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Draft guidance consultation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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using fenfluramine in the NHS in England.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

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