nil
NIPlease disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
Name of commentator person completing form:	Lisa Suchet

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	As a carer of potential recipient of this drug I would say that this drug may well be a future consideration for us. Sodium Valproate luckily stopped our son's drop seizures, but he is now on 5 meds and none of them fully control his seizures. Given he only eats homous I suspect also he effectively keeps himself in ketosis (he was brought up on the ketogenic diet for 18months as a

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Fenfluramine for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 February 2024. Please submit via NICE Docs.

	baby). If our son's seizures get worse, and certainly if the drop seizures returned, having Fenfluramine as an add on would potentially be a very helpful option. It could also be helpful to other patients where side effects and toxicity are barriers to the other AEDs currently available. For example, we never tried Topiramate due to risks of side effects impacting speech for example, which we have spent years trying to improve with therapy. Plus any drug which doesn't cause depression/suicidal thoughts as a side effect (as many antiepileptic drugs do) is going to be a plus.
2	I would absolutely attest that carer burden is not mild to moderate - it is severe. My partner and I have very little semblance of a normal life compounded by regular broken nights. We cannot go to busy places (shops/cafes); we cannot be involved with family or social gatherings; we cannot spend the whole day out as a family of four. Physically our son can do almost nothing for himself (washing, dressing, getting a drink etc).
3	Carer burden is absolutely sensitive to seizure change. Between seizures life can carry on fairly normally (e.g. pottering around the house). Seizures mean everything stops: the seizure has to be managed (e.g. our son is made safe from falling, constantly checked for medical severity, comforted until it has passed) and then he is supported to recover, this could mean sitting in a dark room for an hour or managing meltdowns (crying, screaming, kicking, throwing).
4	Carer impact upon patient death I would surmise to be pretty immense: • loss of child / grief • reiteration of the loss of all original hopes for the child • a sense you failed them by bringing them into the world with a disease • a sense you failed them by not being able to cure them or give them a better life • a loss of identity for yourself • years worth of lost earnings and professional advancement due to caring responsibilities • PTSD (a friend whose disabled child died had to have therapy for this) • Fear in trying to re-find your purpose in life and figuring out what next
5	Carer hours being reduced to 0.7 when patient is in a residential home due to visits home - but they will still be cared for at home during those visits. My son would demand and require the same number of carer hours in any and every setting. It cannot be reduced by location. Simply the person or people doing the caring changes identity. The number of hours would absolutely remain the same. Our son demands and requires 1:1 care wherever he goes, whether it is provided or not!
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Fenfluramine for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 21 February 2024. Please submit via NICE Docs.

- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

Rhys Thomas – NICE Fenfluramine comments

Has all of the relevant evidence been taken into account?

There are no head to head data of cannabidiol plus clobazam v fenfluramine. This is always the case when anti seizure medication (ASM) is trialled, and evaluated by NICE. Because the regulators do not demand this evidence, it is not created. Trial designs however and outcome measures are broadly similar, because the regulators demand similar outcome measures. This allows an imperfect measure of drug v drug – taking in to account relevant features of the trial design such as the population studied and the placebo response.

There are no ASMs with clinically meaningful age, sex, or ethnicity treatment effects.

How well does fenfluramine work in the long term?
Thankfully people who take medication for their epilepsy do not need dose increases over time, or changes in their medication because it becomes less efficacious over time. Instead, early efficacy with ASMs predicts late efficacy. The patient expert quite rightly points out that drugs can appear to have a 'honeymoon' effect, with medicines seeming to lose their efficacy over time. This is best accounted for by placebo effect and return to the mean than any pharmacokinetic/ pharmacodynamic effect.

We have no data to suggest that this is not the case with fenfluramine. Indeed we have evidence to suggest that there is good long term efficacy, perhaps even that the late efficacy is better than the early efficacy. This is best evidenced in the open label extension study (Knupp et al. Epilepsia 2023). In addition clinical experience in the UK prescribing fenfluramine for Dravet syndrome supports these data.

There are a number of uncertainties in the economic model. This is commonly the case. The assumptions tend to be conservative as it hard, for example, to quantity the social benefits of improved sleep quality for parents and carers, or the wider economic benefits to the health system such as fewer unscheduled care visits (ambulances, emergency departments and intensive care support). I understand that the committee downgraded the carer QALYs from the model, but this does not reflect my experience of speaking to the parents and carers of people looking after loved ones with LGS.

When discussing treatment options (3.2) it must be noted that ketogenic diet support for adults in the UK is very hard to access, almost non-existent. This is a non-sedating treatment strategy for people with LGS. The need for options that are minimally sedating in LGS for adults is therefore greater. Similarly, the number of adults who have surgery for LGS is very small indeed but this is not from loss of access to surgery.

The comment about '*the proportion of people ineligible for cannabidiol*' is not quite right – it is not that the person with LGS is ineligible, but that after consultation and a consideration

of risks and benefits, it is decided to not start cannabidiol and clobazam for someone with LGS. This may be for many reasons but these include: prior adverse reaction to clobazam (typically sedation, or paradoxical agitation); neuro muscular disorder or sleep disorder where a sedating benzodiazepine is potentially harmful; patients on super-poly-therapy – someone on four ASMs is rarely improved by adding two new medications; drug-drug interaction. In summary there is a cohort of people with LGS for whom cannabidiol plus clobazam is not a safe choice, but fenfluramine may be as fenfluramine is minimally sedating.

Cannabidiol plus clobazam has been available for more than four years and there was intense public awareness of this. Most diagnosed LGS adult patients for whom cannabidiol plus clobazam could be started have had this discussion already.

The comment that fenfluramine does not have a disease modifying effect on LGS means that when fenfluramine is stopped one would expect the anti-seizure effect of the drug to cease also, probably abruptly; there would be no long term benefit to the person with LGS if they had a time-limited treatment with fenfluramine. The comment was not to discount the possibility that fenfluramine may have better efficacy months to years after reaching the maintenance dose, as appears to be the case for some people with Dravet.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes, on balance. There are a number of assumptions, most of these are common to ASM studies and NICE submissions and there is nothing egregious here, indeed a number of the assumptions are anti-competitive, cautious. For example the use of the eDiary will under report seizures and therefore the true benefit of any drug change.
Similarly and importantly the Markov model relying on drop seizure improvement is ultra-conservative as fenfluramine in the RCT and OLE is effective at improving the frequency of all LGS seizure types, including those more likely to cause hospitalisation –tonic clonic seizures (3.7)

With regards to the dose range of fenfluramine, this will vary across children and adults and across the person with LGS's lifetime – however it is very common for clinicians to prescribe more cautiously than the SPC. The mantra is start low and go slow – in contrast to an RCT where doses are escalated at speed. Therefore in the real world the optimum dose can be uncovered more slowly, likely to be lower.

Secondly the dose of cannabidiol, like all ASMs will be based on tolerability. If clobazam and cannabidiol is being added in early, to only one existing ASM then higher doses are possible

– this is possible in children. Adults are more likely to be established on many ASMs and so the maximum tolerated cannabidiol dose may be lower. This makes it a challenge to model accurately. The number of people starting cannabidiol for the first time as adults will drop over time, as the cohort of children exposed to cannabidiol grow older. It is therefore probable that the mean maintenance dose for all groups will move from the bottom of the 10mg/kg/day range historically, towards the top of that range over time.
In short, the earlier in a patient's journey that the drug is started, the more the dose can be maximised.

Wastage with cannabidiol is seen but is not a serious issue. In my cohort of 45 adults, we'd lose a bottle a year, maximum due to accidents/breakages.

3.10 – I agree the OLE attrition needs to be accounted for.
3.18 The stopping rules are reasonable

Are the recommendations sound and a suitable basis for guidance to the NHS?

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

3.25 is inaccurate – everyone with LGS has an intellectual disability. Everyone with LGS will need daily support, including accessing healthcare.

Importantly people with intellectual disability and epilepsy die almost 20 years sooner than the population mean. Untreated epilepsy is a barrier to gaining prompt access to health care. The framing bias of people presuming that all new collapses are seizures, that all new symptoms are related to ASM changes means that infectious (such as pneumonia) and non infectious (such as tumours) disorders are diagnosed much later.
Were fenfluramine to not be supported by NICE it would create an international inequity where people with LGS have access to a well-tolerated and efficacious drug in Europe but not in the UK. People with strong advocates (more likely to be less deprived) may be able to negotiate access via IFR routes or self-fund, which is inequitable.

Single Technology Appraisal

Fenfluramine for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Comments on the DG:	

Has all of the relevant evidence been taken into account?

"I believe the most up to date evidence has been considered.
I cannot see reference to the paper by Bishop et al (2023)
https://doi.org/10.1212/WNL.0000000000202479
which shows meaningful change on everyday executive function in adults in 57 patients."

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

"Relative reduction of seizures is significantly more meaningful for patients allowing individualised circumstance and disease burden to be taken into account. Utilising drop seizures as the main measurement model has already been established within TA615.
Unfortunately costs have not been (and cannot adequately be) compared to the reduction in hospital admissions, time in intensive care environment, utility of clinic time as well as greater societal costs including that born by the family (please see my separate comment upon impact to caregivers)."

Are the recommendations sound and a suitable basis for guidance to the NHS?

"I would disagree with the recommendations.
This is an incredibly difficult pharmacoresistant epilepsy to treat. We are limited in the range of drug and non-drug interventions available to use as epileptologists in the UK. There is clear data showing significant impact in seizure reduction compared to placebo. When both the FDA in the USA and EMA have approved its use in LGS it seems that NICE's rationale and interpretation is inconsistent with other comparable areas."

"Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and

maternity?"

Given there has been successful implementation of FFA with Dravet Syndrome, and a similar model exists for the use of CBD in Dravet Syndrome and LGS, combined with use in other comparable international regions it feels counterintuitive of the committee to unnecessarily deliberate upon its application in a pharmacoresistant group with incredibly limited treatment options for which very few would achieve this level of seizure reduction of drop seizures.

In section 3.11, in response to text "It added that clinicians considered that the increased longer-term treatment effect of fenfluramine in Dravet syndrome would also apply to LGS."

I would agree with this sentiment.

In section 3.14, in response to text "So, it considered the company's assumption of equal utility values for patients and carers to be unrealistic and preferred to use carer utility values from Lo et al. The committee noted the limitations with applying carer utility"

"Carer consideration and impact should not be ignored in developmental and epileptic encephalopathies, especially in LGS where comorbid severe learning and intellectual disability preclude the ability of conducting significant and robust evaluations into QoL. It is reasonable to extrapolate familial (including patient) outcomes from similar data sets.
Fairfax et al (2019) undertook a systemic review into families where children have chronic health conditions and identified issues in carers with challenges in childcare, constrained employment opportunities and increased symptoms of depression, physical limitations and chronic health problems. Gibson et al (2014) specifically looked into the impact on carers and families of patients with LGS - I included a summary:
Physical impact: many require specialised wheelchairs and adaptations for moving and handling – which worsens with age. Caregivers often report shoulder/back pain. Caregivers often experience physical exhaustion. Significant chronic fatigue and sleep deprivation.
Emotional: Worry and constant vigilance. Anxiety, stress and depression are common amongst caretakers. Financial burden of disease on the family.
Social impact: Decrease in recreational activities. Routine childcare and respite are difficult to find.
Impact on fathers: greater number of stressful life events and feelings of lower self esteem
Treatment success and its impact on carer QoL and patient QolL (with fenfluramine) can be extrapolated from the Jensen et al (2023) paper based on the early access programme to FFA in Dravet Syndrome.
Non-seizure related outcomes for the patient: (carers/clinicians) cognitive function (84%/100%); focus (76%/94%); alertness (72%100%); speech (70%/75%); academic performance (67%/56%); behaviour (63%/88%); sleep (60%/50%); mood (52%/44%); impulse controle |(44%/56%)

Impact on caregivers (caregiver/clinician): improve sleep quality (62%/56%); mood (68%/81%); feeling overwhelmed (64%/81%); missed work (63%/31%); stress (60%/81%); relationship with partner (52%/31%), time to do things they enjoy (52%/88%).
There are several caregiver comments within this paper and these should be considered when assessing impact on caregivers/families based on the same products impact on seizure control, non-seizure outcomes and the impact of improvements observed."

In section 3.14, in response to text "So, it considered the company's assumption of equal utility values for patients and carers to be unrealistic and preferred to use carer utility values from Lo et al. The committee noted the limitations with applying carer utility"

"Carer consideration and impact should not be ignored in developmental and epileptic encephalopathies, especially in LGS where comorbid severe learning and intellectual disability preclude the ability of conducting significant and robust evaluations into QoL. It is reasonable to extrapolate familial (including patient) outcomes from similar data sets.
Fairfax et al (2019) undertook a systemic review into families where children have chronic health conditions and identified issues in carers with challenges in childcare, constrained employment opportunities and increased symptoms of depression, physical limitations and chronic health problems. Gibson et al (2014) specifically looked into the impact on carers and families of patients with LGS - I included a summary:
Physical impact: many require specialised wheelchairs and adaptations for moving and handling – which worsens with age. Caregivers often report shoulder/back pain. Caregivers often experience physical exhaustion. Significant chronic fatigue and sleep deprivation.
Emotional: Worry and constant vigilance. Anxiety, stress and depression are common amongst caretakers. Financial burden of disease on the family.
Social impact: Decrease in recreational activities. Routine childcare and respite are difficult to find.
Impact on fathers: greater number of stressful life events and feelings of lower self esteem
Treatment success and its impact on carer QoL and patient QolL (with fenfluramine) can be extrapolated from the Jensen et al (2023) paper based on the early access programme to FFA in Dravet Syndrome.
Non-seizure related outcomes for the patient: (carers/clinicians) cognitive function (84%/100%); focus (76%/94%); alertness (72%100%); speech (70%/75%); academic performance (67%/56%); behaviour (63%/88%); sleep (60%/50%); mood (52%/44%); impulse controle |(44%/56%)
Impact on caregivers (caregiver/clinician): improve sleep quality (62%/56%); mood (68%/81%); feeling overwhelmed (64%/81%); missed work (63%/31%); stress (60%/81%); relationship with partner (52%/31%), time to do things they enjoy (52%/88%).
There are several caregiver comments within this paper and these should be considered when assessing impact on caregivers/families based on the

same products impact on seizure control, non-seizure outcomes and the impact of improvements observed."

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Fenfluramine hydrochloride for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

EAG comments on company response to draft guidance

Produced by Kleijnen Systematic Reviews (KSR) Ltd in collaboration with Maastricht University Medical Center+ (UMC+)

Authors
Robert Wolff, Managing Director, KSR Ltd, United Kingdom (UK)
Willem Witlox, Health Economist, Maastricht UMC+, Netherlands (NL)
Mirre Scholte, Health Economist, Maastricht UMC+, NL
Andrea Fernández Coves, Health Economist, Maastricht UMC+, NL
Bradley Sugden, Health Economist, Maastricht UMC+, NL
Mark Perry, Systematic Reviewer, KSR Ltd, UK
Jiongyu Chen, Health Economist/Systematic Reviewer, KSR Ltd, UK
Caro Noake, Senior Information Specialist, KSR Ltd, UK
Rachel Croft, Information Specialist, KSR Ltd, UK
Nigel Armstrong, Health Economics Manager, KSR Ltd, UK
Manuela Joore, Health Economist, Maastricht UMC+, NL

'Clinical efficacy' responses from the Evidence Assessment Group (EAG)

The EAG has provided critique of parts of the company's 'response to draft guidance'[1] that are related to clinical efficacy, as follows.

Section 1.5. Data on the per-arm use of non-pharmacological treatments

The company has provided a table showing the prevalence of different concomitant treatments given alongside the three randomised groups.

Table 1. Proportions of patients per arm on non-pharmacological treatments in study 1601

		Part 1 Treatment Group			All Subjects
		Placebo	FFA 0.2 mg/kg/day	FFA 0.7 mg/kg/day	
All Subjects	N per Group	[redacted]	[redacted]	[redacted]	[redacted]
VNS	N	[redacted]	[redacted]	[redacted]	[redacted]
	% of Group	[redacted]	[redacted]	[redacted]	[redacted]
Ketogenic Diet (Expanded Definition)*	N	[redacted]	[redacted]	[redacted]	[redacted]
	% of Group	[redacted]	[redacted]	[redacted]	[redacted]
Ketogenic Diet	N	[redacted]	[redacted]	[redacted]	[redacted]
	% of Group	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	N	[redacted]	[redacted]	[redacted]	[redacted]
	% of Group	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 2, Company response to draft guidance[1] *Expanded definition includes patients on a modified Atkins diet or a low glycaemic diet
FFA= Fenfluramine ; VNS= Vagus Nerve Stimulation

The company states that, *"Observing the data above, there appears to be little/minimal differences in the use of non-pharmacological treatments per treatment arm. In-line with suggestions by the committee, considering the small patient numbers and variability in the treatment of LGS (using different combinations of pharmacological and non-pharmacological treatments for each patient) it is highly unlikely any of these non-pharmacological treatments have an impact on treatment outcomes"*.[1]

There are some differences in the use of concomitant non-pharmacological treatments between groups, which is a plausible confounder. For example, the proportion of patients using a ketogenic diet (expanded definition) is twice as large in either of the fenfluramine groups compared to the placebo group. The company has correctly not applied inferential statistics to test the null hypothesis that the difference between fenfluramine and placebo arms in the study sample (in terms of concomitant non-pharmacological treatments) is consistent with that sample being part of a sampling distribution where the mean of all the sample differences is zero: whether or not the study sample differences are due to random sampling error, or indicate a more systematic effect, is largely immaterial. The important consideration is whether the within-sample differences in concomitant non-pharmacological treatments are a threat to internal validity. That is, are they of sufficient magnitude to mean that the estimates of treatment effect are invalidated? Estimation of the relative treatment effect as the difference or ratio in outcome between arms assumes that all arms experience the same magnitude of confounding, which is often tenable in a randomised controlled trial (RCT); however, this assumption no longer holds if the

arms differ in a confounding factor (in this case, the number of people receiving concomitant non-pharmacological treatments). Hence the difference between two arms will no longer be solely the treatment effect, but will have contributions from confounding.

The company states that small patient numbers and variability in the treatment of Lennox-Gastaut seizures (LGS) make it *unlikely* that non-pharmacological treatments will have an impact on treatment outcomes (that is, that it is unlikely to affect internal validity). This is not true, as shall be explained. The variability in overall treatments given to patients should not usually be a problem in an RCT: after proper random allocation, each group should theoretically have a similar array of different patient treatment indications. Therefore, all arms should have very similar levels of comparability for concomitant non-pharmacological treatments that have been prescribed in response to these treatment indications. In other words, even if every patient is given a personalised prescription, with a varying degree of concomitant non-pharmacological treatments prescribed alongside their main treatment, the fact that all arms will have a similar profile of characteristics (including very similar treatment indications) should mean that all arms will end up being matched for the number of participants using specific concomitant non-pharmacological treatments. However, for this to occur, fairly large sample sizes are needed (the law of large numbers). So, in smaller samples there may be a tendency for random variations in confounders such as concomitant treatments across arms. Therefore, it is likely that in this trial the small numbers will have caused the random differences in concomitant treatments across arms that were observed. Thus, it can be seen (contrary to the company's argument) that small patient numbers and variability in the treatment of LGS make it *more* likely that non-pharmacological treatments will have an impact on treatment outcomes (that is, they are more likely to affect internal validity). Whilst the extent of any effects on internal validity is unknown, the company do not have any evidence to dismiss the potential risk of bias. The committee should therefore consider the possible risk of bias resulting from uneven levels of concomitant treatments across groups.

Section 2.3. Evidence supporting the validity of the eDiary as a measurement device

The company were criticised in the EAG report for a lack of validation for the e-diary as a measurement device. The company have responded by stating that, *"As per Gray et al., 2022[2] eDiaries are now the gold standard to capture data in epilepsy studies. They enable carers to record seizures quickly, accurately and improve the quality and quantity of data versus the traditional paper diary. This also reduces the risk of bias[2] ….The eDiary used in the trial was developed by Signant Health and the Epilepsy Study Consortium (ESC) validated the quality of the device, acknowledging the manufacturers "considerable experience developing complex eDiaries and conducting epilepsy trials".[3] UCB would like to emphasize that the use of this specific eDiary was validated at the regulatory approval stage via both the FDA and EMA. In the NICE appraisal of FFA for Dravet Syndrome[4] the use and validity of eDiaries was not commented on as a potential issue".*

The EAG would reiterate its original criticism, as the company has still not provided direct evidence of measurement validity. The citations provided above do not strongly demonstrate in any scientific way that the eDiary measures what it is supposed to measure.

Section 2.4. External validity of the trial being unclear

The EAG had previously pointed out in its report that the external validity of the trial in terms of age, gender or ethnicity was unclear. It had been explained that for greater understanding of external validity, more information would be required from sub-group analyses investigating whether age, gender or ethnicity affect outcome. If any of age, gender or ethnicity were to affect outcome, then it would also be important to know about the similarity of age, gender or ethnicity in the trial and the UK target

population. However, the company did not provide sub-group analyses, nor any information on the characteristics of the population in England and Wales.

In their response to the EAG, the company state that, *"UCB is not aware of any clinical expert opinion that may suggest age, gender and/or ethnicity may be treatment effect modifiers in LGS. Such concerns have not been raised as potential issues within previous HTA appraisals for DS and LGS (TA808, TA614 and TA615). Furthermore, UCB believe that the entire eligible population is relevant, and all should obtain equal access to new epilepsy products such as FFA, particularly considering that US, EU and MHRA labelling for the product indicate its use within a broad population"*.[1]

The EAG does not think this answers their concerns. The EAG would like to see objective data relating to effect modification from these variables, and not have to rely on (absent) expert clinical opinion alone. For example, the EAG would like to see the company's data for the exploratory sub-group analyses that had been reported to have been carried out, so that the EAG can make a judgement on the validity of the company's decision to not present sub-group analyses in the company submission (CS). Furthermore, whether or not these issues have been raised in previous appraisals is irrelevant. Finally, equal access to drugs is not the same issue as questioning provision of drugs to a population who may respond differently to the population in which the drugs were originally trialled; there are issues of safety and cost effectiveness to be considered. In conclusion, the EAG does not think that the company has adequately addressed the issue of the external validity of trial findings.

Section 3.2: An indirect treatment comparison for cycles 2-5

The EAG's comments refer to both section 3.2 of the company response to draft guidance, as well as the technical report of the network meta-analysis (NMA).[5]

The company summarises the results of the indirect treatment comparison (ITC) with the following table.

Table 2: Summary of efficacy results comparing FFA and CBD with placebo, fixed effects, all time points

	Treatment Arm	
Health State	**RR FFA versus Placebo (95% CrI)**	**RR CBD versus Placebo (95% CrI)**
Timepoint: After 3 months in OLE study (weeks 1-12)		
≥ 25% response	[redacted]	[redacted]
≥ 50% response	[redacted]	[redacted]
≥ 75% response	[redacted]	[redacted]
Timepoint: After 6 months in OLE study (weeks 13-24)		
≥ 25% response	[redacted]	[redacted]
≥ 50% response	[redacted]	[redacted]
≥ 75% response	[redacted]	[redacted]
Timepoint: After 9 months in OLE study (weeks 25-36)		
≥ 25% response	[redacted]	[redacted]
≥ 50% response	[redacted]	[redacted]
≥ 75% response	[redacted]	[redacted]

Timepoint: After 12 months in OLE study (weeks 37-48)		
≥ 25% response	[redacted]	[redacted]
≥ 50% response	[redacted]	[redacted]
≥ 75% response	[redacted]	[redacted]
Based on Table 1 of the technical report of the NMA[5] CBD= Cannabidiol; CrI= Credible Interval; FFA= Fenfluramine; OLE= Open-Label Extension; RR= Risk Ratio		

The company conclude that the effects of fenfluramine are comparable to those of cannabidiol.

Technical issues

A burn-in of 25,000 is used, which is shorter than the 50,000 often used by the Decision Support Unit (DSU).[6] No plots are provided to demonstrate convergence at this point.

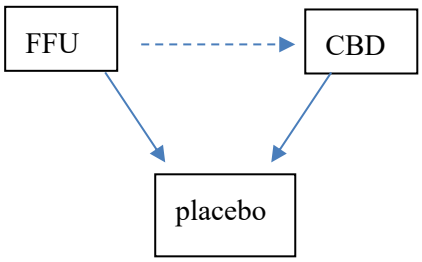
General issues

Network of evidence

For each outcome (e.g., ≥25% response after 6 months), the company appear to have have performed a simple indirect treatment comparison between fenfluramine and cannabidiol, using two direct estimates with a common comparator. The direct estimates are:

- Fenfluramine (FFA) versus Placebo
- Cannabidiol (CBD) versus Placebo

The network diagram is therefore (where the dashed arrow indicates an indirect estimate):



The purpose of an indirect comparison is to provide an indirect estimate, but the company have not done this. The company have instead produced results tables of each treatment against placebo (Table 2), but it is difficult to see, in the absence of a meta-regression, how these tables provide any more information than would be provided by the direct estimates alone. In an NMA where closed loops are present, then robustness and precision of estimates will be gained by combining direct estimates with indirect estimates. This will allow all data in a network (including any head-to-head data) to be included in the combined estimate of each treatment in the network against a common reference treatment. However, in the ITC performed by the company there are no closed loops of evidence and therefore it is not possible to derive indirect estimates which can be combined with the direct estimates. In other words, despite the analysis involving 30,000 Bayesian Monte Carlo Markov Chain iterations, it does not appear as though the results in Table 2 should differ much from the data that has been input into the model. In fact, the EAG have calculated the direct estimates of RR (from the raw trial data that

the company stated that they used in Appendix A). The results calculated in this way are similar, but not identical to those produced by the company's NMA [e.g., [redacted], [redacted] and [redacted] vs. 1.77, 3.57 and 3.52 for the RR for ≥ 25% response, ≥ 50% response and ≥ 75% response of fenfluramine with NMA vs. direct respectively]. These have been uploaded in an excel file [ITC_Direct vs NMA]. However, the main problem with the method used by the company is the assumption that the placebo value for both trials remains unchanged from that estimated at 12 weeks. The company provided the following justification: *"There is no evidence to suggest, or any plausible explanation to believe that a placebo drug will directly provide any improvements or decrements in efficacy, therefore a maintained effect was assumed as the most appropriate for the purposes of the ITC."* (p.12) However, this appears to misunderstand the purpose of the placebo arm, which is to attempt to provide the same conditions as would be experienced in the intervention arm except for the effect of the intervention itself. This enables the effect of these conditions e.g. of just being in a trial, often referred to as the placebo effect, to be cancelled out when estimating the treatment effect i.e. intervention vs. placebo. Of course, it might be the case that the placebo effect, as indicated by the outcome in the placebo arm, remains unchanged. What is also crucial to understand is that an unchanged placebo effect means that the conditions by which response at each level (25% to 75% can occur remain unchanged, and, if they do then this means that further response is possible i.e. an unchanged placebo effect is consistent with an increase in response and not unchanged number/risk of responders. The EAG cannot reach a conclusion as to the pattern of change in placebo effect given that it has not been observed. However, a more conservative and plausible assumption might be to assume that the treatment effect i.e. RR vs. placebo remains unchanged rather than the risk of response in the placebo arm. The effect of this can be understood by noting that the RRs at all levels (25% to 75%), as estimated by the company (see Table 2) for fenfluramine are highest at 12 months, whereas they reach a peak at 9 months for cannabidiol.

Comparators

The company has compared to cannabidiol alone rather than cannabidiol + clobazam, which contradicts the decision problem. The company has also not included in the NMA other comparators deemed by the EAG to be important: clobazam alone, rufinamide and topiramate. The EAG has previously argued in the EAG report of the company submission that the company's justifications for excluding these comparators are insufficient [p103, EAG report]. Furthermore, an NMA that included the excluded comparators (produced by the company after an EAG request during clarification) provides information suggesting that some clinical benefits of other 3rd line anti-seizure drugs may be superior to those of fenfluramine. Given the importance of including all relevant comparators, the EAG therefore thinks that the revised ITC provided by the company does not provide particularly useful information.

Stable event rate in placebo group

The assumption that the event rate in the placebo arm would not change over time is based upon the company's belief that "*There is no evidence to suggest, or any plausible explanation to believe that a placebo drug will directly provide any improvements or decrements in efficacy"*.[1] It is true that a placebo drug will not be able to cause any improvements or decrements in true *treatment* effect (because the true *treatment* effect will always be zero in the case of a true placebo), but it is false to conclude that the observed empirical effect on the outcome *in the placebo drug group* will not change. There are two mechanisms by which the placebo group event rate could change.

Firstly, the placebo effect itself could change over time, perhaps because of a change in belief on the part of patients as the trials progress. Let's assume the placebo effect increases in both arms (e.g. fenfluramine and placebo groups) over time, which is highly plausible as it is likely that in a blinded placebo-controlled RCT (where both arms will believe that they are receiving a beneficial therapy) any

such effect would occur to a similar extent in both arms. Given this, it could be argued that this increased placebo effect is the cause of all or some of the increase in the event rates observed in the fenfluramine and/or cannabidiol groups over time (Appendix A, NMA technical report).[5] However, the false assumption of no change in the outcome of the placebo group (who have no data after 12 weeks and so rely on imputation after this point) will mean that the corresponding increase in event rate that would actually be expected to occur in the placebo group is not reflected by the imputed data. There will therefore be a spurious increase in the contrast between intervention and placebo groups, which will be wholly interpreted as a treatment effect. Very importantly, if such an increase in placebo effect occurred in the fenfluramine trials but not the cannabidiol trials, or vice-versa, (or to a differing extent in either direction) then this could spuriously affect any indirect estimate of fenfluramine versus cannabidiol. Such a differential effect might be expected across trials given the different conditions related to each.

Secondly, extraneous factors other than the placebo effect (or in addition to it) could change in the placebo group over time. These could be related to the natural course of disease or may other reasons. Because these effects would be expected to affect the event rate in both arms within a blinded RCT equally, exactly the same mechanisms for spurious improvement explained above could apply.

These arguments show that it is incorrect to assume that the placebo group should remain at the same event rate, with the potential for serious bias. In turn, this means that the running of an NMA using open-label extension (OLE) drug data supplemented by placebo data from the randomised portion is not a good approach. There are benefits to using longer term data, but these benefits appear to be overwhelmed by the potential disadvantages described above.

Clinical heterogeneity

No assessment of consistency is possible in the model because of the lack of closed loops, and for this reason it is particularly important that a proper assessment of clinical heterogeneity is made between the two comparisons. However, this does not appear to have been properly investigated or reported in the technical document, other than the brief statement that, *"The fenfluramine and cannabidiol trials and OLE were conducted in North America and Europe, and the patient selection criteria in these trials were similar to the indications suggested by the FDA or EMA labels"*.[5]

Summary

In summary, the choice of comparators, the assumption of a stable placebo event rate and the lack of full consideration of clinical heterogeneity reduce the EAG's confidence in the findings from the ITC.

Health economic responses from the EAG

The company's revised base-case

The company provided an overview of model assumptions and the revised base-case results in Tables 8, 9 and 10 of their response to the draft guidance. In an addendum, the company also shared details of how each individual change was implemented in the revised model, and the cumulative impact of each change on their original base-case results. The EAG can verify that it could reproduce the company's initial base-case results in the revised model. However, for the analyses related to 1) the correction for the modelling of the 6 months stopping rule and 2) the modelling of the treatment effect in model cycles 2-5, the EAG needed to retrieve information from the company's clarification model to replace cells in the company's revised model. Therefore, it would be helpful if the company could provide an updated model (preferably the EAGs non-confidential model) including switches for these analyses, as was provided for the other changes that the company implemented. In addition, the EAG would like to see an overview of the individual impact of each company change on their original base-case results, rather than the cumulative impact as was provided in the addendum.

Treatment waning (sections 1.3 and 4.2)

Treatment waning was implemented in the model by considering two elements: 1) the proportion of patients that was assumed to experience treatment waning (5.2% in the company base case based on the last 3 months of the fenfluramine OLE study) and 2) the deteriorating transition probabilities that describe how patients transit when they experience treatment waning. In the model, these two elements are combined by multiplication. In response to the draft guidance, the company aligned the approach to calculate the deteriorating transition probabilities with the EAGs preferred approach by using all people on treatment from the last 3 months of the Study 1601 OLE, rather than only including the people that stayed in their health state or deteriorated. Nevertheless, the company remains assuming that 5.2% of patients experience treatment waning, which they consider reasonable by highlighting one observational study in which FFA patients with LGS discontinue due to lack of efficacy at a low rate in the real-world (6.8%). However, the EAG still considers the company's assumption of 5.2% treatment waning to be implausibly low as this translates to observed percentages of 0.58% and 0.48% of patients experiencing treatment waning in model cycle 10 for FFA and CBD respectively (see Table 3 below).

Table 3: Comparison treatment waning inputs and observed treatment waning in model cycle 10.

	Treatment waning input (%)	**Observed % of FFA patients experiencing treatment waning in the model in cycle 10**	**Observed % of CBD patients experiencing treatment waning in the model in cycle 10**
Company base case after draft guidance	5.2%	0.58%	0.48%
Company scenario 4	19.6%	2.18%	1.81%
Company scenario 5	30%	3.34%	2.77%
EAG suggested scenario	80%	8.92%	7.38%

	Treatment waning input (%)	Observed % of FFA patients experiencing treatment waning in the model in cycle 10	Observed % of CBD patients experiencing treatment waning in the model in cycle 10
Assumption that all deteriorating patients experience treatment waning	100%	11.14%	9.22%
* the observed % of patients experiencing treatment waning in cycle 10 is obtained by multiplying the treatment waning % (column 2) by the deteriorating transition probabilities (column 3) by the cohort in cycle 10. Finally, the patients that transited to a lower health state were the patients with 'observed treatment waning'.			

Additionally, the company states that UK clinical experts could not define the proportion of patients experiencing waning in either treatment arm and that they consider it conservative to assuming equal waning in both arms. It is unclear to the EAG what the true percentage of treatment waning should be and whether assuming equal waning in both arms is a conservative approach, but results of the company's scenario analyses demonstrate that assumptions regarding treatment waning have a substantial impact on the cost-effectiveness results.

Average maintenance dose of CBD (sections 1.4 and 4.4)

The company argues that the average dose of CBD is underestimated as CBD was provided at a mean modal dose of 24 mg/kg/day in the real-world OLE study. At the first appraisal committee meeting, two clinical experts stated the average CBD dose in clinical practice is likely to be between 14-16 mg/kg/day, while a third clinical expert mentioned a dose closer to 12 mg/kg/day. The company further states that it agrees with the committee that a dose between 12-16 mg/kg/day is plausible, and therefore the average dose used within the new company base case has been revised to 14 mg/kg/day. As per the committee's request, the company provided additional scenario analyses exploring CBD maintenance doses of 12, 13, 15 and 16 mg/kg/day. The EAG agrees that based on expert opinion the likely CBD maintenance dose is between 12 and 16 mg/kg/day. However, it is unclear to the EAG what the true dose is and hence the range of ICERs between 12-16 mg/kg/day should be considered for decision making.

Modelling of the treatment effect in cycles 2-5 (response sections 2.1, 3.1, 3.2)

The company clarified that in their initial modelling approach the CBD OLE data used to populate the CBD + CLB + SoC health states for cycles 2 to 5 was based on the treated population data available within the trial publication.

The committee in its draft guidance requested analyses using the same methodology and assumptions used to account for missing data points in the Study 1601 OLE data analysis, applied to the cannabidiol OLE data as well. Specifically, 1) state occupancy data for fenfluramine at months 3, 6, 9 and 12 assuming that those who drop out of the Study 1601 OLE did so with a less than 25% improvement in DSF, as opposed to assuming they are missing at random; and 2) state occupancy data for cannabidiol at months 3, 6, 9 and 12 that accounts for attrition in a similar manner. If limitations in accessible data

from the cannabidiol OLE study are a limiting factor, basing attrition assumptions on fenfluramine OLE attrition data is preferable to assuming patients who leave the sample are missing at random. The EAG notes that these analyses were not provided by the company in its response.

Alternatively, the company identified available ITT data for CBD within the appendix of its clinical trial publication, where there are reported response rates for drop seizures based on Last Observation Carried Forward (LOCF) analyses. To enable a like-for-like comparison with FFA patients, the company performed an ITT analysis with LOCF imputation (to match FFA's analysis with CBD's) using all patients who received open-label FFA, or equivalently, the safety population. It is, however, unclear whether the average FFA maintenance dose in this safety population is in line with the currently modelled dose of 0.413 mg/kg/day and the EAG would like to see evidence for this.

In its revised base-case, the company used a Bayesian anchored ITC (in line with the approach in model cycle 1) using the ITT state occupancy data identified for both FFA and CBD. Contrary to the company's initial approach, which resulted in higher total patient and carer QALYs gained in the observed period for CBD+clobazam+SoC compared to FFA+SoC, the company current approach using the Bayesian anchored ITC favoured FFA (Table 4). The EAG would like to reiterate that the choice of comparators, the assumption of a stable placebo event rate and the lack of full consideration of clinical heterogeneity reduce the EAG's confidence in the findings from the ITC.

Table 4: Patient and caregiver QALYs in the observed trial period

	FFA + SoC	**CBD+clobazam+SoC**
Company's initial approach (cycles 2-5 FFA: TPs based on Study 1601 OLE, CBD: state occupancy based on CBD + CLB + SoC trial OLE)		
Patient QALYs gained	0.25	0.26
Caregiver QALYs gained	0.47	0.48
Company's revised approach (state occupancies derived from the ITC using the ITT data of both FFA and CBD OLE studies using LOCF in both arms)		
Patient QALYs gained	0.25	0.22
Caregiver QALYs lost*	-0.97	-1.00
*In the company's revised model a caregiver disutility approach was used (resulting in caregiver QALY lost), contrary to the company's initial model using a caregiver utility approach (resulting in caregiver QALY gains).		

Average maintenance dose of FFA (sections 2.2 and 4.3)

The company provided the mean daily doses of FFA within the OLE in Table 4 of the draft guidance response, which amounts to [redacted] mg/kg/day. Patients that received >0.7 mg/kg/day were excluded from the average maintenance dose that was used by the company in its revised model (0.413 mg/kg/day), justified by stating that clinicians will not exceed the maximum stated dose within clinical practice.

The EAG agrees that the maximum dose will likely not be exceeded in clinical practice, but noted that the company did include patients with a mean daily dose lower than the initial titration dose (0.2 mg/kg/day) in their calculation. Next to that, patients that received >0.7 mg/kg/day were included in the analysis to inform FFA treatment effectiveness and hence the EAG considers it reasonable to also include these patients in the costing of FFA. Therefore, also in line with the committee's preference of using the mean dose from the Study 1601 OLE, the EAG considers the average FFA maintenance dose of [redacted] mg/kg/day to be the most appropriate for use in the economic model.

Extrapolation of the FFA treatment effect (cycles 6-9) and assumptions for cycle 10 onwards (response section 3.3)

Given the limited available observed data post 15 months, the company's revised base case analysis assumes that treatment effect is maintained from cycles 6-9, based on the last observed efficacy from cycle 5 for both treatment arms. The same methodology is applied to FFA + SoC and CBD + clobazam + SoC and waning is applied from cycle 10 onwards.

Two alternative scenarios were tested by the company in order to explore the uncertainty around the treatment effect of cycles 6-9. First, a scenario assuming treatment effect would be maintained at the average effect observed in cycles 2-5. A second scenario assumed treatment effect duration would be maintained up until 15 months (instead of 27 months in the base case) and waning would start from month 16 onwards (instead of as from moth 28 onwards in the base case).

The EAG agrees that assuming a maintained treatment effect for both arms seems more plausible than the company's initial approach where an increased treatment effect for FFA and a maintained treatment effect for CBD+clobazam+SoC was assumed. However, all of the newly provided analyses for the modelling of FFA and CBD+clobazam+SoC in model cycles 6-9 are conditional on the modelling in cycles 2-5 (i.e. the Bayesian ITC). Hence, the limitations mentioned above also add uncertainty to the extrapolation of the FFA and CBD+clobazam+SoC treatment effect in cycles 6-9.

Wastage costs associated with both CBD and FFA treatment (section 4.5)

The committee requested scenarios which account for the expected wastage costs associated with CBD and FFA in the draft guidance. The company provided scenarios assuming 1) 5% wastage for both treatment arms, 2) 5% wastage for FFA and 10% wastage for CBD, and 3) 0% wastage for FFA and 10% for CBD. The EAG appreciates the scenarios provided by the company but notes that the assumed wastage percentages were not justified. The EAG is therefore unsure whether any of the provided scenarios is reflective of UK clinical practice.

Correction related to implementation of the stopping rule at 6 months in the model (section 4.6)

The stopping rule at 6 months in the company's original base case model was implemented by discontinuing patients from health state 0 (and a percentage of health state 1 in the case of less than 30% and 50% reduction in drop seizure frequency) every 6 months. The EAG believed that this implementation was not optimal as there was a possibility of patients that had experienced sub-optimal response for less than 6 months to discontinue treatment as well.

The company states that tracking of patients (i.e. for how long patients have been in a particular health state) is not possible, and therefore estimated the proportion of patients remaining in health state 0 and health state 1 from the transition probabilities of FFA treated patients during the OLE study. On average, 61.2% of patients in health state 0 remain in health state 0, while 37.9% of patients in health state 1 remains in health state 1 the following cycle.

It is unclear to the EAG 1) how the company's new 6 month stopping rule analysis was exactly implemented in the economic model, 2) what the individual impact of this analysis is on the cost-effectiveness results, and 3) how the company's initial implementation of the 6 months stopping rule can be reproduced in the revised model. In addition, the EAG questions whether the average number of patients that stays in HS0 in the observed period (which is used to inform the number of patients using the stopping rule) is representative for long-term treatment discontinuation. During the observed period patients may have a treatment effect (i.e. move from HS0 to HS1, 2 and 3), and therefore the percentage of patients that is expected to remain in HS0 is lower early on in the model as compared to later model cycles. The EAG therefore, although also suboptimal, prefers using the company's initial approach of modelling the 6 month stopping rule.

Application of carer disutilities (section 4.7)

The company acknowledges the committee preference to use carer disutility values in a manner that do not result in negative QALYs. However, the company states that it was not feasible to present results in another way.

In their revised base-case, the company adopted the disutility approach using estimates from Lo et al. as per the EAGs preference.

[1] UCB Pharma S.A. *Fenfluramine hydrochloride for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]: UCB response to draft guidance. Answers to Committee's requests* 2024 [accessed 22.2.24]

[2] Gray TE, Hirsch LJ, Quraishi IH. Electronic seizure diaries for clinical care and research. Epileptic Disord 2022; 24(5):803-11

[3] Signant Health. *Press Release: Signant Health debuts standardized electronic seizure diary developed in collaboration with The Epilepsy Study Consortium [Internet]*, 2023 [accessed 26.2.24] Available from: https://www.signanthealth.com/news/signant-health-debuts-standardized-electronic-seizure-diary-developed-in-collaboration-with-the-epilepsy-study-consortium/

[4] National Institute for Health and Care Excellence. Fenfluramine for treating seizures associated with Dravet syndrome: NICE Technology appraisal guidance 808 [Internet]. London: NICE, 2022 [accessed 27.7.23]. Available from: https://www.nice.org.uk/guidance/ta808

[5] Marsh S, Taieb V. *Network meta-analysis of FINTEPLA® vs cannabidiol in Lennox-Gastaut Syndrome: open label extension. Technical Report (V1.0) [Report provided by the company]*, 2024 [accessed 22.2.24]

[6] Dias S, Welton NJ, Sutton AJ, Ades AE. *NICE DSU Technical Support Document 2: A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials*. Sheffield: Decision Support Unit, ScHARR, 2011. 98p. Available from: https://www.sheffield.ac.uk/sites/default/files/2022-02/TSD2-General-meta-analysis-corrected-2Sep2016v2.pdf

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Fenfluramine hydrochloride for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651] – updated EAG base-case

Produced by Kleijnen Systematic Reviews (KSR) Ltd in collaboration with Maastricht University Medical Centre (UMC+)

Authors
Robert Wolff, Managing Director, KSR Ltd, United Kingdom (UK)
Willem Witlox, Health Economist, Maastricht UMC+, Netherlands (NL)
Mirre Scholte, Health Economist, Maastricht UMC+, NL
Andrea Fernández Coves, Health Economist, Maastricht UMC+, NL
Bradley Sugden, Health Economist, Maastricht UMC+, NL
Mark Perry, Systematic Reviewer, KSR Ltd, UK
Jiongyu Chen, Health Economist/Systematic Reviewer, KSR Ltd, UK
Caro Noake, Senior Information Specialist, KSR Ltd, UK
Rachel Croft, Information Specialist, KSR Ltd, UK
Nigel Armstrong, Health Economics Manager, KSR Ltd, UK
Manuela Joore, Health Economist, Maastricht UMC+, NL

Correspondence to
Robert Wolff, Kleijnen Systematic Reviews Ltd
Unit 6, Escrick Business Park
Riccall Road, Escrick
York, YO19 6FD
United Kingdom

Date completed 23/10/2023

Source of funding: This report was commissioned by the National Institute for Health and Care Research (NIHR) Evidence Synthesis Programme as project number STA 13/06/79.

Declared competing interests of the authors: None.

Acknowledgements

The Evidence Assessment Group (EAG) thank Dr Christin Eltze for her work as the Clinical Expert.

Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Confidential comparator prices are highlighted in green throughout the report.

Any de-personalised data are highlighted in pink throughout the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Wolff R, Witlox W, Scholte M, Fernández Coves A, Sugden B, Perry M, Chen J, Noake C, Croft R, Armstrong N, Joore M. Fenfluramine hydrochloride for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2023.

Contributions of authors

Robert Wolff acted as project lead and systematic reviewer on this assessment, critiquing the clinical effectiveness methods and evidence and contributing to the writing of the report. Willem Witlox acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Mirre Scholte, Andrea Fernández Coves, Bradley Sugden, Nigel Armstrong, and Manuela Joore acted as health economists on this assessment, critiquing the company's economic evaluation and contributing to the writing of the report. Jiongyu Chen acted as health economist on this assessment, critiquing the company's economic evaluation and contributing to the writing of the report, and also acted as systematic reviewer, critiquing the clinical effectiveness methods and evidence and contributing to the writing of the report. Mark Perry acted as systematic reviewer, critiquing the clinical effectiveness methods and evidence and contributing to the writing of the report. Caro Noake and Rachel Croft acted as information specialists on this assessment, critiquing the search methods in the submission and contributing to the writing of the report.

Table 1: Deterministic EAG base-case – pairwise results

Technology	Total costs (£)	Patient QALYs	Caregiver QALYs	Total QALYs	Total QALYs (incl. SM)	Incremental costs (£)	Incremental QALYs	Incremental QALYs (incl. SM)	ICER (£/QALY)	ICER (£/QALY) (incl. SM)	NHB (£30,000 threshold)	NHB (£30,000 threshold) with SM
Initial EAG base case												
Fenfluramine + SoC	[redacted]	1.16	-19.94	-18.78	-17.97							
Cannabidiol with clobazam + SoC	[redacted]	1.23	-19.94	-18.71	-17.85	[redacted]	-0.07	-0.11	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.60	-20.57	-19.96	-19.54	[redacted]	1.18	1.57	[redacted]	[redacted]	[redacted]	[redacted]
Updated EAG base case (including [redacted] mg/kg/day average fenfluramine maintenance dosage)												
Fenfluramine + SoC	[redacted]	1.16	-19.94	-18.78	-17.97							
Cannabidiol with clobazam + SoC	[redacted]	1.23	-19.94	-18.71	-17.85	[redacted]	-0.07	-0.11	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.60	-20.57	-19.96	-19.54	[redacted]	1.18	1.57	[redacted]	[redacted]	[redacted]	[redacted]
EAG Analysis 12. Exploratory Scenario - Treatment waning applied to 80% of patients												
Fenfluramine + SoC	[redacted]	0.87	-20.34	-19.48	-18.87							
Cannabidiol with clobazam + SoC	[redacted]	0.91	-20.33	-19.42	-18.78	[redacted]	-0.06	-0.09	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.60	-20.57	-19.96	-19.54	[redacted]	0.49	0.67	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG = External assessment group; ICER = incremental cost-effectiveness ratio; NHB = net health benefit; QALY = quality-adjusted life year; SoC = Standard of care; SM = severity modifier

Table 2: Probabilistic EAG base-case – pairwise results

Technology	Total costs (£)	Patient QALYs	Caregiver QALYs	Total QALYs	Total QALYs (incl. SM)	Incremental costs (£)	Incremental QALYs	Incremental QALYs (incl. SM)	ICER (£/QALY)	ICER (£/QALY) (incl. SM)	NHB (£30,000 threshold)	NHB (£30,000 threshold) with SM
Initial EAG base case												
Fenfluramine + SoC	[redacted]	1.18	-20.27	-19.09	-18.27							
Cannabidiol with clobazam + SoC	[redacted]	1.24	-20.26	-19.02	-18.16	[redacted]	-0.07	-0.11	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.61	-20.91	-20.30	-19.87	[redacted]	1.21	1.60	[redacted]	[redacted]	[redacted]	[redacted]
Updated EAG base case (including [redacted] mg/kg/day average fenfluramine maintenance dosage)												
Fenfluramine + SoC	[redacted]	1.18	-20.27	-19.09	-18.27							
Cannabidiol with clobazam + SoC	[redacted]	1.24	-20.26	-19.02	-18.16	[redacted]	-0.07	-0.11	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.61	-20.91	-20.30	-19.87	[redacted]	1.21	1.60	[redacted]	[redacted]	[redacted]	[redacted]
EAG Analysis 12. Exploratory Scenario - Treatment waning applied to 80% of patients												
Fenfluramine + SoC	[redacted]	0.88	-20.68	-19.80	-19.18							
Cannabidiol with clobazam + SoC	[redacted]	0.93	-20.66	-19.74	-19.09	[redacted]	-0.06	-0.09	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.61	-20.91	-20.30	-19.87	[redacted]	0.50	0.69	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG = External assessment group; ICER = incremental cost-effectiveness ratio; NHB = net health benefit; QALY = quality-adjusted life year; SoC = Standard of care; SM = severity modifier