NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Fenfluramine for treating Lennox-Gastaut seizures 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: January 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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using fenfluramine in the NHS in England.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: 21 February 2024
- Second evaluation committee meeting: 6 March 2024
- 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 clinician consider it appropriate to stop. For children or young people, this decision should be made jointly by the clinician, 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 that collectively make up standard care. 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. There is no evidence directly comparing fenfluramine with cannabidiol plus clobazam. But, an indirect comparison suggested that fenfluramine may be more effective than cannabidiol plus clobazam in reducing the number of drop seizures.

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 above what NICE considers an acceptable use of NHS resources and highly uncertain. 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 anti-epileptic 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 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 (GTC) seizures are particularly severe, and uncontrolled and frequent GTC 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. Also, the anxiety that a child with LGS may be injured because of a drop seizure can significantly affect the mental wellbeing of their family members. 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 offering sodium valproate first. If seizures are inadequately controlled, lamotrigine is recommended as a second-line add-on treatment or by itself. If second-line treatment is unsuccessful, cannabidiol plus clobazam, clobazam alone, rufinamide and topiramate are recommended as third-line add-on treatment options. If all other treatment options are unsuccessful, add-on treatment with felbamate (unlicensed use) is recommended, 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. For example, some people cannot have cannabidiol plus clobazam because of drug–drug interactions. The committee noted that it would be useful to see data on the proportion of people ineligible for cannabidiol plus clobazam in NHS clinical practice. The clinical experts noted that LGS can be difficult to diagnose and that by the time people are adults 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 drugs 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. It would also like to see data on the proportion of people ineligible for cannabidiol plus clobazam.

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 comparators included in the company submission were cannabidiol plus clobazam (plus standard care [SC]) and 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. Therefore, 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 (ASMs), except cannabidiol plus clobazam plus SC. It added that cannabidiol plus clobazam plus SC is the only treatment with sufficient 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 see scenarios that considered clobazam, rufinamide and topiramate as separate comparators. It added that data about the proportion of people with LGS using those treatments in the NHS would also be helpful. But, it acknowledged that most of the studies for these treatments were conducted over 20 years ago and so 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 against these treatments may not be robust and clinically meaningful. 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.

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 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 ASM 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 for

fenfluramine). It acknowledged that the most common treatment-emergent adverse events were decreased appetite, somnolence 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.

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 conducted a series of network meta-analyses (NMA). Outcomes assessed were:

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

Following the company's systematic literature review and feasibility assessment, 3 RCTs were identified (that covered only fenfluramine, cannabidiol and placebo). The company conducted 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 GTC 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 analysis. The company's base case NMA results suggested that fenfluramine plus SC is superior to placebo plus SC and cannabidiol plus

clobazam plus SC for all outcomes assessed, except the 75% or more reduction in DSF. The exact NMA results 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 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. The company also considered that cannabidiol plus clobazam plus SC and SC alone were the only relevant comparators (see section 3.3). Results from the NMA that comprised the 9 RCTs in the network suggested that, overall, the clinical benefits of some other third-line ASMs may be 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 company's base case NMA suggests that fenfluramine plus SC demonstrates superior efficacy to cannabidiol plus clobazam plus SC and SC alone for the outcomes:

- median percentage reduction in frequency of GTC seizures
- reductions in DSF of:
  - 25% or more and
  - 50% or more.

But, fenfluramine did not demonstrate superior efficacy for the 75% or more reduction in DSF outcome. And the lack of robust data to enable indirect comparisons with rufinamide, topiramate and clobazam results in uncertainty.

Study 1601 validity

3.6 The EAG noted that the company had not provided data on the per-arm use of non-pharmacological treatments, so the internal and external

validity of the trial was unclear. They also noted that specific interactions between fenfluramine and the other ASMs might create differences in outcomes in comparisons between fenfluramine and placebo. Subgroup analyses would therefore be helpful to assess this. The committee recalled that the choice of treatment regime is highly individualised in LGS and that the treatment population is heterogeneous (see section 3.2). It concluded that subgroup analyses with different combinations of medications are unlikely to resolve any potential uncertainty about the impact on outcomes of particular combination of concomitant medications. The EAG also noted other potential issues with study validity:

- the validity of the efficacy measures depends on the measurement validity of the eDiary. It did not believe the studies provided by the company provided convincing evidence supporting the validity of the eDiary as a measurement device
- the external validity of the trial was unclear, because the company had not done subgroup analyses by age, gender or ethnicity.

The committee concluded that this may add uncertainty to the validity of the evidence.

Economic model

Company's modelling approach

3.7 The company presented a 6-state cohort-based Markov model with a lifetime time horizon of 86 years. 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 NMA. 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 transition probabilities and state occupancies varied from cycles 2 to 9 for fenfluramine plus SC and cannabidiol plus clobazam plus SC (see section 3.10 and section 3.11). After cycle 9, the change in state occupancy was based on treatment waning, discontinuation and death

Health states based on relative reductions in drop seizures

3.8 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 health care resource use data from TA615, based on absolute drop seizure frequency categories. The committee noted that 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 noted other limitations that would have been present with a model with health states based on absolute DSF categories. So, the committee accepted the company's model structure for decision-making. But it concluded that the model structure added uncertainty to the cost-effectiveness estimates.

Exclusion of non-drop seizures in model

3.9 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 from the model adds to the uncertainty around the economic analysis.

Modelling treatment effect during the OLE period

3.10 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, the company used patient-level data from the Study 1601 OLE to generate transition probabilities for cycle 2 to cycle 5. There was a lack of patient-level data for the cannabidiol OLE. So, health state occupancy for cannabidiol plus clobazam plus SC for cycle 2 to cycle 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. 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. The company stated that the modelled health state occupancy was based on a treated population (the model includes a separate health state to accommodate people that have discontinued treatment). The EAG noted that it was inconsistent to consider the treated population for fenfluramine plus SC (instead of the ITT population), while the ITT population was used for cannabidiol plus clobazam plus SC. 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 raised concerns that state occupancy data with fenfluramine was only available for people who had a report measured at each time point and the potential bias this introduced (see section 3.11). The committee would like clarification on whether the cannabidiol OLE data used to populate the cannabidiol plus clobazam plus SC health states for cycles 2 to 5 was based on the treated population or the ITT population. The committee considered that it would prefer the ITT population to be used, and that if only the treated population was used then this could result in bias. If the data was based on the ITT population, the committee would like clarification on the methodology and assumptions used to account for missing data points. It would also like to see analyses that include all 247 people that entered the Study 1601 OLE, including people who did not complete the OLE or were lost to follow up. For consistency, the committee would like to see analyses using the same methodology and assumptions used to account for missing data points in the Study 1601 OLE data analysis, applied to the cannabidiol OLE data as well. Specifically:

- State occupancy data for fenfluramine at months 3, 6, 9 and 12 assuming that those who drop out of the Study 1601 OLE did so with a

less than 25% improvement in DSF, as opposed to assuming they are missing at random.

- State occupancy data for cannabidiol at months 3, 6, 9 and 12 that accounts for attrition in a similar manner. If limitations in accessible data from the cannabidiol OLE study are a limiting factor, basing attrition assumptions on fenfluramine OLE attrition data is preferable to assuming patients who leave the sample are missing at random.

The committee considered that any revised cost-effectiveness analyses should account for OLE attrition as described above, and account for the expected implications for treatment effect extrapolation assumptions, as explained in section 3.11.

Extrapolation of fenfluramine treatment effect

3.11 The company's model had a lifetime time horizon of 86 years. Fifteen months of data for fenfluramine plus SC were available from Study 1601 and the OLE. So, extrapolation of treatment effect was required beyond the trial period. For fenfluramine plus SC, the company assumed that the transition probabilities for cycle 6 to cycle 9 in the model equalled the transition probabilities of cycle 4 to 5, which were based on the last 3 months of the Study 1601 OLE. That is, it was assumed that the treatment effectiveness for fenfluramine increased after the observed trial period. In contrast, the company assumed the treatment effect for cannabidiol plus clobazam plus SC was stable for cycle 6 to cycle 9. The EAG noted that this assumption is important because, in the model, the quality-adjusted life years (QALYs) accumulated during the observed trial period are higher for cannabidiol plus clobazam plus SC than for fenfluramine plus SC. And so, the incremental QALYs in favour of fenfluramine plus SC in the company's base case over the lifetime horizon (see section 3.22) were obtained in the unobserved period. This assumption was based on state occupancy data of fenfluramine and cannabidiol from their 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. Whereas cannabidiol's efficacy plateaus with state occupancy remaining fixed for almost 6 months (from month 6 to 12 of the cannabidiol OLE). The company also stated that long-term data and clinician experience in Dravet syndrome suggests that efficacy of fenfluramine continues to improve until at least months 25 to 30. It added that clinicians considered that the increased longer-term treatment effect of fenfluramine in Dravet syndrome would also apply to LGS. The EAG agreed that the effectiveness of fenfluramine plus SC seemed to increase over time during the trial period. But it was uncertain about the prolongation of treatment effect after the trial period. It 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). One clinical expert stated that they were not aware of a disease-modifying effect of fenfluramine. So it seemed unlikely that fenfluramine's efficacy would continue to improve beyond the trial period. Another clinical expert agreed and added 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. 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. It added that the missing data points may have been treated as missing at random. People lost to follow up are likely systematically different from people continuing treatment, which the committee considered biased the data. 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. The committee concluded that neither the company's preferred assumption of increasing treatment effect, nor the EAG's preferred assumption of maintained treatment effect, were consistent with Study 1601 OLE data when accounting for attrition. The preferred assumptions were also not consistent with the clinical experts' expectations for treatment effectiveness over time. The committee considered that an analysis accounting for missing data points as detailed in section 3.10 is needed to inform the treatment effect for fenfluramine plus SC for cycle 6 to cycle 9. It requested analyses with treatment effect assumptions for cycle 6 to cycle 9 based on the conclusions of the imputation analyses detailed in section 3.10.

Treatment waning

3.12 The company applied treatment waning after cycle 9 in the model. The company calculated the proportion of people in each cycle that experience treatment waning (5.2%) based on the last 3 months of the Study 1601 OLE. The transition probabilities applied to people experiencing waning were then calculated based on people who stayed in their health state or moved into a worse health state (deteriorating transition probabilities) in last 3 months of the Study 1601 OLE. This was applied to both fenfluramine plus SC and cannabidiol plus clobazam plus SC due to lack of treatment waning data for cannabidiol plus clobazam plus SC. The EAG considered that the company's method results in an overestimation in the proportion of people with deteriorating transition probabilities because it is not calculated over the total number of people on treatment. The EAG preferred to use all people on treatment from the last 3 months of the Study 1601 OLE (rather than only including the people that stayed in their health state or deteriorated) to calculate the treatment waning transition probabilities in its base case. The committee noted that in TA615, the company assumed that people on cannabidiol stayed in the

same health state beyond 9 cycles (27 months). That is, the treatment effect of cannabidiol was maintained until the person stopped treatment or died. In TA615, the company also considered that it had captured reduced effectiveness over time in a scenario analysis in which it increased the annual rate at which people in all health states (except the seizure-free health state) stopped cannabidiol. Specifically, it increased the stopping rate from 5% to 10% of people per year. In the current appraisal, the committee considered there was uncertainty about the most appropriate approach. But, it noted that the choice of approach had a small impact on the cost-effectiveness results. The EAG considered that the proportion of people experiencing treatment waning per cycle (5.2%) was extremely low. This was based on the proportion of people that had discontinued treatment at 12 months in the fenfluramine and cannabidiol OLEs. The EAG produced a scenario in which 80% of people experienced treatment waning. This had a larger impact on the cost-effectiveness results. The committee would like to see additional data or evidence to support the company's assumption of 5.2% of people experiencing treatment waning after cycle 9. It recalled issues with the assumption that Study 1601 OLE data were missing at random (see section 3.10 and section 3.11). It considered that any analysis of OLE data to inform treatment waning assumptions should account for data attrition as requested in section 3.10, as opposed to assuming data are missing at random. It also requested additional scenarios exploring different proportions of people experiencing treatment waning and a scenario with 10% of people per year discontinuing treatment as explored in TA615.

Patient utility values

3.13 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 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

3.14 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 used for people with LGS from Verdian et al. (see section 3.13). 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. Additionally, the company's carer utility approach 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. However, 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 committee concluded that it preferred the EAG's assumptions around carer utility values, but applied in a manner that did not result in negative QALYs.

Fenfluramine maintenance dose

3.15 The summary of product characteristics (SPC) for fenfluramine recommends increasing the dose of fenfluramine as tolerated up to the recommended maintenance dosage of 0.7 mg/kg/day. In its initial model, the company implemented a base case maintenance dosage for fenfluramine of 0.5 mg/kg/day. This was based on data from the Study 1601 OLE and validated during an advisory board meeting with UK clinical experts. But, at the clarification stage, the company lowered the base case fenfluramine dosage to 0.413 mg/kg/day. It stated that the updated dosage was based on the average mean daily dosage for fenfluramine for all people in the Study 1601 OLE, in which efficacy continued to improve at lower average doses than used in Study 1601. It added that the

updated dosage is more reflective of clinical practice because in the Study 1601 OLE, dosages were titrated based on safety and tolerability. It also suggested that the updated 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. But, it considered that the justification for the decrease in dosage seemed to contradict the clinical experts' statements originally provided by the company. It also noted that both the original dosage and updated dosages were lower than the maintenance dosage recommended in the SPC (that is, 0.7 mg/kg/day). Both dosages 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 therefore preferred using 0.5 mg/kg/day for fenfluramine in its base case. The committee requested the mean daily dosage from Study 1601 for the fenfluramine 0.7 mg/kg/day arm (that was used to inform the indirect treatment comparison). The committee noted that both the 0.5 mg/kg/day dosage and the 0.413 mg/kg/day dosage provided at clarification were from the Study 1601 OLE. The committee requested that it would like clarification on how the 0.5 mg/kg/day dosage and the updated 0.413 mg/kg/day dosage were calculated and the rationale for the discrepancy. The committee was minded to prefer the use of the mean dose from the Study 1601 OLE as this dose is likely to be most reflective of clinical practice. But, the committee would also like to see a scenario in which the dose in cycle 1 reflects the mean dose in the 0.7 mg/kg/day arm in Study 1601. This is because this was the dataset used to inform the indirect treatment comparison that informed efficacy in cycle 1 of the model.

Cannabidiol maintenance dose

3.16 The SPC for cannabidiol states that the dosage can be increased from a maintenance dosage of 10 mg/kg/day to 20 mg/kg/day. In its initial model, the company implemented a base case maintenance dosage for cannabidiol of 14 mg/kg/day. This was based on real-world use of

cannabidiol for Dravet syndrome (Silvennoinen 2021) and expert opinion stating that the dosage is not expected to exceed 14 mg/kg/day. But, at the clarification stage, the company increased the base case cannabidiol dosage to 16 mg/kg/day. The company considered that 16 mg/kg/day is conservative based on UK expert clinical opinion and the cannabidiol OLE study. The mean modal dosage within the cannabidiol OLE was 24 mg/kg/day. It acknowledged that in clinical practice some people have 10 to 12 mg/kg/day, but stated that adequate reductions in DSF are rarely seen at lower cannabidiol dosages. The EAG considered that the justification for the increase in dosage appeared to contradict the previous statement by clinical experts provided by the company. The previous statement suggested that an appropriate approach would be to assume a dosage of 14 mg/kg/day. The EAG also 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. So, the EAG modelled an average maintenance dosage of 12 mg/kg/day for cannabidiol in its base case. The clinical experts stated that in their experience the average maintenance dosage of cannabidiol was around 12 to 15 mg/kg/day. They added that cannabidiol is an oily substance and is provided in a glass bottle. So there can be wastage due to the glass bottle breaking or some cannabidiol being leftover in the bottle. They also noted that there may be less wastage of fenfluramine in practice. The committee noted that the company's updated base case cannabidiol dosage was supported by evidence from the cannabidiol OLE study. The committee considered that the appropriate cannabidiol maintenance dosage for the model was likely between 12 and 16 mg/kg/day. It would like to see scenario analyses exploring the impact on cost effectiveness for the range of cannabidiol maintenance dosages it considered plausible. It also requested that the company provide further data on the average maintenance dosage of cannabidiol used in NHS clinical practice. Given that all the company's or EAG's analyses assume zero wastage, the committee would also like to see scenarios which account for the

expected wastage costs associated with both cannabidiol and fenfluramine treatment. Based on the expectations and rationale for different wastage levels across cannabidiol and fenfluramine, the committee would like to see scenarios in which greater wastage is assumed for cannabidiol and in which equal wastage is assumed for fenfluramine and cannabidiol.

Residential care

3.17 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 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-seizures 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 the vast majority of 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.

Stopping rule

3.18 The marketing authorisation for fenfluramine does not specify a stopping rule. But, the company 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, clinicians 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 that were in health state 0 for 6 months. As a result, people that were in health state 0 for only 3 months also discontinued. The committee requested that the company resolve this issue in the model. 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.

Pulmonary hypertension

3.19 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 pre-treatment echocardiograms and consideration of other risk factors. In contrast, the maximum daily dosage 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. Also, 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.

Severity

3.20 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', with absolute and relative QALY shortfall thresholds 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.

Cost-effectiveness estimates

Uncertainties in evidence and modelling assumptions

3.21 The committee noted that there were uncertainties in the evidence base and modelling assumptions, 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 internal and external validity of Study 1601 because of the uncertainty associated with the use of concomitant medications and non-pharmacological treatments (see section 3.6).
- Whether age, gender or ethnicity are treatment effect modifiers (see section 3.6).
- The appropriateness of the company's model structure based on relative reduction in DSF (see section 3.8).
- The appropriateness of only using drop seizures in the modelling, and not other seizure types (see section 3.9).

- Whether the data used to model the cannabidiol plus clobazam plus SC treatment effect for cycles 2 to 5 was based on ITT population data or treated population data (see section 3.10).
- The appropriateness of the data used to inform state occupancy between cycles 2 and 5 (see section 3.10).
- Fenfluramine's long-term treatment effect and the appropriateness of the data used by the company to justify an increasing treatment effect between cycles 6 and 9 (see section 3.11).
- Whether it was appropriate to calculate treatment waning transition probabilities based on people who stayed in their health state or moved into a worse health state in the last 3 months of the Study 1601 OLE (see section 3.12).
- The proportion of people who experience treatment waning after cycle 9 (see section 3.12).
- The appropriateness of the patient utility values presented in the company submission (see section 3.13).
- The maintenance dosages and wastage with fenfluramine and cannabidiol in NHS clinical practice (see section 3.15 and section 3.16).

Company and EAG cost-effectiveness estimates

3.22 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 base case incremental cost-effectiveness ratios (ICERs) for the comparisons with cannabidiol plus clobazam plus SC and with SC alone were within the range normally considered an acceptable use of NHS resources. In the EAG's base case analysis, for the comparison with cannabidiol plus clobazam plus SC, fenfluramine plus SC was dominated (that is, it was less effective and more expensive). 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

3.23 The committee preferred the model to:

- base the treatment effect assumptions for cycles 2 to 5, and for cycles 6 to 9 on the conclusions of the imputation analyses (see section 3.10 and section 3.11). Specifically,
  - State occupancy data for fenfluramine at months 3, 6, 9 and 12 assuming that those who drop out of the Study 1601 OLE did so with a less than 25% improvement in DSF, as opposed to assuming they are missing at random.
  - State occupancy data for cannabidiol at months 3, 6, 9 and 12 that accounts for attrition in a similar manner. If limitations in accessible data from the cannabidiol OLE study are a limiting factor, basing attrition assumptions on fenfluramine OLE attrition data is preferable to assuming patients who leave the sample are missing at random.
- account for data attrition, as detailed in section 3.10, in any analysis of data used to inform treatment waning assumptions
- use the Verdian et al. (2008) utility values to model patient utility (see section 3.13)
- use a carer disutility approach using the Lo et al. (2021) carer utility values, but applied in a manner that does not result in negative QALYs (see section 3.14)
- use the mean dose from the Study 1601 OLE as the fenfluramine maintenance dose (see section 3.15)
- assume 10% of people with LGS reaching 18 will need residential care (see section 3.17)
- include residential-care costs and assume 0.7 carers for people who need residential care (see section 3.17)
- 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 3.18)

- not include treatment costs for pulmonary hypertension (see section 3.19)
- use a severity weight of 1.7 applied only to patient QALYs (see section 3.20).

The committee's requests for additional analyses

3.24 The committee could not arrive at a preferred ICER because the high level of uncertainty in the modelling assumptions. Particularly the assumptions used to model treatment effect for fenfluramine plus SC and cannabidiol plus clobazam plus SC. But the committee noted that the cost-effectiveness estimates with its preferred assumptions would likely be above the range NICE normally considers to be an acceptable use of NHS resources. The committee would like to see the following additional exploratory or confirmatory work:

- Additional data:
  - on the proportion of people:
    - ineligible for cannabidiol plus clobazam in NHS clinical practice (see section 3.2).
    - with LGS using clobazam, rufinamide and topiramate in NHS clinical practice (see section 3.3).
  - to support the company's assumption of 5.2% of people experiencing treatment waning after cycle 9 (see section 3.12).
  - on the average maintenance dosage of cannabidiol used in NHS clinical practice (see section 3.16).
- Clarification on:
  - whether the cannabidiol OLE data that was used to populate the cannabidiol plus clobazam plus SC health states for cycles 2 to 5 was based on the treated population or the ITT population. If based on the ITT population, the committee would also like clarification on the methodology and assumptions used to account for missing data points (see section 3.10).

  - how the company's original base case maintenance dosage for fenfluramine of 0.5 mg/kg/day was calculated, how the updated maintenance dosage was calculated and the rationale for the discrepancy between the dosages (see section 3.15).
- Scenario analyses:
  - in which clobazam, rufinamide and topiramate are considered separately as comparators in the cost-effectiveness analysis (see section 3.3).
  - exploring different proportions of people experiencing treatment waning and a scenario with 10% of people discontinuing treatment as explored in TA615 (see section 3.12).
  - in which the fenfluramine dose in cycle 1 reflects the mean dose in the 0.7mg/kg/day arm of Study 1601 (see section 3.15).
  - exploring the impact on cost-effectiveness for the range of cannabidiol maintenance dosages the committee considered plausible (see section 3.16).
  - Incorporating wastage costs associated with both cannabidiol and fenfluramine treatment. That is, a scenario in which greater wastage is assumed for cannabidiol and a scenario in which equal wastage is assumed for fenfluramine and cannabidiol (see section 3.16).
- Resolve the issue related to the implementation of the stopping rule at 6 months in the model (see section 3.18).

Other factors

Equality

3.25 The clinical experts highlighted that people with LGS may 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 expert noted that some of the tests potentially required 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 treatment.

Uncaptured benefits

3.26 The committee did not identify any additional benefits of fenfluramine not captured in the economic modelling. So, the committee concluded that all additional benefits of fenfluramine had already been taken into account.

Conclusion

3.27 The committee agreed that further information was needed to decide all its preferred modelling assumptions and to understand the full impact of the uncertainties. But, the most plausible cost-effectiveness estimates that include some of the committee's preferred assumptions are above the range that NICE usually considers an acceptable use of NHS resources. It concluded that it was not possible to recommend fenfluramine for treating LGS 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.

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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

Megan John

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.

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Technical lead

Lizzie Walker

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