NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING
MAY 2019

Fenfluramine hydrochloride for treatment of seizures associated with Lennox-Gastaut syndrome

NIHRIO ID	15020	**NICE ID**	9878
Developer/Company	Zogenix International Ltd	**UKPS ID**	Not available

Licensing and market availability plans	Currently in phase III clinical trial.

SUMMARY

Fenfluramine hydrochloride is in clinical development as a treatment for paediatric and adult patients with Lennox-Gastaut syndrome. Lennox-Gastaut syndrome is a rare and severe form of epilepsy that is most commonly found in children. It is characterised by slow mental development and various types of seizures that are difficult to treat. As patients enter into adulthood, the emergent comorbidities associated with the syndrome (such as impaired mobility, learning and behaviour) become more apparent and add further burden to the patient and their careers, alongside management of their seizures. Lennox-Gastaut syndrome can be difficult to diagnose when children are young due to the evolving nature of the seizures experienced. Lennox-Gastaut syndrome is highly resistant to antiepileptic drugs.

Fenfluramine belongs to a class of drugs called the selective serotonin releasing agonists which stimulates multiple 5-HT receptor sub-types through the release of serotonin. Fenfluramine may also act on other receptors and these actions may help to reduce the frequency of seizures. When added to other standard anti-epileptic treatments, fenfluramine hydrochloride has shown preliminary evidence of reducing seizure frequency. If licensed, fenfluramine hydrochloride may offer an additional treatment option for patients with Lennox-Gastaut syndrome.

PROPOSED INDICATION

Treatment of seizures associated with Lennox-Gastaut syndrome in children aged 2 years to 17 years and adults.[a]

TECHNOLOGY

DESCRIPTION

Fenfluramine hydrochloride (ZX-008; low-dose fenfluramine) is an amphetamine derivative and sympathomimetic stimulant which stimulates the release of serotonin and modulates serotonin transporter function.[1] Fenfluramine is a selective serotonin releasing agent, and thereby stimulates multiple 5-HT receptor sub-types through the release of serotonin. Fenfluramine may reduce seizures by acting as an agonist at specific serotonin receptors in the brain, including the 5-HT1A, 5-HT1D, 5-HT2A, and 5-HT2C receptors.[a] Additionally, fenfluramine has been shown to have effects on sigma 1 receptors, which have been implicated as having a role in epilepsy.[2] Through this function, fenfluramine is considered to exert its anticonvulsant effect, although the exact mechanism of action is yet to be elucidated.[3]

Fenfluramine is currently in phase III clinical development as a therapy for the treatment of uncontrolled seizures in children and adults with Lennox-Gastaut syndrome (LGS). In a phase III clinical trial (NCT03355209), fenfluramine hydrochloride was supplied as an oral solution and participants received one of the two doses of fenfluramine hydrochloride (either 0.2 mg/kg/day or 0.8 mg/kg/day). There is no maximum duration for study treatment reported on the trial registry.[4]

INNOVATION AND/OR ADVANTAGES

Patients with LGS rarely achieve complete seizure control despite available therapeutic options. Achieving a reduction in seizure frequency usually requires polypharmacy with an individualized regimen.[2] Better treatment options are an urgent unmet need among the patient with LGS.

Fenfluramine hydrochloride is considered to have anticonvulsant properties.[3] Use of fenfluramine hydrochloride as an additional therapy in patients (3-18 years old) with refractory LGS has demonstrated sustained meaningful seizure reduction.[2]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Fenfluramine hydrochloride does not currently have Marketing Authorisation in the EU/UK for any indication.

Fenfluramine is currently in phase III clinical development for the treatment of Dravet syndrome.[7]

Fenfluramine hydrochloride was granted orphan drug designation in the EU in February 2017 for Lennox-Gastaut syndrome.[5]

Fenfluramine hydrochloride was granted orphan drug designation in the US in June 2017 for Lennox-Gastaut syndrome.[6]

[a] Information provided by Zogenix International Ltd.

PATIENT GROUP

DISEASE BACKGROUND

Lennox-Gastaut syndrome (LGS) is a severely debilitating form of generalised paediatric epilepsy that begins in early childhood between the ages of 2 and 7 years.[8,9] The condition is characterised by a symptomatic triad of diffuse slow interictal spike wave in the waking electroencephalogram (< 3 Hz), fast rhythmic burst (10 Hz) during sleep, and several types of epileptic seizures.[9] These seizure types include tonic seizures (muscle contraction lasting few seconds to minutes), atypical absence seizures (during which the person has a blank stare but is still partly aware of their surroundings) and drop seizures (brief loss of muscle tone and consciousness, causing abrupt falls).[5] Tonic seizures are considered the most common of all, and are prerequisite in the diagnosis of the condition, whilst atypical absence seizures are the second most common type of seizures experienced.[10] Behavioural disorders are further associated with the condition; these include aggressiveness and hyperactivity as well as some forms of learning disability and personality disorder.[5]

LGS can be defined as either cryptogenic, which appears without any antecedent history or brain pathology evidence, or symptomatic, which is associated with pre-existing brain damage such as perinatal asphyxia, tuberous sclerosis, meningoencephalitis sequelae, cortical dysplasia, cranial trauma, and more rarely tumours or metabolic diseases.[9] Cryptogenic cases tend to have a later onset than symptomatic cases and account for up to 30% of those with Lennox-Gastaut syndrome.[11]

LGS belongs to epileptic encephalopathies and is highly refractory to all antiepileptic drugs.[12] The diagnosis of LGS can also be difficult as the electroencephalogram features can take time to develop in young patients and may evolve over time making it difficult to identify the seizure types associated with the condition.[13] As seizures can persist into adulthood, the concerns for social integration and appropriate care make the condition one of the most complex epileptic disorders to manage for both specialists in epilepsy and neurologists.[10] Despite reported incidence of LGS being rare in adolescence, patients are rarely relieved of seizures, and over time, mental and psychiatric conditions become worse and can disturb a patient's quality of life.[14,15]

CLINICAL NEED AND BURDEN OF DISEASE

The incidence of LGS is estimated at 0.1/100,000 children in Europe.[16] The incidence is five times higher in males than females.[17]

In England, LGS has an estimated prevalence of approximately 5,000 people.[18]

LGS-related mortality is estimated at around 5%.[8]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

LGS is considered one of the most difficult sub-types of epilepsy to treat as the seizures associated with it are generally refractory to current treatment options available.[11] LGS is primarily managed with anti-epileptic drugs, and may be supported by a ketogenic diet or vagus nerve stimulation.[8]

CURRENT TREATMENT OPTIONS

NICE recommendations regarding treatment for LGS in children, young people and adults are as follows:[19]

- Offer lamotrigine as adjunctive treatment to children, young people and adults with LGS if first-line treatment with sodium valproate is ineffective or not tolerated.
- Discuss with a tertiary epilepsy specialist if adjunctive treatment is ineffective or not tolerated. Other antiepileptic drugs that may be considered by the tertiary epilepsy specialist are rufinamide and topiramate.
- Only offer felbamate in centres providing tertiary epilepsy specialist care and when treatment with all of the antiepileptic drugs listed above has proved ineffective or not tolerated.

PLACE OF TECHNOLOGY

If licensed, fenfluramine hydrochloride could be an additional treatment option for patients with LGS, who have an inadequate response to antiepileptic drugs.

CLINICAL TRIAL INFORMATION

Trial	ZX008-1601, NCT03355209, EudraCT 2017-002628-26; aged 2-35 years; part I: fenfluramine hydrochloride (dose 1) or fenfluramine hydrochloride (dose 2) vs placebo, part II: fenfluramine hydrochloride (dose 1) or fenfluramine hydrochloride (dose 2); phase III
Sponsor	Zogenix International Ltd.
Status	Ongoing
Source of Information	Trial registry[4,20]
Location	EU (not including the UK), United States, Canada, and other countries
Design	Part I: randomised, double-blind, parallel group, placebo-controlled study Part II: open-label extension
Participants	n=225 (planned); aged 2-35 years; clinical diagnosis of Lennox-Gastaut syndrome, where seizures that result in drops are not completely controlled by current antiepileptic treatments; must be receiving at least 1 concomitant antiepileptic drugs and up to 4 concomitant anti-epileptic treatments.
Schedule	Part I: randomised to receive one of two doses of fenfluramine hydrochloride (0.2mg/kg/day or 0.8mg/kg/day) or placebo Part II: open label and participants receive fenfluramine hydrochloride at either 0.2mg/kg/day or 0.8mg/kg/day
Follow-up	The participants were followed for up to 20 weeks in the first part of the study and up to 12 months in the second part.
Primary Outcomes	Change from baseline in frequency of seizures that result in drops in subjects receiving fenfluramine hydrochloride compared to placebo [time frame: up to 20 weeks maintenance and taper period]
Secondary Outcomes	Adverse events and related safety parameters in subjects receiving fenfluramine hydrochloride compared to placebo (time frame: up to 12 months open label)
Key Results	-

Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as for December 2019.

Trial	FFA-LGS, NCT02655198, EudraCT 2015-004008-46; aged 3-18 years; fenfluramine hydrochloride; phase II
Sponsor	KU Leuven
Status	Ongoing
Source of Information	Trial registry[2,21,22]
Location	Belgium
Design	Single arm, open-label
Participants	n=13; aged 3-18 years; minimum requirements (based on International League Against Epilepsy (ILAE) epilepsydiagnosis.org); drug resistant; males or non-pregnant, non-lactating females.
Schedule	Patients received escalating doses of fenfluramine hydrochloride (0.2, 0.4 and 0.8 mg/kg/day), max 30 mg. There is no maximum duration for study treatment, as reported on the trial registry.
Follow-up	Treatment duration: 20 weeks. The participants were followed for up to 20 weeks.
Primary Outcomes	Efficacy of add-on FFA in Lennox Gastaut epilepsy: number of responders and seizure free patients after each period and at each dosage assessed (time frame: 8, 12, 16 and 20 weeks)
Secondary Outcomes	Time frame 20 weeks: • Seizure frequency change per patient and per major seizure type (tonic clonic seizures (TCS), tonic seizures (TS), atonic seizures (AS), focal seizures (FS)) • Adverse events • Sleep quality • Clinical global impression scale at last visit , by patient/caregiver and treating physician
Key Results	-
Adverse effects (AEs)	Thirteen patients were enrolled (mean age = 11.7 years, range = 3-17). Ten (77%) patients completed 20 weeks of treatment. There was a 53% median reduction (N = 13) in convulsive seizures (CS); median reduction was 60% in the 10 completers. Eight patients (62%) had a ≥50% CS reduction; three (23%) patients had a ≥75% reduction. Nine (69%) patients entered the long-term extension study. At 15 months (n = 9), median reduction in CS was 58%; six (67%) patients had a ≥50% reduction, and three (33%) patients had a ≥75% reduction. The most common adverse events were decreased appetite (n = 4, 31%) and decreased alertness (n = 2, 15%). No echocardiographic signs of cardiac valvulopathy or pulmonary hypertension were observed.
Expected reporting date	Primary completion date reported as for September 2018.

ESTIMATED COST

The cost of fenfluramine hydrochloride is not known yet.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Cannabidiol for adjuvant treatment of seizures associated Lennox-Gastaut syndrome (ID1308). Expected publication date to December 2019.
- NICE guideline. Epilepsies: diagnosis and management (CG137). January 2012. Updated April 2018.
- NICE quality standard. Epilepsy in children and young people (QS27). February 2013.
- NICE interventional procedures guidance. Vagus nerve stimulation for refractory epilepsy in children (IPG50). March 2004.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Paediatric Neurosurgery. E09/S/a.
- NHS England. 2013/14 NHS Standard Contract for Paediatric Neurosciences: Neurology. E09/S/b.
- NHS England. 2013/14 NHS Standard Contract for Paediatric Neurosciences: Neurodisability E09/S/c.
- NHS England. 2014/14 NHS Standard Contract for Paediatric Neurosciences: Neurorehabilitation. E09/S/d.
- NHS England. 2013/14 NHS Standard Contract for Children's Epilepsy Surgery Service (CESS). E09/S/e.
- NHS England. April 2013 NHS Clinical Commissioning Policy: Vagal Nerve Stimulation for Epilepsy. NHSCB/D04/P/d.

OTHER GUIDANCE

Cross et al. Expert opinion on the management of Lennox–Gastaut syndrome: treatment algorithms and practical considerations. 2017.[13]

ADDITIONAL INFORMATION

Zogenix Inc did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

REFERENCES

1 National Cancer Institute (NCI). *Fenfluramine (Code C81418).* Available from: https://ncit.nci.nih.gov/ncitbrowser/ConceptReport.jsp?dictionary=NCI_Thesaurus&version=18.08d&ns=ncit&code=C81418&key=229728652&b=1&n=null [Accessed 21 March 2019].

2 Lagae L, Schoonjans AS, Gammaitoni AR, Galer BS, Ceulemans B. A pilot, open-label study of the effectiveness and tolerability of low-dose ZX008 (fenfluramine HCl) in Lennox-Gastaut syndrome. *Epilepsia*. 2018 Oct;59(10):1881-8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30146701 10.1111/epi.14540.

3 Schoonjans AS, Lagae L, Ceulemans B. Low-dose fenfluramine in the treatment of neurologic disorders: experience in Dravet syndrome. *Ther Adv Neurol Disord*. 2015 Nov;8(6):328-38. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26600876 10.1177/1756285615607726.

4 ClinicalTrials.gov. *A Study to Investigate the Efficacy and Safety of ZX008 (Fenfluramine Hydrochloride) as an Adjunctive Therapy in Children and Adults With Lennox-Gastaut Syndrome. Trial ID: NCT03355209*. Available from: https://clinicaltrials.gov/ct2/show/NCT03355209 [Accessed 21 March 2019].

5 European Medicines Agency (EMA). *Public summary of opinion on orphan designation - Fenfluramine hydrochloride for the treatment of Lennox-Gastaut syndrome.* Report No.: EMA/71973/2017. Available from: https://www.ema.europa.eu/en/documents/orphan-designation/eu/3/17/1836-public-summary-opinion-orphan-designation-fenfluramine-hydrochloride-treatment-lennox-gastaut_en.pdf.

6 US Food and Drug Administration. *Fenfluramine.* Available from: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=584217 [Accessed 21 March 2019].

7 ClinicalTrials.gov. *Fenfluramine - phase III.* Available from: https://clinicaltrials.gov/ct2/results?cond=&term=Fenfluramine&cntry=&state=&city=&dist=&recrs=a&recrs=b&recrs=d&recrs=e&recrs=f&phase=2 [Accessed 21 March 2019].

8 National Institute for Health and Care Excellence (NICE). *Cannabidiol for adjuvant treatment of seizures associated with LennoxGastaut syndrome - Final scope.* Available from: https://www.nice.org.uk/guidance/gid-ta10410/documents/final-scope [Accessed 25 April 2019].

9 Orphanet. *Lennox-Gastaut syndrome.* Available from: https://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=885&Disease_Disease_Search_diseaseGroup=Lennox-Gastaut-syndrome&Disease_Disease_Search_diseaseType=Pat&Disease(s)/group%20of%20diseases=Lennox-Gastaut-syndrome&title=Lennox-Gastaut-syndrome&search=Disease_Search_Simple [Accessed 21 March 2019].

10 Arzimanoglou A, French J, Blume WT, Cross JH, Ernst JP, Feucht M, et al. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. *Lancet Neurol*. 2009 Jan;8(1):82-93. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19081517 10.1016/S1474-4422(08)70292-8.

11 National Organisation for Rare Disorders. *Lennox-Gastaut Syndrome.* Available from: https://rarediseases.org/rare-diseases/lennox-gastaut-syndrome/ [Accessed 21 March 2019].

12 van Rijckevorsel K. Treatment of Lennox-Gastaut syndrome: overview and recent findings. *Neuropsychiatr Dis Treat*. 2008 Dec;4(6):1001-19. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19337447.

13 Cross JH, Auvin S, Falip M, Striano P, Arzimanoglou A. Expert Opinion on the Management of Lennox-Gastaut Syndrome: Treatment Algorithms and Practical Considerations. *Front Neurol*. 2017;8:505. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29085326 10.3389/fneur.2017.00505.

14 Gibson PA. Lennox-Gastaut syndrome: impact on the caregivers and families of patients. *J Multidiscip Healthc*. 2014;7:441-8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25336963 10.2147/JMDH.S69300.

15 Hancock EC, Cross HH. Treatment of Lennox-Gastaut syndrome. *Cochrane Database Syst Rev*. 2009 Jul 8(3):CD003277. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19588340 10.1002/14651858.CD003277.pub2.

16 Orphanet Report Series - Rare Diseases collection. *Prevalence and incidence of rare diseases: Bibliographic data.* Available from:

https://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf [Accessed 25 April 2019].

17 Patient. *Lennox-Gastaut Syndrome.* Available from: https://patient.info/doctor/lennox-gastaut-syndrome [Accessed 22 March 2019].

18 National Institute for Health and Care Excellence. *B58 Block Scoping Reports.* Available from: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/Block-scoping-reports/batch-58-block-scoping-report.pdf [Accessed 22 March 2019].

19 National Institute for Health and Care Excellence (NICE). *Anti-epileptic drugs to offer based on epilepsy syndrome.* Available from: https://pathways.nice.org.uk/pathways/epilepsy/anti-epileptic-drugs-to-offer-based-on-epilepsy-syndrome#content=view-node%3Anodes-lennoxgastaut-syndrome [Accessed 25 April 2019].

20 Europe Clinical Trial Register. *A Two-Part Study of ZX008 in Children and Adults with Lennox-Gastaut Syndrome (LGS); Part 1: A Randomized, Double-blind, Placebo-controlled Trial of Two Fixed Doses of ZX008 (Fenfluramine Hydrochloride) Oral Solution as Adjunctive Therapy for Seizures in Children and Adults with LGS, Followed by Part 2: An Open-label Extension to Assess Long-Term Safety of ZX008 in Children and Adults with LGS.* Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-002628-26/BE [Accessed 25 April 2019].

21 ClinicalTrials.gov. *Add-on Therapy With Low Dose Fenfluramine in Lennox Gastaut Epilepsy (FFA-LGS)*. *Trial ID: NCT02655198*. Available from: https://clinicaltrials.gov/ct2/show/NCT02655198 [Accessed 25 April 2019].

22 EU Clinical Trial Register. *Add-on fenfluramine in Lennox Gastaut epilepsy*. *Trial ID: 2015-004008-46*. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-004008-46/BE [Accessed 25 April 2019].

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.