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

Confidential information redacted

Third appraisal committee meeting

Technology appraisal committee D [15 January 2025]

Chair: Raju Reddy

Lead team: Will Sullivan, Raju Reddy, Paul Caulfield

External assessment group: Kleijnen Systematic Reviews (KSR)

Technical team: Emma McCarthy, Lizzie Walker, Lorna Dunning

Company: UCB

NICE

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

- ✓ **Appraisal history and appeal points**
- ❑ Consultation responses
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Summary

NICE National Institute for Health and Care Excellence

Appraisal history

2nd draft guidance: Fenfluramine is not recommended for treating seizures associated with Lennox–Gastaut syndrome (LGS) as an add-on to other antiseizure medicines for people 2 years and over

Draft guidance issued	Final draft guidance issued	Appeal outcome	Actions following appeal
1st committee meeting: January 2024	2nd committee meeting: March 2024	Appeal September 2024	Guidance reissued for consultation October 2024
Not recommended – uncertainty in long term treatment effect and modelling, not cost effective	Revised company base case and additional analysis Not recommended – uncertainty in evidence and modelling, not cost effective	6 appeal points upheld – 5 from company, 1 from RCP (relating to procedural points wastage, waning and appropriate comparators)	Post-appeal analyses: Revised company base case using cost minimisation approach and results of clinician survey (n=14)

3rd committee meeting: January 2025

NICE

Abbreviations: ACM, appraisal committee meeting; DG, draft guidance; FDG, final draft guidance; RCP; Royal College of Physicians

Recap: appeal outcome

11 appeal points - 6 points upheld, 5 dismissed – evaluation remitted to committee to address concerns

Appeal points	Topic	Outcome	Appeal panel comments
Company 1a.2	No ACM3 scheduled	Upheld	Change in the committee preferred method for comparative data analysis at the 2nd committee meeting was significant enough to require a 3rd meeting.
Company 1a.6	Time required for new analyses	Upheld	Requirement for UCB to produce new analyses within a short time frame before committee meeting was procedurally unfair.
Company 2.2	Treatment waning	Upheld	Clinical experts at the appeal suggested that treatment waning is not seen in clinical practice. Committee approach of applying transition probabilities from last 3 months of study 1601 to 100% of people on treatment in model unreasonable
Company 2.3	Wastage	Upheld	Clinical experts indicated that small amounts of wastage does occur for both drugs. Wastage should be included, but noted this was a small consideration in economic modelling.
Company 2.4, RCP 2.1	Standard care as comparator	Upheld	Clinical experts at appeal considered standard care (SC) alone was not a relevant comparator and does not reflect current clinical practice. Unreasonable to include SC alone as a comparator. Comparison with SoC informative only if evidence-based.

Abbreviations: ACM, appraisal committee meeting; RCP, Royal College of Physicians; SC, standard of care

Recap: appeal outcome

11 appeal points - 6 points upheld, 5 dismissed – evaluation remitted to committee to address concerns

Appeal point	Topic	Outcome	Appeal panel comments
Company 1a.1	No technical engagement	Dismissed	Not procedurally unfair not to hold technical engagement
Company 1a.4	Approach to use of ITT data for comparative efficacy	Dismissed	Not procedurally unfair for committee to change preferred approach
TSA 1a.2 and 2.2	Change in wording of guidance	Dismissed	Change in wording of guidance following consultation is procedurally fair and reflects high uncertainty
Company 2.1	Preference for naïve comparison	Dismissed	Not unreasonable for committee to prefer naïve comparison on basis of high uncertainty

Abbreviations: ITT, intention-to-treat; TSA, Tuberous Sclerosis Association

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

- ❑ Appraisal history and appeal points
- ✓ **Consultation responses**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Summary

NICE National Institute for Health and Care Excellence

Consultation responses to draft guidance 2 (post appeal) [1]

Unmet need

UCB (company), TSA, Young Epilepsy, Epilepsy Action, ILAE, Epilepsy Society, ABN, web comments

- LGS impacts patients + caregiver beyond seizures alone – e.g. cognitive impairment, difficulty communicating + mobility
- Patients do not usually achieve control over seizures with current treatments
- Fenfluramine significantly improves quality of life for patients and carers and reduces LGS-related mortality
- Fenfluramine is well tolerated, safer, fewer interactions and easier to use than cannabidiol – do not need to use with clobazam (which is associated with drowsiness)

Treatment pathway and comparators

UCB (company), ILAE, ABN, web comments, Jazz Pharma (comparator company)

- LGS is a long-term condition; adults have multiple therapies over decades – not appropriate to consider 1st, 2nd and 3rd-line
- Many suggest that standard care alone does not exist in practice; Jazz Pharma considers SC alone is an appropriate comparator.
  - Note that some SC treatments are included in NICE guidance because of available evidence, not because of clinical use or utility
- Committee's request for data on % who would NOT have cannabidiol + clobazam in clinical practice may not be knowable

NICE

LGS, Lennox-Gastaut syndrome; TSA, Tuberous Sclerosis Association; ABN, Association of British Neurologists; ILAE, International League Against Epilepsy; SC, standard care

Consultation responses to draft guidance 2 (post appeal) [2]

Treatment waning

Company (UCB), ABN, ILAE, web comments, Jazz Pharma (comparator company)

- Treatment waning may not be a true pharmacological effect but due to disease course – generally little to no waning effect would be expected for fenfluramine, supported by clinical opinion
- Loss of efficacy is accounted for using a stopping rule in the modelling
- If there are no data from the study open-label extension period showing a need to increase dosage, then this would also support a sustained treatment effect

Wastage

Company, TSA, ILAE, web comments, Jazz Pharma (comparator company)

- Most patient and professional organisation comments suggest wastage is a bigger issue for cannabidiol than fenfluramine
- Jazz Pharma: appropriate to assume no wastage for either cannabidiol or fenfluramine – breakage not a regular issue

Clinical effectiveness

UCB (company), Epilepsy Action, ILAE, Epilepsy Society, ABN, web comments

- Conclusion that fenfluramine is less efficacious than cannabidiol may not be appropriate since this is based on a naïve comparison with further consideration of confounders needed
- May be appropriate to assume equal efficacy between fenfluramine and cannabidiol
- Fenfluramine would be expected to have good clinical efficacy for other types of seizures in addition to drop seizures

LGS, Lennox-Gastaut syndrome; TSA, Tuberous Sclerosis Association; ABN, Association of British Neurologists; ILAE, International League Against Epilepsy;

Equality considerations

Equality issue raised at second draft guidance consultation

Equality issue raised at consultation by Epilepsy Society:

- Fenfluramine is available for use in other similar conditions (such as Dravet syndrome) so inequality issue if not available in LGS

Equality considerations from initial submissions included in appendix

LGS, Lennox-Gastaut syndrome;

Key issues at ACM3

Issue	Impact on cost-effectiveness results
Comparators: Is standard care alone an appropriate comparator? If yes, would an optimised recommendation for people who would otherwise have cannabidiol plus clobazam be appropriate?	Large
Comparative efficacy assumptions: Is it appropriate to assume equal efficacy for fenfluramine plus standard care and cannabidiol plus clobazam plus standard care?	Large
Treatment waning: Is it appropriate to assume no treatment waning?	Moderate
Maintenance dose of cannabidiol: What is the appropriate cannabidiol maintenance dose to use in decision making?	Moderate
Wastage	Small – included in appendix
Pulmonary arterial hypertension	Unknown – included in appendix

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

- ❑ Appraisal history and appeal points
- ❑ Consultation responses
- ✓ **Clinical effectiveness**
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Key issue: Standard care alone as comparator

Company considers that standard care alone not an appropriate comparator

Committee position from ACM2 + appeal panel view

- Some people cannot have CBD + CLB + SC but could have fenfluramine, so SC relevant comparator
- Appeal panel: Unreasonable to require comparison with SC alone. Comparison with standard case would be informative if evidence based, but since most of the relevant studies for SC treatments were done over 20 years ago they do not reflect current clinical practice.

Company

- SC not a relevant comparator – did not provide comparisons vs SC
- If CBD + CLB already considered, failed or unsuitable, only alternative treatment is surgery or clinical trials

EAG comments

- Most clinical experts in survey considered SC alone not appropriate; survey phrased in leading way

Draft guidance 2 consultation responses

- Most responses indicated SC alone is NOT part of clinical practice
- Jazz Pharma (manufacturer of cannabidiol) - SC alone is appropriate comparator based on expert opinion and NG217

ACM, appraisal committee meeting; CBD, cannabidiol; CLB, clobazam; NG, NICE guidance; SC, standard care

Treatment pathway

Fenfluramine positioned at 3rd line, same place in pathway as cannabidiol + clobazam. TA615 recommends cannabidiol + clobazam if drop seizures are not controlled well enough after trying 2 or more antiepileptic drugs

Pharmacological therapy

1st line

Valproate

↓↑ ✚

2nd line

Lamotrigine
Monotherapy
or add-on

↓↑ ✚

3rd line

Fenfluramine | Cannabidiol + clobazam | Clobazam | Rufinamide | Topiramate

↓↑ ✚

Felbamate (unlicensed)

↓↑ Switch treatment upon failure to reduce seizures
✚ Add-on treatment upon failure to reduce seizures

Non-pharmacological therapy

✚

- Ketogenic diet
- Vagus nerve stimulation
- Resective surgery
- Callostomy

Further treatment options

Proposed positioning

Included in SC basket

Is SC alone an appropriate comparator? If yes, would an optimised recommendation for people who would otherwise have CBD + CLB be appropriate? Is it possible to define clinical criteria for people who could have CBD +CLB?

CBD, cannabidiol; CLB, clobazam; SC, standard care

Key issue: Revised company approach to efficacy

New company base case assumes equivalent clinical efficacy for FFA+SC and CBD+CLB+SC

Committee position from ACM2 and appeal panel view

- Committee preference for modelling treatment effect = naïve comparison from open-label extensions of FFA and CBD
- At ACM1, committee noted treated population may be biased; requested analyses using ITT population from OLE. But, at ACM2, committee considered that company's NMA approach using ITT population not suitable
- Appeal panel: change in committee preferences significant, so need 3rd committee meeting to consider updated approach

Company

- Revised base case uses new cost minimisation approach – assumes that FFA and CBD equivalent efficacy, waning, adverse events and discontinuation rates (not previously proposed)
- Results from ITC favour FFA but have large and overlapping credible intervals that encompass 1
- Cost minimisation approach supported by 93% (13/14) of surveyed clinical experts
- New approach reduces uncertainty compared to naïve comparison and updated clinical trial OLE NMA

ACM, appraisal committee meeting; CBD, cannabidiol; CLB, clobazam; FFA, fenfluramine; ITC, indirect treatment comparison; ITT, intention to treat; NMA, network meta-analysis; OLE, open-label extension; SC, standard care

Key issue: Revised company approach to efficacy

New company base case from company assumes equivalent clinical efficacy for FFA+SC and CBD+CLB+SC

EAG comments

- Updated company approach ignores observed clinical differences between FFA and CBD in clinical trial data – but also limitations to naïve comparison and OLE NMA alternatives so best approach is unclear
- EAG maintains approach from ACM2 of using OLE-treated population data for cycles 2 to 5 and maintains difference between FFA and CBD
- Noted differences in disease management costs in company base case due to differing proportions of generalised tonic-clonic seizures in FFA and CBD populations in trial data – so company's approach does not assume completely equal efficacy

Is it appropriate to assume equal efficacy for FFA + SC vs CBD + CLB + SC? Is the company's approach suitable?

ACM, appraisal committee meeting; CBD, cannabidiol; CLB, clobazam; FFA, fenfluramine; NMA, network meta-analysis; OLE, open-label extension; SC, standard care

Scenario analysis with revised approach to missing data when indirectly comparing treatments

Revised approach to missing data favours FFA, but may introduce bias due to more missing data than for CBD

Committee position from ACM2

- Requested analyses that assume people who drop out of Study 1601 OLE and the cannabidiol OLE had <25% reduction in frequency of drop seizures

Company

- Analysis outlined above provided as a scenario analysis and applied to both OLE studies
- Placebo effect assumed stable over time and assessed from respective phase 3 studies

EAG comments

- More missing data for CBD, so new missing data approach may bias in favour of FFA compared with original method of last observation carried forward – may be reasonable if data not missing at random
- Company's approach assumes no further events in placebo arm after 12 weeks
  - Not same as 'placebo effect is assumed to remain stable over time'
  - Placebo effect should apply to both arms, so company approach may bias in favour of intervention

Draft guidance 2 consultation responses

- ABN query if people who drop out have lowest efficacy –short-term intolerability most likely cause of drop out

NICE

Is the company scenario appropriate for decision making?

ABN: Association of British Neurologists; CBD, cannabidiol; FFA, fenfluramine; OLE, open-label extension; NMA, network meta-analysis

Alternative approaches to model clinical efficacy

Choice of approach for incorporating clinical efficacy impacts overall direction of results

Clinical equivalence Company base case at ACM3	**Naïve comparison of treated populations in OLEs** Committee at ACM2	**NMA of ITT populations in OLEs** Company scenarios at ACM2 and ACM3
Clinical equivalence between FFA and CBD	**FFA+SC and CBD+CLB+SC efficacy:** State occupancies based on naïve comparison of **treated** population of FFA and CBD open-label extension trials **SC efficacy:** Assume no change from cycle 1	**FFA+SC and CBD+CLB+SC efficacy:** State occupancies based on NMA of **ITT** population of FFA and CBD open-label extension trials **SC efficacy:** Assume no change from cycle 1 **Imputation:** LOCF (at ACM2); non-random (people who dropped out of the OLE had a less than 25% improvement in DSF) (at ACM3)
Equal efficacy for FFA+SC and CBD+CLB+SC No results provided vs SC	Favours CBD+CLB+SC vs FFA+SC and SC	Favours FFA+SC vs CBD+CLB+SC and SC

What is the committee's preferred approach to model clinical efficacy?

ACM, appraisal committee meeting; CBD, cannabidiol; CLB, clobazam; DSF, drop-seizure frequency; LOCF, last observation carried forward; FFA, fenfluramine; ITT, intention-to-treat; NMA, network meta-analysis; OLE, open-label extension; SC, standard care

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

- ❑ Appraisal history and appeal points
- ❑ Consultation responses
- ❑ Clinical effectiveness
- ✓ **Modelling and cost effectiveness**
- ❑ Summary

NICE National Institute for Health and Care Excellence

Key issue: Treatment waning

Revised base case from company assumes no treatment waning for FFA or CBD

Committee position from ACM2 and appeal panel view

- Apply transition probabilities from last 3 months of study 1601 to 100% of people on treatment in model. Appeal panel: committee approach unreasonable
- Clinical experts at appeal – waning not seen in practice in people on antiepileptic treatments
- Post-appeal committee conclusion – approach for calculating treatment waning uncertain. Need evidence-based scenarios and company needs to justify its modelling

Company

- No treatment waning in revised base case and does not provide scenario analyses
- 2/14 clinicians mention short waning period– but consider already accounted for by stopping rule

EAG comments

- 64% of experts in survey agreed no treatment waning in clinical practice – but leading question
- EAG base case applying transition probabilities from last 3 months of study 1601 to 5.2% of people on treatment in model (5.2% = % patients stopping treatment in months 9-12 of OLE study)

Draft guidance 2 consultation response

- Multiple patient organisations indicate that treatment waning not observed or rare in practice for FFA or CBD - people do not need later drug trials or increasing doses

NICE

Should treatment waning be included in the model?

ACM, appraisal committee meeting; SC, standard care; FFA, fenfluramine; CBD, cannabidiol; OLE, open label extension

Key issue: Maintenance dose of CBD

Company updated maintenance dose of CBD from 14 to 16 mg/kg/day

Committee position from ACM2

- Appropriate to consider range of CBD maintenance dosages between 12 and 16 mg/kg/day

Company

- Updated base case CBD maintenance dose from 14 mg/kg/day to 16 mg/kg/day
- Expert opinion from supplementary question in survey (n=7) – responses range from 15 to 20 mg/kg/day
- Considers 16 mg/kg/day is a highly conservative assumption (also notes OLE mean modal dose was 24 mg/kg/day).

EAG comments

- Notes that at ACM1, clinical experts estimated lower average CBD maintenance doses (2 estimated 14 to 16 mg/kg/day, while 1 estimated ~12 mg/kg/day)
- In TA615, CBD maintenance dose of 12 mg/kg/day used
- EAG models 2 base cases
  1. CBD maintenance dose of 12 mg/kg/day
  2. CBD maintenance dose of 16 mg/kg/day

What is the appropriate CBD maintenance dose to use in decision making?

ACM, appraisal committee meeting; CBD; cannabidiol; OLE, open-label extension; SC, standard care

Summary of changes to assumptions

ACM, appraisal committee meeting; CBD, cannabidiol; FFA, fenfluramine; LOCF, last observation carried forward; SC, standard care;

Input	Company base case at ACM2	Revised company base case	EAG preferred assumption
Source of efficacy of fenfluramine	**Cycles 2-5**: Network meta-analysis of extension studies (missing data approach – LOCF) **Cycles 5-9**: maintained efficacy	**Cycle 2-5**: health state proportions from FFA extension study **Cycles 5-9**: maintained efficacy	**Cycle 2-5**: health state % from treated population of Study 1601 extension **Cycles 5-9**: maintained efficacy
Source of efficacy of cannabidiol + clobazam	**Cycle 1**: Network meta-analysis clinical trial **Cycles 2-5**: Network meta-analysis extension study (missing data approach – LOCF) **Cycles 5-9**: maintained efficacy	Equal efficacy with FFA for all cycles	**Cycle 2-5**: health state % from treated population of Study 1601 extension **Cycles 5-9**: maintained efficacy
Efficacy of standard care	Not comparator	Not comparator	**Cycle 1**: transition probabilities directly from SC arm of Study 1601 **Cycles 2+**: no change in state occupancy (except death)
Maintenance dose fenfluramine	0.413 mg/kg/day	0.416 mg/kg/day	0.416 mg/kg/day
Maintenance dose cannabidiol	14 mg/kg/day	16 mg/kg/day	1. 12 mg/kg/day 2. 16 mg/kg/day
Treatment waning	5.2% of patients	None	5.2% of patients
Wastage	0%	FFA: [redacted]%, CBD: [redacted]%	FFA: [redacted]%, CBD: [redacted]%

Cost-effectiveness results

All results are reported in Part 2 slides because they include confidential comparator discounts

Results presented in part 2 include (but not limited to):

- Deterministic company base case (cost comparison approach) – FFA + SC is cost saving vs CBD + CLB + SC
- Deterministic EAG base cases:
  - 12 mg/kg/day CBD maintenance: FFA + SC dominated by CBD + CLB + SC
  - 16 mg/kg/day CBD maintenance: FFA + SC cost effective vs CBD + CLB + SC
- No EAG scenarios are cost effective against SC alone (company did not submit scenarios comparing with SC alone)

SC, Standard care; FFA, fenfluramine; CBD, cannabidiol; CLB, clobazam

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

- ❑ Background and key issues
- ❑ Consultation responses
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Summary**

NICE National Institute for Health and Care Excellence

Summary of questions for committee

- Is standard care alone an appropriate comparator? If yes, would an optimised recommendation for people who would otherwise have CBD + CLB be appropriate?
- Is it appropriate to assume equal efficacy for fenfluramine plus standard care and cannabidiol plus clobazam plus standard care?
- Is it appropriate to assume no treatment waning?
- What is the appropriate cannabidiol maintenance dose to use in decision making?

SC, standard care; FFA, fenfluramine; CBD, cannabidiol

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

Supplementary appendix

NICE National Institute for Health and Care Excellence

Key issue: Wastage

Appeal panel considered appropriate to include wastage costs – company use mean values from clinician surgery, EAG use median values

Committee position from ACM2 and appeal panel view

- Committee noted that CBD is an oily substance provided in glass bottles and FFA is a liquid provided in plastic bottles – so it considered there may be more treatment wastage of CBD than of FFA. But, noted that no evidence-based scenarios provided
- Appeal panel considered unreasonable to exclude wastage

Company

- Revised company base case includes treatment wastage of [redacted]% for CBD and [redacted]% for FFA – based on mean values of wastage estimates from clinician survey calculated

EAG comments

- Company survey responses may be influenced by leading question bias – but EAG overall considers that informing wastage in model based on survey results is reasonable
- EAG preference is to use median values for wastage to reflect non-normal distribution of survey results – assuming [redacted]% wastage for FFA and [redacted]% for CBD

What is the committee's preferred method for incorporating treatment wastage for FFA and CBD?

NICE

SC, standard care; FFA, fenfluramine; CBD, cannabidiol

Key issue: Pulmonary arterial hypertension (PAH)

Background and committee position from ACM2

- Committee questioned whether PAH would be a cumulative dose-related AE in the long term (when using FFA for more than 5 years) – but concluded it was not appropriate to model the cost of PAH at the time
- Committee concluded to consider whether this was still appropriate based on latest data

Company

- PAH has not been previously seen in LGS – reported in 1 child having FFA for Dravet syndrome and resolved on discontinuation
- Model accounts for regular monitoring and early identification of potential PAH by including costs of echocardiograms

Does the model appropriately account for costs associated with PAH?

ACM, appraisal committee meeting; AE, adverse event; FFA, fenfluramine; LGS; Lennox-Gastaut syndrom