National Institute for Health and Care Excellence

Health Technology Evaluation

Fenfluramine hydrochloride for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651] Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Association of British Neurologists	Appropriate in light of recent published trial data and similar approval by the FDA and European Medicines Agency CHMP.	Thank you for your comment. No action needed.
	Epilepsy Action	We would welcome this topic being referred to NICE for appraisal and evaluation for marketing authorisation as an adjunctive therapy for Lennox-Gastaut syndrome	Thank you for your comment. No action needed.
	Jazz Pharmaceuticals	There is a substantial unmet need for additional treatment options for LGS seizures, particularly for patients unable to achieve seizure control with currently available treatments. For this reason, it is appropriate for this technology to be appraised by NICE.	Thank you for your comment. No action needed.
	UCB Pharma Ltd	NICE's intention to evaluate this technology through its Single Technology Appraisal process seems appropriate and accurate.	Thank you for your comment. No action needed.

Section	Stakeholder	Comments [sic]	Action
	Young Epilepsy	N/A	No action needed.
Wording	Association of British Neurologists	Remit appropriately says…"To appraise the clinical and cost effectiveness of fenfluramine hydrochloride ….. for treating Lennox-Gastaut seizures in people aged 2 and over".	Thank you for your comment. No action needed.
	Epilepsy Action	Yes	Thank you for your comment. No action needed.
	Jazz Pharmaceuticals	N/A	No action needed.
	UCB Pharma Ltd	Yes	Thank you for your comment. No action needed.
	Young Epilepsy	N/A	No action needed.
Timing Issues	Association of British Neurologists	Should be evaluated before further approval. Already available for treatment of other epilepsy syndromes (Dravet syndrome).	Thank you for your comment. In any appraisal NICE aims to publish guidance as close as possible to the granting of a marketing authorisation. No action needed.

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	Epilepsy Action	As this treatment is intended to treat people with current uncontrolled seizures, we would welcome an urgent appraisal in order to assess this potential treatment.	Thank you for your comment. In any appraisal NICE aims to publish guidance as close as possible to the granting of a marketing authorisation. No action needed.
	Jazz Pharmaceuticals	LGS is a severe and treatment-resistant rare epilepsy syndrome. We welcome the availability of new treatment options that can support people with LGS.	Thank you for your comment. No action needed.
	UCB Pharma Ltd	As per the background stated within the Draft scope, patients managed with anti-epileptic drugs have seizures which are often resistant to treatment and have relatively few treatment options available. Due to this, it is likely that healthcare resource utilisation (HCRU) (eg general practitioner visits, secondary care referrals and hospitalisations) is high considering the increased HCRU in patients with epilepsy and increased seizure frequency (Chin et al, 2021). This continued high cost and time impact upon the NHS's resources can be reduced for patients that may be suitable and maintained on an alternative treatment option. The high disease burden, multiple co-morbidities and unmet treatment needs often results in patients requiring costly tertiary care, where multiple disciplinary teams are required to support. Some patients also resort to surgery, which alone incurs high costs to the NHS with questionable treatment outcomes.	Thank you for your comment. In any appraisal NICE aims to publish guidance as close as possible to the granting of a marketing authorisation. No action needed.

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		The burden on carers in supporting such patients is also high, resulting in high levels of disutility and further impact to the NHS's resources. [redacted]There is therefore an urgency to enable the availability of additional treatment options such as fenfluramine to help alleviate some of the above-mentioned challenges that the NHS is facing.	
	Young Epilepsy	N/A	No action needed.
Additional comments on the draft remit	Association of British Neurologists	N/A	No action needed.
	Epilepsy Action	N/A	No action needed.
	Jazz Pharmaceuticals	N/A	No action needed.
	UCB Pharma Ltd	The section named 'The technology' states Zogenix as the relating company to the product. Following the completed acquisition of Zogenix in 2022, can this please be changed to 'Fintepla, Zogenix - part of the UCB group of companies'.	Thank you for your comment. The wording of the remit has been updated to UCB Pharma.
	Young Epilepsy	N/A	No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Association of British Neurologists	Background information on this technology might include an account of the drug's development and safety concerns. Fenfluramine is a derivative of amphetamine approved in 1973 as a dieting and weight loss drug in the United States. The drug was later withdrawn from use by the FDA due to cardiovascular concerns including potentially fatal pulmonary hypertension. In subsequent studies for epilepsy, patients were required to have screening with echocardiograms before treatment.	Thank you for your comment. The background section is intended as a brief overview of the disease area. No action needed.
	Epilepsy Action	We would suggest including a link to further information regarding the use of sodium valproate, given the established teratogenic risks of taking that AED during pregnancy. In addition, reference to the updated MHRA advice on topiramate would be useful and welcome. We also would welcome the inclusion of further available information here, including how the drug is administered, its efficacy and currently known side-effects and contraindications	Thank you for your comment. The background section is intended as a brief overview of the disease area. No action needed.
	Jazz Pharmaceuticals	In addition to the factors mentioned in the background information, patients with LGS are at high risk of Sudden Death in Epilepsy (SUDEP). Further, LGS is associated with a substantial caregiver burden and has an impact the wider family, including siblings and other family members. Adequate seizure control for the patient has a positive impact on the wider family unit and on caregiver wellbeing.	Thank you for your comment. The background section is intended as a brief overview of the disease area. No action needed.
	UCB Pharma Ltd	This information mostly appears to be accurate. It would be beneficial to highlight that most patients are often resistant to polytherapy treatment,	Comment noted. The background section is intended as a brief

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		resulting in variable outcomes following treatment and consequently patients often live with seizures into adulthood (Chin et al, 2021). As per NICE guidance and the comparators list, can surgery and Levetiracetam also be mentioned as possible treatment options.	overview of the disease area, therefore few amendments required. Levetiracetam has been included as a comparator.
	Young Epilepsy	"Crash to the ground" may be better described as "fall suddenly to the ground". "Anti-epileptic drugs" should be referred to as "anti-seizure medication".	Comment noted. The text in the background information section has been amended as suggested.
Population	Association of British Neurologists	Approval should include a clear definition of LGS to facilitate identification of suitable patients.	Thank you for your comment. The technology will be appraised in line with the marketing authorisation and company's positioning. No action needed.
	Epilepsy Action	Yes	Thank you for your comment. No action needed.
	Jazz Pharmaceuticals	Yes the population is appropriately defined.	Thank you for your comment. No action needed.

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	UCB Pharma Ltd	Yes	Thank you for your comment. No action needed.
	Young Epilepsy	N/A	No action needed.
Subgroups	Association of British Neurologists	Trial evidence supporting the use of fenfluramine demonstrated effectiveness considered to be clinically meaningful in reducing drop seizures and generalised tonic clonic seizures. In line with NICE guidelines for Dravet syndrome and randomised trial data, approval for use should be based on a carer's ability to reliably monitor seizure activity and adverse events prospectively (through diaries) with specialist follow up and clear criteria for discontinuation. However, there does not seem to be any particular subgroup that needs to be considered separately.	Thank you for your comment. No action needed.
	Epilepsy Action	We believe that people with both epilepsy and a learning disability should be given particular consideration given the established association with severe learning and behavioural disorders.	Thank you for your comment. No action needed.
	Jazz Pharmaceuticals	N/A	No action needed.
	UCB Pharma Ltd	Although subgroups could be considered, the heterogeneity of the disease results in difficulty in defining a clearly established sub-group. The limited number of patients and therefore data available also limits the depth and accuracy of analysis that can be conducted. Sub-group analysis within Lennox-Gastaut syndrome raises equity of access concerns due restrictions in patients meeting criteria for access.	Thank you for your comment. No action needed.

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	Young Epilepsy	N/A	No action needed.
Comparators	Association of British Neurologists	Yes However, felbamate is rarely used in UK and may be less relevant for NHS.	Thank you for your comment. No action needed.
	Epilepsy Action	Yes	Thank you for your comment. No action needed.
	Jazz Pharmaceuticals	We believe that levetiracetam needs to be included as a potential treatment effect modifier, as this was most commonly co prescribed treatment in the Phase 3 trial	Thank you for your comment. Levetiracetam has been included as a comparator.
	UCB Pharma Ltd	To clarify: fenfluramine is expected to be used as an add-on treatment following failure of combinations of any of the standard of care treatments listed apart from cannabidiol plus clobazam. Fenfluramine is expected to be provided as an alternative treatment option to cannabidiol plus clobazam (as per fenfluramine's EMA Orphan Maintenance Assessment Report Jan 2023).	Thank you for your comment. No action needed.
	Young Epilepsy	N/A	No action needed.
Outcomes	Association of British Neurologists	See above. Quality of life and assessment of a meaningful benefit requires clinical input rather than simple seizure counting.	Thank you for your comment. The outcomes listed include HRQOL. The committee

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			will seek the views of clinical and patient and carer experts throughout the appraisal process.
	Epilepsy Action	Yes	Thank you for your comment. No action needed.
	Jazz Pharmaceuticals	It is important to note that even with current treatment options, achieving complete seizure freedom is challenging and that treatment often aims to achieve optimal seizure control. Reducing the frequency of seizures has a substantial positive effect on patients, carers and the wider family unit.	Thank you for your comment. No action needed.
	UCB Pharma Ltd	A carers quality of life is a key outcome measure for Lennox-Gastaux syndrome (NICE TA615). Can health-related quality of life therefore be mentioned as applicable to both patients and carers. Can executive functioning also be included as a potential outcome measure.	Thank you for your comment. HRQOL has been amended to include patients and carers.
	Young Epilepsy	N/A	No action needed.
Equality	Association of British Neurologists	People with LGS often have very difficult to treat epilepsy and considering further treatments for this disorder is likely to have a positive rather than negative impact on this group. However, the target population which would have a degree of intellectual disability may have difficulty communicating	Thank you for your comment. The committee will consider this potential equality

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		adverse effects and therefore this should be carefully monitored by carers and medical attendants.	issue. No changes to the scope required.
	Epilepsy Action	N/A	No action needed.
	Jazz Pharmaceuticals	Up to 95% of patients with LGS have cognitive impairment; further, developmental delays and behavioural disturbances are common. LGS associated cognitive and behavioural difficulties may prevent children from achieving independence in adult life and in some cases, adult patients with LGS may be institutionalised. It is important to consider the population of people with LGS living in long term care and/or those with LGS associated cognitive impairment and/or learning disability and ensure that there are no barriers to access to the available treatments for LGS.	Thank you for your comment. The committee will consider this potential equality issue. No changes to the scope required.
	UCB Pharma Ltd	The draft remit and scope do not need to be changed in order to meet the aims listed.	Thank you for your comment. No action needed.
	Young Epilepsy	N/A	No action needed.
Other considerations	Association of British Neurologists	The need for ongoing cardiac monitoring.	Thank you for your comment. The committee will consider the drug within its MA including any monitoring

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			requirements. No further actions required.
	Epilepsy Action	N/A	No action needed.
	Jazz Pharmaceuticals	N/A	No action needed.
	UCB Pharma Ltd	N/A	No action needed.
	Young Epilepsy	N/A	No action needed.
Questions for consultation	Association of British Neurologists	N/A	No action needed.
	Epilepsy Action	N/A	No action needed.
	Jazz Pharmaceuticals	**Which treatments are considered to be established clinical practice in the NHS for the treatment of Dravet syndrome?** We believe that Dravet Syndrome has been mentioned in error and that this should refer to LGS. The treatments considered established clinical practice for LGS are as outlined in NICE CG21, Section 6.2. **Where do you consider fenfluramine hydrochloride will fit into the existing care pathway for Lennox-Gastaut syndrome, as described in NICE clinical guideline 217?**	Thank you for your comment. No action needed.

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		Per NICE CG21, we consider fenfluramine to fit into the existing pathway as a Third-Line Treatment, per NICE CG217 sections 6.2.5 and 6.2.6.	Thank you for your comment. No action needed.
		Will people with Lennox-Gastaut syndrome continue to use fenfluramine hydrochloride in adulthood? LGS also affects adults therefore it is anticipated that some people will continue to use fenfluramine hydrochloride in adulthood.	Thank you for your comment. No action needed.
		Have all relevant comparators for fenfluramine hydrochloride been included in the scope? As mentioned above, we believe that levetiracetam needs to be included as a potential treatment effect modifier.	Thank you for your comment. No action needed.
		Is fenfluramine hydrochloride likely to require additional monitoring for the risk of adverse cardiovascular outcomes such as heart valve disease? As outlined in the SmPC for fenfluramine hydrochloride, section 4.4, “prior to starting treatment, patients must undergo an echocardiogram to establish a baseline prior to initiating treatment (see section 4.3) and exclude any pre-existing valvular heart disease or pulmonary hypertension. Echocardiogram monitoring should be conducted every 6 months for the first 2 years and annually thereafter.” The SmPC also describes the Fintepla controlled access programme to 1) prevent off-label use in weight management in obese patients and 2) confirm that prescribing physicians have been informed of the need for periodic cardiac monitoring in patients taking Fintepla.	Thank you for your comment. No action needed.

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		Echocardiogram monitoring is not a routine part of care for people with LGS, therefore this constitutes additional monitoring for this indication. However, this monitoring is already a requirement for people with Dravet Syndrome.	
	UCB Pharma Ltd	**Will people with Lennox-Gastaut syndrome continue to use fenfluramine hydrochloride in adulthood?** Yes **Would fenfluramine hydrochloride be a candidate for managed access?** UCB does not consider fenfluramine a candidate for managed access. **Is fenfluramine hydrochloride likely to require additional monitoring for the risk of adverse cardiovascular outcomes such as heart valve disease?** Yes, the same monitoring will be required as per the current SmPC. Whereby echocardiogram monitoring should be conducted every 6 months for the first 2 years and annually thereafter. Please note fenfluramine will be supplied by generating a controlled access portal (CAP) Prescriber ID and be provided alongside a risk management program. **Do you consider that the use of fenfluramine hydrochloride can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** Yes, there are numerous benefits of fenfluramine that cannot be captured in the health economic model, UCB will mention and aim to substantiate these benefits within the HTA submission. For example, the benefit of fenfluramine	Thank you for your comment. No action needed. Thank you for your comment. No action needed. Thank you for your comment. No action needed.

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		in reducing the duration and length of seizures, the benefits on non-drop seizures and the benefit on the quality of life of the siblings of children or young people with Lennox-Gastaux Syndrome. Other benefits not captured include executive functioning, cognitive and behavioural impacts. **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** UCB will provide any clinical trial data and real-world evidence that could not be included in the model as well as qualitative evidence from clinical experts and patient advisory groups.	Thank you for your comment. No action needed. Thank you for your comment. No action needed.
	Young Epilepsy	N/A	No action needed.
Additional comments on the draft scope	Association of British Neurologists	N/A	No action needed.
	Epilepsy Action	N/A	No action needed.
	Jazz Pharmaceuticals	**Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?** Yes – there are 3-year open label extension data for cannabidiol, and data from the BECOME study showing the efficacy and safety for cannabidiol beyond seizures, which have been presented at congresses.	Thank you for your comment. No action needed.

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	UCB Pharma Ltd	Please see comments below on UCB's suggestion for evaluating this technology via the cost-comparison process: **Would it be appropriate to use the cost-comparison methodology for this topic?** No, it is unlikely this would be appropriate for fenfluramine. **Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?** Yes, Cannabidiol plus clobazam **Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?** Yes, the primary outcome measure, 'change in baseline in frequency of seizures that result in drops in subjects receiving fenfluramine compare to placebo' is still clinically relevant. A secondary outcome measure observing response rates was used to inform the model and is deemed as more clinically relevant for the assessment. **Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?**	Thank you for your comment. No action needed. Thank you for your comment. No action needed. Thank you for your comment. No action needed.

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		The results of the long-term open-label extension trial of cannabidiol (NCT02224573) had been published after its health technology appraisal (TA615). The results of this trial will be implemented within the submission for fenfluramine. There are no important ongoing trials reporting in the next year.	Thank you for your comment. No action needed.
	Young Epilepsy	The appraisal should consider what treatment people would transfer on to if fenfluramine hydrochloride was not continued into adulthood, as well as the benefits and risks of this course of action.	Thank you for your comment. No action needed.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

- **Eisai**
- **Neonatal and Paediatric Pharmacist Group (NPPG)**