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SMC2723

fenfluramine oral solution (Fintepla®)

UCB Pharma Ltd

10 January 2025

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, advises NHS Boards and Area Drug and Therapeutics Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

fenfluramine (Fintepla®) is accepted for restricted use within NHSScotland.

Indication under review: treatment of seizures associated with Lennox-Gastaut syndrome as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older.

SMC restriction: patients whose seizures have not been controlled after trying two or more anti-epileptic medicines.

In a randomised, double-blind, phase III study, fenfluramine significantly reduced drop seizure frequency in patients (aged 2 to 35 years) with Lennox-Gastaut syndrome that was inadequately controlled by current anti-epileptic medicines, compared with placebo.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Fenfluramine is a serotonin releasing agent, which stimulates multiple 5-HT receptor subtypes. The precise mode of action of fenfluramine in Lennox-Gastaut syndrome (LGS) is not known but it may reduce seizure frequency by acting on certain serotonin receptors in the brain and by acting on the sigma-1 receptor. Fenfluramine is administered as an oral solution at doses ranging between 0.2 to 0.7 mg/kg/day in two divided doses; further details on maximum dosing are in the Summary of Product Characteristics (SPC).[1]

1.2. Disease background

LGS is a rare and severe epilepsy disorder that usually begins in early childhood, between 3 and 5 years of age.[2, 3] Patients with LGS account for 5% to 10% of children with seizures with an estimated prevalence of 0.58 per 10,000 in the UK.[4] It is characterised by multiple severe seizure types such as tonic, atonic, and atypical absence seizures. Drop seizures (those that result in sudden falls causing serious injury and/or hospitalisation) are common but patients can also experience milder seizures that do not result in falls, such as myoclonic seizures, focal seizures, and non-convulsive status epilepticus. Nearly all patients with LGS have treatment resistant, lifelong epilepsy, accompanied with cognitive and behavioural impairments. Patients with LGS have an increased risk of death (between 3% and 7%) during their lifetime, including the risk of sudden unexpected death in epilepsy (SUDEP).[2, 3, 5]

1.3. Company proposed position

The submitting company has requested that fenfluramine is positioned for use in patients whose seizures have not been controlled after trying two or more anti-epileptic medicines.

1.4. Treatment pathway and relevant comparators

Patients are generally managed with sodium valproate first-line.[6, 7] Lamotrigine[8] is recommended as a second-line treatment option, either as monotherapy or as an adjunct, if sodium valproate is unsuitable, ineffective or not tolerated.[6]

If second-line treatment is unsuccessful then other treatment options include: cannabidiol (in conjunction with clobazam)[9], clobazam[10], rufinamide[11], or topiramate[12]. Non-pharmacological treatments such as ketogenic diet and vagus nerve stimulation (VNS) can also be added onto the treatment pathway at this stage. Polytherapy is common and seizure control is difficult to achieve with current therapies.[6] SMC has accepted cannabidiol plus clobazam (SMC2263) and rufinamide (SMC2146) as adjunctive therapy in the treatment of seizures associated with LGS; though rufinamide is restricted to use in patients who have failed treatment with or are intolerant of other anti-epileptic medicines.

In the population covered by the proposed positioning, the submitting company considers cannabidiol plus clobazam to be the only relevant comparator. However, SMC clinical experts suggested that rufinamide may be another potential comparator.

1.5. Category for decision-making process

Eligibility for a PACE meeting

Fenfluramine meets SMC orphan criteria.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of fenfluramine for the indication under review comes from Study 1601 Part 1. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant study.

Criteria	Study 1601 Part 1.[2, 13]
Study design	International, randomised, double-blind, parallel-group, placebo-controlled phase III study.

Eligible patients	• Patients aged 2 to 35 years of age who had an Epilepsy Study Consortium-confirmed diagnosis of LGS who met the following criteria:
	  ○ Onset of seizures at ≤ 11 years of age.
	  ○ Multiple seizure types that result in drops including: GTC, SGTC, TS, AS, TA, or FS.
	  ○ Abnormal cognitive development.
	• Experienced ≥ 8 drop seizures in the 4-week baseline period (immediately prior to screening with ≥ 2 drops per week).
	• Receiving ≥ 1 to 4 concomitant anti-epileptic medicines, which were stable for ≥4 weeks prior to screening and expected to remain stable throughout the study.
	• No concomitant cannabidiol use.

Treatments & Randomisation	After the 4-week baseline period to establish seizure frequency, patients were randomised equally to receive oral: fenfluramine 0.2 mg/kg/day[a] (n=89), fenfluramine 0.7 mg/kg/day[a] (n=87), or placebo (n=87). A 2-week titration period[b] was followed by a subsequent maintenance period, where all patients remained at their assigned dose for 12 weeks. Total treatment time from the beginning of the titration period through the end of the maintenance period was 14 weeks. At the end of the maintenance period (or early discontinuation), all subjects underwent the blinded 2-week Taper or Transition Period depending on whether they exited the study or were enrolled in Study 1601, Part 2 (the long-term open-label extension study), respectively. Concomitant use of KD and VNS were permitted but changes to these therapies, as well as anti-epileptic medicines were not permitted during the study. Randomisation was stratified by weight (< 37.5 kg or ≥ 37.5 kg).
Primary outcome	Percentage change in median DSF per 28 days from baseline to the combined 14-week treatment period (titration and maintenance) for fenfluramine 0.7 mg/kg/day compared with placebo.
Secondary outcomes	• Proportion of patients with a ≥ 50% reduction in DSF (from baseline to the combined 14-week treatment period) for fenfluramine 0.7 mg/kg/day compared with placebo. • Proportion of patients with improvement[c] on the CGI-I (investigator rating) at visit 12 for fenfluramine 0.7 mg/kg/day compared with placebo.
Statistical analysis	The predefined primary efficacy analysis was conducted on the mITT population (all randomised patients who received ≥ 1 dose of fenfluramine or placebo and ≥ 1 week of electronic diary data were available). A hierarchical testing procedure was applied to the primary and key secondary outcomes (in the order above) with no formal testing after the first non-significant outcome in the hierarchy.

Abbreviations: AS = atonic seizure; CGI-I = clinical global impression of change-improvement rating; CS = clonic seizures; DSF = drop seizure frequency; EEG = electroencephalogram; FS = focal seizure; GTC = generalised tonic-clonic seizure; Hz = hertz; KD = ketogenic diet; LGS = Lennox-Gastaut Syndrome; mITT = modified intention-to-treat; MS = myoclonic seizure; SGTC = secondary generalised tonic-clonic seizure; TA = tonic/atonic seizure; TS = tonic seizure; VNS = vagus nerve stimulation.

[a] Up to a maximum of 26 mg per day.

[b] Patients in the 0.7 mg/kg/day fenfluramine group were titrated to the target dose, whereas patients in the other two treatment groups started at their target dose.
[c] The CGI-I scale ranges from 1 (very much improved) to 7 (very much worse). Improvement would be classed as a score of 1 (very much improved), 2 (much improved), or 3 (minimally improved).

In Study 1601 Part 1, fenfluramine 0.7 mg/kg/day was significantly more effective than placebo for the primary outcome and the key secondary outcome (proportion of patients with a ≥ 50% reduction in DSF from baseline to the combined 14-week treatment period). Results for the CGI-I investigator rating outcome numerically favoured fenfluramine 0.7 mg/kg/day over placebo, but this was not statistically significant; this meant that reported results for outcomes further down the hierarchy were not deemed to be statistically significant. The licensed target maintenance dose is 0.7 mg/kg/day, therefore efficacy results for the 0.2 mg/kg/day will not be discussed further. Details of results are presented in Table 2.2.

Table 2.2. Results for primary and key secondary outcomes in Study 1601 Part 1 in the modified intention-to-treat (mITT) population.[2, 13]

	Fenfluramine 0.7 mg/kg/day (n=87)	**Placebo (n=87)**
Primary outcome: Percentage change in median DSF per 28 days from baseline to the combined 14-week treatment period (titration and maintenance).		
Median DSF at baseline (per 28 days)	83	53
Median DSF at week 14 (per 28 days)	55	47
Median percentage change in median DSF from baseline at week 14	-26.5%	-7.6%
Median difference versus placebo (95% CI), p-value	-19.9% (-31.0 to -8.7), p=0.001	
Key secondary outcome: Proportion of patients with a ≥ 50% reduction in DSF from baseline to the combined 14-week treatment period (titration and maintenance).		
Percentage of patients who achieved ≥ 50% reduction in DSF, % (n)	25% (22/87)	10% (9/87)
Odds ratio versus placebo (95% CI), p-value	2.87 (1.23 to 6.70), p=0.015	
Key secondary outcome: Proportion of patients with improvement on the CGI-I (investigator rating) at visit 12.		
Percentage of patients with improvement on the CGI-I Investigator Rating at visit 12, % (n)	49% (39/80)	34% (27/80)
Odds ratio versus placebo (95% CI), p-value	1.86 (0.98 to 3.52), NSS	

Abbreviations: CGI-I = clinical global impression of change-improvement rating; CI = confidence interval; DSF = drop seizure frequency; NSS = not statistically significant.

The results of an analysis for the primary outcome using the maintenance period (12 weeks), for the fenfluramine 0.7 mg/kg/day group (-27.2%) compared with the placebo group (-7.3%), were similar to those of the analysis for the combined 14-week treatment period (titration and maintenance). Additionally, no significant increases in any individual seizure types, no notable difference in new seizure types or incidence of status epilepticus are reassuring.[2]

In the seizure type subgroup analyses, fenfluramine 0.7 mg/kg/day reduced the frequency (from baseline) of the five drop seizure types (GTC, SGTC, tonic, atonic, tonic/atonic) to a greater or similar extent compared with the placebo group. Fenfluramine had the largest treatment effect in reducing GTC frequency compared with placebo (-45.7% versus -5.5%).[2, 13]

2.2. Evidence to support the positioning proposed by the submitting company

The enrolled patients (n=263) had prior treatment failure with a median of seven prior anti-epileptic medicines (range: 1 to 20) which included clobazam, lamotrigine, rufinamide, topiramate, and sodium valproate. Most patients (95%) used 2 to 4 anti-epileptic medicines as background therapy during the study. The most concomitantly used medicines with fenfluramine (n=176) in the study were: sodium valproate (98/176, 56%); clobazam (81/176, 46%); lamotrigine (59/176, 34%); rufinamide (35/176, 20%); felbamate (27/176, 15%) and topiramate (23/176, 13%). However, it is noted that 27% (72/263) of patients had previously been treated (and failed treatment) with cannabidiol.[2, 5]

2.3. Health-related quality of life (HRQoL) outcomes

HRQoL was measured using the Quality of Life in Childhood Epilepsy-16 item questionnaire (QOLCE-16) at randomisation and at visit 12 (end of the combined 14-week treatment period); this is a parent-proxy reported epilepsy-specific instrument that has been validated to assess how epilepsy affects day-to-day functioning of children in various areas, including physical activities, wellbeing, cognition, social activities, behaviour, and general health.[15, 16] Overall, the results for the QOLCE in the fenfluramine groups suggest no significant differences in the overall score between the fenfluramine and placebo groups.

2.4. Supportive studies

LGS patients who completed Study 1601 Part 1 could participate in the ongoing Study 1601 Part 2.[17] Study 1601 Part 2 was an open-label, 52-week, flexible-dose extension study; all patients (even those on 0.7 mg/kg/day fenfluramine in Part 1) had to be treated initially with 0.2 mg/kg/day for 1 month (transition period) to assess effectiveness of this dose. The dose was titrated (from month 2 onwards) as necessary. The primary objective of Part 2 was to assess the long-term safety and tolerability of fenfluramine at doses ranging from 0.2 mg/kg/day to 0.7 mg/kg/day; only 68/247 patients received a mean daily dose of ≥ 0.6 mg/kg/day.[2, 17] A total of 143 patients have completed the study, 19 patients are ongoing, and 85 patients have withdrawn. The most common reason for discontinuation was lack of efficacy (55 [22%]), adverse event (13 [5.3%]), and patient withdrawal (13 [5.3%]).[1] Over the entire open-label extension (n=241), the median percentage change in monthly DSF was -28.6%, whilst 31% of patients experienced a ≥ 50% reduction in DSF.[17]

2.5. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of head-to-head evidence against cannabidiol with clobazam, the submitting company presented two indirect treatment comparisons (ITCs). Firstly, a Bayesian Network Meta-Analysis (NMA) which focussed on the safety and efficacy of fenfluramine versus cannabidiol with clobazam; this comparison was used to inform cycle one (months 1 to 3) of the cost-effectiveness model. Secondly, an ITC of the open-label extension (OLE) period was conducted which focussed on a modified intention-to-treat population (mITT); these were patients that had received ≥ 1 dose

of treatment, had a valid estimate of the frequency of seizures that resulted in drop seizures from Study 1601 Part 1, and had at least one month of valid seizure data during the OLE (Study 1601 Part 2).

Table 2.3: Summary of indirect treatment comparison.

Criteria	Overview
Design	Bayesian NMA following: **Cycle one**: comparing efficacy of treatments in a 14-week randomised comparison period. **Cycles two to five:** using OLE studies for 48-week period.
Population	Patients ≥ 2 years old with a diagnosis of LGS and uncontrolled seizures, taking one to four anti-seizure medicines, evidence of more than one type of seizure and at least two drop seizures per week during the baseline period.
Comparators	Cannabidiol 10 mg/kg/day (plus clobazam); cannabidiol 20 mg/kg/day (plus clobazam); and fenfluramine. All comparisons were presented relative to placebo (reference treatment in the analyses), and not with each other.
Studies included	Knupp et al. 2022: fenfluramine 0.2 mg/kg/day; fenfluramine 0.7 mg/kg/day versus placebo.[13] Thiele et al. 2018 (GWPCARE4): cannabidiol 20 mg/kg/day versus placebo.[18] Devinsky et al. 2018 (GWPCARE3): cannabidiol 10 mg/kg/day; cannabidiol 20 mg/kg/day versus placebo.[19]
Outcomes	**Cycle one: randomised treatment period** 1. Median percentage reduction in frequency of generalised tonic-clonic seizures. 2. ≥ 25% reduction in drop seizure frequency. 3. ≥ 50% reduction in drop seizure frequency. 4. ≥ 75% reduction in drop seizure frequency. **Cycles two to five: OLE (assessed at weeks 12, 24, 36 and 48)** 1. ≥ 25% reduction in frequency of drop seizures. 2. ≥ 50% reduction in frequency of drop seizures. 3. ≥ 75% reduction in frequency of drop seizures.
Results	**Cycle one** For outcomes 1, 2, and 3: all three treatments were likely superior to placebo. Fenfluramine was ranked first using SUCRA measurements though all credible intervals overlapped, suggesting similar effects. For outcome 4: only cannabidiol 20 mg/kg/day (plus clobazam) was likely superior to placebo. The SUCRA ranking indicated that cannabidiol 20 mg/kg/day (with clobazam) was the highest ranked treatment. However, the credible intervals overlapped, suggesting similar effects. **Cycles two to five** Rates of outcomes from the placebo group were carried forward into the OLE NMA to allow for comparison with fenfluramine. Outcomes 1 and 2: fenfluramine and cannabidiol plus clobazam were likely superior to placebo at all time points for these outcomes. Fenfluramine was ranked first using SUCRA measurements though all credible intervals overlapped (at all time points), suggesting similar effects. Outcome 3: fenfluramine and cannabidiol plus clobazam were likely superior to placebo at all time points. Using the SUCRA ranking, fenfluramine (at weeks 12 and 48) and cannabidiol plus clobazam (at weeks 24 and 36) were ranked first at different time points. However, all credible intervals overlapped (at all time points), suggesting similar effects.

Abbreviations: DSF = Drop seizure frequency; GTC = generalised ITC = indirect treatment comparison; LGS = Lennox-Gastaut Syndrome; OLE = open-label extension; OLE ITC = open-label extension indirect treatment comparison; SUCRA = surface under the cumulative ranking curve.

An additional NMA report which explored broader networks with other potential comparators contained results of pairwise comparisons (using fixed effects model) of relative risk (in comparison to placebo) for the outcomes: ≥ 25%, ≥ 50%, and ≥ 75% reduction in frequency of drop seizures; for these outcomes, fenfluramine was compared with rufinamide (as well as with cannabidiol 10 mg/kg/day plus clobazam and cannabidiol 20 mg/kg/day plus clobazam). The 95% credible intervals for these comparisons overlapped for all three outcomes, suggesting similar efficacy between all of these treatments. Overall, the submitting company deemed these comparisons to be inappropriate based on their feasibility assessment and excluded it from their base case in the original submission.

3. Summary of Safety Evidence

In Study 1601 Part 1 the safety population was defined as all randomised patients who received at least one dose of fenfluramine 0.7 mg/kg/day (n=87), 0.2 mg/kg/day (n=89) or placebo (n=87), during the combined 14-week treatment period (titration and maintenance). During this double-blind period, the incidence of: treatment-related adverse events (AEs) (55%, 35%, 39%), severe treatment-emergent AEs (3.4%, 1.1%, 1.1%), and treatment-emergent AEs leading to discontinuation (5.7%, 4.5%, 1.1%); were all notably higher in 0.7 mg/kg/day group, compared with the 0.2 mg/kg/day and placebo groups respectively. The most common treatment-emergent AEs (occurring ≥ 10% of patients in either fenfluramine group and were more common than the placebo group) were: decreased appetite (36%, 20%, 12%); fatigue (18%, 9.0%, 10%); somnolence (17%, 10%, 10%); and diarrhoea (13%, 11%, 4.6%).[2, 13]

In Study 1601 Part 2, the most common treatment-emergent serious AEs in the double-blind through the open-label treatment periods (n=262) were: change in seizure presentation (3.8%), status epilepticus (3.8%), pneumonia (3.1%), pneumonia aspiration (3.1%), seizure (1.5%), somnolence (1.5%), vomiting (1.1%), and dehydration (1.1%).[2]

Cardiac effects could occur in longer exposure as they are related to cumulative exposure. The LGS population is usually young and requires long-term treatment. The SPC recommends that cardiac monitoring is performed using echocardiogram before starting fenfluramine, then every 6 months for the first 2 years and then annually during treatment. A patients and caregivers alert card is also available.[1]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In Study 1601 Part 1, fenfluramine 0.7 mg/kg/day showed a 20% decrease, compared with placebo, in the median DSF from baseline to the end of a 14-week treatment period (primary outcome);[2, 13] these findings were supported by findings for the key secondary outcome.[2]
- Study 1601 Part 1 was a well-conducted controlled phase III study at low risk of bias due to randomisation, stratification and blinding of patients and investigators. The study design also aligned with regulatory recommendations for investigating medicines for treating epilepsy disorders.[14]

- Most study patients broadly reflect the proposed population in terms of prior and concomitant anti-epileptic treatments. Of note, just over a quarter of study patients had prior treatment with cannabidiol, which the submitting company considers to be the most relevant comparator

4.2. Key uncertainties

- There is no direct evidence comparing fenfluramine with any treatment options for this positioning. The submitting company provided two ITCs comparing fenfluramine with cannabidiol plus clobazam. The ITCs had some limitations, including heterogeneity across the placebo groups and a lack of placebo control during the OLE phase. The submitting company claimed that the ITCs provided evidence that fenfluramine was superior to cannabidiol, however, it seems more reasonable to conclude that fenfluramine and cannabidiol (with clobazam) have similar efficacy over both time periods (cycle 1, and cycles 2 to 5).
- Expert responses from those contacted by SMC outlined that rufinamide was a possible comparator. An additional NMA provides some reassurance that fenfluramine has similar efficacy to rufinamide.
- There appeared to be large differences between the baseline median DSF (per 28 days), which was higher in the fenfluramine 0.7 mg/kg/day group (83) compared to placebo (53).[2, 13] For context, in the GWPCARE3[19] and GWPCARE4[18] studies (registration studies for cannabidiol for LGS), the differences between the median DSF (per 28 day) for the treatment groups and placebo were < 7. It is therefore uncertain if these differences were large enough to influence the study outcomes.
- There is a lack of controlled data beyond 14 weeks, and there is uncertainty in longer term outcomes.

4.3. Clinical expert input

Expert responses from those contacted by SMC consider fenfluramine to be a therapeutic advancement and fulfil an unmet need as it offers a treatment option to reduce seizure frequency when other existing treatments are ineffective or not tolerated. They indicated that it would be used as per the company's positioning in place of cannabidiol (with clobazam) and possibly rufinamide.

4.4. Service implications

Expert responses from those contacted by SMC highlighted that there could be significant service implication due to the requirement for a baseline and regular (every 6 months for the first two years then annually thereafter) echocardiograms.[1]

5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from the Tuberous Sclerosis Association and UK rare epilepsies together (UKRET). Tuberous Sclerosis Association is a registered charity and UKRET is a charitable unincorporated organisation.

- Tuberous Sclerosis Association has received 11.2% pharmaceutical company funding in the past two years, with none from the submitting company. UKRET has not received any pharmaceutical company funding in the past two years.
- LGS is associated with often severe and prolonged seizure activity that is poorly controlled by anti-epilepsy medicines. Uncontrolled seizures can result in numerous unplanned hospital admissions and medical interventions. Living with LGS can result in failure to thrive due to nutritional challenges. Children may lose weight and stop growing. LGS also impacts the wider family. Parents and caregivers report trauma and mental health diagnoses, including post-traumatic stress disorder from events associated with their children's LGS. Siblings are reported to experience attachment issues and behavioural challenges along with mental health diagnoses.
- LGS is challenging to treat with currently available anti-epileptic medicines. Children and adults with LGS will be prescribed multiple medications at any one time and will have typically tried between 15 to 20 different anti-epileptic medications, many of which can result in side-effects that reduce quality of life.
- This new medicine is important to patients and carers as many families will have exhausted all currently available treatment options, including pharmacological, surgical and dietary interventions, yet seizures may still not be under control. If fenfluramine were to reduce the frequency of drop seizures a patient had this could have a huge impact on patients and families.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

Details of the economic case are summarised in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis (CUA) and a cost-minimisation analysis (CMA)
Time horizon	Lifetime horizon up to a maximum of 86 years, based on a mean starting age of 13.7 years.
Population	Patients aged 2 or older with treatment resistant LGS associated seizures which have not been controlled after treating with two or more ASMs.
Comparators	Cannabidiol with clobazam plus Standard of Care (SoC) was the sole comparator included in the economic model.
Model description	All patients entered the model via an initial titration plus maintenance (T+M) phase lasting one cycle. From cycle 2 onwards, patients entered the maintenance or discontinuation phase. Maintenance phase consisted of four health states based on percentage reduction in DSF from baseline: • state 0, for people with a less than 25% decrease in DSF (no response) • state 1, for people with a 25% to less than 50% decrease in DSF (low response) • state 2, for people with a 50% to less than 75% decrease in DSF (medium response) • state 3, for people with a 75% or greater decrease in DSF (best response) The model included two additional health states. One for people who discontinued treatment and an absorbing death state. Discontinuation could occur at titration and at any cycle after that throughout the time horizon due to adverse events, lack of efficacy or stopping rule.

Clinical data	The main source of clinical evidence was Study 1601 Part 1 and the associated OLE study (Part 2). There were no direct head-to-head studies comparing fenfluramine with cannabidiol plus clobazam. ITCs were therefore conducted to assess relative treatment effect.
Extrapolation	State occupancy between cycles 2 to 9 varied based on efficacy data from the clinical evidence. In the absence of direct head-to-head comparative data for fenfluramine and cannabidiol plus clobazam, the RCT ITC provided efficacy inputs for the first cycle and OLE ITC provided efficacy inputs for cycles 2 to 5. State occupancies were maintained from cycles 6 to 9 and assumed equal to the latest observed efficacy data in cycle 5 based on OLE ITC. From cycle 10 onwards, state occupancy was based on treatment waning, discontinuation and death. Discontinuation started from cycle 2 and was captured by a stopping rule when patients' response is below 30% reduction in DSF, evaluated every 6 months. A proportion of patients were assumed to undergo treatment waning using deteriorating transition probabilities estimated from cycles 4 to 5 from the fenfluramine OLE study. All-cause mortality was applied using a background mortality rate applied to all patients. In addition, all patients were at risk of SUDEP. SUDEP mortality was assumed to be dependent on health states and the frequency of seizures per 28 days.
Quality of life	Trial-based utilities could not be used due to unavailability of a mapping algorithm to convert a childhood epilepsy questionnaire scores into EQ-5D utilities. Vignette based utility scores from a 2008 conference abstract were used instead, since these were applied in previous LGS studies and aligned with the model's relative health state structure. The utility scores were 0.020, 0.10, 0.50 and 0.596 for health states 0, 1, 2 and 3 respectively.
Costs and resource use	Medicine costs in the model included those for acquisition, administration and subsequent treatments. Costs for managing adverse events, monitoring echocardiograms, terminal care, residential care and health state specific resource use were all included in the model. Treatment wastage was assumed for cannabidiol plus clobazam but not for fenfluramine.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. A PAS discount is in place for cannabidiol and this was included in the results used for decision-making by using estimates of the comparator PAS price.

ASM = anti-seizure medicines; DSF = drop seizure frequency; LGS = Lennox-Gastaut Syndrome; OLE = open-label extension; RCT = randomised controlled trial; SoC = standard of care; SUDEP = sudden unexpected death in epilepsy.

6.2. Results

SMC considered results for decision-making that took into account all relevant PAS. SMC is unable to present these results due to competition law issues.

The Committee did not agree with the claimed greater comparative efficacy of fenfluramine versus cannabidiol (with clobazam) and the results of the CUA were therefore not a key consideration for the purpose of decision-making.

The Committee did find it reasonable to conclude that fenfluramine and cannabidiol (with clobazam) have similar efficacy. Hence, results of the CMA, which assumes treatment equivalency in terms of efficacy, AEs, and discontinuation rates in all cycles, were considered more relevant for decision-making. The CMA predicted savings with fenfluramine, making it the preferred treatment on cost-minimisation grounds. The majority of savings were attributed to reduced medicine treatment costs.

6.3. Sensitivity analyses

The company conducted one-way sensitivity analysis, probabilistic sensitivity analysis and scenario analysis to explore uncertainty. Long-term treatment effect of fenfluramine, cannabidiol maintenance dosage and the utility values applied were key drivers of the ICER in the CUA.

Cannabidiol maintenance dosage and wastage assumptions were key drivers of incremental costs in the CMA.

A range of sensitivity and scenario analyses were considered, and descriptions of these key scenarios are provided in table 6.2 below.

Table 6.2 Scenario analysis

	Parameter	Base case	Scenario analyses	Incremental QALYs
	Base case	-	-	0.42
1	Time horizon	Lifetime	15 years	0.39
2A	Utilities for patients	Verdian EQ-5D	Verdian (2008) TTO	0.26
2B			Verdian (2008) VAS	0.48
2C			Lo (2021) TTO	0.29
3	Utilities for caregivers	Excluded	Included (2 caregivers)	0.76
4A	Cannabidiol Dose	16 mg/kg/day	12 mg/kg/day	0.42
4B			15 mg/kg/day	0.42
4C			20 mg/kg/day	0.42
5A	Cannabidiol wastage	10%	0%	0.42
5B			5%	0.42
6	Waning efficacy	Included	Excluded	0.54
7	Scottish-specific cost data	N/A	N/A	0.42

Abbreviations: QALYs = Quality-adjusted life years; TTO = time trade-off; VAS = visual analogue scale.

6.4. Key strengths

- The modelled population matches the licensed indication.
- The study data from Study 1601 Part 1 is promising and suggests meaningful clinical benefit relative to placebo.
- The economic model is structurally sound and costing is comprehensive.

6.5. Key uncertainties

- The absence of direct evidence comparing fenfluramine with cannabidiol (plus clobazam) has led to a reliance on ITCs to estimate relative treatment effect. The company conducted two NMAs and concluded that these offer robust evidence of fenfluramine having superior efficacy outcomes compared to all alternatives. The company's conclusion does not align with overlapping credible intervals of the indirect comparisons presented in the submission. It is not feasible to conclude that either treatment is objectively more effective than the other due to significant limitations in the evidence base underpinning the analyses (see section 2.5). The Committee therefore considered results of the CUA to be of limited relevance in the context of decision-making.

- The results of the ITCs suggested it was reasonable to conclude that fenfluramine and cannabidiol (with clobazam) have similar efficacy over both time periods (cycle 1, and cycles 2 to 5). However, the OLE ITC was especially uncertain, owing to the lack of OLE data for placebo patients, the method applied for imputation and potential imbalances in effect modifiers for participants. Any long-term projections of treatment effect are therefore subject to substantial uncertainty. The most reasonable conclusion inferred from the ITC is one of similar efficacy between fenfluramine and cannabidiol (with clobazam). The supplied CMA is of greater relevance in the context of decision-making.

- From cycle 10 onwards, in both treatment arms, a proportion of patients were assumed to undergo treatment waning. The proportion was calculated based on the 5.2% of patients in the OLE study (Part 2) who stopped treatment in the last three months due to lack of efficacy. This amounted to only 0.58% and 0.48% of people moving to a worse health state in the fenfluramine and cannabidiol arms of the model respectively. The level of treatment waning applied in the model is a key driver of QALY gains in the CUA and cost savings in the CMA. The impact of a more conservative assumption was explored. When assuming 100% of patients stopping treatment in the final three months of the OLE experiencing waning, the CMA results still favoured fenfluramine.

- There is some uncertainty about the maintenance dose of both fenfluramine and cannabidiol applied in the model. The recommended maintenance dose for fenfluramine in the SPC is 0.7 mg/kg/day.[1] However, a mean dose of 0.4 mg/kg/day was applied in the base case, reflecting the limitations of Study 1601 outlined in section 4.2. Similarly, the recommended maintenance dosage for cannabidiol in the SPC is between 10 to 20 mg/kg/day[9], with a dose of 16 mg/kg/day applied in the company base case. Changes to the cannabidiol maintenance dose had a noticeable impact on incremental costs in the CMA.

- 10% medicines wastage during the administration process was applied to cannabidiol in the model whilst no wastage was assumed for patients receiving fenfluramine. The rationale for the unequal wastage was that cannabidiol is an oily liquid sold in glass bottles which is assumed slippery and easily broken if dropped, whereas fenfluramine is not oily and sold in plastic bottles. It is unclear if this is a reasonable assumption to be making. Assuming no wastage of cannabidiol in the CMA led to an approximately 40% decrease in predicted cost savings.

- Relative reduction in DSF is the only outcome included in the model. It is unclear what impact the inclusion of other types of seizures might have on the cost-effectiveness of fenfluramine. Furthermore, the cost-effectiveness of fenfluramine against other comparators such as rufinamide was not explored.

7. Conclusion

After considering all the available evidence, the Committee was able to accept fenfluramine for use in NHSScotland.

8. Guidelines and Protocols

The National Institute of Health and Clinical Excellence (NICE) published the following guideline in April 2022: Epilepsies in children, young people and adults.[6]

The Scottish Intercollegiate Guidelines Network (SIGN) published the following guidelines in May 2021: Epilepsies in children and young people: investigative procedures and management.[20]

9. Additional Information

9.1. Product availability date

05 July 2023

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Fenfluramine 2.2 mg/mL oral solution	**0.2 to 0.7 mg/kg/day**	**For a 12 kg child: 6,009 to 20,778** **For a 70 kg adult: 35,006 to 64,528[a]**

Costs from BNF online on 17 October 2024. Costs do not take any patient access schemes into consideration.
[a]The maximum recommended daily dose of fenfluramine for this indication is 26 mg.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 128 patients eligible for treatment with fenfluramine in each year to which confidential uptake rates were applied. A discontinuation rate of 50% applied in year 1 reducing to 7% in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including **13 December 2024.**

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.