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

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Contents:

The following documents are made available to stakeholders:

1. **Draft Guidance Document (DG 2)** as issued to consultees and commentators

2. **Comments on the Draft Guidance 2 from the company,** UCB Pharma
   a. Draft guidance response form
   b. Draft guidance response
   c. Survey on treatment pathways

3. **Consultee and commentator comments on the Draft Guidance 2** from:
   a. Epilepsy Action
   b. Epilepsy Society
   c. Tuberous Sclerosis Association
   d. Young Epilepsy
   e. Association of British Neurology
   f. International League Against Epilepsy UK
   g. Jazz Pharma

4. **Comments on the Draft Guidance 2 received through the NICE website**

5. **External Assessment Group critique of company response to the Draft Guidance 2**

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

Draft guidance consultation

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using fenfluramine in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation 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 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 age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: October 2024

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using fenfluramine in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 26 November 2024
- Third evaluation committee meeting: 15 January 2025
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Fenfluramine is not recommended, within its marketing authorisation, for treating seizures associated with Lennox–Gastaut syndrome (LGS) as an add-on to other antiseizure medicines for people 2 years and over.

1.2 This recommendation is not intended to affect treatment with fenfluramine that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop. For children or young people, this decision should be made jointly by the healthcare professional, the child or young person, and their parents or carers.

Why the committee made these recommendations

People with LGS are offered a range of antiseizure medicines. If this does not control their seizures, other treatments can be introduced, including cannabidiol plus clobazam.

Evidence from a clinical trial shows that people who have fenfluramine have fewer drop seizures per month than people who have standard care without cannabidiol plus clobazam. There is no evidence directly comparing fenfluramine with cannabidiol plus clobazam. The results of an indirect comparison comparing fenfluramine with cannabidiol plus clobazam are uncertain.

The economic evidence for fenfluramine has some uncertainties, including how well it works in the long term and around some of the assumptions used to estimate cost effectiveness. Even when considering the condition's severity and its effect on quality and length of life, the most likely cost-effectiveness estimates are highly uncertain and above what NICE considers an acceptable use of NHS resources. So, fenfluramine is not recommended.

2 Information about fenfluramine

Marketing authorisation indication

2.1 Fenfluramine (Fintepla, UCB) is indicated for 'the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) as an add-on therapy to other antiepileptic medicines for patients 2 years of age and older'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for fenfluramine.

Price

2.3 The list price for fenfluramine is £1,802.88 for the 120-ml (2.2 mg/ml) bottle and £5,408.65 for the 360-ml bottle (excluding VAT; BNF online accessed January 2024).

2.4 The company has a commercial arrangement. This makes fenfluramine available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The evaluation committee considered evidence submitted by UCB, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of the condition

3.1 Lennox–Gastaut syndrome (LGS) is a severe, lifelong and treatment-resistant form of epilepsy that begins in early childhood, generally before the age of 8 years. It is characterised by a specific electroencephalogram (EEG) pattern and developmental delay or cognitive impairment. It is also characterised by frequent seizures of different types. Drop seizures result in a loss of muscle tone or stiffening of muscles, which may result in falls, serious injury, pain, hospitalisation and death. Generalised tonic–clonic seizures are particularly severe. Uncontrolled and frequent generalised tonic–clonic seizures correlate to an increased risk of death. Non-drop seizures are typically not as severe as drop seizures and do not generally result in hospitalisation. The patient carer expert noted that LGS can also result in behavioural issues such as hyperactivity, anxiety, aggression, sleep disturbances and depression. They also noted that LGS has a substantial impact on families and carers, with some reporting feelings of despair and helplessness. People with the condition need round-the-clock care, and help with almost all aspects of daily life. Families and carers may find that it prevents them from leading normal lives and prevents family activities. The anxiety that a child with LGS may be injured because of a drop seizure can also significantly affect the mental wellbeing of their

family. The patient carer expert explained that they must be within catching distance of their child at all times because their child could have a drop seizure at any moment. The committee concluded that LGS severely affects the quality of life of people with the condition, their families and carers.

Clinical management

Treatment options

3.2 The NICE guideline on epilepsies in children, young people and adults (from here referred to as NG217) recommends considering sodium valproate first. If seizures are inadequately controlled, NG217 recommends considering lamotrigine as a second-line add-on treatment or by itself. If second-line treatment is unsuccessful, cannabidiol plus clobazam, clobazam alone, rufinamide and topiramate can be considered as third-line add-on treatment options. If all other treatment options are unsuccessful, add-on treatment with felbamate (unlicensed use) can be considered, under the supervision of a neurologist with expertise in epilepsy. Non-pharmacological treatment options include vagus nerve stimulation, a ketogenic diet and surgery. The clinical experts stated that the NG217 treatment pathway for LGS is broadly reflective of clinical practice in the NHS. But, they noted that the choice of treatment regime is highly individualised and based on effectiveness, adverse effects, sedative effects and drug–drug interactions. The committee noted that it would be useful to see data on the proportion of people who would not have cannabidiol plus clobazam in NHS clinical practice. The company and clinical experts were unable to provide an estimate of the proportion of people who would not have cannabidiol plus clobazam because of the heterogeneity of LGS and the treatment options, and the rarity of LGS. The clinical experts noted that LGS can be difficult to diagnose because not all people display the characteristic symptoms (see section 3.1) at onset or at any one time. By the time people are diagnosed they have often already had most third-line treatment options. They also stated that

current treatments often do not control seizures associated with LGS. The patient carer experts noted that the currently available drugs that comprise standard care (SC) that initially work, can lose efficacy. The committee concluded that LGS is a heterogenous condition and there is an unmet need for treatments that reduce the number of drop seizures without markedly increasing adverse events.

Proposed positioning and comparators

3.3 The company positioned fenfluramine as a third-line add-on therapy, in line with the positioning of cannabidiol plus clobazam. Based on this positioning, the comparator included in the company submission was cannabidiol plus clobazam (plus SC). The company also provided a scenario comparing fenfluramine with SC alone. SC comprised a basket of treatments that included:

- clobazam
- levetiracetam
- valproate
- lamotrigine
- topiramate and
- rufinamide.

The EAG noted that clobazam, rufinamide and topiramate are recommended as third-line treatment options in NG217. So they should also be considered separately as comparators and not just within the basket of treatment options. The company highlighted the refractory nature of LGS and the heterogeneity of the treatment population. It noted that it is therefore not clinically or statistically meaningful to compare fenfluramine plus SC with individual or specific combinations of antiseizure medications, except cannabidiol plus clobazam plus SC. It added that it believed that cannabidiol plus clobazam plus SC is the only treatment with enough trial data to permit a robust comparison. The company also referenced the NICE technology appraisal guidance on

cannabidiol with clobazam for treating seizures associated with Lennox–Gastaut syndrome (from here referred to as TA615). In that appraisal, cannabidiol plus clobazam plus SC was compared with SC alone (referred to as 'current clinical management' in TA615 and defined as a 'basket of choices of antiepileptic drugs'). The committee recalled that the treatment pathway in LGS, particularly after second-line treatment, can be heterogeneous (see section 3.2). The committee considered that it would be helpful to have seen scenarios that considered clobazam, rufinamide and topiramate as separate comparators, if data was available. It added that data about the proportion of people with LGS using those treatments in the NHS would also be helpful. The company stated that it was unable to provide an estimate of the proportion of people using clobazam, rufinamide and topiramate in the NHS because of the heterogeneity of LGS and treatment options. It noted that these treatments are considered within the basket of treatments in the SC arm of Study 1601. It added that the healthcare professionals who were consulted considered the proportions of these treatments in the SC arm of Study 1601 to be reflective of clinical practice. The committee acknowledged that most of the studies where these treatments are considered separately, rather than in a basket of antiepileptic drugs, were conducted over 20 years ago. So, they do not reflect current clinical practice (see section 3.5). Because of this and the heterogeneity in the treatment population, it accepted that any comparisons where these treatments are considered separately may not be robust and clinically meaningful. At the first committee meeting, the committee concluded that the positioning of fenfluramine plus SC in the treatment pathway in line with cannabidiol plus clobazam plus SC was appropriate. It also concluded that cannabidiol plus clobazam plus SC and SC alone are appropriate comparators. In response to the draft guidance, the company stated that it did not consider SC alone to be an appropriate comparator. This is because data for the SC alone arm is only available for 3 months and so extrapolation beyond this relies on assumptions. It added that because of the heterogenous treatment pathway resulting in

various SC drugs being used, with varying costs and efficacy, the comparison with SC alone is much more uncertain than the comparison with cannabidiol plus clobazam plus SC. At the appeal panel meeting after the second committee meeting, clinical experts noted that there are some people for whom cannabidiol plus clobazam is unsuitable or ineffective and these people would instead have some other combination of treatments. But they noted that, because of the highly heterogenous nature of the disease, these treatments are also very heterogeneous. So, the clinical experts at the appeal panel meeting considered that SC alone was not a relevant comparator for fenfluramine plus SC. At the second committee meeting, the committee concluded that cannabidiol plus clobazam plus SC was a relevant comparator for fenfluramine plus SC and that most people who were eligible for fenfluramine plus SC would receive cannabidiol plus SC if fenfluramine was not available. But, it considered that fenfluramine would be suitable for some people who cannot have cannabidiol plus clobazam. It noted that it had not seen any evidence to suggest that it was possible to define any subpopulations that would be expected to receive a particular comparator, and so could not consider such subgroups separately. The committee understood that the data for SC from Study 1601 was only available for 3 months and that the extrapolation from short-term studies is inherently uncertain. So, there was substantial uncertainty associated with the comparison with SC alone. But, it considered that a comparison with a basket of SC treatments, as represented in Study 1601, would be informative for decision making, if evidence based.

Clinical effectiveness

Study 1601 and Study 1601 open-label extension

3.4 The primary clinical evidence for fenfluramine plus SC came from Study 1601 and an interim analysis of the Study 1601 open-label extension (OLE) study. Study 1601 was a phase 3, double-blind, international randomised controlled trial (RCT). It compared the efficacy

and safety of fenfluramine 0.2 mg/kg/day (n=89) and fenfluramine 0.7 mg/kg/day (n=87) as an add-on therapy to SC, with placebo plus SC (n=87). The trial period was 20 weeks. It recruited people aged between 2 and 35 years, with Epilepsy Study Consortium-confirmed LGS diagnoses, on stable antiseizure medication regimens. The EAG noted that the final scope outcomes included seizure frequency (overall and by seizure type) and seizure severity. But, it noted that the company reported seizure frequency for only drop seizures and seizure severity was not collected in the trial. The primary outcome was percentage reduction from baseline in drop-seizure frequency (DSF) per 28 days in the fenfluramine 0.7 mg/kg/day arm. At week 14 of the titration and maintenance period, the median percentage change from baseline in DSF was a 26.5% reduction in the fenfluramine 0.7 mg/kg/day arm. This was compared with a 7.6% reduction in the placebo arm (p=0.001). At week 14, the proportion of people with a reduction in DSF of 50% or more was 25.3% in the fenfluramine 0.7 mg/kg/day arm and 10.3% in the placebo arm (p=0.015). Study 1601 OLE (n=247) is an ongoing flexible-dose, single-arm study to assess the safety and efficacy of fenfluramine plus SC for people who completed Study 1601. All people were initially started on 0.2 mg/kg/day fenfluramine and after 1 month were titrated by effectiveness and tolerability, which were assessed at 3-month intervals. At the latest data cut, 142 people had completed 12 months of follow up. At year 1 of the OLE, the median percentage reduction in DSF from baseline was 51.8% (p<0.0001). The committee concluded that fenfluramine as an add-on to SC is more effective at reducing DSF than SC alone. The committee also noted the adverse events reported in Study 1601 (available in the summary of product characteristics [SPC] for fenfluramine). It acknowledged that the most common treatment-emergent adverse events were decreased appetite, drowsiness and fatigue, which occurred at a higher rate in the fenfluramine 0.7 mg/kg/day arm than in the fenfluramine 0.2 mg/kg/day arm.

RCT network meta-analyses

3.5 Because there was no direct head-to-head evidence for fenfluramine plus SC compared with cannabidiol plus clobazam plus SC, the company did a series of network meta-analyses (NMAs). Outcomes captured between 10- and 20-week timepoints were considered. Outcomes assessed were:

- median percentage reduction in frequency of generalised tonic–clonic seizures
- reductions in DSF of:
  - 25% or more
  - 50% or more
  - 75% or more
- discontinuation due to adverse events.

After the company's systematic literature review and feasibility assessment, 3 RCTs were identified (covering fenfluramine, cannabidiol and placebo only). The company did an NMA with these 3 RCTs, each with intention-to-treat (ITT) populations, referred to as the 'ITT data NMA'. But not everyone in the RCT for cannabidiol was also having clobazam. So, the company performed an additional NMA analysis using cannabidiol plus clobazam subgroup data, based on data published by the German health technology assessment body, the GBA (The Federal Joint Committee). This was referred to as the 'GBA data NMA'. The GBA data did not include sufficient data on the median reduction in frequency of generalised tonic–clonic seizures or the discontinuation due to adverse events. So, the ITT data NMA was used for these outcomes. Together, the ITT data NMA and the GBA data NMA formed the company's base-case NMA. The company stated that its base-case NMA point-estimate results at 14 weeks suggest that fenfluramine plus SC is most likely to be superior to placebo plus SC and cannabidiol plus clobazam plus SC for all outcomes assessed, except the 75% or more reduction in DSF. For all outcomes the credible intervals for fenfluramine and cannabidiol overlap. The exact credible intervals are considered confidential by the company and cannot be reported here. The EAG disagreed with the exclusion

following the feasibility assessment of 6 RCTs that included rufinamide, lamotrigine, clobazam and topiramate. It noted that rufinamide, topiramate and clobazam are recommended for consideration as third-line treatments in NG217. The company's rationale for the exclusion was that the 6 RCTs did not report all outcomes of interest or all key patient characteristics. It added that most of the excluded studies included data that was 20 to 30 years old and so do not capture improvement in LGS treatment. In its initial submission, the company considered that cannabidiol plus clobazam plus SC was the only relevant comparator (see section 3.3). It also provided a scenario analysis where SC alone was included as a comparator. Results from the NMA that comprised the 9 RCTs in the network suggested that, overall, some clinical benefits of some other third-line antiseizure medications used as monotherapies may be numerically superior to those of fenfluramine. The committee acknowledged the challenges of robust data collection in people with LGS (see section 3.3). The committee concluded that the comparative clinical effectiveness of fenfluramine plus SC and cannabidiol plus clobazam plus SC is uncertain. This was because of the mixed direction of results for the efficacy outcomes assessed at 14 weeks (titration and maintenance phase) and the overlapping credible intervals. It also noted the lack of robust data for rufinamide, topiramate and clobazam. So, the results of the indirect comparisons including these comparators as monotherapies were very uncertain.

Open-label extension

Method of imputation

3.6 At the first committee meeting, the committee noted that 247 people entered the Study 1601 OLE, but the number of people with data at 12 months was much lower. It noted that the data presented by the company did not account for people who did not complete the OLE or were lost to follow up. The committee considered that people lost to follow up are likely systematically different to people who continue treatment,

which the committee considered would bias the data. So it would have preferred to see analyses using the ITT populations, using the same methodology and assumptions to account for missing data in the Study 1601 OLE and cannabidiol OLE data. Specifically:

- State occupancy data for fenfluramine at months 3, 6, 9 and 12, assuming people who dropped out of the Study 1601 OLE had a less than 25% improvement in DSF, and not that they are missing at random.
- 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 people who leave the sample are missing at random.

In response to the draft guidance, the company identified available ITT data for the cannabidiol OLE, where there are reported response rates for drop seizures based on last observation carried forward (LOCF) analyses. For consistency, the company imputed missing values from the Study 1601 OLE data also using the LOCF method to produce ITT data for fenfluramine plus SC. The committee noted that the company had not done the imputation analyses that it had requested at the first committee meeting and considered that the LOCF method assumes people who leave the sample are missing at random. The company stated that because the LOCF method was used for both fenfluramine and cannabidiol OLE data, this alleviates any concern of bias. The committee considered that the analysis could be subject to bias but that the direction of bias was unclear. This is because of the difference in drop-out rates between the cannabidiol and fenfluramine OLE studies and because the LOCF assumes data is missing at random. It also considered that the LOCF imputation analyses used to derive the OLE ITT data could subsequently bias the results of the OLE NMA (see section 3.7). It concluded that it would like to see analyses assuming people who

dropped out of the Study 1601 OLE and the cannabidiol OLE had a less than 25% improvement in DSF.

NMA

3.7 The company did an additional NMA in response to consultation, based on the ITT populations of the OLE studies for fenfluramine and cannabidiol. The LOCF imputation method was used to derive the ITT populations for both fenfluramine and cannabidiol data (see section 3.6). Outcomes captured at week 1 to 12, weeks 13 to 14, weeks 25 to 36 and weeks 37 to 48 of the OLEs were considered. Outcomes assessed were reductions in DSF frequency of:

- 25% or more
- 50% or more
- 75% or more.

The OLE studies did not include a placebo control arm. So, the company assumed that the placebo response rates observed in the randomised controlled period would continue during the OLE period for each respective treatment. The company stated that its OLE NMA point-estimate results suggest that fenfluramine plus SC is most likely to be superior to placebo plus SC and cannabidiol plus SC for all outcomes assessed, except the 75% or more reduction in DSF. For all outcomes the credible intervals for fenfluramine and cannabidiol overlap. The credible intervals are considered confidential by the company and cannot be reported here. The EAG noted the following limitations with the OLE NMA within the context of the appraisal, which reduced its confidence in the results:

- Cannabidiol alone rather than cannabidiol plus clobazam was included as a comparator in the OLE NMA. The company noted that this was because data is not publicly available for people taking cannabidiol plus clobazam.

- The purpose of a placebo arm is to determine the true treatment effect on an intervention. Potential changes in the placebo response during the trials, for example because of changes in the participants' beliefs or the natural history of the disease, were not accounted for. This is a potential source of bias.
- Clinical heterogeneity between the populations does not appear to have been properly investigated and meta-regression (a statistical method to adjust for differences between trials in key characteristics) was not used.

The committee agreed with the limitations highlighted by the EAG. It also noted the limitations with the imputation method used by the company in the ITT analysis (see section 3.6). It concluded that because of the limitations with the imputation analyses and the OLE NMA methodology, the results of the OLE NMA were highly uncertain. Because of these limitations, the committee considered that the results were not sufficiently robust for decision making. The committee considered that it would be helpful to see an updated approach to the OLE NMA, which addressed its concerns with the methodology.

Economic model

Company's modelling approach

3.8 The company presented a 6-state cohort-based Markov model with a lifetime time horizon of 86 years. The model compared fenfluramine plus SC with cannabidiol plus clobazam plus SC and SC alone. Four health states were based on percentage reduction in DSF from baseline:

- state 0, for people with a less than 25% decrease in DSF
- state 1, for people with a 25% to less than 50% decrease in DSF
- state 2, for people with a 50% to less than 75% decrease in DSF
- state 3, for people with a 75% or greater decrease in DSF.

The model included 2 additional health states. One for people who discontinued treatment and an absorbing death state. In the model, there were 3 main phases:

- titration and maintenance
- treatment and
- subsequent follow up.

The titration and maintenance phase was modelled for a duration of 2 weeks (titration) and 3 months (maintenance). State occupancy was based on drop-seizure distribution at baseline in Study 1601. The model assumed that people remain in these health states during the titration and maintenance phase unless they either discontinue due to adverse events or die. After the titration and maintenance phase, people moved to the corresponding health state based on the efficacy data from the RCT NMA (see section 3.5). The model cycles lasted 3 months. For the SC arm, it was assumed that there was no change in state occupancy from cycle 2 onwards, except for people who die. Data informing state occupancies varied from cycles 2 to 9 for fenfluramine plus SC and cannabidiol plus clobazam plus SC (see section 3.12 and section 3.13). After cycle 9, the change in state occupancy was based on treatment waning, discontinuation and death (see section 3.14).

Health states based on relative reductions in drop seizures

3.9 The EAG highlighted concerns with basing health states on the relative reductions in drop seizures. It noted that this results in people with different numbers of absolute drop seizures being in the same health state, despite having significant differences in health-related quality of life (HRQoL) and costs. It added that this model structure based on relative reduction in drop seizures deviated from other published models in LGS and from the model used in TA615. So, it would prefer a model based on absolute reduction in drop seizures. The company stated that a modelling approach using absolute reductions in drop seizures was not feasible

because of the lack of absolute trial data for cannabidiol plus clobazam plus SC. It also highlighted that in its model, relative reduction in the percentage of DSF was translated to absolute DSF using the midpoint approach in Neuberger et al. (2020). This allowed the incorporation of healthcare resource use data from TA615, based on absolute DSF categories. The committee noted the very large interquartile ranges for the baseline median DSF in Study 1601 (2 to 1,761 and 7 to 1,803 for placebo and fenfluramine 0.7 mg/kg/day, respectively). It questioned the plausibility of using a relative approach, given the large difference in the absolute number of drop seizures for the treatment population. The committee noted that, as a result, it is highly uncertain to assume people in the same relative reduction in DSF health state have the same utility values and healthcare resource use. It considered that a model based on absolute reduction in DSF would be more robust. But it acknowledged other limitations that would have been present with a model with health states based on absolute DSF categories. So, although the committee had significant reservations about the appropriateness of the model structure, it agreed to use it to inform its decision making. It concluded that the model structure added uncertainty to the cost-effectiveness estimates.

Exclusion of non-drop seizures in model

3.10 The committee noted that the model only included drop seizures, and so did not include the impact of fenfluramine on other seizure types. It noted that it was unclear whether the exclusion of non-drop seizures from the model would favour fenfluramine or the comparators. It recognised that reducing non-drop seizures is important to people with LGS and their carers. But it understood that non-drop seizures are harder to measure and verify than drop seizures. It concluded that the absence of non-drop seizures in the model adds to the uncertainty around the economic analysis.

Modelling treatment effect during the OLE period

State occupancies versus transition probabilities

3.11 The treatment effect for cycles 2 to 5 was informed by the OLE studies for both fenfluramine plus SC and cannabidiol plus clobazam plus SC. For fenfluramine plus SC, in its initial modelling approach the company used patient-level data from the Study 1601 OLE to generate transition probabilities for cycles 2 to 5. There was a lack of patient-level data for the cannabidiol OLE. So, health-state occupancy for cannabidiol plus clobazam plus SC for cycles 2 to 5 was directly derived from state occupancies reported for the cannabidiol OLE. The EAG noted that for fenfluramine plus SC, there was a discrepancy between clinical trial state occupancy and the modelled state occupancy (derived using transition probabilities based on patient-level data from the Study 1601 OLE). This caused an overestimation of people in health states with better relative response in the fenfluramine plus SC arm and potentially an overestimation of the fenfluramine plus SC treatment effect. So, the EAG preferred to directly use the clinical trial state occupancy of fenfluramine plus SC in the model in its base case. The committee acknowledged the lack of patient-level data for the cannabidiol OLE, which prevented the company from calculating transition probabilities for the cannabidiol plus clobazam plus SC arm. It considered that it would prefer a consistent approach between fenfluramine plus SC and cannabidiol plus clobazam plus SC. It concluded that it would consider Study 1601 state occupancy data directly to determine health-state occupancy for fenfluramine plus SC for cycle 2 to cycle 5 for decision making.

Use of NMA data

3.12 At the first committee meeting, the committee noted that the data the company used to generate the transition probabilities for cycles 2 to 5 in the fenfluramine plus SC arm was based on treated-population data. That is, data based on people who were still having treatment at each respective timepoint. The company clarified that the cannabidiol OLE data that was used to populate the cannabidiol plus clobazam plus SC health

states was also based on treated-population data. The committee noted that using the treated population may be subject to bias. In response to the draft guidance, the company used the results of the OLE NMA analysis based on the ITT population (see section 3.7) to populate health states for fenfluramine plus SC and cannabidiol plus clobazam plus SC for cycles 2 to 5. The EAG noted that the company's initial modelling approach resulted in higher total patient and carer quality-adjusted life years (QALYs) gained in the observed period (cycle 2 to 5) for cannabidiol plus clobazam plus SC compared with fenfluramine plus SC. Whereas, the company's updated approach using OLE ITC data favours fenfluramine plus SC. Given the limitations of the OLE NMA highlighted by the EAG (see section 3.7), the EAG preferred to retain its original modelling approach. That is, modelling cycles 2 to 5's state occupancies for fenfluramine plus SC and cannabidiol plus clobazam plus SC based on the treated population in the fenfluramine and cannabidiol OLEs, respectively. The committee noted the potential bias introduced by using the treated population, rather than the ITT population, because the treated-population data does not account for people lost to follow up (see section 3.6). But it also noted the potential bias introduced by using LOCF imputation (see section 3.6). It also considered that the choice of imputation method (LOCF) would bias the comparison with SC alone in favour of fenfluramine plus SC. This is because in the placebo arm of Study 1601, which was used to model SC-alone treatment effectiveness, only a small proportion of people (4 out of 87) dropped out during the RCT period. Whereas in the Study 1601 OLE, 33.6% of people (83 out of 247) dropped out. The committee also noted that the methodological limitations with the OLE NMA also added to the uncertainty associated with the company's preferred method for modelling treatment effect for cycles 2 to 5. It noted that it would be helpful to see an updated approach to the OLE NMA which addressed its concerns with the methodology. But in the absence of this, it concluded that it was appropriate to use the OLE

treated-population data for modelling treatment effect for cycles 2 to 5 as a basis for decision making, despite its limitations.

Extrapolation of treatment effect

3.13 The company's model had a lifetime time horizon of 86 years. But, only 15 months of data for fenfluramine plus SC was available from Study 1601 and the OLE. So, extrapolation of treatment effect was needed beyond the trial period. For fenfluramine plus SC, the company's initial modelling approach assumed that the transition probabilities for cycles 6 to 9 equalled the transition probabilities of cycles 4 to 5, which were based on the last 3 months of the Study 1601 OLE. That is, it was assumed that the treatment effect for fenfluramine plus SC increased after the observed trial period. In contrast, the company assumed the treatment effect for cannabidiol plus clobazam plus SC was stable for cycles 6 to 9. This assumption was based on the experience of healthcare professionals using fenfluramine to treat Dravet syndrome and state occupancy data of fenfluramine and cannabidiol from the respective OLE studies. 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. The EAG highlighted that in NICE's technology appraisal guidance on fenfluramine for treating seizures associated with Dravet syndrome (from here referred to as TA808) a maintained treatment effect of fenfluramine was modelled based on the efficacy data. The EAG preferred to model a maintained treatment effect for fenfluramine plus SC treatment during cycle 6 to cycle 9 in its base case (in line with the assumed maintained treatment effect for cannabidiol plus clobazam plus SC). A clinical expert stated that the peak effect with fenfluramine is achieved quickly and would likely be achieved within the trial period. The committee analysed the Study 1601 OLE data that the company provided to support an increased treatment effect after the trial period. The committee noted from figure 9 of the company submission that 247 people entered the OLE study. But the

number of people with data at 12 months was substantially reduced, which the committee considered biased the data (see section 3.6). The company acknowledged this limitation with the Study 1601 OLE data. So, the committee was not convinced that the data supported an increasing treatment effect for fenfluramine after the trial period. After the first committee meeting, the company did imputation analyses based on all people who received open-label fenfluramine and used resulting data to perform an additional NMA (see section 3.7). The results of the NMA were used to populate health states for cycles 2 to 5 for fenfluramine plus SC and cannabidiol plus clobazam plus SC (see section 3.12). It also updated its base-case assumption for fenfluramine plus SC, assuming that treatment effect is maintained from cycles 6 to 9, in line with cannabidiol plus clobazam plus SC. That is, people stay in same health state as cycle 5 for cycles 6 to 9. The committee recalled that it had not seen OLE ITT data that appropriately accounted for attrition (see section 3.6). So it considered that there was substantial uncertainty regarding the plausibility of the extrapolation of treatment effect for cycles 6 to 9. It noted that the company's updated base-case analysis and EAG's base-case analysis both assumed a maintained treatment effect for fenfluramine plus SC and cannabidiol plus clobazam plus SC for cycles 6 to 9. Based on the lack of robust evidence to suggest an increased treatment effect for fenfluramine, the committee concluded that it would use the following as a basis for its decision making:

- a maintained treatment effect assumed for cycles 6 to 9 (for fenfluramine plus SC and cannabidiol plus clobazam plus SC)
- state occupancy based on the cycle 5 state occupancies for fenfluramine plus SC and cannabidiol plus clobazam plus SC in the EAG's base-case model.

But the committee considered that the uncertainty around a maintained treatment effect for cycles 6 to 9 had not been fully explored (for example, whether a decreasing treatment effect might be more appropriate).

Treatment waning

3.14 From cycle 10 onwards in the model, people in the fenfluramine plus SC and cannabidiol plus clobazam plus SC arms stayed in the same health state unless they experienced treatment waning, stopped treatment, or died. The company calculated the proportion of people experiencing treatment waning by:

- taking the proportion of people stopping because of lack of efficacy in the last 3 months of the Study 1601 OLE, which was 5.2%
- multiplying this proportion with the deteriorating transition probabilities based on all people on treatment from last 3 months of the Study 1601 OLE.

This was applied to both the fenfluramine plus SC arm and cannabidiol plus clobazam plus SC arm because of a lack of treatment waning data for the latter. The EAG explained that applying this to the health-state occupancies in cycle 10 resulted in only 0.58% and 0.48% of people moving to a worse health state for fenfluramine plus SC and cannabidiol plus clobazam plus SC, respectively. The EAG considered that this was extremely low. The EAG did a scenario in which the deteriorating transition probabilities from the last 3 months of Study 1601 were applied to 80% of people. This translated to observed percentages of 8.92% and 7.38% of people experiencing treatment waning in model cycle 10 for fenfluramine plus SC and cannabidiol plus clobazam plus SC, respectively. This had a large impact on the cost-effectiveness results. The committee noted that in TA615 the company assumed that people on cannabidiol stayed in the same health state from cycle 10 onwards (27 months) unless they stopped treatment or died. The company in that appraisal did a scenario analysis where 10% of people in all health states (except the seizure-free health state) stopped cannabidiol. The committee in TA615 concluded that this scenario captured some, but not all, of the treatment effect diminishing over time. In the current appraisal, the company provided 3 alternative scenarios:

- Applying the deteriorating transition probabilities from the last 3 months of the Study 1601 OLE to 19.6% of people from cycle 10 onwards. This proportion was based on the discontinuation of people who reported 'no effect' as the reason to end treatment with cannabidiol (as part of a long-term real-world evidence study in Germany on various epilepsy types).
- Applying the deteriorating transition probabilities from the last 3 months of the Study 1601 OLE to 30% of people from cycle 10 onwards. The company considered this to be a high assumption for this parameter.
- Assuming 10% discontinuation per cycle (a similar approach was explored in TA615 but in that appraisal the scenario assumed 10% discontinuation per year). This was implemented assuming equal percentage discontinuation from all health states.

The company also provided 1 observational study (Polega et al. 2022). It showed, based on pharmacy records, that during a 2-year period 6.8% of people with LGS having fenfluramine stopped because of lack of efficacy. The company stated that this provided evidence that applying the deteriorating transition probabilities from the last 3 months of Study 1601 to 5.2% of people in its base case was realistic. The committee noted that the value from Polega et al. was also much higher than the proportion of people who moved to a worse health state in cycle 10 in the company's base-case model, as described above. The committee considered that the key uncertainty was whether the company's approach of calculating treatment waning was appropriate, rather than whether the proportion of people stopping treatment because of lack of efficacy in the last 3 months of the Study 1601 OLE was reflective of clinical practice. Also, it noted that the figure from Polega et al. was based entirely on a US population. Whereas Study 1601 and the OLE also included people from centres outside of the US. So, it was unclear how applicable the figure is to UK clinical practice. The company also added that it considers assuming equal treatment waning for fenfluramine plus SC and cannabidiol plus clobazam plus SC to be a conservative assumption to reduce bias. At the

second committee meeting, a clinical expert stated that it is reasonable to use the last 3 months of the Study 1601 OLE to estimate the proportion of people experiencing treatment waning in the long term. The committee agreed that it was reasonable to use deteriorating transition probabilities based on the last 3 months of the Study 1601 OLE to model treatment waning for cycle 10 onwards. But, it considered that the way treatment waning had been applied in the company's base case (where these deteriorating transition probabilities were only applied to 5.2% of people each cycle) underestimated the level of treatment waning that was likely to occur in clinical practice. The committee noted that increasing the proportion of people experiencing treatment waning also increases the proportion of people stopping because of the stopping rule (see section 3.21). But it noted that this applied to the fenfluramine plus SC and cannabidiol plus clobazam plus SC treatment arms. At the appeal panel meeting after the second committee, clinical experts stated that treatment waning is not seen in clinical practice in people having antiepileptic treatments. So, the evidence from that last 3 months of the Study 1601 OLE may not be applicable to clinical practice. All scenarios that the committee had seen were based on evidence from the last 3 months of the Study 1601 OLE. So, it concluded that the most appropriate approach for calculating treatment waning in the model was uncertain. It considered that it needed to see evidence-based scenarios and additional justification for the company's preferred approach for modelling treatment waning.

Patient utility values

3.15 The company collected data from responses to the Quality of Life in Childhood Epilepsy-16 item questionnaire (QOLCE-16) in Study 1601 and the OLE. But it did not use the data in its model. It stated that the QOLCE-16 is a disease-specific measure and that long-term data was not yet available. The company used EQ-5D utility values from Verdian et al. (2008), a vignette-based conference abstract, to inform patient utility values. It chose this because it matched NICE's EQ-5D reporting

requirements, had been used previously in LGS models and aligned with the model's relative health-state structure. The company also considered 2 other studies reporting relevant utility values (Auvin et al. 2021 and Lo et al. 2021) but these were deemed less appropriate. Auvin et al. examined various types of epilepsies, including Dravet syndrome, which did not align with the patient population. Lo et al. did not align with the model's structure because it reported utilities for health states based on the total number of drop seizures per month. The EAG noted that the vignette approach used by Verdian et al. is condition-orientated and so may not capture all aspects that influence dimensions of the EQ-5D. Also, the values are not directly from people living with LGS. The company highlighted that vignette-based utility values may be useful in rare conditions such as LGS, where it is not possible to recruit a large enough representative sample. The EAG also considered the utility values to be relatively low and lack face validity when compared with the mean baseline QOLCE-16 scores from Study 1601. Also, it noted that the overall quality-of-life domain and most other domains of the QOLCE-16 showed hardly any clinically relevant change at visit 12 (end of study or end of treatment) compared with baseline. This indicates that the HRQoL of people with LGS may not be very sensitive to improvements in DSF. So, it considered that the large differences in utility values between the health states in the model seemed to lack face validity. The EAG used the Verdian et al. utility values in its base case, but considered that none of the sources of utility values in the company submission were ideal for informing HRQoL for people with LGS. The committee considered that all utility values presented in the company submission were associated with limitations. But, it recognised the challenges associated with obtaining robust utility values in rare conditions such as LGS. The committee concluded that the Verdian et al. utility values are associated with substantial uncertainty. But, they are likely the best available source of utility values given the use of health states based on relative reductions in drop seizures.

Carer utility values

3.16 The committee recalled that caring for someone with LGS has a substantial impact on carers' quality of life (see section 3.1). It considered that capturing this in the model is appropriate. The company included carer utilities for each health state in its base case by applying the same utility values from Verdian et al. (2008) used for people with LGS (see section 3.15). The company assumed 1.8 carers per person with LGS. The company assumed that the utility value of carers equalled that of people with LGS. This was because of a lack of LGS carer utility values in the literature and the substantial impact of LGS on carers who provide round-the-clock care. The EAG considered this assumption to be unrealistic. It highlighted that Auvin et al. (2021) and Lo et al. (2021) reported higher utility values for carers compared with people with LGS. It also noted that the Zarit Caregiver Burden Inventory results in Study 1601 suggested a mild to moderate carer burden and that carer burden may not be sensitive to changes in seizure frequency. The company's carer utility approach also meant that when a person with LGS in the model died, the corresponding carer utility value is set to 0. This overestimates this impact of mortality, given that the carer does not die together with the person they care for. The company also provided a scenario analysis in which carer disutility values were used (instead of utility values). The disutility values were obtained by calculating the difference between the visual analogue scale utility value for the UK general population and the UK carer utility scores for LGS estimated in Auvin et al. The resulting disutility value was then used to calculate a decrement applied to the QALYs for each treatment. Given the limitations with the carer utility approach, the EAG preferred to use the carer disutility approach in its base case. But, the EAG preferred to use disutility values calculated from Lo et al. in its base case (rather than Auvin et al.). This was because it considered that:

- the time trade-off approach from Lo et al. is better aligned with the NICE reference case (stating that a choice-based method should be used) than the visual analogue scale approach used by Auvin et al.
- the sample size of Lo et al. (n=150) was larger than the sample size of Auvin et al. (n=30)
- the DSF categories in Lo et al. better aligned with the DSF categories in the model compared with the DSF categories Auvin et al.

The committee considered that the responsibility for carers was substantial but would expect that the HRQoL for people living with the condition themselves to be lower than carers. 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 values, rather than disutility values. But, it noted that the EAG's application of the disutility approach resulted in negative total QALYs for all treatments. It considered that this lacked face validity given that no person or carer in the model is assumed to experience negative utility. The company stated that negative QALYs were inherent to the disutility approach in this case, considering that people with LGS have very low QALYs and require more than 1 carer. It clarified 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. The committee acknowledged the company's rationale for negative QALYs with the carer disutility approach and considered this was appropriate in this case. The committee concluded that it preferred to use the carer disutility approach in its base case, using disutility values calculated from Lo et al.

Fenfluramine maintenance dosage

3.17 The SPC for fenfluramine recommends increasing the dose of fenfluramine as tolerated up to the recommended maintenance dosage of 0.7 mg/kg/day. The company implemented a base-case maintenance

dosage for fenfluramine of 0.413 mg/kg/day. It stated the dosage was based on the mean daily dosage for fenfluramine for people in the Study 1601 OLE, in which efficacy continued to improve at lower average doses than used in Study 1601. This mean daily dosage excluded people who had dosages of more than 0.7 mg/kg/day (maximum licensed dosage) in the OLE. The company considered that the OLE dosage is more reflective of clinical practice than those in Study 1601 because dosages were titrated based on safety and tolerability in the OLE. It also suggested that the dosage was comparable to the average dosage of people with Dravet syndrome who are not on stiripentol. The EAG agreed that in clinical practice, dosages will be titrated based on tolerability, efficacy and safety. It noted that the mean daily dosage was lower than the maintenance dosage recommended in the SPC (that is, 0.7 mg/kg/day). The dosage also differed from the dosages that people had in Study 1601 (see section 3.4), which was used to inform the indirect treatment comparison. The EAG disagreed with the company's rationale for excluding people who had mean dosages of more than 0.7 mg/kg/day in the OLE from the calculation. It noted that people with a mean daily dose lower than the initial titration dosage (0.2 mg/kg/day) were included in company's calculation. And that people who had more than 0.7 mg/kg/day were included in clinical-effectiveness data used in the model. So the EAG preferred using the mean daily dosage for fenfluramine for all people in the Study 1601 OLE (including those who had more than 0.7 mg/kg/day), which was 0.416 mg/kg/day. The committee concluded that it preferred to use the mean dose from the Study 1601 OLE as this dose is likely to be most reflective of clinical practice. It agreed with the EAG's rationale that the maintenance dosage calculation should include people that had mean dosages of more than 0.7 mg/kg/day. So, the committee preferred to include a mean daily dosage for fenfluramine of 0.416 mg/kg/day.

Cannabidiol maintenance dosage

3.18 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. At the first committee meeting, the company assumed a base-case maintenance dosage for cannabidiol of 16 mg/kg/day. The company considered that 16 mg/kg/day is conservative based on clinical expert opinion and the cannabidiol OLE study. It highlighted that the mean modal dosage within the cannabidiol OLE was 24 mg/kg/day. The EAG noted that an average dosage of 12 mg/kg/day was used in TA615. It highlighted that the company also used the same data to model cannabidiol efficacy as that used in TA615. The clinical experts stated that in their experience the average maintenance dosage of cannabidiol was around 12 mg/kg/day to 15 mg/kg/day. The committee requested scenario analyses exploring a range of cannabidiol maintenance dosages from 12 mg/kg/day to 16 mg/kg/day. After the first committee meeting, the company provided these scenarios and updated its base-case maintenance dosage for cannabidiol to 14 mg/kg/day. But it considered that the mean maintenance dosage in practice is closer to 16 mg/kg/day. But the committee noted that cannabidiol RCTs demonstrated a statistically significant reduction in the number of drop and non-drop seizures at 10 mg/kg/day. The EAG modelled an average maintenance dosage of 12 mg/kg/day for cannabidiol in its base case. But it noted that this was uncertain and considered that the range between 12 mg/kg/day and 16 mg/kg/day should be considered for decision making. Based on clinical expert opinion and data from the cannabidiol OLE, the committee considered that it was appropriate to consider a range of cannabidiol maintenance dosages between 12 mg/kg/day and 16 mg/kg/day for decision making.

Treatment wastage

3.19 At the first committee meeting, clinical experts stated that there may be treatment wastage caused by bottle breakages or leftover liquid medicine in the bottle. Because the company's and EAG's initial analyses all assumed no wastage, the committee requested scenarios accounting for

the expected wastage costs associated with both cannabidiol and fenfluramine. The company provided scenarios in which it assumed:

- 5% wastage for both treatment arms
- 5% wastage for fenfluramine and 10% wastage for cannabidiol
- 0% wastage for fenfluramine and 10% wastage for cannabidiol.

The EAG noted that the assumed wastage percentages provided by company were not justified and so it was uncertain whether any of the scenarios were reflective of clinical practice. A patient carer expert stated that wastage of liquid treatments for LGS is often caused by the person having the treatment knocking it out of a carer's hand, which is not specific to the drug used. The clinical experts stated that some drug wastage does happen for both fenfluramine and cannabidiol, but that this is relatively small. A clinical expert estimated that they would typically lose 1 bottle of cannabidiol per year due to accidents or breakages, in their cohort of 45 adults. The committee noted that cannabidiol is an oily substance that is provided in glass bottles and that fenfluramine is a liquid that is provided in plastic bottles. So, it considered that there may be more treatment wastage of cannabidiol than of fenfluramine. But, the committee noted that it had not seen evidence-based scenarios for treatment wastage. For example, scenarios aligning with clinical expert opinion on how often wastage happens for fenfluramine and cannabidiol in clinical practice. So, it considered that the approach to incorporating treatment wastage in the model was uncertain.

Residential care

3.20 In its submission the company stated that most people will need residential care. The company did not include the impact of residential care in its initial base-case model but provided a scenario analysis including residential-care costs applied to 10% of people who reach age 18. This approach was similar to that used in TA615. In that appraisal, 10% of people experiencing seizures were assumed to need

residential care by the time they were 18 compared with 2% for people who were drop-seizure free. The EAG preferred to include the cost of residential care in its base case. It used the residential-care rate of 10% provided by the company, but noted that it was uncertain whether this figure was representative of NHS clinical practice. The EAG also considered that the impact of residential care on carer HRQoL should be modelled. In its base case it assumed that people who need residential care will need 0.7 carers (rather than 1.8). This was calculated based on the proportion of days per year that people who need residential care are expected to be at home. The patient carer experts explained that they would expect that most carers would prefer to look after people with LGS themselves rather than opting for residential care. The committee considered that some carers may not be able to provide adequate care because of their own health and so residential care may be the only option. The committee concluded that it was appropriate to assume 10% of people with LGS reaching 18 years old will need residential care. It also concluded that it was appropriate to include residential-care costs and to assume 0.7 carers for people needing residential care, to account for the reduced carer responsibility. The company updated its base-case model after the first committee meeting to align with the committee's preferences for residential care.

Stopping rule

3.21 The marketing authorisation for fenfluramine does not specify a stopping rule. But the company initially proposed a stopping rule whereby treatment is stopped if DSF has not reduced by at least 25% from baseline, assessed every 3 months. The EAG noted that in TA808, the committee recommended a stopping rule for people who had less than 30% reduction in DSF over a period of 6 months. This stopping rule was also in line with current practice for cannabidiol plus clobazam in LGS. At the clarification stage, healthcare professionals consulted by the company considered it reasonable to stop treatment if the reduction in DSF was

less than 25% to 30%. They also agreed it would be reasonable to assess outcomes every 6 months. The EAG preferred to apply the stopping rule applied in TA808. But, it noted that the stopping rule at 6 months appeared to be incorrectly implemented in the model. It explained that all people from health state 0 discontinued every 6 months, instead of only the people who were in health state 0 for 6 months. As a result, people who were in health state 0 for only 3 months also discontinued. In response to the draft guidance, the company stated that tracking people in the model in the cannabidiol plus clobazam plus SC arm would not be possible without transition probabilities, because patient-level data would be needed. The company implemented a revised stopping rule but the EAG considered this also had limitations and so preferred the company's initial approach. The committee concluded a stopping rule whereby fenfluramine is stopped if the DSF has not reduced by at least 30% from baseline, assessed every 6 months is reasonable. The company updated its base case after the first committee meeting to align with the committee's preferred stopping rule, whereby fenfluramine is stopped if the DSF has not reduced by at least 30% from baseline, assessed every 6 months.

Pulmonary hypertension

3.22 There were no cases of pulmonary arterial hypertension or valvular heart disease reported at any point in Study 1601 and its OLE. But, the committee were aware of a previous study by Souza et al. (2008). In that study, which analysed a cohort of fenfluramine-associated pulmonary hypertension cases, there was a median of 4.5 years between exposure and onset of symptoms. The committee questioned whether pulmonary arterial hypertension could be a cumulative dose-related adverse event and could potentially be an issue after using fenfluramine for more than 5 years. It considered whether the cost of treating pulmonary hypertension should be included in the model. The company highlighted that fenfluramine, when previously used as a weight-loss medication, was

prescribed at 60 mg/day, with dosages as high as 220 mg/day. And the association with heart disease was complicated by the lack of pretreatment echocardiograms and consideration of other risk factors. In contrast, the maximum daily dose of fenfluramine for LGS is 26 mg. The company explained that, based on the latest data, fenfluramine has been exposed for 5,203-patient years globally and there have been no confirmed cases of pulmonary arterial hypertension. After the second committee meeting, the company noted that pulmonary arterial hypertension has now been reported in 1 child having fenfluramine (at a dosage of 10.12 mg/day) for Dravet syndrome. When the child stopped taking fenfluramine, the reaction resolved. The committee considered that it would be helpful to have more information about pulmonary arterial hypertension in this population to understand if the associated costs should be included within the model. The company noted that as part of the controlled access programme stipulated by the Medicines and Healthcare products Regulatory Agency, people must have an echocardiogram every 6 months for the first 2 years on fenfluramine and annually thereafter. If an abnormality is detected, then fenfluramine would be stopped. The committee concluded that, based on the latest available data, it is appropriate not to model the cost of treatment for pulmonary arterial hypertension, but they would consider if this was still appropriate based on the most up to date data available.

Severity

3.23 The committee may apply a greater weight to QALYs (a severity modifier) if technologies are indicated for conditions with a high degree of severity (using an objective definition of severity), as set out by NICE. In NICE's health technology evaluations manual, severity is defined as the 'future health lost by people living with the condition with standard care in the NHS'. Absolute and relative QALY shortfall thresholds are then used to define sufficient future health loss for severity weighting. Based on the patient QALYs generated from the company's and EAG's models, the

company and EAG agreed that a severity modifier of 1.7 was appropriate. The company considered that this should be applied to people with LGS and their carers and so applied the severity modifier to both patient and carer QALYs in its base case. The EAG considered that carer QALYs should not be weighted so only applied the severity modifier to patient QALYs in its base case. The committee noted that in the NICE draft technology appraisal guidance on ganaxolone for treating seizures caused by CDKL5 deficiency disorder in people 2 years and over the committee concluded that the severity weighting should only be applied to people with the condition. It also noted that there is no evidence that society values QALY gains for carers of people with severe conditions above QALY gains for carers of people with 'non-severe' conditions. The committee noted that the absolute and proportional QALY shortfall calculations were based on people with LGS. It considered that the severity modifier could only potentially be applied to carer QALYs as well if they met the absolute and proportional requirements for the application of the severity modifier, and if this was supported by evidence. The company did not provide evidence to suggest that this was the case. So, the committee concluded that only applying the severity weight of 1.7 to the patient QALYs was appropriate. The company updated its base case after the first committee meeting to align with the committee's preference of only applying the severity modifier to patient QALYs.

Cost-effectiveness estimates

Acceptable incremental cost-effectiveness ratio

3.24 NICE's manual for health technology evaluations notes that judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the incremental cost-effectiveness ratio (ICER). The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee noted concerns around the high level of uncertainty, specifically:

- The lack of clinical-effectiveness and cost-effectiveness data for fenfluramine plus SC compared with rufinamide plus SC, topiramate plus SC and clobazam plus SC (see section 3.3 and section 3.5).
- The lack of clinical-effectiveness data for fenfluramine on seizure severity and frequency of seizure types other than drop seizures (see section 3.4).
- The results of the OLE NMA and the comparative clinical effectiveness of fenfluramine plus SC and cannabidiol plus clobazam plus SC (see section 3.7).
- The appropriateness of the company's model structure based on relative reduction in DSF (see section 3.9).
- The appropriateness of only using drop seizures in the modelling, and not other seizure types (see section 3.10).
- The lack of fenfluramine and cannabidiol ITT OLE data that account for data attrition in an appropriate manner, leading to uncertainty about:
  - The appropriateness of the data used to inform state occupancy between cycles 2 and 5 for the fenfluramine plus SC and cannabidiol plus clobazam plus SC arms (see section 3.12).
  - The appropriateness of assuming a maintained treatment effect between cycles 6 and 9 for the fenfluramine plus SC and cannabidiol plus clobazam plus SC arms (see section 3.13).
- The appropriateness of the patient utility values presented in the company submission (see section 3.15).

The committee needed more evidence and additional scenarios regarding:

- SC alone as a comparator for fenfluramine plus SC (see section 3.3)
- treatment waning in the economic model, including evidence-based scenarios and additional justification for the company's preferred approach (see section 3.14)

- treatment wastage in the economic model, evidence-based scenarios to be explored and additional justification for the company's preferred approach (see section 3.19).

The committee noted that decisions about the acceptability of the technology as an effective use of NHS resources should take account of the degree of certainty around the value for money. It noted that evidence generation in LGS is difficult because LGS is a rare condition impacting children. It took this into account in its decision making and considered how the nature of the condition affects the ability to generate high-quality evidence. It considered whether the uncertainties were a result of the nature of the condition or whether the uncertainties were resolvable. It considered that some of the uncertainties were associated with the rarity of the condition, such as the patient utility values (see section 3.15). But it considered that some of the uncertainties were potentially resolvable such as the use of ITT OLE data that does not assume data points are missing at random (see section 3.12). The committee was aware it should be cautious in accepting a higher degree of uncertainty in circumstances when the highest standard of evidence generation that should be expected in the circumstances has not been achieved and agreed no additional flexibility should be applied. Because of the high level of uncertainty in the clinical and economic evidence, the committee agreed that an acceptable ICER would be towards the lower end of the range NICE considers a cost-effective use of NHS resources.

Company and EAG cost-effectiveness estimates

3.25 In response to the draft guidance, the company only presented cost-effectiveness results against cannabidiol plus clobazam plus SC. But, in its response, the EAG included cost-effectiveness results, with the company's preferred assumptions, against cannabidiol plus clobazam plus SC and SC alone, for committee consideration. Because of confidential commercial arrangements for fenfluramine, the comparators and other treatments in the model, the exact cost-effectiveness estimates

are confidential and cannot be reported here. The company's deterministic base-case ICER for the comparison with cannabidiol plus clobazam plus SC was above the range normally considered an acceptable use of NHS resources. In the EAG's deterministic base-case analysis, for the comparison with cannabidiol plus clobazam plus SC, fenfluramine plus SC was dominated (that is, fenfluramine generated fewer QALYs and was more expensive than cannabidiol plus clobazam plus SC). The EAG's base ICER for the comparison with SC alone was higher than the range normally considered an acceptable use of NHS resources.

The committee's preferences

3.26 As a basis for decision making, the committee preferred the model to:

- use the OLE treated-population data for modelling treatment effect for cycles 2 to 5 for fenfluramine plus SC and cannabidiol plus clobazam plus SC (see section 3.11 and section 3.12)
- assume a maintained treatment effect for cycles 6 to 9 for fenfluramine plus SC and cannabidiol plus clobazam plus SC (see section 3.13)
- use the Verdian et al. (2008) utility values to model patient utility (see section 3.15)
- use a carer disutility approach using the Lo et al. (2021) carer utility values (see section 3.16)
- use the mean dose from the Study 1601 OLE as the fenfluramine maintenance dose, including people who received a mean dosage of more than 0.7 mg/kg/day (see section 3.17)
- consider a range of cannabidiol maintenance doses of 12 mg/kg/day to 16 mg/kg/day (see section 3.18)
- assume 10% of people with LGS reaching 18 years will need residential care (see section 3.20)
- include residential-care costs and assume 0.7 carers for people who need residential care (see section 3.20)

- include a stopping rule whereby treatment with fenfluramine is stopped if DSF has not reduced by at least 30% from baseline, assessed every 6 months (see section 3.21)
- not include treatment costs for pulmonary hypertension (see section 3.22)
- use a severity weight of 1.7 applied only to patient QALYs (see section 3.23).

The committee noted that there remained outstanding uncertainties in the economic modelling approach, including whether SC alone was an appropriate comparator and the appropriate assumptions for incorporating treatment waning and wastage. The committee would value further clinical input in response to consultation, and evidence-based scenarios for these issues that it could consider at a third committee meeting.

Other factors

Equality

3.27 The clinical experts highlighted that people with LGS have learning disabilities, so support is needed at appointments. A clinical expert also considered fenfluramine treatment will be started by specialists. But, because adults with LGS may not be under the care of a specialist, they may not have access to new treatments. A patient carer expert noted that some of the tests potentially needed to start fenfluramine may be traumatic for people with LGS who have sensory issues. The committee was aware of the need for equitable access to fenfluramine if it is recommended, but noted that access to treatments is an implementation issue that cannot be addressed in a technology appraisal recommendation. It was also aware of monitoring requirements for fenfluramine and noted that these should be considered before starting fenfluramine.

Uncaptured benefits

3.28 The committee also considered potential benefits of fenfluramine that were not included in the economic model. The company stated that there are a number of benefits not captured in the economic model, such as:

- reductions in:
  - duration of drop and non-drop seizures
  - losses to work productivity, which may also provide wider societal benefit
- improvements in:
  - the quality of life of siblings and other family members of people with LGS
  - the intellectual development of children with LGS, due to fewer seizures
  - motor function and
  - executive function.

The committee considered that it was unclear whether including these in the model would favour fenfluramine or the comparators. It concluded that any of these potential uncaptured benefits were unlikely to outweigh the committee's concerns about the cost-effectiveness estimates and the degree of uncertainty around the ICER.

Conclusion

3.29 The committee noted that there remained outstanding uncertainties in the economic modelling approach, including whether SC alone was an appropriate comparator and the appropriate assumptions for incorporating treatment waning and wastage. So, the committee could not arrive at a preferred ICER. But, the committee noted that company's deterministic base-case ICERs for the comparisons with cannabidiol plus clobazam plus SC was above the range normally considered an acceptable use of NHS resources. Also, in the EAG's deterministic base-case analysis, for the comparison with cannabidiol plus clobazam plus SC, fenfluramine plus SC was dominated (that is, fenfluramine generated fewer QALYs and was

more expensive than cannabidiol plus clobazam plus SC). So, fenfluramine could not be recommended for treating seizures associated with LGS as an add-on to other antiseizure medicines in people 2 years and over.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Raju Reddy

Vice chair, technology appraisal committee D

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Dilan Savani

Technical lead

Lizzie Walker

Technical adviser

Kate Moore

Project manager

Linda Landells, Lorna Dunning

Associate director

ISBN: [to be added at publication]

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 4pm on 3 December 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):	UCB Pharma Ltd

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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.	N/A
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	UCB overall comment: The response to the updated draft guidance is principally based on an updated base case which now assumes equal efficacy between fenfluramine with standard of care (FFA + SC) and its comparator, cannabidiol + clobazam + SC (CBD + CLB + SC). A separate response document called 'ID1651_Fenfluramine_LGS_response to DG2_3rd December 2024' provides UCB's overall response the updated draft guidance together with the updated base case and scenario analysis which incorporates the requested imputation analysis.

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NICE National Institute for Health and Care Excellence

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2	**Section 3.3. Proposed positioning and comparators** **Remaining uncertainty on whether SC alone is an appropriate comparator** UCB comment: Based on UCB's initial proposal, the evidence provided during the appeal hearing and the evidence from survey responses. UCB states the only appropriate comparator is CBD + CLB. Further description and analysis have been provided in the response document called 'ID1651_Fenfluramine_LGS_response to DG2_3rd December 2024 [CON]'.
3	**Section 3.7 NMA** **Request for imputation analysis.** "The committee considered that it would be helpful to see an updated approach to the OLE NMA, which addressed its concerns with the methodology." UCB comment: UCB has performed this imputation analysis and conducted the NMA based on this. The results of this are incorporated as a scenario and provided within 'ID1651_Fenfluramine_LGS_response to DG2_3rd December 2024 [CON]'.
4	**Section 3.14 Treatment waning** "It considered that it needed to see evidence-based scenarios and additional justification for the company's preferred approach for modelling treatment waning" UCB comment: UCB has further explored the subject of waning by surveying clinicians to gain a better understanding of the real-life effects of CBD and FFA. The results of the survey further led to the conclusion that waning should not be applied in the model. Further description and analysis have been provided within 'ID1651_Fenfluramine_LGS_response to DG2_3rd December 2024 [CON]'.
5	**Section 3.18 Cannabidiol maintenance dosage** "the committee considered that it was appropriate to consider a range of cannabidiol maintenance dosages between 12 mg/kg/day and 16 mg/kg/day for decision making." UCB comment: Further consideration and- a stronger evidence base is required for the base case as a dosage range between 12 mg/kg/day to 16 mg/kg/day risks heavily underestimating the true costs to the NHS for patients that are maintained on cannabidiol. UCB acknowledge some patients may be controlled on lower doses of cannabidiol. However, UCB obtained additional clinical expert opinion that stated most patients are dosed towards 20 mg/kg/day and therefore has updated the base case to reflect the upper limit of the dosage range the committee consider appropriate to consider (16 mg/kg/day). Further evidence has been provided within 'ID1651_Fenfluramine_LGS_response to DG2_3rd December 2024 [CON]'.
6	**Section 3.19 Treatment wastage** "The committee noted that cannabidiol is an oily substance that is provided in glass bottles and that fenfluramine is a liquid that is provided in plastic bottles. So, it considered that there may be

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

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	more treatment wastage of cannabidiol than of fenfluramine. But, the committee noted that it had not seen evidence-based scenarios for treatment wastage" UCB comment: To quantify wastage, the expert clinician survey gathered more evidence by asking clinical experts across England and Wales to estimate wastage for CBD and FFA. The resulting average assumptions of wastage have been applied in the base case, alongside a scenario for median wastage values within 'ID1651_Fenfluramine_LGS_response to DG2_3rd December 2024 [CON]'.
7	**Section 3.22 Pulmonary hypertension** "The committee concluded that, based on the latest available data, it is appropriate not to model the cost of treatment for pulmonary arterial hypertension, but they would consider if this was still appropriate based on the most up to date data available." UCB comment: Further detail has been provided in 'ID1651_Fenfluramine_LGS_response to DG2_3rd December 2024 [CON]'.
8	**Section 3.24 Cost-effectiveness estimates** **"But it considered that some of the uncertainties were potentially resolvable such as the use of ITT OLE data that does not assume data points are missing at random (see section 3.12).". "the committee agreed that an acceptable ICER would be towards the lower end of the range NICE considers a cost-effective use of NHS resources."** UCB comment: Given that UCB has been given the opportunity to attempt the imputation analysis, and therefore potentially resolve the uncertainty mentioned above, UCB request the committee consider revising the above wording to the effect that "an acceptable ICER would be within the full range that NICE considers a cost-effective use of NHS resources, if the company were to resolve issues around the use of ITT OLE data." Taking into full consideration the severe nature of LGS and the life limiting impact if has on patients and families. In addition, the- very real challenges of gathering data in this rare disease.

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If

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confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.

- 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.

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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 updated Draft Guidance with new base case based on equal efficacy and safety (cost-minimisation approach)

December 2024

File name	Version	Contains confidential information	Date
ID1651_Fenfluramine_LGS_Response to DG2_3rd December 2024 [Redacted]	1.0	Yes	3rd December 2024

Executive Summary

UCB's response to draft guidance 2 (DG2) is principally based on an updated base case which assumes equal efficacy between fenfluramine with standard of care (FFA + SC) and its comparator, cannabidiol + clobazam + SC (CBD + CLB + SC), i.e. a cost-minimisation approach. This approach is overwhelmingly supported by the opinion of clinical experts in the UK and acknowledges the different results produced by a naïve comparison (which results in less quality-adjusted life years – QALYs) and through an indirect treatment comparison (ITC) (resulting in more QALYs for FFA + SC compared with CBD + CLB + SC). Assuming equal efficacy enables a fair, reasonable and patient focused approach to support patients suffering from Lennox–Gastaut syndrome (LGS) by allowing another treatment option to be available. It reduces the uncertainties which have been highlighted by the committee with regards to comparison of efficacy between FFA and CBD.

The updated draft guidance refers to a number of perceived uncertainties, based on the "*economic modelling approach, including whether SC alone was an appropriate comparator and the appropriate assumptions for incorporating treatment waning and wastage*". UCB has aimed to provide additional evidence related to these uncertainties, and also the new proposal of equal efficacy; an expert healthcare professional (HCP) survey (hereafter mentioned as "HCP survey" see report attached to UCB response) was conducted in November 2024 which asked the opinion of 14 clinicians (that treat approximately 700 patients suffering from LGS within England and Wales). This represents a large cohort of expert HCP opinion, considering the rarity of LGS. Data from this survey was used in conjunction with the real-world evidence provided by clinicians during the appeal hearing to validate UCB's approach.

UCB acknowledges that the committee has requested submission of an imputation analysis applied to the open-label extension (OLE) network meta-analysis (NMA). UCB has conducted this analysis and provided it as a scenario, alongside the updated base case. In addition, UCB has [redacted]. Applying the [redacted] to the revised base case assumptions [redacted] alternative to the National Health Service (NHS) up to an

assumed discount of [redacted]% for CBD (see section 2.). It also enables FFA to be cost-effective up to a discount of [redacted]% for CBD (assuming a threshold of £[redacted] per QALY gained) and up to as discount of [redacted]% for CBD assuming a threshold of £[redacted] per QALY gained, when applying the imputation analysis to the OLE NMA (see scenario in section 3.).

UCB believes the updated proposition enables FFA + SC to be cost-effective vs CBD + CLB + SC in the ranges normally considered an acceptable use of NHS resources. There is a substantial need for further treatment options for this severe condition to mitigate its debilitating effects on the lives of children and adults. In these circumstances, UCB submit that FFA should now be accepted for NHS use based on the [redacted] and the scenarios that have been provided.

[redacted]

This response document is accompanied by 7 attachments, 4 Word reports and 3 Excel models:

- Draft Guidance Comments Form “ID1651 fenfluramine DG2 response form [noCON]”
- Report of the HCP survey “Survey on Treatment Pathways and Options for Patients in England and Wales with Lennox-Gastaut Syndrome 28 Nov 2024”
- Report of the OLE NMA “UCB Data on File, OLE NMA report 2024 - CONFIDENTIAL”
- Updated model: “ID1651_Fenfluramine_LGS_CEM_ Base Case Cost Min Analysis_Answers to DG2 _CON”

- Redacted version of the updated model: “ID1651_Fenfluramine_LGS_CEM_ Base Case Analysis_Answers to DG2_REDACTED”
- Scenario Analysis on OLE NMA “ID1651_Fenfluramine_LGS_CEM_ Scenario Analysis on OLE NMA_Answers to DG2 _CON”
- Updated confidentiality checklist form ” ID1651 Fenfluramine Confidential information checklist (DG) [noCON].docx”

1. Remaining uncertainties requiring evidence-based analyses

1.1. Comparison versus SC alone

The committee acknowledge that there is "*substantial uncertainty associated with the comparison with SC alone*", however there is still mention that "*a comparison with a basket of SC treatments, as represented by Study 1601, would be informative for decision making, if evidence based*." (2).

Summary comment and UCB's approach

As per the response to the draft scope, UCB maintains that "*fenfluramine is expected to be used as an add-on treatment following failure of combination of any of the standard of care treatments listed apart from cannabidiol plus clobazam. Fenfluramine is positioned to be provided as an alternative treatment option to cannabidiol plus clobazam* (as per fenfluramine's EMA Orphan Maintenance Assessment Report Jan 2023 (3))". This positioning has been confirmed by expert clinicians in committee meetings and appeal panel hearing.

The remaining uncertainty within DG2 appears to be based on FFA being suitable for some people who cannot have CBD + CLB. However, if CBD + CLB has already been considered, failed or deemed unsuitable, the only alternative treatment options at this stage of the pathway are invasive surgery or clinical trials (this was confirmed during the appeal hearing and further by the HCP survey; see the description of the results further below).

Expert clinicians have explained that the NICE treatment pathway does not reflect how patients are treated in clinical practice in the NHS. At the second appraisal committee meeting (6 March 2024), it was highlighted that standard SC treatments provide seizure control in ~0.7% of people with LGS, this means >99% of patients remain uncontrolled. It was also mentioned that "*people often increase dosage and/or increase number of medications to try to achieve seizure control*", which reflects the heterogenerity and therefore uncertainty in treating LGS (4).

UCB are reiterating, that at the stage of the treatment pathway where FFA or CBD are considered, patients have already been considered for or failed multiple SC combinations, and this has specifically been confirmed by patient expert testimonies

during the appeal hearing as well as HCPs based in England and Wales whom completed the HCP survey.

Based on this evidence which clarifies FFA's position in the pathway and alternative treatment options available, UCB have not incorporated any scenarios assuming a basket of SC drugs to be a comparator to FFA + SC.

The additional supporting evidence provided below provides concrete and substantial arguments supported by clinicians on why SC alone cannot be considered as a comparator to FFA + SC.

Clinical expert opinion at the appeal hearing (September 2024)(5)

On 6 September 2024, during the appeal hearing, the appeal panel discussed the appeals submitted by UCB, the Royal College of Physicians (RCP) and the Tuberous Sclerosis Association (TSA). All of which supported that SC alone is not a relevant comparator to FFA + SC, as this comparison is unreasonable and does not reflect NHS clinical practice. (5)

Prominent HCPs during the appeal hearing provided real-world evidence based on NHS clinical practice as to why CBD + CLB +SC is the only relevant comparator to FFA + SC. The panel concurred with the clinicians, patients, and UCB, stating that "*it was unreasonable for the committee to insist on an additional comparison of fenfluramine with standard of care alone*."(5). This decision was informed by significant input from clinical experts and patients.

The use of CBD +CLB as the only relevant comparator for FFA is supported by submitted evidence in response to the DG2 and testimonies made during the hearing of the appeal panel.

However, prior to the appeal hearing, the issue pending was regarding the treatment of patients when CBD +CLB was unsuitable or ineffective, leading the committee to assume that patients would revert to SC alone.

The RCP explained that, for those patients, "*given the highly heterogenous nature of the disease and current clinical practice in managing patients with LGS* […] *comparing fenfluramine and SC with SC alone had no clinical relevance*". Furthermore, the RCP agreed on the notion that "*a patient in a world without FFA who could not have CBD with clobazam would have SC is an oversimplification*" (5).

There is inconsistent evidence on how many patients fail CBD+CLB or are unsuitable for it, however, it remains true that the alternative treatment option for these patients are not SC drugs, but invasive surgeries or clinical trials.

Clinical expert opinion from the survey conducted by UCB (November 2024)

To reinforce the real-life experience of UK clinical and patient experts, as previously expressed by the RCP and TSA during the panel hearing, UCB conducted a structured expert elicitation in the form of a survey in November 2024 with 14 HCPs in England and Wales experienced in treating LGS (see details of all responses in the report attached to UCB response (6)).

- The survey findings indicate that, in response to Question 4, respondents estimated that an average of only 14% of patients are contraindicated to the combination of CBD + CLB. This highlights that the proportion of patients that are unsuitable for CBD + CLB is very low in clinical practice. Clinicians mentioned that "*very few cannot take cannabidiol*" and that its "*well maintained*", however others mentioned that patients had to "*withdraw due to side effects as well as ineffectiveness*".

- The majority of clinicians, 12 out of 14 (86%), confirmed that if patients cannot take CBD + CLB, the remaining options would be invasive surgeries or clinical trials (Question 5). This provides evidence that patients who stop taking/have failed or are unsuitable for CBD + CLB will not revert to a basket of SC treatment, but rather have the options available to them as above. Furthermore, for the 2 clinicians (14%) who answered 'No', they mentioned that a ketogenic diet or VNS could be options. We can see that those who answered 'No' did so specifically because of considering a ketogenic diet alongside surgeries or trials, opposed to them being considered for SC which have not yet been considered or reverting back to a basket of SC treatments. All these answers make comparing to SC alone irrelevant at this stage of the treatment pathway.

- When asked if the only relevant comparator to FFA + SC should be CBD + CLB + SC, a majority of clinicians, 12 out of 14 (84%), agreed (Question 6). For the two clinicians (14%) who answered 'No', one clinician mentioned that "*reasonable comparators would be FFA vs valproate+ clobazam or valproate + lamotrigine*", however, this same clinician agreed to the previous question, which asked if, when CBD + CLB + SC cannot be used, invasive surgeries or clinical trials were the only

remaining options. Therefore, the SC drugs mentioned as reasonable comparators, would only be reasonable if FFA were to be considered/positioned alongside SC treatments, and therefore before CBD + CLB + SC, which it is not. The remaining clinician responded that cenobamate should be considered, however this is can only be used in LGS as an unlicensed drug.

Based on the evidence provided during the appeal panel hearing and the supportive evidence from survey responses, UCB's base case approach is to only consider CBD + CLB as a comparator.

1.2. Waning

In DG2 post appeal, it is stated that the committee *"considered that it needed to see evidence-based scenarios and additional justification for the company's preferred approach for modelling treatment waning"* (Section 3.14, page 23) (2).

Summary comment and UCB's approach

UCB has further explored the subject of waning by surveying with clinicians to gain a better understanding of the real-life effects of CBD and FFA, ultimately concluding that there was no waning in clinical practice and should not be applied in the model.

If treatment waning is observed for CBD or FFA, it is during the '*honeymoon*' period (as described during the appeal panel hearing). A loss of efficacy during this period is accounted for in clinical practice by using the stopping rule, and that stopping rule is replicated in the model and applied every 6 months along the entire model duration. When considering the integration of efficacy waning in the cost-effectiveness model, it is important to note that the stopping rule has an active role and the highest impact on the simulation of patients being removed from treatment in the absence of (or insufficient) efficacy. Please see Appendix 1 for detailed explanation.

After the appeal, UCB explored further the topic of waning and through the HCP survey collected relevant information and provide evidence to justify its selection of input for waning in the model. As detailed below, the results of the HCP survey showed clinical experts do not experience waning for CBD or FFA.

Clinical expert opinion at the appeal hearing (September 2024)(5)

On 6 September 2024, during the appeal hearing, the appeal panel answered the appeal submitted by UCB regarding the committee's conclusions in relation to the waning of the treatment effects associated with FFA and CBD. Aligned with UCB's current position on waning, *"the panel were persuaded, having heard the opinions of other clinical experts that spoke in the hearing, that treatment waning is not seen in their clinical practice in patients receiving anti-epileptic treatment at this stage in the care pathway*" (5)

Dr Micheal Taylor, explained clearly during the meeting *"that lack of efficacy in some patients is managed through a stopping rule. In LGS clinical opinion is that waning is not routinely seen especially after two years. Indeed, in his and colleagues' experience nationally, if there is a persistent effect after a honeymoon period of 6 months there is no proof of declining efficacy. Everyday clinical practice suggests waning is not being seen after that point. Dr Taylor stated he had never been to a scientific epilepsy meeting or seen a paper about waning and there is good data saying that at 6 months a response to the drug predicts long term response*.". (5)

Clinical expert opinion from the survey conducted by UCB (November 2024)

The HCP survey further demonstrated that waning of efficacy is not seen by a majority of HCPs (see details of all responses in the report attached to UCB response).

When asked about treatment waning in clinical practice for patients taking CBD or FFA (question 7), nine out of fourteen experts confirmed there is no waning, and 4 mentioned some waning of efficacy. Among those 4 experts, two reported waning occurring in CBD patients but mentioned this was not observed for FFA:

"*I have not seen waning in children on FFA for seizures (admittedly using this for Dravet syndrome), but with cannabidiol this is possibly more marked*"

"*Waning does occur with CBD in my experience*"

Two other experts, commented on the 'honeymoon' period where waning "*may occur over a couple of weeks or a couple of months*". However, this is already captured in

the model through the observed data and stopping rule applied. There is no evidence of waning after this point.

Based on the evidence provided during the appeal hearing, the absence of evidence of waning from literature, supported by evidence from survey responses, UCB's base case approach for modelling treatment waning is to apply no waning (0%), applicable to both treatment groups (which aligns with the equal efficacy assumption in the cost-minimisation analysis).

1.3. Wastage

In DG2, the Committee continues to express concern regarding the issue of wastage: "*it considered that the approach to incorporating treatment wastage in the model was uncertain*" (Section 3.14, page 29) (2).

Summary statement and UCB's approach

In the initial base case provided by UCB, treatment wastage was not considered. At the first appraisal committee meeting (11 January 2024), clinical experts stated that there is treatment wastage caused by bottle breakages or leftover liquid medicine in the bottle for CBD only. UCB therefore submits that there is some wastage associated with CBD, while the wastage for FFA is minimal/non-existent. (7)

The appeal panel was aligned with this position, given the fact that CBD is an oily substance provided in glass bottles and FFA is a liquid provided in plastic bottles, the consequences of accidents or an inability to aspirate all of the contents of the vial are likely to be greater for CBD than for FFA. The appeal panel determined that "*it was unreasonable for the committee to conclude that drug wastage does not occur at all and that this is equally the case for fenfluramine and CBD*". Further details on the appeal are described below(2).

In order to validate UCB position and quantify the wastage, the HCP survey gathered more evidence by asking clinical experts across England and Wales to estimate wastage for CBD and FFA.

Further information has been provided below on the context, and how wastage for CBD and FFA was calculated.

Clinical expert opinion at the appeal hearing (September 2024) (5).

On 6 September 2024, during the appeal hearing, the appeal panel answered the appeal submitted by UCB regarding NICE's conclusion that it should assume no treatment wastage between FFA and CBD is inconsistent with the available evidence and therefore unreasonable. The appeal panel upheld this appeal. (5)

The appeal panel concluded that although drug wastage, in practice, is relatively small for both drugs, it does nonetheless occur. Particularly given that CBD is an oily substance provided in glass bottles and FFA in a liquid provided in plastic bottles, the consequences of accidents or an inability to aspirate all the contents of the vial are likely to be greater for CBD than for FFA. Although the panel accepted that this is likely to be a relatively small consideration regarding the economic modelling and its outcomes, it considered that it was unreasonable for the committee to conclude that "*drug wastage does not occur at all (0%) and that this is equally the case for FFA and CBD*". (5)

Clinical expert opinion from the survey conducted by UCB (November 2024)

In response to comments within DG2, a question was included into the HCP survey for both FFA and CBD (see details of all responses in the report attached to UCB response).

To the question about the number of bottles wasted per patient per year for CBD (Question 8), the median value from these results is [redacted] bottle ([redacted]%) wasted of CBD per patient per year (calculated by diving [redacted] by 22 bottles used per year[1]) and the mean wastage is [redacted]% (calculated by diving the average number of bottles used [redacted] by 22 bottles used per year).

To the question about the number of bottles wasted per patient per year for FFA (Question 9), the median value from these results is no (0) wastage, per patient per year and the mean wastage is[redacted]% (calculated by diving the average number of

[1] For CBD: an average of 22 bottles of cannabidiol (containing 10,000 mg) are used per year for an average patient weight of 42.8kg, and average dose of 14mg/kg/day"

bottles used [redacted] by 25 bottles used per year[2]). Most clinicians (11 out of 14) estimated there to be [redacted] for FFA.

Based on this evidence, a wastage assumption of [redacted]% for CBD and [redacted]% for FFA has been applied within the base case and median values were applied in scenario analysis.

1.4. Pulmonary arterial hypertension (PAH)

The committee initially questioned whether pulmonary arterial hypertension could be a cumulative dose-related adverse event that could be an issue after using FFA for more than 5 years, based on the results of a previous study by Souza et *al*. (2008) (8). Following provision of data, the committee concluded at the time that it is appropriate not to model the cost of treatment for pulmonary arterial hypertension. After the second committee meeting, UCB noted that pulmonary arterial hypertension has now been reported in 1 child having FFA (at a dosage of 10.12 mg/day) for Dravet syndrome. When the child stopped taking FFA, the reaction resolved. The committee considered that it would be helpful to have more information about pulmonary arterial hypertension in this population to understand if the associated costs should be included within the model (Section 3.22) (2).

As of August 2024, more than 8,000 patients around the world have been treated with Fintepla with only 1 resolvable case of PAH. UCB confirms that a case of PAH associated with Fintepla® (10.12 mg/day) was reported in a child with Dravet syndrome, as per the update within the most recent Summary of Product Characteristics (SmPC) (9). The patient discontinued treatment, and the reaction resolved post-discontinuation. UCB is not aware of additional costs and so treatment costs for pulmonary hypertension should continue to not be included. Regular echocardiogram monitoring allows an early identification of a potential PAH, and before associated physical signs. The symptoms of PAH develop slowly - a patient may not notice them for months or even years - therefore monitoring by physicians before, during, and after treatment with FFA ensures that any potential issues are detected early, and the appropriate remedial action is taken. As part of the controlled access programme stipulated by the Medicines and Healthcare products Regulatory

[2] For FFA: an average of 25 bottles of fenfluramine (containing 264 mg) are used per year based on an average patient weight of 42.8kg and average dose of 0.416mg/kg/day”

Agency, people must have an echocardiogram every 6 months for the first 2 years on FFA and annually thereafter; this is currently incorporated into the model.

PAH has not been observed in the LGS clinical programme and so far, no other post-marketing cases of PAH associated to FFA have been reported to date. Routine and additional pharmacovigilance activities are closely monitoring the safety profile of FFA around the world, including the conduct of EU, US and Japanese cardiovascular safety registry studies.

1.5 CBD maintenance dose

UCB acknowledges that the committee considers it is appropriate to consider a range of CBD maintenance dosages between 12 mg/kg/day and 16 mg/kg/day for decision making and has reconsidered the application of the average dose within the base case (Section 3.18) (2).

The EAG modelled a dose of 12 mg/kg/day as it noted the average dosage of 12 mg/kg/day was used in TA615 and that the 12 mg/kg/day is based on clinical experts stating that the average maintenance dose of CBD was around 12 mg/kg/day to 15 mg/kg/day. It should be noted that the 12 mg/kg/day dose applied within TA615 was based on assumptions made over 5 years ago and prior to long-term experience in the use of CBD that clinicians now have.

The average dose of 24 mg/kg/day dose observed within the open-label trial was generally consistent across each 12-week period as well as in the last 12 weeks of data for each patient (10). Furthermore, CBD has an uncapped dosing regimen, and as observed in the Open Label Extension (OLE) study, some patients are dosed up to 30 mg/kg/day.

Given the accepted maintenance dose of FFA is based on the average dose within its open-label trial (0.416 mg/kg/day), for consistency, the average maintenance dose for CBD within its open-label trial (24 mg/kg/day) should also be used. However, UCB attempted to gain further insight from UK clinicians as per below.

On Friday 29th November, UCB asked all 14 clinicians that answered the HCP survey a supplementary question on the average patient dose for their patients taking CBD.

Of the 7 clinicians that responded, three of the clinicians stated the maximum dose of 20 mg/kg/day is the average, three stated a range from 15 mg/kg/day to 20 mg/kg/day (two aiming for the maximum and another specifying 18 mg/kg/day) and another provided a dose range based on ml/day, equating to approximately 15 mg/kg/day to 20 mg/kg/day based on an average patient weight of 42.8kg. Table 1 presents the quotes shared by the clinicians in response to the supplementary question.

Table 1. Supplementary question: **For the patients well maintained on CBD, what would you say is the average patient dose (mg/kg/day)? (n=7)**

Respondent	Answer
Birmingham childrens hopsital	our maximum dose is usually 20mg/kg/day. The average dose is usually somewhere between 15 and 20mg/kg/day, say 18mg/kg/day.
Queen Elizabeth Hospital Birmingham	20 mg/kg/day
NUTH Newcastle	Most of my patients are on 7 to 10ml/daily (700mg to 1000mg a day) - I no longer prescribe by weight: 24/mg/kg would be 9ml bd - much higher than any dose I use in adults
Great Ormond Street Hospital, London	Most patients are on 20mg/kg/day, which is the maximum BNF recommended dose for LGS"
Bristol Royal Hospital for Children	The average patient dose is around 15-20mg/kg/day (as seizure freedom is almost never observed I tend to continue to increase the dose of CBD up to a max of 20mg/kg/day unless there are problematic side effects).
University Hospital of Wales	The children I have on CBD at the moment have a dosage that varies from 15mg/kg/d to 20mg/kg/d. I would probably aim for this as the maximum, and if either it was not effective or there were side-effects, then I would withdraw it after a period.
Great Ormond Street Hospital	the average dose is 20mg/kg/day

UCB acknowledge that some patients may be well maintained on lower doses, such as 12 mg/kg/day to 15 mg/kg/day. However, most clinicians treat patients between 15 mg/kg/day to 20 mg/kg/day and thus closer to the maximum recommended dose stated within the SmPC of 20 mg/kg/day (9). UCB acknowledges the committee's statement that it is appropriate to consider a range of CBD maintenance dosages between 12 mg/kg/day and 16 mg/kg/day for decision making. It was decided that the upper limit of NICE's acceptable range for CBD (16 mg/kg/day) be applied to the base case which utilises the cost-minimisation approach and is based on the real world evidence provided.

Scenarios for 12-15 mg/kg/day have also been provided to reflect the committee's request. However, considering the evidence base presented, assuming a dose of 16 mg/kg/day would remain a highly conservative assumption that underestimates the true cost of CBD to the NHS for patients that are currently maintained on this treatment option.

2. *New base case proposal*

UCB proposes a revised base case analysis using a cost-minimisation approach to mitigate uncertainties remaining with the naïve comparison approach as well as the updated OLE NMA (based on the requested imputation analysis) (see section 3.).

A naïve comparison between the trials inherently carries the largest uncertainty. Particularly as described at the appeal meeting, a naïve comparison is *"inconsistent with NICE's preference for using adjusted data*". (5) The naïve comparison is flawed to a worser extent to an ITC and does not account for uncertainty by providing a range via credible intervals, as opposed to an ITC approach. UCB acknowledge the committees request regarding the imputation analysis for the ITC. Comparing FFA to CBD does show that relative risks favour FFA, however, the credible intervals have a large overlap and there remains large uncertainty on the incremental QALYs that are produced. Large 95% CrI that encompass 1 may also suggest that the assumption of equal efficacy between FFA and CBD cannot be ruled out. A pragmatic and reasonable approach considering the evidence base, is to assume equal efficacy and safety, particularly in the absence of long-term data.

The cost-minimisation approach required expert clinical input for validation, and therefore is something that expert clinicians were asked in the HCP survey; whether it would be appropriate to assume equal efficacy between FFA and CBD for decision-making purposes (Question 10, see details of all responses in the see details of all responses in the report attached to UCB response).

The large majority, 93% (13/14), of the consulted clinicians agreed that this would be a suitable approach to take for decision making purposes. Specifically, clinicians commented the following.

“In my clinical experience fenfluramine is better tolerated and more effective than CBD. In terms of data from trials the differences are so small that it is not possible to determine statistically which is more effective.”

Using the equal efficacy and safety assumption, and considering the revised assumptions on waning, wastage and CBD’s dosage, [redacted]

Table 2. Summary of latest model assumptions compared to last base case

Input	UCB's last base case	Revised base case (cost-minimisation)	Commentary/ rationale
PAS discount for FFA	[redacted]	[redacted]	[redacted]
PAS discount for CBD	[redacted]	[redacted]	Unknown discount
FFA + SC efficacy	Cycle 1: NMA of RCT Cycles 2-5: NMA of OLE studies using LOCF Cycles 5-9: Maintained efficacy	Cycle 1: NMA of RCT Cycle 2-5: state occupancies from FFA OLE study Cycles 5-9: Maintained efficacy	Based on ITC results: large 95% CrI of encompassing 1 and expert opinion (from the survey n=14)
CBD + CLB + SC efficacy	Cycle 1: NMA of RCT Cycles 2-5: NMA of OLE studies using LOCF Cycles 5-9: Maintained efficacy	Equal efficacy as FFA for all cycles	Based on ITC results: large 95% CrI of encompassing 1 and expert opinion (from the survey n=14)
Safety & discontinuation	AEs & discontinuation rates from respective FFA and CBD studies	AEs & discontinuation rates from FFA study (equal between the two treatment groups)	Needed for a cost-minimisation assumption
Treatment waning	Applied to 5.2% of the patients	No waning in either treatment group	Based on expert opinion (from the survey n=14) and aligned with the cost-minimisation approach
Severity modifier application	Applied at the 1.7 level	No severity modifier applied	Not applicable to equal efficacy and safety approach
FFA maintenance dose	0.413 mg/kg/day	0.416 mg/kg/day	Including FFA patients taking the dosage above the daily cap as per committee preferred assumptions
CBD maintenance dose	14 mg/kg/day	16 mg/kg/day (varied from 12 up to 15mg)	Based on expert opinion (supplementary questions following the survey n = 7). Varied as requested within DG2
Wastage	0%	[redacted]% for CBD and [redacted]% for FFA	Based on expert opinion (from the survey, n=14)

Abbreviations: AE, Adverse Events; CBD, Cannabidiol; CBD + CLB, Cannabidiol with Clobazam; CrI, Credible Intervals; DG2, 2nd Draft Guidance; DSF, Drop Seizure Frequency; FFA, Fenfluramine; ITC, Indirect Treatment Comparison; LOCF, Last Observation Carried Forward; mg/kg/d, milligrams per kilogram per day; NMA, Network Meta-Analysis ; OLE, Open-Label Extension; PAS, Patient Access Scheme; SC, Standard of Care; QALYs, Quality-Adjusted Life Years; RCT, Randomised Clinical Trial.

The updated base case cost-minimisation results are presented below in Table 3 and Table 4.

The cost-minimisation analysis assumes equal efficacy and safety for both treatment arms (FFA + SC and CBD + CLB + SC), which implies that FFA and CBD are considered equivalent in terms of efficacy, waning, AEs and discontinuation rates across all cycles. Table 3presents the results of this analysis. As a result, the analysis focuses solely on the costs associated with each treatment arm at each cycle. The results demonstrate that FFA is [redacted] compared to CBD, with [redacted] amounting to [redacted] per patient. These [redacted] are mainly driven by [redacted] treatment costs ([redacted]) associated with FFA, with [redacted] from a reduced need for treating seizures (-£905).

Table 3. Updated base-case cost-minimisation results: FFA + SC (at PAS price) versus CBD + CLB + SC (at list price)

Cost types	Intervention cost (£) (FFA + SC)	Comparator cost (£) (CBD + CLB + SC)	Increment (£)
Treatment costs	[redacted]	[redacted]	[redacted]
Monitoring costs	521	0	521
Disease management cost – seizure-associated care	29,219	30,124	-905
ASM cost	1,981	3,303	-1,322
Total	[redacted]	[redacted]	[redacted]

Abbreviations: ASM, Antiseizure Medication; CBD + CLB, Cannabidiol with Clobazam; FFA, Fenfluramine; PAS, Patient Access Scheme; SC, Standard of Care.

With [redacted], and in-keeping with the assumptions presented above, FFA [redacted] to CBD until a [redacted] discount is applied to CBD (see Table 4).

Table 4. Updated base-case cost-minimisation results: FFA + SC (at PAS price) versus CBD + CLB + SC (at different discount levels)

CBD discount level	Technologies	Incremental costs
5%	FFA + SC vs CBD + CLB + SC	[redacted]
10%	FFA + SC vs CBD + CLB + SC	[redacted]
15%	FFA + SC vs CBD + CLB + SC	[redacted]
20%	FFA + SC vs CBD + CLB + SC	[redacted]
25%	FFA + SC vs CBD + CLB + SC	[redacted]
30%	FFA + SC vs CBD + CLB + SC	[redacted]
35%	FFA + SC vs CBD + CLB + SC	[redacted]
40%	FFA + SC vs CBD + CLB + SC	[redacted]
45%	FFA + SC vs CBD + CLB + SC	[redacted]

CBD discount level	Technologies	Incremental costs
50%	FFA + SC vs CBD + CLB + SC	[redacted]
55%	FFA + SC vs CBD + CLB + SC	[redacted]
60%	FFA + SC vs CBD + CLB + SC	[redacted]
65%	FFA + SC vs CBD + CLB + SC	[redacted]
70%	FFA + SC vs CBD + CLB + SC	[redacted]
75%	FFA + SC vs CBD + CLB + SC	[redacted]
80%	FFA + SC vs CBD + CLB + SC	[redacted]
85%	FFA + SC vs CBD + CLB + SC	[redacted]
90%	FFA + SC vs CBD + CLB + SC	[redacted]
95%	FFA + SC vs CBD + CLB + SC	[redacted]

Abbreviations: CBD + CLB, Cannabidiol with Clobazam; FFA, Fenfluramine; PAS, Patient Access Scheme; SC, Standard of Care.

Scenario on treatment wastage (Scenario A) and CBD OLE dosage (Scenario B) are presented in tables Table **5** and Table 6.

Scenario A: Wastage of FFA and CBD treatments

This alternative scenario examines the impact of adjusting the wastage for CBD and for FFA, considering [redacted]% wastage for FFA and [redacted]% wastage for CBD (as per the median values). The results show a minimal impact of considering median values versus average values for wastage of FFA and CBD.

Table 5. Scenario on treatment wastage results: FFA + SC (at PAS price) versus CBD + CLB + SC (at list price)

Scenario description	Updated base case Average wastage parameters		Scenario Median wastage parameters		Incremental costs	
	FFA	CBD	FFA	CBD	Updated base case	Scenario
Treatment wastage	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]	[redacted]

Abbreviations: CBD, Cannabidiol; CBD + CLB, Cannabidiol with Clobazam; FFA, Fenfluramine; PAS, Patient Access Scheme; SC, Standard of Care.

Scenario B: CBD dosages for the OLE period

Four scenarios are conducted based on different dosages of CBD during the OLE period: varied from 12 mg/kg/day up to 15 mg/kg/day, considering that the updated base case dosage for CBD was at 16 mg/kg/day (see Table 6). Treatment with FFA compared to CBD [redacted]

Table 6. Scenario on CBD OLE dose results: FFA + SC (at PAS price) versus CBD + CLB + SC (at list price)

Scenario description	Updated base case Parameters	Scenario Parameters	Incremental costs	
	CBD OLE dose	CBD OLE dose	Updated base case	Scenario
Varying CBD OLE dose from 12mg/kg/d up to 15mg/kg/d	16 mg/kg/d	15 mg/kg/d	[redacted]	[redacted]
	16 mg/kg/d	14 mg/kg/d	[redacted]	[redacted]
	16 mg/kg/d	13 mg/kg/d	[redacted]	[redacted]
	16 mg/kg/d	12 mg/kg/d	[redacted]	[redacted]

Abbreviations: CBD, Cannabidiol; CBD + CLB, Cannabidiol with Clobazam; FFA, Fenfluramine; mg/kg/d, milligrams per kilogram per day; OLE, Open Label Extension; PAS, Patient Access Scheme; SC, Standard of Care.

Sensitivity analyses around the updated base case were conducted and presented below.

Deterministic Sensitivity Analyses

The tornado diagram plotting the 20 parameters with most impact on the cost-savings in the cost-minimisation analysis is displayed in 1 and highlights that FFA [redacted] throughout variation in all parameters.

The tornado diagram shows that the three most impactful parameters influencing the incremental costs is weight for all age groups (12-17 years, 18-35 years, >35 years).

Figure 1. Updated tornado diagram for the drivers of cost-minimisation analysis: FFA + SC (at PAS price) vs CBD + CLB + SC (at list price)

Abbreviations: CBD + CLB, Cannabidiol with Clobazam; FFA, Fenfluramine; GTC, Generalised Tonic-Clonic; HCRU, Healthcare Resource Use; PAS, Patient Access Scheme; SC, Standard of Care; SUDEP, Sudden Unexpected Death in Epilepsy; T+M, Titration and Maintenance.

3. Scenario with imputation applied to OLE NMA in the cost-effectiveness analysis

3.1. Imputation method for the OLE period data & OLE NMA

In response to consultation, UCB has submitted new analyses to address the limitations with the imputation of missing data.

UCB acknowledge that the committee "*would like to see analysis assuming people who dropped out of the study 1601 OLE and the CBD OLE has a less than 25% improvement in DSF*" and "*considered that it would be helpful to see an updated approach to the OLE NMA, which addressed its concerns with the methodology*".

As a first step, a new imputation method was implemented accounting for people who did not complete the OLE or were lost to follow up. Patients with missing data at a given timepoint were assumed to have less than 25% reduction in frequency of drop seizures at that timepoint, so that the total number of patients in a given arm was the

same at each timepoint (247 and 364 patients for FFA and CBD respectively). The same methodology was applied to both OLE studies. Table 7 below reflects the new datasets used for each OLE studies. (11-13) The placebo effect is assumed to remain stable over time and was assessed from the respective phase III studies. (14, 15) The corresponding results of the NMA can be found in Table 8, and were inserted in the cost-effectiveness model.

More details on the OLE NMA can be found in OLE NMA report 2024 (see details the report attached to UCB response) (16).

Table 7. OLE NMA datasets using new imputation method

Study	Treatment arm	Outcome	Timepoint (weeks)	N (number of patients)	R(number of events)
Thiele 2019	PLACEBO	≥ 25% REDUCTION	12	161	70
Thiele 2019	CANNABIDIOL	≥ 25% REDUCTION	12	364	251
ZX008	PLACEBO	≥ 25% REDUCTION	12	87	27
ZX008	FENFLURAMINE	≥ 25% REDUCTION	12	247	136
Thiele 2019	PLACEBO	≥ 50% REDUCTION	12	161	31
Thiele 2019	CANNABIDIOL	≥ 50% REDUCTION	12	364	178
ZX008	PLACEBO	≥ 50% REDUCTION	12	87	8
ZX008	FENFLURAMINE	≥ 50% REDUCTION	12	247	81
Thiele 2019	PLACEBO	≥ 75% REDUCTION	12	161	9
Thiele 2019	CANNABIDIOL	≥ 75% REDUCTION	12	364	106
ZX008	PLACEBO	≥ 75% REDUCTION	12	87	3
ZX008	FENFLURAMINE	≥ 75% REDUCTION	12	247	30
Thiele 2019	PLACEBO	≥ 25% REDUCTION	24	161	70
Thiele 2019	CANNABIDIOL	≥ 25% REDUCTION	24	364	244
ZX008	PLACEBO	≥ 25% REDUCTION	24	87	27
ZX008	FENFLURAMINE	≥ 25% REDUCTION	24	247	128
Thiele 2019	PLACEBO	≥ 50% REDUCTION	24	161	31
Thiele 2019	CANNABIDIOL	≥ 50% REDUCTION	24	364	187
ZX008	PLACEBO	≥ 50% REDUCTION	24	87	8
ZX008	FENFLURAMINE	≥ 50% REDUCTION	24	247	81
Thiele 2019	PLACEBO	≥ 75% REDUCTION	24	161	9
Thiele 2019	CANNABIDIOL	≥ 75% REDUCTION	24	364	110
ZX008	PLACEBO	≥ 75% REDUCTION	24	87	3
ZX008	FENFLURAMINE	≥ 75% REDUCTION	24	247	34
Thiele 2019	PLACEBO	≥ 25% REDUCTION	36	161	70
Thiele 2019	CANNABIDIOL	≥ 25% REDUCTION	36	364	229
ZX008	PLACEBO	≥ 25% REDUCTION	36	87	27
ZX008	FENFLURAMINE	≥ 25% REDUCTION	36	247	123
Thiele 2019	PLACEBO	≥ 50% REDUCTION	36	161	31

Study	Treatment arm	Outcome	Timepoint (weeks)	N (number of patients)	R(number of events)
Thiele 2019	CANNABIDIOL	≥ 50% REDUCTION	36	364	179
ZX008	PLACEBO	≥ 50% REDUCTION	36	87	8
ZX008	FENFLURAMINE	≥ 50% REDUCTION	36	247	81
Thiele 2019	PLACEBO	≥ 75% REDUCTION	36	161	9
Thiele 2019	CANNABIDIOL	≥ 75% REDUCTION	36	364	113
ZX008	PLACEBO	≥ 75% REDUCTION	36	87	3
ZX008	FENFLURAMINE	≥ 75% REDUCTION	36	247	37
Thiele 2019	PLACEBO	≥ 25% REDUCTION	48	161	70
Thiele 2019	CANNABIDIOL	≥ 25% REDUCTION	48	364	155
ZX008	PLACEBO	≥ 25% REDUCTION	48	87	27
ZX008	FENFLURAMINE	≥ 25% REDUCTION	48	247	119
Thiele 2019	PLACEBO	≥ 50% REDUCTION	48	161	31
Thiele 2019	CANNABIDIOL	≥ 50% REDUCTION	48	364	119
ZX008	PLACEBO	≥ 50% REDUCTION	48	87	8
ZX008	FENFLURAMINE	≥ 50% REDUCTION	48	247	79
Thiele 2019	PLACEBO	≥ 75% REDUCTION	48	161	9
Thiele 2019	CANNABIDIOL	≥ 75% REDUCTION	48	364	75
ZX008	PLACEBO	≥ 75% REDUCTION	48	87	3
ZX008	FENFLURAMINE	≥ 75% REDUCTION	48	247	41

Table 8. Results of OLE NMA with requested imputation method

3.2. Results of scenario with imputation applied to NMA

For the scenario analysis using the updated OLE NMA with the requested method for imputation analysis, FFA is considered at the [redacted] ([redacted]) and CBD at list price.

In this scenario, in Table 9, treatment with FFA vs CBD is [redacted]. When applying discounts to the CBD price in 5% increments (ranging from 5% to 95%), FFA (at its PAS price) remains cost-effective compared to CBD until a discount level of [redacted], see Table 10.

Table 9. Scenario (using updated OLE NMA) results with severity modifier applied: FFA + SC (at PAS price) versus CBD + CLB + SC (at list price)

Technologies	Total costs (£)	Total LYG	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
FFA + SC	[redacted]	20.30	-18.45	[redacted]	0.09	0.57	[redacted]
CBD + CLB + SC	[redacted]	20.21	-19.02	-	-	-	-

Abbreviations: CBD + CLB, Cannabidiol with Clobazam; FFA, Fenfluramine; ICER, Incremental Cost-Effectiveness Ratio; LYG, Life Years Gained; QALYs, Quality-Adjusted Life Years; PAS, Patient Access Scheme; SC, Standard of Care.

Table 10. Scenario (using updated OLE NMA) results with severity modifier applied: FFA + SC (at PAS price) versus CBD + CLB + SC (at different discount levels)

CBD discount level	Technologies	Incremental costs	Incremental QALYs	ICER
5%	FFA + SC vs CBD + CLB + SC	[redacted]	0.57	[redacted]
10%	FFA + SC vs CBD + CLB + SC	[redacted]	0.57	[redacted]
15%	FFA + SC vs CBD + CLB + SC	[redacted]	0.57	[redacted]
20%	FFA + SC vs CBD + CLB + SC	[redacted]	0.57	[redacted]
25%	FFA + SC vs CBD + CLB + SC	[redacted]	0.57	[redacted]
30%	FFA + SC vs CBD + CLB + SC	[redacted]	0.57	[redacted]
35%	FFA + SC vs CBD + CLB + SC	[redacted]	0.57	[redacted]
40%	FFA + SC vs CBD + CLB + SC	[redacted]	0.57	[redacted]
45%	FFA + SC vs CBD + CLB + SC	[redacted]	0.57	[redacted]
50%	FFA + SC vs CBD + CLB + SC	[redacted]	0.57	[redacted]
55%	FFA + SC vs CBD + CLB + SC	[redacted]	0.57	[redacted]
60%	FFA + SC vs CBD + CLB + SC	[redacted]	0.57	[redacted]
65%	FFA + SC vs CBD + CLB + SC	[redacted]	0.57	[redacted]
70%	FFA + SC vs CBD + CLB + SC	[redacted]	0.57	[redacted]
75%	FFA + SC vs CBD + CLB + SC	[redacted]	0.57	[redacted]
80%	FFA + SC vs CBD + CLB + SC	[redacted]	0.57	[redacted]

CBD discount level	Technologies	Incremental costs	Incremental QALYs	ICER
85%	FFA + SC vs CBD + CLB + SC	[redacted]	0.57	[redacted]
90%	FFA + SC vs CBD + CLB + SC	[redacted]	0.57	[redacted]
95%	FFA + SC vs CBD + CLB + SC	[redacted]	0.57	[redacted]

Abbreviations: CBD + CLB, Cannabidiol with Clobazam; FFA, Fenfluramine; ICER, Incremental Cost-Effectiveness Ratio; NMA, Network Meta-Analysis; OLE, Open Label Extension; PAS, Patient Access Scheme; QALYs, Quality-Adjusted Life Years; SC, Standard of Care.

The alternative scenarios on treatment wastage (Alternative scenario A) and CBD dosage (Alternative scenario B) are presented in Table 11 and Table 12.

Alternative scenario A: Wastage of FFA and CBD treatments applied to the OLE NMA cost-effectiveness analysis

This alternative scenario examines the impact of adjusting the wastage for CBD and for FFA, considering [redacted]% wastage for FFA and [redacted]% wastage for CBD (as per the median values). The results show a minimal impact of considering median values versus average values for wastage of FFA and CBD.

Table 11. Alternative scenario (using updated OLE NMA) on treatment wastage results: FFA + SC (at PAS price) versus CBD + CLB + SC (at list price)

Scenario description	Reference scenario Average wastage parameters		Alternative scenario Median wastage parameters		Reference scenario Results			Alternative scenario Results		
	FFA	CBD	FFA	CBD	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Treatment wastage	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]	0.57	[redacted]	[redacted]	0.57	[redacted]

Abbreviations: CBD, Cannabidiol; FFA, Fenfluramine; ICER, Incremental Cost-Effectiveness Ratio; PAS, Patient Access Scheme; QALYs, Quality-Adjusted Life Years SC; Standard of Care.

Alternative scenario B: CBD dosages for the OLE period applied to the OLE NMA cost-effectiveness analysis

Four alternative scenarios are conducted based on different dosages of CBD during the OLE period: varied from 12 mg/kg/day up to 15 mg/kg/day, considering that the updated base case dosage for CBD was at 16 mg/kg/day (see Table 6). Treatment with FFA compared to CBD is [redacted].

Table 12. Alternative scenario (using updated OLE NMA) on CBD OLE dose results: FFA + SC (at PAS price) versus CBD + CLB + SC (at list price)

Scenario description	Reference scenario Parameters	Alternative scenario Parameters	Reference scenario Results			Alternative scenario Results		
	CBD OLE dose	CBD OLE dose	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Varying CBD OLE dose from 12mg/kg/d up to 15mg/kg/d	16 mg/kg/d	15 mg/kg/d	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	16 mg/kg/d	14 mg/kg/d	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	16 mg/kg/d	13 mg/kg/d	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	16 mg/kg/d	12 mg/kg/d	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CBD, Cannabidiol; FFA, Fenfluramine; mg/kg/d, milligrams per kilogram per day; ICER, Incremental Cost-Effectiveness Ratio; OLE, Open Label Extension; PAS, Patient Access Scheme; QALYs, Quality-Adjusted Life Years SC; Standard of Care.

Sensitivity analyses around the scenario using the updated OLE NMA were conducted and presented below.

Probabilistic Sensitivity Analyses

Results from the PSA are presented in Table 13 and Figure 2.

The cost-effectiveness plane for FFA + SC versus CBD + CLB + SC indicates the following: [redacted] of the simulations are located in the [redacted] quadrant, where FFA + SC is associated with [redacted] QALYs and [redacted] costs compared to CBD + CLB + SC; [redacted] fall in the [redacted] quadrant where FFA + SC is associated with [redacted] QALYs but also [redacted] costs; and [redacted] fall in the [redacted] quadrant (Figure 2).

Table 13. Scenario (using updated OLE NMA) average results from the probabilistic sensitivity analysis: FFA + SC (at PAS price) versus CBD + CLB + SC (at list price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Probabilistic ICER (£/QALY)
FFA + SC	[redacted]	-18.56	[redacted]	0.60	[redacted]
CBD + CLB + SC	[redacted]	-19.17	-	-	-

Abbreviations: CBD + CLB, Cannabidiol with Clobazam; FFA, Fenfluramine; ICER, Incremental Cost-Effectiveness Ratio; PAS, Patient Access Scheme; QALYs, Quality-Adjusted Life Years; SC, Standard of Care.

Figure 2. Scenario (using updated OLE NMA) cost-effectiveness plane: FFA + SC (at PAS price) versus CBD + CLB + SC (at list price)

Abbreviations: CBD + CLB, Cannabidiol with Clobazam; FFA, Fenfluramine; PAS, Patient Access Scheme; QALYs, Quality-Adjusted Life Years; SC, Standard of Care.

Deterministic Sensitivity Analyses

In the scenario using the new imputation method for the OLE NMA, the tornado diagram shows that the six most impactful parameters are related to efficacy in the OLE period (cycles 2 to 5), specifically the risk ratios obtained from the OLE NMA used to determine state occupancy of patients during this period, and weight in patients aged 12 to 17 years and 18 to 35 years. The uncertainty related to the OLE NMA risk ratios is related to the [redacted] used as lower and upper bound for these parameters (please refer to Table 8).

Figure 3. Scenario (using updated OLE NMA) tornado diagram: FFA + SC (at PAS price) versus CBD + CLB + SC (at list price)

Abbreviations: CBD + CLB, Cannabidiol with Clobazam; FFA, Fenfluramine; GTC, Generalised Tonic-Clonic; HCRU, Healthcare Resource Use; PAS, Patient Access Scheme; SC, Standard of Care; SUDEP, Sudden Unexpected Death in Epilepsy; T+M, Titration and Maintenance.

Placebo Sensitivity Analyses

One of the uncertainties raised within DG2 regarding the assumption on placebo, mentioned "*Potential changes in the placebo response during the trials, for example because of changes in the participants' beliefs or the natural history of the disease, were not accounted for. This is a potential source of bias*" (2) UCB has therefore tested alternative assumptions on the placebo effect in the NMA, by considering various percentages of reduction (up to 10%) in the placebo response during the OLE phases compared to the blinded phases of both trials. The details on the methodology and results can be found within the attached OLE NMA report 2024 (16).

Risk ratio estimates (vs placebo) were generally higher for almost all combinations of percentage reductions in placebo response rate compared to the base case (constant placebo effect in both trials). Overall, for a given outcome and timepoint, the treatments ranking obtained using risk ratio estimates were similar to results from the

base case for each combination of percentage reductions in placebo response rates. It is expected that the placebo effect variations (as tested in the report) will not change the conclusions of the cost-effectiveness analysis comparing FFA to CBD while integrating the OLE NMA results.

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Appendix 1

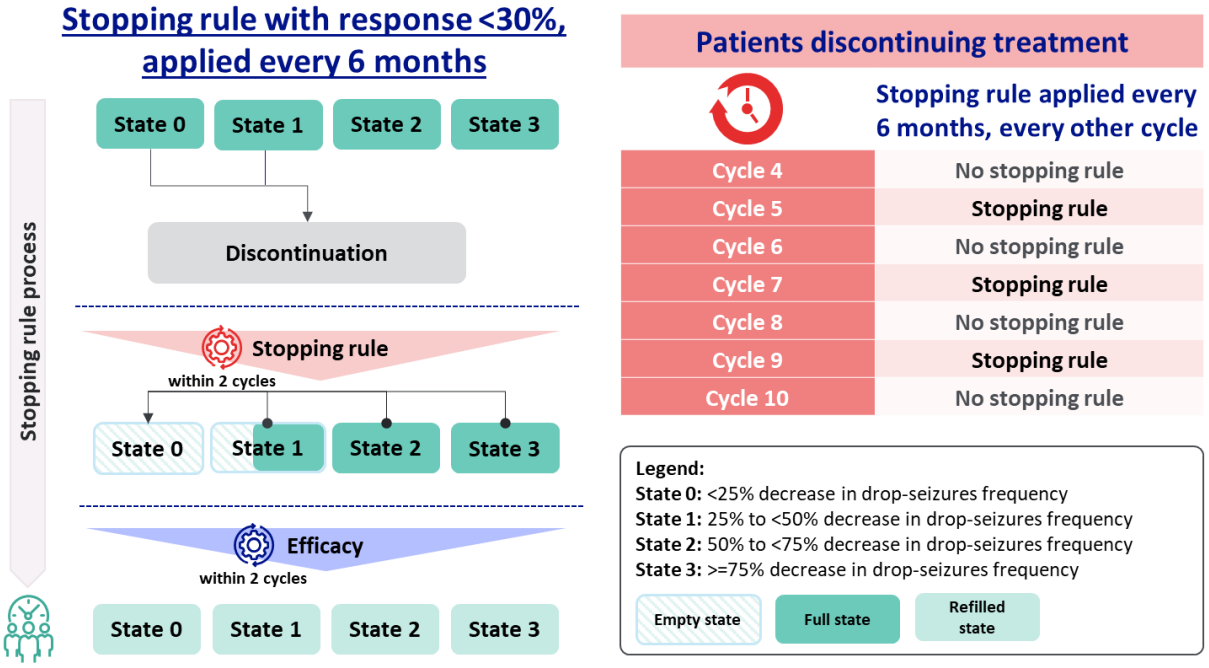
Description of the stopping rule mechanism

In the model after cycle 2, discontinuation due to lack of efficacy is captured by a stopping rule, applied to patients with response below 30% reduction in drop-seizures frequency (DSF), evaluated every 6 months (see Figure 4). The stopping rule is applied equally to both treatment arms, FFA + SC and CBD + CLB + SC.

A particularity of the stopping rule relates to how patients are redistributed in the treated health states (states 0 - 3) after discontinued patients are moved to the respective discontinued state. The stopping rule is expected to result in the discontinuation of patients whose response is not clinically relevant. However, in the model all discontinued patients (AEs, lack of efficacy, and stopping rule) are accounted for together and removed equally from all the treated health states (for example, if 20% of patients discontinue treatment in a given cycle, the number of patients in states 0 – 3 will be reduced by 20%). When the model applies state occupancy data (coming or not from the NMA) to determine the proportion of patients in each treated health state (states 0 - 3), it effectively results in a refilling of state 0 (and state 1), which the stopping rule would have emptied due to lack of clinically relevant response. This is illustrated in Figure 4.

This effect of the stopping rule causes a deterioration of the general health of the cohort, as it artificially mimics treatment waning by removing patients from better health states (states 2 and 3), when it was meant to cause discontinuation of patients in worse health states (state 0 and possibly 1).

Figure 4. Stopping rule mechanism in the cost-effectiveness model



Appendix 2

While clinical practice and expert opinion indicate that waning is not observed for CBD or FFA, it should be noted how clinicians would manage hypothetical waning. The 14 HCP's that answered the survey were further asked a question, and almost all (6 out of the 7) clinicians that responded, confirmed that if waning were to occur (hypothetically), they would increase dosage to try and maintain initial efficacy.

Table 14. Supplementary question: If waning were to be observed (after the honeymoon period), which of the three situations would be the most common course of action in clinical practice (n=7)

1) increase dose to try and maintain initial efficacy
2) remove treatment
3) continue dose and patients have lower efficacy

Respondent	Answer
Birmingham childrens hopsital	Usually 1, as long as still scope to increase the dose and no side effects. If dose maximised or side effects then 2, in order to then try another treatment.
Queen Elizabeth Hospital Birmingham	1) increase dose to try and maintain initial efficacy
NUTH Newcastle	IF waning occurred you'd up the dose first
Great Ormond Street Hospital, London	1) increase dose to try and maintain initial efficacy
Bristol Royal Hospital for Children	The most likely first step on observing waning of the effectiveness of CBD is to increase the dose.
University Hospital of Wales	If there is waning with CBD then I would withdraw it, as I would not expect there to be any further beneficial effect with dosage increment(s).
Great Ormond Street Hospital	increase dose but if this continues after max dose used I would remove the CBD treatment

Healthcare Professional Expert Survey on Treatment Pathways and Options for Patients in England and Wales with Lennox-Gastaut Syndrome (LGS)

Prepared for: UCB
By: Syneos Health
November 2024

This document was generated using the Qualtrics platform, leveraging its advanced survey design, data collection, and reporting tools to ensure accurate and comprehensive analysis.

Presentation of the survey

Context

Fenfluramine is currently being appraised by NICE for its use in the treatment of Lennox-Gastaut Syndrome (LGS) in individuals aged 2 years and older (ID1651). LGS is a severe rare form of epilepsy characterised by drug-resistant seizures and significant developmental challenges, making effective treatment options critically important for improving patient outcomes. After two appraisal committee meetings NICE Committee D issued a negative recommendation regarding the use of fenfluramine for LGS. UCB appealed the against the recommendation. Other appellants were the Royal College of Physicians, and the Tuberous Sclerosis Association (TSA) patient organization. The NICE appeal panel convened to discuss and decided specific points, including assumptions about treatment comparators, efficacy waning, and drug wastage. Following the appeal, NICE subsequently issued a revised Draft Guidance 2 and invited stakeholders to provide comments. This provided an opportunity for stakeholders, including UCB, clinicians, and patient organizations, to offer further input and evidence that could inform NICE's final recommendations.

Objective

As part of its response to the new Draft Guidance, UCB commissioned a survey of clinical experts in England and Wales to gather robust, real-world data and insights regarding the treatment of Lennox-Gastaut Syndrome (LGS) patients. This additional evidence aims to address areas of uncertainty highlighted in the National Institute of Health and Care Excellence (NICE) Single Technology Appraisal (STA) ID1651.

Methodology

- Participant selection: A total of 24 HCPs specialising in paediatric, adult, or both fields of neurology, with experience in treating patients with LGS, were invited via email to participate in the study. These specialists were selected from the pool of neurologists practicing in rare epilepsies across NHS England and Wales to determine eligibility.

- Survey design: An electronic survey comprising 10 questions was developed using Qualtrics. The survey began with a short summary outlining its purpose, followed by three screening questions gathering background information, one question on contraindications, one on the treatment pathway, one on standard of care as a comparator, one on treatment waning, two on treatment wastage, and one on assumptions regarding efficacy. Responding to each question was mandatory in order to proceed to the next. Free text responses were permitted.

- Data collection: In early November 2024, an initial email was sent to a list of neurologists to organise the administrative aspects of the survey. The survey went live on Monday, 25th November, and the link to the Qualtrics website was shared via email. The cut-off for data collection was at 9:00 am (GMT) on Thursday, 28th November. Due to the short notice of the survey, a maximum of two reminder emails were sent to participants.

Results

By 9:00 am (GMT) on Thursday 28th November, 14 participants had completed the survey. The full survey text, along with the questions and responses, are presented in the remainder of this document.

Background questions

1. Please provide the name of your main hospital of clinical practice

NUTH Newcastle
University Hospital of Wales
Leeds Children's Hospital
National Hospital for Neurology and Neurosurgery
Nottingham University Hospitals
Evelina London Children's Hospital
Birmingham Children's Hospital
Queen Elizabeth Hospital Birmingham
Birmingham Children's Hospital
Barberry Regional epilepsy service, Birmingham and Queen Elizabeth University Hospital Birmingham
GOSH
Great Ormond Street Hospital, London
Great Ormond Street Hospital
Great Ormond street Hospital for children

2. Please specify your title and specialisation. (e.g., Paediatric, Neurologist.)

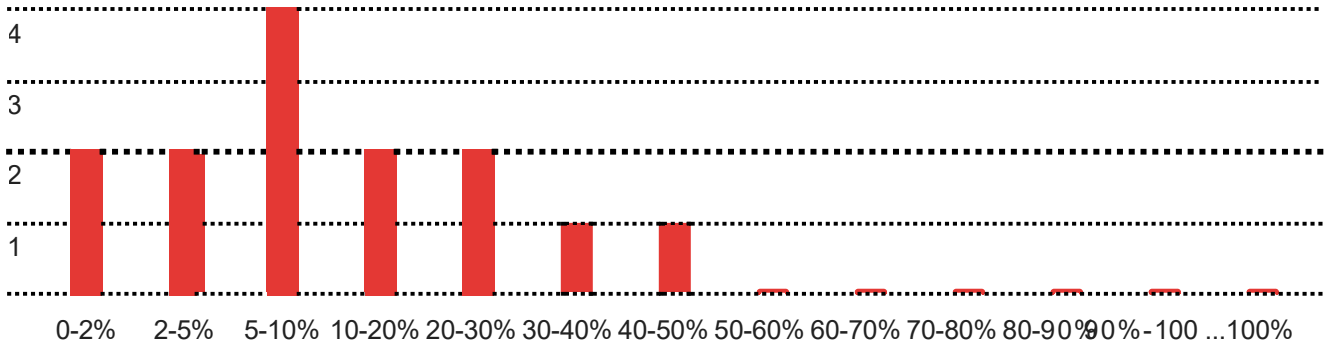
Consultant Paediatric Neurologist (n= 5)
Paediatric Neurologist (n=4)
Adult Neurologist (n=3)
Epilptologist and neuropsychiatrist (n=1)
Paediatric Neurologist with a special interest in complex epilepsy (n=1)

3. How many patients do you currently treat for LGS

10	18	21	70	In excess of 100
12	20	Approx 30-40	80	150
15-20	20	50	approx 100	

Contraindications

4. What is the proportion of patients that are contraindicated to cannabidiol + clobazam?



- Choice Count

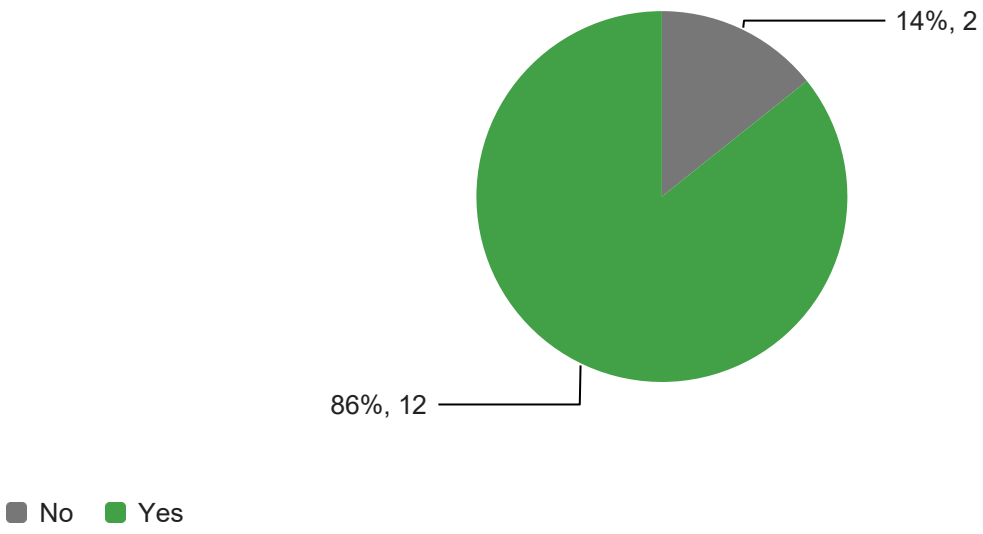
The average proportion of patients has been calculated as 14.21%.

Please provide any further information below

0-2%	Very few are contraindicated, it is often tolerability which is the issue (with clobazam)
0-2%	I do not believe that any of these patients are contraindicated to CBD and clobazam. However there is a significant proportion of patients who have not responded to these treatments or had dide effects. Many patients have still not been tried on CBD and clobazam because their epilepsy is considered to be 'reasonably' well controlled or their families are accepting of their current epilepsy control. Some parents are not keen for their child to be on CBD.f
2-5%	raised LFTs with CBD
2-5%	Very few cannot take cannabidiol. Well maintained.
5-10%	Issues with liver dysfunction (usually related to MASLD) and also intake (such as weight loss): these mean that CBD (especially) is not an option
5-10%	some patients are clobazam intolerant and therefore in-elligible for cannabidiol
5-10%	n/a
5-10%	Estimating for patients in whom significant liver issues or issues with historic clobazam use for which co-prescribing in mandated
10-20%	Main issue has been either abnormal LFTs or increased ammonia preventing addition of CBD or intolerance of Clobazam due to over sedation
10-20%	sleepiness, intolerance due to GI side effects
20-30%	i have commmemced patients on cannabidiol and have had to withdraw due to side effects as well as ineffectiveness.
20-30%	Nil
30-40%	Clobazam causing tonic seizures or poor prior experience with CLOB
40-50%	Many patients already failed a Cannabidiol trial. Another proportion of patients do not tolerate Clobazam (side effects).

Treatment pathway

5. If Cannabidiol + Clobazam + SoC cannot be taken, at this stage of the treatment pathway patients have already been exposed to multiple SoC drugs and the remaining treatment options would be interventions such as invasive surgeries and consideration for clinical trials. Do you agree? - Selected Choice



Yes, please comment:

Yes (n=12)

Surgical options such as callosotomies (which are not without complications and their own set of morbidities) or VNS, which has an unclear response rate in children with LGS, and is not thought to be an option by our 'adult' colleagues here
By the time we consider CBD and CLob patients will have received more than 2 (typically 4 or more SoC drugs and be considered for ketogenic diet or VNS if surgery has not been an option
VNS or resection would be an option
Or recycling meds with little effect
VNS, ketogenic diet , Callosotomy and newer Antis seizure medications
Many of our patients cohorts has VNS implanted & failed multiple ASM
ketogenic/ VNS the main alternatives
SoC products are given before. No other treatment options left after CBD so, as above
Yes usually they have tried multiple standard ASMs, next options would depend if there are significant drop seizures (callosotomy) or a surgical target (not very often)
Without another option surgeries eg callostomy, VNS, DBS or trials are the only options. The other option is palliation.
by the time patients go on CBD+clobazam, SoC drugs are pretty much exhausted
VNS or possibly callosotomy, not resective surgery

No, please provide a description of how these patients are treated:

No (n=2)

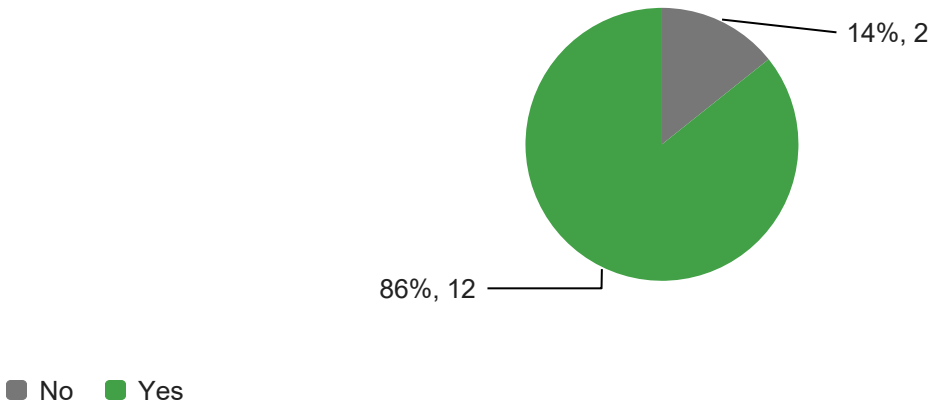
also option of ketogenic diet but severe lack of capacity only 3 centres in UK take adult patients and also option of VNS (this is an extracranial procedure and well tolerated)
Ketogenic diet may also be an option but this is not a suitable / preferred option for many patients due to the impact on lifestyle of being on the diet.

Standard of care as a comparator

UCB positioned fenfluramine + SoC as a direct comparator only to cannabidiol + clobazam + SoC.

The outcome from the NICE appeal panel stated that 'it was unreasonable of the committee to insist that fenfluramine should additionally be compared to SoC alone.'

6. Do you agree that the only relevant comparator to fenfluramine + SoC should be cannabidiol + clobazam + SoC?



If No, please include a detailed description of which basket of SoC alone drugs would be appropriate to compare against fenfluramine + SoC. Further explain your answer, as to why you think this comparison would be appropriate:

No (n=2)

Cenobamate
reasonable comparators would be fenfluramine vs valproate+ clobazam or valproate +lamotrigine

Treatment waning

Waning is known where “attenuation of treatment effects over time” (ref 1[1]). The appeal outcome specifies that “clinical experts stated treatment waning is not seen in clinical practice in people having antiepileptic treatments”. Based on your clinical practice, please answer the following questions:

7. Do you agree that treatment waning is not seen in clinical practice for patients taking cannabidiol or fenfluramine ?

If no, please provide detail on what time does treatment waning occur and what proportion of patients experience this? Please comment

No (n=5)

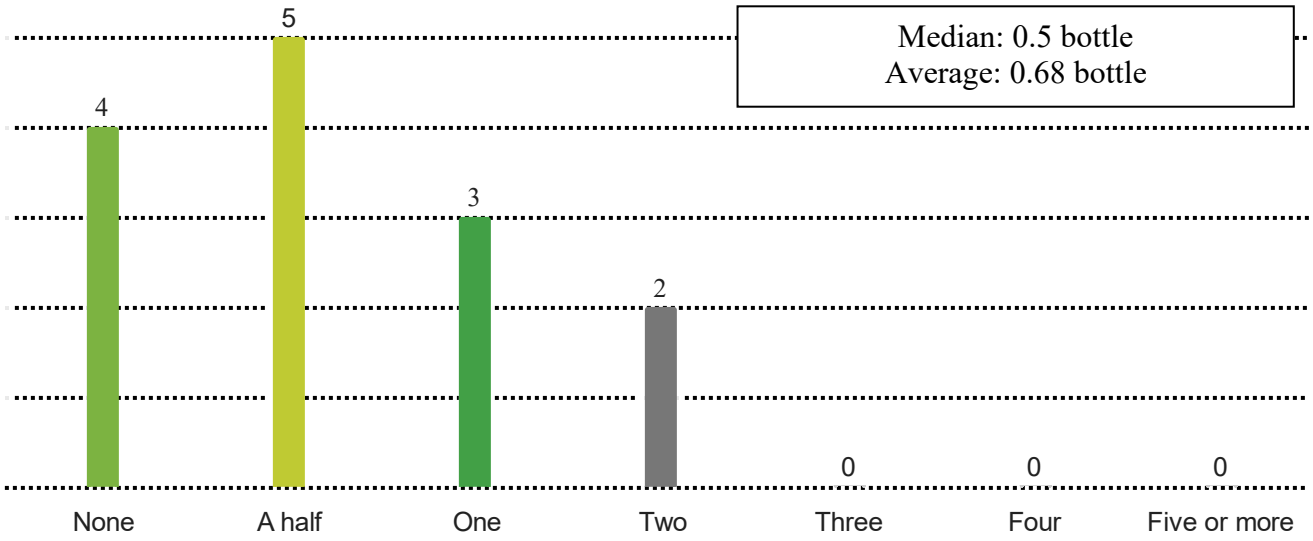
tretament waning can occur anytime, however in my practice I have commonly seen this after 6 months. in 1/3 rd of patients.
This question is poorly phrased, as it lumps CBD and fenfluramine together. Waning does occur with CBD in my experience, over months-years, in perhaps 1/3 patients
Unfortunately with many treatments in epilepsy you see a 'honeymoon' period where seizure control improves when the ASM is started or when the dose is increased, and the benefits are not maintained. The time taken varies from patient to patient. The treatment waning may occur over a couple of weeks or a couple of months.
we often see a so called 'honeymoon period' where an initial response to treatment is not sustained in the longer term. I have specifically seen this with cannabidiol/ clobazam
I have not seen waning in children on fenfluramine for seizures (admittedly using this for Dravet syndrome), but with cannabidiol this is possibly more marked, given that we have used cannabidiol for children with Dravet syndrome (where it usually has not demonstrated any effect, or an element of waning) and Lennox Gastaut syndrome, where waning is possibly more pronounced (but I have no data for this although it does seem to be a consideration)

[1] Reference 1: Taylor et al. "Treatment Effect Waning in Immuno-oncology Health Technology Assessments: A Review of Assumptions and Supporting Evidence with Proposals to Guide Modelling" Pharmacoeconomics Actions Search in PubMed Search in NLM Catalog Add to Search . 2024 Nov;42(11):1181-1196. doi: 10.1007/s40273-024-01423-6. Epub 2024 Aug 23. https://pmc.ncbi.nlm.nih.gov/articles/PMC11499331/

Treatment wastage

The appeal decision document describes that, “given the fact that CBD is an oily substance that is provided in glass bottles and fenfluramine is a liquid that is provided in plastic bottles, the consequences of accidents or an inability to aspirate all of the contents of the vial are likely to be greater for CBD than for fenfluramine”. Please provide an estimate, based on your clinical experience, of the average number of bottles which are lost due to wastage (for any reason, including breakages, liquid left in bottles or other)

8. Cannabidiol: please estimate the number of bottles wasted (broken/ smashed/ oily substance left in bottle), per patient, per year. Note: an average of 22 bottles of cannabidiol are used per year based on an average patient weight of 42.8kg (ref 2[2])



Please give your reasoning

None (n=4)

I am not aware of this data
Families are very cautious with their medications & no accidents happened so far.
I am not aware of any wastage
No reported instances from patients

A half (n=5)

never had a patient request replacement for a broken bottle
This does occur, and is infrequent (possibly 1-2 bottles per year in our population); the liquid also seems to 'creep out' of the bottle according to one parent
I have only had one patient who broke a bottle
one bottle every few patients - ie 1/2 per patient on average
It is rare but does happen

One (n=3)

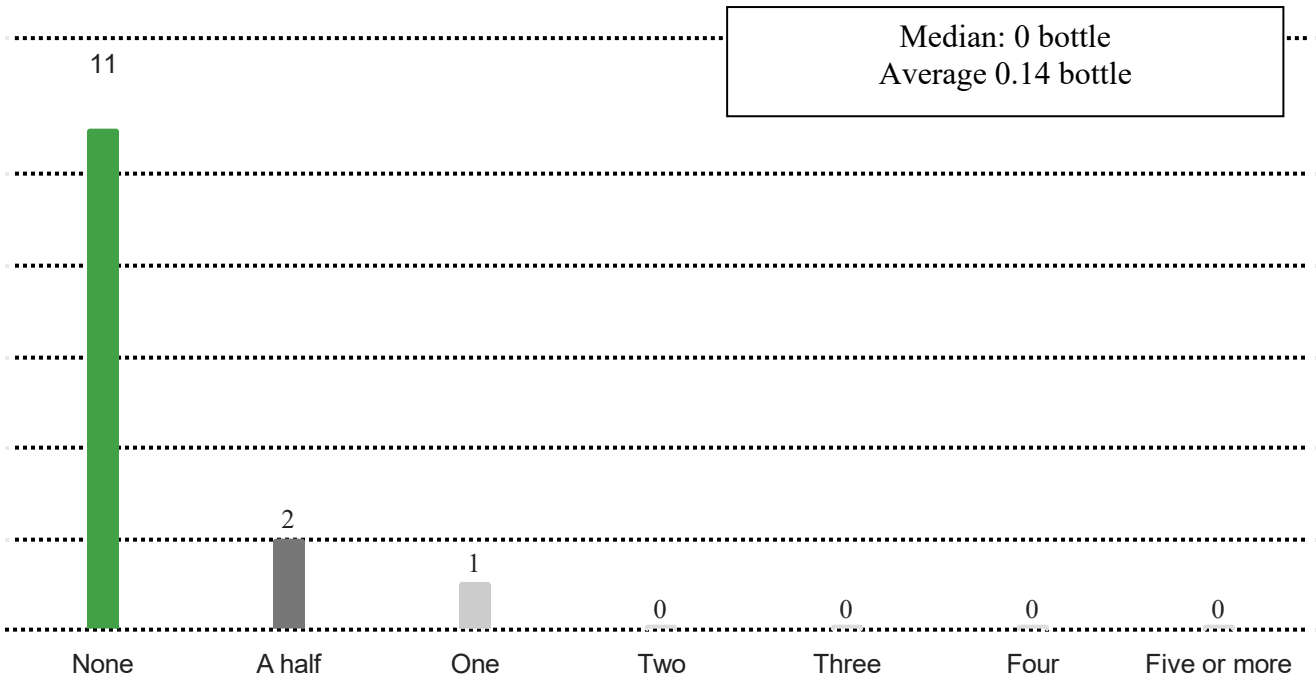
clinical experience
We will only be informed if final bottle is smashed or earlier prescription, approximate estimate based on experience. Also note CBD is oily and therefore more difficult to ensure all extracted - this causes patients to order a little earlier than the prescribed 'three months'.
This is based on anecdotal experience requesting a repeat prescription

Two (n=2)

[2] Reference 2: Knupp K.G et al. "Efficacy and Safety of Fenfluramine for the Treatment of Seizures Associated With Lennox-Gastaut Syndrome: A Randomized Clinical Trial" JAMA Neurol 2022; 79(6):554–64

Spilt medication, smashed bottles or new bottle being started before all content of existing bottle used. Also wastage due to patients not tolerating medication and stopping it.
This is an observation, not subject to reasoning

9. Fenfluramine: estimate the number of bottles of wasted (broken/ smashed/ substance left in bottle), per patient, per year. Note: an average of 25 bottles of fenfluramine are used per year based on an average patient weight of 42.8kg (ref 2)



Please give your reasoning

None (n=11):

clinical experience, not a glass bottle
We have not had any requests I remember for this need in the children on fenfluramine for Dravet syndrome (I am the 'authorised signatory' for fenfluramine for children in South Wales)
No glass, and no clear issue with drawing up.
I have never had a patient report this
not aware
plastic bottles
Not heard of it happening
No reported events from parents and caregivers
None so far
I am not aware of any wastage
As for CBD

A half (n=2)

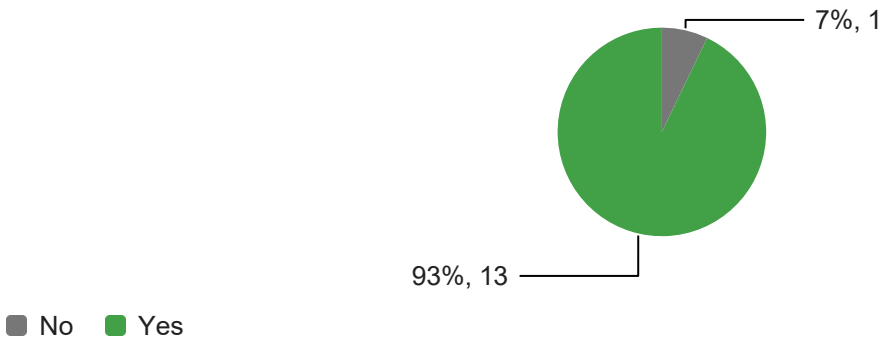
I would predict very little wastage for fenfluramine as in my experience with CBD
Medication not being tolerated and thus stopped. Spilt medication.

One (n=1)

This is an observation, not subject to reasoning

Assuming equal efficacy

10. . Do you agree that it would be appropriate to assume equal efficacy between fenfluramine and cannabidiol for decision making purposes?



Please give your reasoning

Yes (n=13)

there is still individual variability, in the absence of head to head trials this is reasonable, my personal clinical experience from dravet syndrome would favour fenfluramine
I am unclear what this is asking, so perhaps need to be an outlier on this: I think that fenfluramine does have some element of disease modifying activity for Dravet syndrome at least, that cannabidiol does not confer. I presume that the same should hold for LGS, but this is clearly not what you are asking here.
as above
Methods used do not allow determination of a clear difference
It is unreasonable and not viable for a head to head trial (and this is against any previous models ever required). Depending on models naive vs ITT fenfluramine or CBD come out as greater efficacy, with the lack of ability in a rare disorder to undertake a head to head trial and modelling being so contentious the only reasonable thing is to assume equal efficacy. They can and should only be compared to each other and no compared to SoC.
In my clinical experience fenfluramine is better tolerated and more effective than CBD. IN terms of data from trials the differences are so small that it is not possible to determine statistically which is more effective.
if this is chosen in the correct subset of patients - yes
though fenfluramine is more efficacious for prolonged seizures than CBD and I would use Fenfluramine first in this scenario
As above
Indirect comparison of data suggests so
considering differences in placebo response is important in the comparisons
I agree with the above. But more clinical experience with CBD
Both treatments are likely to be efficacious and tolerated in at least some patients and not in others. This is the case with other ASMs too. We need to find the treatment which suits the patient and allows best QoL when considering efficacy and side effects

No (n=1)

We need to have direct comparison trials for cannabidiol and fenfluramine

Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BT

26th November 2024

Dear NICE Technology Appraisals Team,

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

Lennox-Gastaut syndrome (LGS) is a severely debilitating form of generalised paediatric epilepsy.

The impact of LGS goes beyond seizures and includes cognitive impairment, communication difficulties, psychiatric symptoms, sleep and behavioural challenges, and mobility problems. All of these issues significantly impact both patients' and caregivers' quality of life. Overall mortality and Sudden Unexpected Death in Epilepsy (SUDEP) are also major concerns for people living with LGS and their loved ones.

Patients with LGS rarely achieve complete seizure control despite available therapeutic options. Achieving a reduction in seizure frequency usually requires polypharmacy with an individualized regimen.

New treatment options are needed for patients with LGS, a profoundly impairing, treatment-resistant, developmental and epileptic encephalopathy.

In England, LGS has an estimated prevalence of approximately 5,000 people. LGS-related mortality is estimated at around 5%.

We urge NICE to fully take into account wider benefits from the adoption of fenfluramine, such as reducing demands on NHS services, and supporting unpaid carers. Fenfluramine represents a potential new treatment option for patients with LGS for whom current treatment options are not working to control their seizures, and given the proven effectiveness of fenfluramine this could represent long term cost savings by reducing hospital admissions.

In addition, we do not believe that the summaries of clinical effectiveness take full account of the positive results of existing studies into the effectiveness of fenfluramine. As highlighted in our appeal letter, a decision was made that fenfluramine is less efficacious than cannabidiol on a naive comparison between open-label trials, without considering confounding variables that may have been affecting the trials.

We also disagree with the assertion in the recommendations that "people with LGS are offered a range of antiseizure medicines". There is a serious unmet need for more treatments for this condition, given that people with LGS rarely achieve seizure control on current available treatments.

Given the link between LGS and learning disabilities, special consideration should be given to the potential impact of fenfluramine on quality and length of life.

In conclusion, we support the adoption of fenfluramine as a treatment for LGS and believe that it would offer real benefits to people with LGS and their families.

Many thanks,

[redacted]

[redacted]

[redacted]

Epilepsy Action

[redacted]

NICE National Institute for Health and Care Excellence

Name	[redacted]
Organisation	Epilepsy Society
Comments on the DG:	

Has all of the relevant evidence been taken into account?

At the original review of fenfluramine, we were not registered stakeholders and were therefore not asked to comment. Comment below from our Director or Genomic Research who treats many of the people with Dravet syndrome in the UK:
"It is inequitable in my view that people with LGS will not have access to FFA, whilst other people with serious epilepsies (ie Dravet syndrome) do. Some people with DS have done very well on the drug, when nothing else has worked, and trial data support its use in LGS too. Therefore, denying people with LGS the opportunity to try FFA is inequitable and difficult to justify."

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

Please see answer to first question.

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 age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

The numbers of people with Lennox Gastaut syndrome in the UK is thought to be relatively low but the burden of the disease is high. Like Dravet syndrome, LGS is a Developmental and Epileptic Encephalopathy which is very difficult to treat with current anti-seizure medications. For most people with LGS, it is a lifetime condition. Unlike Dravet syndrome, there is no support group to advocate for those with LGS, but their need to benefit from new treatment options is just as great. We feel that a decision not to allow people with LGS access to fenfluramine would unfairly disadvantage this group, not giving them the opportunity to improve quality of life through a repurposed drug which is already benefiting others.

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 26 November 2024. Please submit via NICE Docs.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Tuberous Sclerosis Association

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

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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 would like to emphasise the impact seizures have on the whole family, not just the person living with the condition. Seizures are a frightening experience for all involved. Affected children are often too young to understand what is happening to them. Seizures also impact younger

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	siblings who become very distressed seeing their family member having a seizure. 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. Outings, childcare, school trips and any activities that children would usually take part in take a vast amount of organisation. Often, parents will feel unable to leave their child with anyone but trained professionals, which means that 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. Family life can be disrupted by having a child with severe health needs who will need many trips to doctors and hospitals for ongoing monitoring, intervention and emergency care. The frequent long distance hospital visits require special childcare arrangements for patients' siblings, may be very expensive to get to, and may require a parent to stay overnight. This can make it very difficult for both of their parents to maintain a full-time job; parents may have to limit their working hours to ensure their child can get to the hospital. The costs of care for the child may impact significantly on the financial position of the family; this is exacerbated if one parent has to stay at home. Any reduction in the frequency of seizures will have a significant impact on the quality of life of the individual, parents/carers and the family as a whole.
2	Twenty one people with epilepsy die weekly in the UK, many of which are in young and otherwise healthy people (Mbvizo, G et al. Epilepsy-Related Deaths Are A Major Public Health Problem: Results From A National Study Using Linked Administrative Health Data To Determine The Burden Of Epilepsy-Related Deaths And The Proportion That Are Potentially Avoidable. Epilepsia 2019;60(S2): S5-S248). 50% of all epilepsy deaths are thought to be potentially avoidable. Research published by Public Health England (PHE) in 2018 (Deaths Associated with Neurological Conditions) has found that the number of annual deaths of epilepsy patients, including those from Sudden Unexpected Death in Epilepsy (SUDEP), 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 have the potential to further reduce the number of annual deaths related to LGS epilepsy in England.
3	The Tuberous Sclerosis Association along with SUDEP Action is supportive of the proposal that fenfluramine should be funded for people with LGS-associated seizures. The addition of fenfluramine treatment will have a vast positive impact on equality and health inequality in this patient group. The experience amongst families and the evidence from natural history studies show that the better controlled epilepsy is, and the younger the age at which this occurs, the better the outcome for intellectual development, with amelioration of the above-mentioned problems. In general, this patient group has previously had poor access to care because of the variety and severity of their problems. The availability of effective treatments like fenfluramine will vastly improve their health outcome; especially for those who are least able to advocate for themselves (or whose families are less able to articulate their needs). *"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 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"*

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	"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."
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

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- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- 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.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Young Epilepsy

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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	We urge the evaluation committee to take into account the evidence highlighting the unmet needs of those living with Lennox-Gastaut syndrome, the need for new treatment options for this community and the wider impact this syndrome has on the lives of those affected. In particular, we would like to draw the following evidence to the committee's attention: **A comprehensive systematic literature review of the burden of illness of Lennox-Gastaut syndrome on patients, caregivers, and society (Cross et al, 2024)** https://onlinelibrary.wiley.com/doi/full/10.1111/epi.17932 This review highlighted that reducing the high burden of clinical symptoms could increase quality of life for both people living with Lennox-Gastaut syndrome and their caregivers. It is common to experience pharmacoresistance with this syndrome and most people need multiple types of medcation as well as changing treatment over time.The review identified that there is often a high cost for healthcare resource and medication associated with the syndrome. **The psychosocial impact of epilepsy on young children and their families: The Sussex Early Epilepsy and Neurobehaviour (SEEN) Study (Young Epilepsy, 2017)** https://www.youngepilepsy.org.uk/reports/seen-study-2017 Early onset epilepsy is often associated with frequent epileptic seizures which are difficult to treat, as well as additional developmental and behavioural needs. This can have a significant impact on everyday life at home and school. Parents shared the significant impact that epilepsy has on family functioning, including the impact caused by seizures. They also highlighted the negative impact on siblings, as well as the negative impact on family finances and employment. Mothers of children with epilepsy face a higher risk of depression, anxiety, general stress and fatigue, compared to mothers of children with non-epilepsy related neurodisability.
2	We urge the committee to recommend the use of fenfluramine for seizures associated with Lennox-Gastaut syndrome given the committee's conclusion that '*LGS is a heterogenous condition and there is an unmet need for treatments that reduce the number of drop seizures without markedly increasing adverse events'.*

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- 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.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Association of British Neurology

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[Insert disclosure here]
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	In section 3.2 There is no true first line, second line or third line pathway for LGS. It is a flawed and compromised process to use these terms. We recognise that some medications are typically used early in a patient's life – such as sodium valproate, and recognise some drugs are licenced for LGS such as cannabidiol with clobazam.

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2	In section 3.2 The International League Against Epilepsy only ratified the definition of LGS in 2021 (Specchio et al, Epilepsia). This has a number of consequences: i) many clinicians have not been confident to diagnose or re-diagnose people with LGS, particularly adults with complex epilepsy; ii) the epidemiology of LGS in the UK has never been recorded.
3	In section 3.2 "The committee noted that it would be useful to see data on the proportion of people who would not have cannabidiol plus clobazam in NHS clinical practice" This is unknowable for certain and published estimates vary. The Chin et al study (Seizure 2021) identifies how underdiagnosed LGS is in the UK, and how the term is underutilised. Cannabidiol with clobazam is not a useful option for some adults with LGS. Sedating medications, particularly GABA-ergic anti-seizure medications such as clobazam commonly exacerbate tonic seizures. Tonic seizures can cluster, often occur from sleep and can cause sudden drops leading to injury. There is an unrecorded population of patients who will not be able to use cannabidiol because the licence demands that clobazam must be co-prescribed.
4	In section 3.2 The waning of effect of medications is reported, colloquially called 'honeymooning'. It is speculated that for many that this is not a true pharmacological effect, but instead the natural waxing and waning disease course. Most people who are established on effective medication remain on this combination and do not need later drug trials or gradual increasing doses.
5	In Section 3.3 As above, the concept of 'third-line' is spurious and strident adherence to this term and the modelling that utilises this concept will create inaccurate modelling data. Clobazam, rufinamide and topiramate are not medications that commonly lead to seizure freedom or seizure control in LGS. They are recommended in NG217 due only to the fact that they have been studied in cohorts of patients with LGS and therefore NICE could appraise these data. It is true that these medications are used for LGS in the UK but they are not sufficiently efficacious to be used as a comparator. These are long-standing medications and treatment with these alone leads to the poor outcomes and treatment needs (treatment gap) stated above in 3.2, as identified by patient carers and clinicians.
6	In Section 3.3 Standard care is not a safe or appropriate comparator. SC is not a static or steady state. We do not accept a state where patients are constantly seizing with complex behavioural needs. SC is not a steady state and patients will commonly be offered more expensive later treatments such as vagus nerve stimulation. They will also have higher emergency care costs and higher costs for emergency medications such as buccal midazolam. Cannabidiol plus clobazam is an appropriate comparator. Patients being considered for this will have failed more than two appropriately chosen treatments, will have seen a specialist who can recognise and diagnose LGS.
7	Section 3.3 Clinical subgroups are identifiable The goal for treatment will vary for all patients, Clobzam has a sedative and anti-anxiety effect and so some patients may be prescribed this with cannabidiol for the secondary benefits of clobazam. Although not recognised in the modelling, all treatment choices are joint and patient preference is a factor. Some patient carers are attracted to the plant-based origins of cannabidiol and have seen media coverage, much of it positive about cannabidiol. As stated above, drugs that sedate and particularly GABA-ergic drugs may aggravate tonic seizures (definition above) and so cannabidiol plus clobazam would not be appropriate for them. Similarly excess polytherapy is best avoided and if a patient is already on three anti seizure

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	medications it may be preferable for them to start fenfluramine as a fourth, rather than add in cannabidiol and clobazam and have five prescribed anti-seizure medications.
8	Section 3.4 p11 As stated above, the terms of reference means that NG27 data supporting the use of rufinamide, lamotrigine, clobazam and topiramate are reported for LGS and this has to form the basis of their report. Please do not confuse this with a consensus clinical recommendation or professional guidelines where data that do not meet NICE standards, and clinical experience are used to create a recommendation which truly reflects clinical practice. The comment about the age of these studies is valid.
9	Section 3.6 If the committee speculated that people lost to follow up differed from those that were retained, they could measure this. Can the company produce the demographic and epilepsy related data of these two groups? Has the committee data to prove that the drop out rate is lower than similar studies, how does it compare to the cannabidiol studies?
10	Section 3.6 Does the committee have data to prove that those who drop out of the study have the lowest efficacy? It is our experience that short term tolerability is a more likely cause of drop out. Families have lived with seizures for years and so more seizures is not a surprise or a major issue, but new emergent side effects are a major concern.
11	Section 3.7 Is it fair to ask for data that are not available? The NICE approval of cannabidiol included clobazam because of a sub-group analysis, the RCTs were of adjunctive cannabidiol, not cannabidiol and clobazam.
12	Section 3.7 It is standard for OLEs in epilepsy studies to not have a placebo arm. I know of no data from epilepsy studies that demonstrate a dynamic response to placebo that would need to be taken in to account for OLE data analysis. If the EAG have these data from epilepsy studies, these could be provided to the committee.
13	Section 3.9 The difference between absolute and relative drop seizure reduction is an interesting one and both measures have merit. Clearly increases in drop seizures will reduce HRQoL and a total reduction would move someone in to their best HRQoL state. We know of no data that state that absolute number of drop seizures is proportionate to HRQoL and so this link remains speculative. There are many uncounted factors that will determine how drop seizures affect HRQoL; these would include how able and active the individual is; the impact on the individual of broken teeth, nose, facial lacertations; the time of day of drop seizures; their care package, and carer habits. We do not follow the evidence that relative reduction in drop seizure is an inferior strategy to absolute number of drop seizures. Indeed relative reduction in seizure frequency is the mainstay of epilepsy RCT study design and has been the bedrock of many a NICE appraisal.
14	Section 3.10 The focus on drop seizures is also that treatment options for these seizures is more limited than for generalised tonic clonic seizures, for example.
15	Section 3.13 Do the committee have access to dose changes during the OLE? It is our experience that fenfluramine efficacy is reached early and that doses remain stable. If there are no data showing that ever increasing doses were needed during the OLE then it is safe to presume that early treatment effect is maintained. Decreasing treatment effect is not predicted and is not seen in epilepsy medications.
16	Section 3.14 We note that the EAG consider a waning a drop out of 0.58% and 0.48% to waning to be ‘exceedingly low’. It is our experience that once established on a treatment it is very rare indeed

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	for people to transition away from the treatment. If there are few late emergent side effects, then this figure is very likely to be accurate.
17	Section 3.14 We cannot see where the EAG identified that using the 1601 for 80% of people was justified. The waning estimates of 8.92% and 7.38% are too high, implausible. Significant waning is not our clinical experience, nor is it suspected from our experience and knowledge of anti seizure medications. Indeed waning is not a concept that is broadly discussed in clinical or academic epilepsy meetings because it is presumed that people who respond well to a medication, will respond life-long, with no dose increase needed. We fully support the conclusion that waning modelling needs to be evidence based. Neither the company nor the EAG have always been fully evidence based in their approaches.
18	3.16 It is not clear to us what personal or professional experience the EAG used when determining the 24-hour care needs of a disabled adult. Typically children and adults with LGS will need someone on 'waking nights' meaning a parent or carer awake and alert to support their care needs, administer emergency medication were they to start seizing overnight. Daytime people's care needs can sometimes be met by a single carer, but more typically this rises to two for trips outside of the home or when there may be more complex feed or medication regimens. The description of the carer burden being mild to moderate does not reflect our experience. Children and adults with complex neurodisabiity commonly need support with ventilation, complex feeds and constipation, they may have sensory needs, be visually impaired. There are higher levels of autism spectrum disorder, scoliosis, insomnia, challenging behaviour. The challenges in LGS are greater because on top of this are the side effects of anti seizure medications and the devastating impact of frequent and unpredictable seizures.
19	3.16 Epilepsy related death is common. People with intellectual disability and epilepsy, such as LGS die approximately 20 years before those people the UK average. In addition we see sudden unexpected death in epilepsy (SUDEP). The grief impact of dying suddenly following a seizure cannot be underestimated and the carer utility value set to this must be very great indeed.
20	3.16 We understand that the committee made a judgement based decision that the carer burden on HRQoL was inflated. We disagree with this and do not see the evidence that they used to come to this conclusion. Epilepsy is the most modifiable of the comorbidities associated with LGS which is why addressing it with impactful new treatments is such a priority. However the non-seizure related comorbidities mean that the carer responsibility is life-long, highly complex, multifaceted, twenty-four hours a day and unpredictable. Many parents co-sleep with their child or young adult. The care burden is emotionally and physically exhausting and you live in terror of your child going in to status epilepticus (seizures that do not stop by themselves) or SUDEP. As children age the burden increases as social care provision diminishes; respite opportunities are fewer, college must end and there are financial and legal complexities to navigate.
21	3.19 It is clear that no one knows the correct level of wastage for either fenfluramine or cannabidiol plus clobazam. It is fair to presume that breakages are greater for cannabidiol (oily substance, glass jar) and we know that this does occur. In contrast we have not heard of any such accidents with fenfluramine and so the actual level of breakage with fenfluramine may be zero. In addition we know of at least two situations where the legal status of cannabidiol has been misunderstood by a care home, and fearing that they cannot hold a large amount of stock of a

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

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	prohibited medication, they have returned it to the pharmacy to be destroyed. Clearly this will never happen to fenfluramine. Additionally some parent carers feel that the 'bottom of the bottle' of cannabidiol does not have the same treatment effect, and so have started new bottles sooner than advised. We cannot accurately quantify the wastage of cannabidiol, but it will be higher than fenfluramine where the true wastage figure may approximate to zero.
22	3.23 We strongly feel that the failure to apply the severity modifier to carer QALYs is an error and one that is not evidence based, nor one that reflects the day to day, year to year experience of having a child or adult with LGS. Failure to do so for ganaxolone is not a helpful precedent, and we understand that the appraisal is under an appeal presently. Essentially when people with LGS respond well to anti-seizure medication, it effectively treats three people. The committee has taken a non-evidence based and unsympathetic view. It is demonstrably clear that parents and carers looking after people with LGS will have made significant professional, social and financial compromises to support their child or adult. Furthermore it is evident that the severity of the disorder (multiple care needs, multiple system involvement, multiple specialists, multiple medications) and unpredictability of the disorder means that HRQoL is significantly impacted. This reduction in HRQoL leads to the QALY impact. We do not understand the comment that (paraphrased) 'society does not recognise QALY gains for people with severe conditions above QALY gains for carers of other, less severe disorders'. Society wants to lessen human suffering and support the most vulnerable, of course we would recognise the QALY gains differently in someone who has had a child recover from cancer, versus a child recovering from appendicitis.
23	3.24 With regards to 'uncertainty' for clinical efficacy for 'non-drop' seizures – it is expected from RCT data that fenfluramine will have a modest to good response to other seizure types, variable person to person, with little to no seizure aggravation. That would be sufficient for clinical use.
24	3.28 These wider benefits are helpful to consider. The theme of the excellent tolerability of fenfluramine (aprticualrtly when compared to clobazam – with or without cannabidiol) does not come through in this consultation. This is what prevents tonic seizure aggravation, leads to better HRQoL for patients and carers and leads to a low rate of discontunation.

Insert extra rows as needed

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information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.

- 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.
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Re: Fenfluramine for Treating Seizures Associated with Lennox-Gastaut Syndrome in Individuals Aged 2 Years and Over (ID1651)

Many thanks for the opportunity to comment on the use of fenfluramine in treating Lennox-Gastaut Syndrome (LGS).

Standard of care

The EAG are keen to compare fenfluramine with topiramate, clobazam and rufinamide. This is understandable as they are listed as proposed treatments in the NICE guidance. This however is an unacceptable comparison. It is a quirk that over the last decades people have studied some antiseizure medications in some specific patient groups, and therefore NICE could find evidence for specific medications in LGS. This does not represent clinical use, clinical consensus, not clinical utility of these medicines. Respectfully these are not a true comparator and should not be used for cost efficacy comparison.

The majority of people with LGS are adults and will have been tried on multiple medications over decades; the concept of first, second or third line therapy under these circumstances is spurious. Cannabidiol plus clobazam is a late treatment and so is a **true comparator** for fenfluramine.

The economic model is conservative and under-represents the real-world benefits of fenfluramine

Cannabidiol has a number of clinically **meaningful drug interactions** which impacts its tolerability and safety. These are rarely seen in regulatory studies, but apparent once the medication is available. Fenfluramine has fewer interactions which makes it more tolerable, safer and easier to use than cannabidiol. Effectively there are fewer unscheduled health-care encounters for patients initiating fenfluramine, than those starting cannabidiol.

When cannabidiol is used it must be in conjunction with clobazam, this brings complexity as the side effects of clobazam (drowsiness) mimic other health problems and drug problems. Fenfluramine does not need to be used with clobazam and therefore it is safer and easier to use.

Cannabidiol is an oily liquid that comes in a glass bottle. When a bottle is dropped, the whole 100ml bottle is lost. All clinical and lay experts agreed that wastage is a bigger issue for cannabidiol than fenfluramine.

The concept of waning has been exaggerated by the committee

In conflict with OLE evidence and the clinical experts, they state that discontinuation rates are ‘implausibly low’. As prescribers, we refute this; we experience a very low waning effect in Dravet patients with fenfluramine and expect this to be replicated for LGS.

The evidence overwhelmingly supports that fenfluramine offers a significant improvement in quality of life by reducing the frequency of seizures and hospitalisations compared to existing treatments. The ILAE believes insufficient weight has been given to this evidence in the final recommendation which undermines the clinical data and also compromises patient care standards.

Additionally, comparisons made between fenfluramine and cannabidiol failed to adequately represent fenfluramine's superior profile in terms of **drug interactions and ease of use,** which are crucial for patient compliance and safety. The decision to dismiss the practical challenges associated with cannabidiol, such as wastage due to its packaging, further highlights the unreasonable nature of the recommendation.

The ILAE believes the committee have failed to fully appreciate the benefit to carers in terms of their QALYs. The ILAE believes the committee have taken a very conservative approach to appraising the evidence which does not fully capture clinical practice. In doing so their decision appears unreasonable to stakeholders who would expect a broader interpretation of clinical benefits and an appreciation of patient and **caregiver impacts.**

We fully appreciate the challenges of performing clinica; trials in the clinically heterogenous Lennox Gastaut syndrome, where clincal endpoints and therefore benefits may differ more than in other disorders. We encourage the EAG and committee to therefore be sympathetic to this application as failure to appreciate these challenges and the huge unmet clinical need will prevent the use of an important new treatment for people with LGS, and hinder future investment and innovation in this therapy area.

Sincerely,

[redacted]
British branch of the International League Against Epilepsy

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

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	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

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

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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.	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.
1	**Treatment options – Section 3.3 Proposed positioning and comparators** "*The committee recalled that the treatment pathway in LGS, particularly after second-line treatment can be heterogeneous"* We agree with the committee that the most appropriate comparators would be cannabidiol plus clobazam plus SC but also SC alone. As highlighted by the expert clinicians, treating refractory LGS patients is complex and requires individualised therapy. Patients are taking multiple anti-seizure medications in clinical practice, at many lines of therapy.

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	Considering cannabidiol plus clobazam as sole comparator in the proposed positioning of third-line add-on therapy, would infer that all patients at this line in pathway receive cannabidiol plus clobazam, which is not the case. This would not accurately represent the heterogeneity of the LGS treatment landscape, the evidence given by clinical experts, nor be reflective of clinical guidelines such as NG217. In the NG217 guideline, cannabidiol plus clobazam is not the only treatment recommended as add-on third-line therapy. We therefore agree with the committee that appropriate comparators would be cannabidiol plus clobazam plus SC but also SC alone.
2	**Treatment Waning – Section 3.14** *"clinical experts stated that treatment waning is not seen in clinical practice in people having antiepileptic treatments"* We are in agreement with clinicians in the above statement reported at the appeal committee. As per TA615, we would consider that this would be managed through natural discontinuation of treatment or can be managed through stopping rules.
3	**Treatment Wastage – Section 3.19** We agree with the initial analyses submitted by EAG and company which assumed no wastage for either cannabidiol or fenfluramine and no difference in wastage between products. As per our previous comments submitted to draft guidance consultation in February 2024; the similarities in application of both cannabidiol and fenfluramine are outlined in the summary of product characteristics (SPCs), with cannabidiol being supplied in a glass bottle and fenfluramine in a plastic bottle. Both cannabidiol and fenfluramine are oral solutions, provided in bottles, 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. We note the discussion at appeal hearing of the accumulation of any product at the end of a bottle: as documented in the patient information leaflet, drug extraction is taken from an inverted bottle, assisting with the extraction of the final few millilitres of solution. Furthermore, 100ml bottles of cannabidiol have a fill target level of 102ml (+/- 1 ml). This additional fill is documented in the batch record. As previously stated in our comments on breakage, which was supported by clinical expert comments in both the committee meeting and the appeal committee, breakage is not a regular occurrence. There should be no requirement for any additional wastage calculation.

Insert extra rows as needed

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Single Technology Appraisal

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

Comments on the draft guidance received through the NICE website

Name	[redacted]
Comments on the DG:	

My 29 year old son has been on Fenfluramine since February this year, up until the end of October, I have seen a definite reduction in his seizures, the intensity of his seizures, his hemiplegic episodes, his rescue drugs, his respiratory issues and the need for need for Oxygen and suctioning. He started on 1ml BD and gradually over the following months it has increased to 2.5ml BD, with the scope of increasing the dosage soon. My son is also prescribed:- CBD oil and since February it has been reducing from 3ml BD to now 0.5ml at night and Clobazam from 1.25ml once a day to now 1ml at night. He also takes Phenytoin, Keppra, Sodium Valproate and Cenobamate.
Since my son was 6 months old, he has tried the following drugs: Carbamazepine, Vigabatrin, Gabapentin, Lamotrogine, Acetazolamide ,Topiramate, Oxcarbazepine, Risperidone, Clobazam (when AHC was diagnosed in Sep 2004) Zonisimide. In 2020 -back on Clobazam with CBD oil, Florazarine for AHC.
In Aug 2002 to 2007 He had the VNS implant which reduced his seizures by over 30% . In 2014 he underwent surgery to replace the VNS battery, but the wires in his neck were broken so operation was cancelled.

Towards the end of last year 2023, he was suffering from really bad respiratory problems with an increase in seizures and hospital admissions. As such, his consultants commented, that my son was entering the last phase of his life. But by the end of March 24, since starting Fenfluramine and Acetyleysteine for his respiratory issues, his health has greatly improved

Over the last several months his quality of life has turned around. He is engaging more with his peers and staff, his mobility and transferring is better, he is sleeping reasonably at night, he is not so drowsy and able to participate in activities. His seizures are not as intense and he bounces back much quicker after medication. There is also a reduction in his mouth hemies and shivering episodes. Overall its the best he has ever been.
I will devastated, if he can not get the funding for him to stay on Fenfluramine. I do not want him to regress to the way he used to be.

From January to October 2024, to the same months of last year 2023, these are the improvements on last years figures.
Seizures: -21%, Rescue meds - Buccolam: - 3%, Lorazepam: -58%
Hemiplegia attacks: -49%, Mouth Hemies: -77% and Shivering Episodes': - 16%

Name	[redacted]

Comments on the DG:

Has all of the relevant evidence been taken into account?

Yes

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

No, as detailed in my comments
1) it is not appropriate to compare to 'standards of care'
2) it is only appropriate to compare to CBD, based on modelling it is only appropriate to consider equal efficacy
3) it is appropriate to consider there is wastage in CBD where there is not in FFA
4) there is no evidence of waning in FFA and CBD, the stopping rule takes care of any patients for whom the drug does not work and as such patients will not be continued on this when it does not work

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

No, the only sound and suitable guidance based on the clinical evidence and that of the experts (of which I am one at the appeal) is fenfluramine to be made available in line with CBD and clobazam as a treatment for Lennox Gastaut. Anything less than this is based on unfair bias and 'preferences' of the committee which have no basis.

Comment on section 1.1

The decision by NICE to refuse fenfluramine (FFA) as an add on therapy is in direct contraindication to the evidence as provided by clinicians and the company at the appeal.

Why the committee made these recommendations?
Simply the committee (as made apparent at the appeal) kept applying a concept of 'standard of care' which in clinical practice does not exists. This is predicated on a committee preference with clearly no clinical understanding of pharmacoresistant epilepsies or the DEEs. LGS is such a heterogenous disorder that its treatment cannot follow a singular pathway.

It is also predicated on the idea that fenfluramine must be compared with another therapy and that there must be comparison with CBD in clinical trails. It should only require comparison with placebo. The modelling dependent on preference shows minor advanatges and therefore it should be considered that CBD (and clobazam) and FFA have equal efficacy.

Economic evidence having uncertainity represents a failure on NICE's end to engage withe UCB in technical engagement as was requested prior to the first panel. This decision made no sense and I consider this evidence of the highly prejudicial process this panel had in the review of FFA.

Comment on 'information-about-fenfluramine'

FFA has a clear licence in LGS. There is a clear evidence base.

Comment on Proposed positioning and comparators

As I detailed extensively at the appeal - the standards of care DO NOT exist in clinical practice.
LGS is a highly heterogenous disorder with multiple underlying aetiologies which can alter the drugs used and path to treatment. Specifically by the time children reach tertiary paediatric neurologists such as myself they have often trialled 3-4 drugs within the 'standards of care'. CBD and clobazam are not always suitable and further treatment options are required. Fenfluramine should be compared to CBD and clobazam and not to the other therapies. There is no ability for comparison to each drug separately and FFA placement is in the scenario where these drugs will likely have already been utilised without success, at the same level we would, in practice, trials CBD and clobazam.
It should not be compared with SoC/SC - NICE are very contradictory here stating - 'accepted that any comparisons where these treatments are considered separately may not be robust and clinically meaningful' yet asking for comparison again with Sc when its position means its only true comparator is CBD for which it should be considered to have equal efficacy. The only relevant comparator is CBD and clobazam.
Waning does not exist as every clinical expert told the committee at the meeting - committee preference does not overule clinical expertise. The stopping rule takes care of patients for whom the drug does not work (as happens in CBD and clobazam, and FFA in Dravet Syndrome). 5.2% was a fair number based on data rather than NICEs model and numbers which do not have any clinical basis and did not stand up to ANY scrutiny. Waning simply does not happen - if it will not work we as clinicians will stop it.
To consider this - my first oncall 1 week post this meeting I had a call within 24 hours for a smashed bottle - a real world evidence of a 3rd smashed bottle in a year in a cohort of 5 patients with CBD (my own). Evidence base for this would be interesting but not practical to capture, therefore clinician opinion must be considered.
Why does the committee have a preference for dosing>0.7mg/kg/day when this is maximum dosing? This seems to be a scenario where committee preference is to utilise supratherapeutic doses, hence inflating costs, which would not happen in clinical practice.
It is well documented Jensen MP, Gammaitoni AR, Salem R, Wilkie D, Lothe A, Amtmann D. Fenfluramine treatment for Dravet syndrome: Caregiver- and clinician-reported benefits on the quality of life of patients, caregivers, and families living in Germany, Spain, Italy, and the United Kingdom. Epilepsy Res. that improvement in seizure burden improved quality of life in caregivers. Uncaptured costs include hospital admissions/intensive care, time off work for carers, socioeconomic models of input from epileptologists/epilepsy nurses/GPs and other professionals.

Simply the committee must:
1) Accept comparison and equal efficacy to CBD
2) consider that SoC is not a comparator.
3) Consider there is less wastage than CBD and clobazam
4) Consider there is no waning

Name	[redacted]
Organisation	[redacted]

Comments on the DG:
Has all of the relevant evidence been taken into account? Yes **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Yes **Are the recommendations sound and a suitable basis for guidance to the NHS?** Yes **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 age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?** It is important to recognise he unmet needs of the LGS community, the impact of living with LGS and the need for new treatment options like Fenfluramine.

Name	[redacted]
Organisation	[redacted]
Comments on the DG:	
Comment on 'Details of the condition' section 3.1, wording **Lennox–Gastaut syndrome (LGS) is a severe, lifelong and treatment-resistant form of epilepsy that begins in early childhood, generally before the age of 8 years. It is characterised by a specific electroencephalogram (EEG) pattern and developmental delay or cognitive impairment.'** The above statement is a general characterisation of LGS which is widely accepted. An LGS diagnosis may be given as a primary clinical diagnosis, where no specific cause for the epilepsy has yet been identified and the patient meets the above triad of symptoms - this is the case for many older individuals with an existing LGS diagnosis who may not have benefited from more recent genetic testing for example. However in more recent years, more specifically in the paediatric epilepsy patient population, LGS is given as a secondary diagnosis to the actual cause of the epilepsy, be it a genetic or structural aetiology. When LGS is provided as a diagnosis, it is subjective on the interpretation of ion, the treating clinician as by definition LGS is a heterogeneous form of epilepsy. This is important to note, when considering differing individual's response to treatments such as Fenfluramine or other anti seizure treatment options. **Comment on 'Details of the condition' section 3.1, wording** ***Non-drop seizures are typically not as severe as drop seizures and do not generally result in hospitalisation.*** This is a generalisation and whilst drop seizures may result in physical injury requiring hospitalisation non-convulsive status epilepticus (NCSE) which is another key feature in LGS, if prolonged may equally result in hospitalisation.	

Comment on section 3.1 treatment options

Here I add my views as to why we need new options like Fenfluramine for people living with LGS:
• there is a delicate balance of seizure control vs. side effects to obtain optimum QoL for individuals with LGS. The challenges some individuals experience with CBD+Clobazam C+C e.g. excessive somnolence often experienced with Clobazam and the long term impact of taking this as an addictive Benzo, also some individuals cannot tolerate the oily nature of CBD, Fenfluramine could offer an alternative more suitable treatment option for some individuals.
• the random nature of individual responses to ASM's are unpredictable even to clinicians and researchers, i.e. some individuals respond to certain ASM's whilst others don't and no one knows who will respond and why.

It is therefore imperative that there is a range of treatment options available to people with an LGS diagnosis, because by definition, they are already living with a drug resistant form of epilepsy - way beyond third-line treatment - and certainly SC has not worked. As stated above, C+C may work for some or be tolerated by some individuals, but not for others so for some individuals Fenfluramine may be a more efficacious treatment.

Individuals with LGS need options, else they will continue to live with a life-limiting if not, life-threatening condition.

Name	[redacted]
Organisation	[redacted]
Comments on the DG:	

Has all of the relevant evidence been taken into account?

We believe that the focus of the comparison (fenfluramine vs clobazam & cannabidiol) is too narrow, as the committee itself seems to recognise. This may well be a fault of the manufacturer's presentation and argument, but nevertheless it risks failing to offer what could be a life-changing option for some families.

Within the CHD2 UK group that we represent, a number of our members have been diagnosed with LGS (and this is replicated in the US and other international groups). Because the condition is heterogeneous, no particular treatment has consistent efficacy across patients as a whole, nor across age, sex, ethnicity or other categories. Response is very much on an individual basis. Ruling out potential treatments on a single comparative measure fails to account for the enormous individual impact to the patient (and indeed their family / carers) that a positive response would signify when existing treatments have failed.

The comparison (vs. cannabidiol & clobazam) also lacks some elements of real-world experience as described by our family members. Being prescribed cannabidiol in the UK is far more difficult than being prescribed almost any other anti-epilepsy medication. Even before we get to consider any medical reasons for it not being prescribed, there is still an evident reluctance among many consultants to prescribe cannabis-derived products, regardless of licensing guidelines and theoretical availability. We do not consider it appropriate to argue that fenfluramine is no more effective that cannabidiol & clobazam, when many families are simply not given the option of trying cannabidiol. This indicates that there is an ongoing

need to allow other new treatments to be available when existing standard offerings prove ineffective.

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

We consider that the treatment cost for the medication is comparatively low when set against the devastating impact that LGS has both to an individual and to their wider family. An LGS diagnosis takes over the lives of those affected, with parents and family members unable to work due to needing to devote the majority of their time to a caring role. Any medication that could significantly reduce seizures for some patients would concomitantly allow for a better quality of life for their immediate family and potentially a more productive role beyond that of a carer. Indeed, for those individuals for whom fenfluramine would have a significant positive impact, the reduction in seizure frequency, in combination with the reduction in the extensive associated financial and societal costs, means that the benefits would far outweigh the ongoing cost.

Furthermore, as with other anti-seizure medications, it is usually fairly rapidly apparent when an AED such as fenfluramine is ineffective for the individual; and ineffective AEDs are soon weaned out again and stopped. Therefore, there is little risk of ongoing costs for fenfluramine prescriptions for individuals where there was no obvious, significant improvement.

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 (DG2)

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

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1. Remaining uncertainties requiring evidence-based analyses

1.1. Comparison versus SC alone

The committee stated that a comparison with standard care (SC) alone, as a basket of treatments, would be useful for decision-making. Specifically, this would be where cannabidiol (CBD) + Clobazam + standard of care (SoC) cannot be taken.

However, the company did not provide this comparison, stating that it was not clinically relevant, which was based on clinical expert opinion, including a survey, which found that 12 out of 14 clinicians agreed that such patients would only be eligible for invasive surgeries or clinical trials. The other clinicians mentioned ketogenic diet and one mentioned vagus nerve stimulation (VNS). The survey also found that 12 of 14 clinicians agreed that the only relevant comparator was CBD + clobazam + SoC. One of the other clinical experts mentioned cenobamate and the other mentioned valproate + clobazam or valproate + lamotrigine.

External Assessment Group (EAG) comment: To those two questions related to the relevance of SC alone (questions 5 and 6), only one of 14 clinicians mentioned pharmacotherapy that might be part of a basket of treatments. However, it should be noted that the company expressed the questions as statement that implied that SC alone was not appropriate with which the clinicians were asked whether they agreed.

In addition, it is noteworthy that the stage in the care pathway was not clearly stated in either question e.g., question 5 stating: *"patients have already been exposed to multiple SoC drugs and the remaining treatment options would be interventions such as invasive surgeries and consideration for clinical trials."* It might indeed be the case that at a certain point there are no other options, but CBD + Clobazam + SoC is recommended as early as early as third line. Therefore, a better form of question might have been: *"At third line, what would be the appropriate treatment for those who cannot take CBD + Clobazam + SoC?"*. This means that SC alone in the form of some pharmacotherapy cannot be ruled out.

1.2. Waning

In their updated base-case, the company assumed no treatment effect waning (0.0%) for both fenfluramine (FFA) + SoC and CBD + SoC, based on clinical expert opinion from the appeal hearing and a survey conducted by the company.

EAG comment: The committee in draft guidance 2 requested evidence-based scenarios to support the modelling of treatment waning in the economic model. The company did not provide scenario analyses based on additional data, but assumed no treatment waning for FFA and CBD in their updated base-case using clinical expert opinion as its evidence base. The EAG noted that clinical experts during the appeal hearing and the majority of the clinical experts that responded to the company's survey agreed that treatment waning is not seen in clinical practice for patients taking FFA or CBD (9 respondents agreeing, 5 respondents disagreeing).

However, the clinical expert responses to question 7 of the company's survey may be prone to leading question bias, as the company's question (i.e. *do you agree that treatment waning is not seen in clinical practice for patients taking cannabidiol or fenfluramine*) may imply the answer "yes". The EAG's approach of modelling treatment waning in its base-case therefore remains unchanged, i.e. use all patients on treatment from month 9 to 12 (last cycle of observed data) in the FFA open label extension (OLE) study to calculate the treatment waning probability in the next cycles.

1.3. Wastage

The company informs wastage in their updated economic model based on clinical expert opinion from the appeal hearing and a survey conducted by the company. In response to question 8 about the number of bottles wasted per patient per year for CBD in the company's healthcare professional (HCP) survey, the median and mean were [redacted] and [redacted] respectively wasted per patient per year. For FFA, the median and mean were [redacted] and [redacted] respectively per patient per year (question 9). Based on clinical expert opinion from the appeal hearing and the survey conducted by the company, the company's updated base-case applies [redacted] and [redacted] wastage for CBD and FFA (mean values), respectively, whereas the median values were explored in a scenario analysis.

EAG comment: In line with the committee's request, the company provided additional analyses for treatment wastage based on clinical expert opinion. Although responses to the company's survey may again be prone to leading question bias by stating that "*given the fact that CBD is an oily substance that is provided in glass bottles and fenfluramine is a liquid that is provided in plastic bottles, the consequences of accidents or an inability to aspirate all of the contents of the vial are likely to be greater for CBD than for fenfluramine*", the EAG considers informing wastage in the economic model based on the survey results to be reasonable. However, as the data from the survey seem not normally distributed, the EAG prefers using the median values (i.e. [redacted] wastage for FFA and [redacted] wastage for CBD) in its base-case.

1.4. Pulmonary arterial hypertension (PAH)

1.5. CBD maintenance dose

In its updated base-case, the company assumes a CBD maintenance dose of 16 mg/kg/day based on clinical expert responses to a supplementary question in its survey (Section 1.5 of the response).

EAG comment: The EAG notes that the committee's preferred CBD maintenance dose range of 12 mg/kg/day to 16 mg/kg/day was based on clinical expert opinion and data from the CBD OLE study. The company provided 7 more clinical expert inputs in its response to DG2 document, mostly ranging between 15 and 20 mg/kg/day. The EAG, however, could not find the exact wording of this supplementary question and detailed responses related to the CBD maintenance dose in the survey document that was provided by the company.

The EAG agrees that the clinical expert inputs described by the company suggest that the average CBD maintenance dose may be at the upper end of the committee's range considered appropriate for decision making. However, at the first appraisal committee meeting, two clinical experts stated the average CBD dose in clinical practice is likely to be between 14 to 16 mg/kg/day, while a third clinical expert mentioned a dose closer to 12 mg/kg/day. Considering this diversity of clinical expert inputs, the EAG prefers modelling two base-cases: 1) assuming a CBD maintenance dose of 12 mg/kg/day and 2) assuming a CBD maintenance dose of 16 mg/kg/day.

2. New base case proposal

The company's revised base case analysis includes a cost-minimisation approach (which implies that FFA and CBD are considered equivalent in terms of efficacy, waning, AEs and discontinuation rates across all cycles) to mitigate uncertainties remaining with the naïve comparison approach as well as the updated OLE NMA (based on the requested imputation analysis). A summary of the company's latest modelling assumptions compared to its last base-case is presented in Table 1 below.

Table 1: Comparison of base-case assumptions

Input	Last company base case	Revised company base case	Commentary/rationale
PAS discount for FFA	[redacted]	[redacted]	[redacted]
PAS discount for CBD	[redacted]	[redacted]	Unknown discount
FFA + SC efficacy	Cycle 1: NMA of RCT Cycles 2-5: NMA of OLE studies using LOCF Cycles 5-9: Maintained efficacy	Cycle 1: NMA of RCT Cycle 2-5: state occupancies from FFA OLE study Cycles 5-9: Maintained efficacy	Based on ITC results: large 95% CrI of encompassing 1 and expert opinion (from the survey n=14)
CBD + CLB + SC efficacy	Cycle 1: NMA of RCT Cycles 2-5: NMA of OLE studies using LOCF Cycles 5-9: Maintained efficacy	Equal efficacy as FFA for all cycles	Based on ITC results: large 95% CrI of encompassing 1 and expert opinion (from the survey n=14)
Safety & discontinuation	AEs & discontinuation rates from respective FFA and CBD studies	AEs & discontinuation rates from FFA study (equal between the two treatment groups)	Needed for a cost-minimisation assumption
Treatment waning	Applied to 5.2% of the patients	No waning in either treatment group	Based on expert opinion (from the survey n=14) and aligned with the cost-minimisation approach

Input	Last company base case	Revised company base case	Commentary/rationale
Severity modifier application	Applied at the 1.7 level	No severity modifier applied	Not applicable to equal efficacy and safety approach
FFA maintenance dose	0.413 mg/kg/day	0.416 mg/kg/day	Including FFA patients taking the dosage above the daily cap as per committee preferred assumptions
CBD maintenance dose	14 mg/kg/day	16 mg/kg/day (varied from 12 up to 15 mg)	Based on expert opinion (supplementary questions following the survey n = 7). Varied as requested within DG2
Wastage	0%	[redacted]% for CBD and [redacted]% for FFA	Based on expert opinion (from the survey, n=14)

Based on Table 2 of company's response to DG2
AE = adverse event; CBD = cannabidiol; CrI = credible interval; DG2 = draft guidance 2; FFA = fenfluramine; ITC = indirect treatment comparison; LOCF = last observation carried forward; NMA = network meta-analysis; OLE = open-label extension; PAS = Patient Access Scheme; SC = standard care

EAG comment: The company uses a cost-minimisation approach in its updated economic model, assuming that FFA and CBD are equivalent in terms of efficacy, waning, adverse events (AEs) and discontinuation rates. The company justified its approach by the large overlap of credibility intervals surrounding the relative risks that encompass 1, which may suggest equal efficacy between FFA and CBD. In addition, the majority of consulted clinical experts in the company's survey agreed that this would be a suitable approach to take for decision making purposes (see question 10).

Using a cost-minimisation approach, the company aims to mitigate uncertainty related to the modelling of treatment effectiveness during the OLE period (cycles 2-5). This was initially modelled using a naïve comparison between the trials, followed by a network meta-analysis (NMA) including last observation carried forward (LOCF). In its current response to draft guidance 2, the company explored a scenario analysis including an NMA with non-random imputation (i.e. assuming people who dropped out of the study 1601 OLE and the CBD OLE has a less than 25% improvement in drop seizure frequency (DSF) for the modelling of treatment effect in cycles 2-5). The EAG's comments to this scenario analysis are discussed in Section 3 below.

Although the EAG considers the company's cost-minimisation approach to be the simplest modelling alternative, it ignores any observed differences between FFA and CBD in the clinical trial data. The naïve comparison and OLE NMA alternatives (i.e. using LOCF and non-random imputation), however, also suffer from limitations and it is therefore unclear to the EAG what would be the best approach to model treatment effectiveness of FFA and CBD. Hence, the EAG's base-case remains unchanged, i.e. using state occupancies for fenfluramine and CBD in line with their clinical trial data for the modelling of treatment effectiveness in cycles 2-5, and assuming a maintained treatment effect for both after the observed data period.

3. Scenario with imputation applied to OLE NMA in the cost-effectiveness analysis

3.1. Imputation method for the OLE period data & OLE NMA

The company have updated the OLE NMA to incorporate the imputation of missing data by assuming patients with missing data have less than 25% reduction in drop seizures, as suggested in DG2.

The company also stated that: *"The placebo effect is assumed to remain stable over time and was assessed from the respective phase III studies."* (p. 22)

EAG comment: The EAG have compared the drop seizure data as presented in Table 7 with those presented by the company in response to the first draft guidance (referred to as DG1) and critiqued by the EAG. This shows that, as anticipated by imputing missing data as less than a 25% reduction in drop seizure, as opposed to the original method of LOCF, the number of events (R) is reduced in the new dataset and the reduction increases with time (see Table 2). This does not apply to the placebo arm because, as in DG1, it is assumed that there are no more events beyond 12 weeks. As stated in the EAG critique of DG1, it continues to be questionable that this is consistent with the company assertion that the; "*The placebo effect is assumed to remain stable over time"*. In fact, if the placebo effect was to remain stable then, if there had been follow-up of the placebo arm patients, this effect would have been observed in both the intervention and comparator arms of the trials. This is the basis of the inclusion of a placebo arm i.e. because the placebo effect applies to the intervention arm. Assuming no further events in the placebo arm implies that there is in fact no placebo effect beyond the follow-up period rather than it being stable, but this is only applied to the placebo arm, which might produce a bias in favour of the intervention. However, this bias has now been to some extent mitigated by the new method of imputation, which diminishes the efficacy of only the interventions. However, the EAG notes that the reduction in R is greater for cannabidiol than fenfluramine, which is presumably due to more missing data for the former. The effect of this is to reduce the efficacy of cannabidiol more than of fenfluramine. This can be seen by observing the change in risk (R/N) and relative risk (risk with intervention/risk with placebo) between the company response to DG1 and DG2 (see Table 3). The EAG are therefore concerned that, although the imputation might reduce any bias in favour of the intervention vs. placebo arm, it might introduce bias in favour of fenfluramine. However, this is difficult to assess given that the reason for the committee recommending this imputation was the belief that the data might not be missing at random, which might imply that the reduction in efficacy and the greater reduction in efficacy of cannabidiol is in fact appropriate.

The EAG also have some concerns regarding the validity of the results. The is because, despite there being no difference in the data used for the NMA at the 12-week timepoint, the risk ratios have changed between the response to DG1 and DG2 (see Table 3).

Table 2: OLE NMA datasets using new imputation method vs. original NMA presented for ACM2

Study	Treatment arm	Outcome	Timepoint	N	R1	R2	R1-R2
Thiele 2019	PLACEBO	≥ 25% REDUCTION	12	161	[redacted]	[redacted]	0
Thiele 2019	CANNABIDIOL	≥ 25% REDUCTION	12	364	[redacted]	[redacted]	0
ZX008	PLACEBO	≥ 25% REDUCTION	12	87	[redacted]	[redacted]	0
ZX008	FENFLURAMINE	≥ 25% REDUCTION	12	247	[redacted]	[redacted]	0
Thiele 2019	PLACEBO	≥ 50% REDUCTION	12	161	[redacted]	[redacted]	0
Thiele 2019	CANNABIDIOL	≥ 50% REDUCTION	12	364	[redacted]	[redacted]	0
ZX008	PLACEBO	≥ 50% REDUCTION	12	87	[redacted]	[redacted]	0
ZX008	FENFLURAMINE	≥ 50% REDUCTION	12	247	[redacted]	[redacted]	0
Thiele 2019	PLACEBO	≥ 75% REDUCTION	12	161	[redacted]	[redacted]	0

Study	Treatment arm	Outcome	Timepoint	N	R1	R2	R1-R2
Thiele 2019	CANNABIDIOL	≥ 75% REDUCTION	12	364	[redacted]	[redacted]	0
ZX008	PLACEBO	≥ 75% REDUCTION	12	87	[redacted]	[redacted]	0
ZX008	FENFLURAMINE	≥ 75% REDUCTION	12	247	[redacted]	[redacted]	0
Thiele 2019	PLACEBO	≥ 25% REDUCTION	24	161	[redacted]	[redacted]	0
Thiele 2019	CANNABIDIOL	≥ 25% REDUCTION	24	364	[redacted]	[redacted]	-14
ZX008	PLACEBO	≥ 25% REDUCTION	24	87	[redacted]	[redacted]	0
ZX008	FENFLURAMINE	≥ 25% REDUCTION	24	247	[redacted]	[redacted]	-9
Thiele 2019	PLACEBO	≥ 50% REDUCTION	24	161	[redacted]	[redacted]	0
Thiele 2019	CANNABIDIOL	≥ 50% REDUCTION	24	364	[redacted]	[redacted]	-10
ZX008	PLACEBO	≥ 50% REDUCTION	24	87	[redacted]	[redacted]	0
ZX008	FENFLURAMINE	≥ 50% REDUCTION	24	247	[redacted]	[redacted]	-2
Thiele 2019	PLACEBO	≥ 75% REDUCTION	24	161	[redacted]	[redacted]	0
Thiele 2019	CANNABIDIOL	≥ 75% REDUCTION	24	364	[redacted]	[redacted]	-6
ZX008	PLACEBO	≥ 75% REDUCTION	24	87	[redacted]	[redacted]	0
ZX008	FENFLURAMINE	≥ 75% REDUCTION	24	247	[redacted]	[redacted]	-1
Thiele 2019	PLACEBO	≥ 25% REDUCTION	36	161	[redacted]	[redacted]	0
Thiele 2019	CANNABIDIOL	≥ 25% REDUCTION	36	364	[redacted]	[redacted]	-29
ZX008	PLACEBO	≥ 25% REDUCTION	36	87	[redacted]	[redacted]	0
ZX008	FENFLURAMINE	≥ 25% REDUCTION	36	247	[redacted]	[redacted]	-14
Thiele 2019	PLACEBO	≥ 50% REDUCTION	36	161	[redacted]	[redacted]	0
Thiele 2019	CANNABIDIOL	≥ 50% REDUCTION	36	364	[redacted]	[redacted]	-18
ZX008	PLACEBO	≥ 50% REDUCTION	36	87	[redacted]	[redacted]	0
ZX008	FENFLURAMINE	≥ 50% REDUCTION	36	247	[redacted]	[redacted]	-5
Thiele 2019	PLACEBO	≥ 75% REDUCTION	36	161	[redacted]	[redacted]	0
Thiele 2019	CANNABIDIOL	≥ 75% REDUCTION	36	364	[redacted]	[redacted]	-11
ZX008	PLACEBO	≥ 75% REDUCTION	36	87	[redacted]	[redacted]	0
ZX008	FENFLURAMINE	≥ 75% REDUCTION	36	247	[redacted]	[redacted]	-1
Thiele 2019	PLACEBO	≥ 25% REDUCTION	48	161	[redacted]	[redacted]	0
Thiele 2019	CANNABIDIOL	≥ 25% REDUCTION	48	364	[redacted]	[redacted]	-103
ZX008	PLACEBO	≥ 25% REDUCTION	48	87	[redacted]	[redacted]	0
ZX008	FENFLURAMINE	≥ 25% REDUCTION	48	247	[redacted]	[redacted]	-22
Thiele 2019	PLACEBO	≥ 50% REDUCTION	48	161	[redacted]	[redacted]	0
Thiele 2019	CANNABIDIOL	≥ 50% REDUCTION	48	364	[redacted]	[redacted]	-74
ZX008	PLACEBO	≥ 50% REDUCTION	48	87	[redacted]	[redacted]	0
ZX008	FENFLURAMINE	≥ 50% REDUCTION	48	247	[redacted]	[redacted]	-11
Thiele 2019	PLACEBO	≥ 75% REDUCTION	48	161	[redacted]	[redacted]	0
Thiele 2019	CANNABIDIOL	≥ 75% REDUCTION	48	364	[redacted]	[redacted]	-41
ZX008	PLACEBO	≥ 75% REDUCTION	48	87	[redacted]	[redacted]	0
ZX008	FENFLURAMINE	≥ 75% REDUCTION	48	247	[redacted]	[redacted]	-3

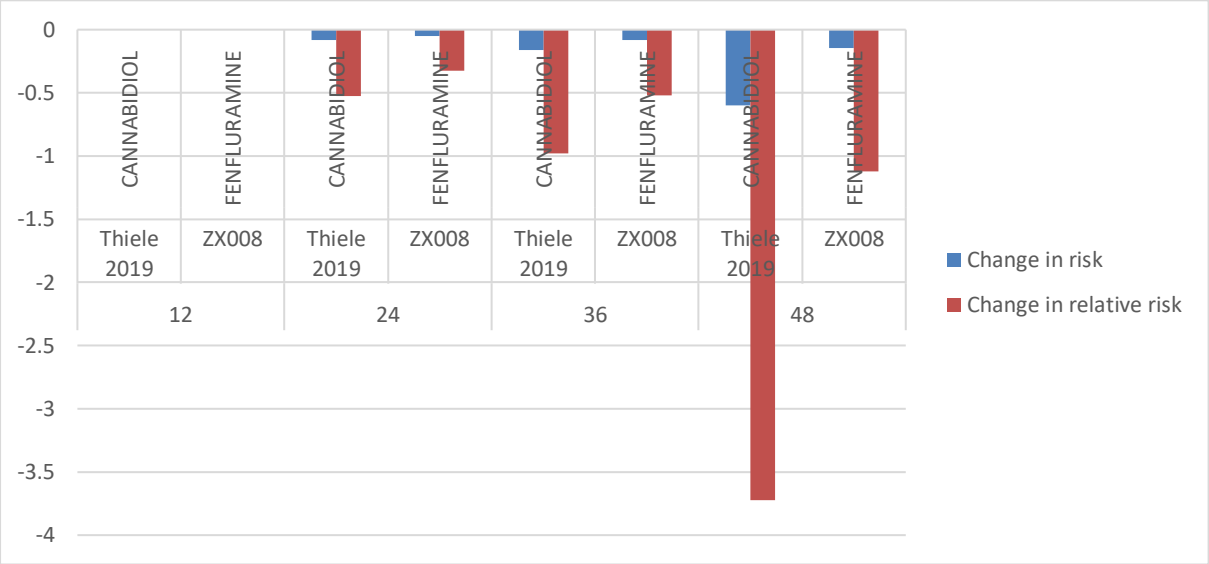
ACM2 = appraisal committee meeting 2; N = total; NMA = network meta-analysis; OLE = open-label extension; R = number of events

Table 3: OLE NMA datasets using new imputation method vs. original NMA presented for ACM2

	Response to DG1		Response to DG2	
	RR FFA versus Placebo (95% CrI)	RR CBD versus Placebo (95% CrI)	RR FFA versus Placebo (95% CrI)	RR CBD versus Placebo (95% CrI)
Timepoint: At week 12 in the OLE study				
≥ 25% response	[redacted]	[redacted]	[redacted]	[redacted]
≥ 50% response	[redacted]	[redacted]	[redacted]	[redacted]
≥ 75% response	[redacted]	[redacted]	[redacted]	[redacted]
Timepoint: At week 24 in the OLE study				
≥ 25% response	[redacted]	[redacted]	[redacted]	[redacted]
≥ 50% response	[redacted]	[redacted]	[redacted]	[redacted]
≥ 75% response	[redacted]	[redacted]	[redacted]	[redacted]
Timepoint: At week 36 in the OLE study				
≥ 25% response	[redacted]	[redacted]	[redacted]	[redacted]
≥ 50% response	[redacted]	[redacted]	[redacted]	[redacted]
≥ 75% response	[redacted]	[redacted]	[redacted]	[redacted]
Timepoint: At week 48 in the OLE study				
≥ 25% response	[redacted]	[redacted]	[redacted]	[redacted]
≥ 50% response	[redacted]	[redacted]	[redacted]	[redacted]
≥ 75% response	[redacted]	[redacted]	[redacted]	[redacted]

Based on EAG critique of company response to DG1, Table 8 of company response to DG2.
CBD = cannabidiol; CrI = credible interval; DG = draft guidance; FFA = fenfluramine; NMA = network meta-analysis; OLE = open-label extension; RR = risk ratio

Figure 1: EAG calculated change in risk and relative risk from original to new OLE NMA



3.2. Results of scenario with imputation applied to NMA (including 1.7x severity modifier)

Table 4: Results of scenario with imputation applied to NMA

Technologies	Total costs (£)	Total LYG	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
FFA + SC	[redacted]	20.30	-18.45	[redacted]	0.09	0.57	[redacted]

Technologies	Total costs (£)	Total LYG	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
CBD + CLB + SC	[redacted]	20.21	-19.02	-	-	-	-
SC alone	[redacted]	20.17	-19.30	[redacted]	0.13	0.85	[redacted]