Report Fintepla® - fenfluramine

Product & Mechanism of action	Authorized indications Licensing status	Essential therapeutic features	NHS impact
Substance: fenfluramine **Brand Name:**Fintepla® **Originator/licensee:**Zogenix ROI Limited **Classification:** NI **ATC code:** N03AX26 **Orphan Status:** **EU:** Yes **US:** Yes **Mechanism of action:** Fenfluramine is a serotonin releasing agent, and thereby stimulates multiple 5-HT receptor sub-typesthrough the release of serotonin. Fenfluramine may reduce seizures by acting as an agonist at specificserotonin receptors in the brain, including the 5-HT1D, 5-HT2A, and 5-HT2C receptors, and also byacting on the sigma-1 receptor. The precise mechanism is notknown [1].	**Authorized Indication:** **EMA:** Fenfluramine is indicated for thetreatment of seizures associated with Dravet syndrome **and Lennox-Gastaut syndrome** as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older [2]. **FDA:** Fenfluramine is indicated for thetreatment of seizures associated with Dravetsyndrome and Lennox-Gastaut syndrome in patients 2 years of age and older. [3] **Route of administration:** OS **Licensing status** **EU CHMP P.O. date:** 15/12/2022 **FDA M.A. date:** 25/03/2022 **EU Speed Approval Pathway:** No **FDA Speed Approval Pathway:** Yes ---------- **ABBREVIATIONS:** AE: adverse event ASM: antiseizure medication CHMP: Committee for Medicinal Products for Human Use ESC: Epilepsy StudyConsortium GTC: generalized tonic-clonic LGS: Lennox-Gastaut syndrome M.A.: marketing authorization P.O.: positive opinion Pts: patients TEAE: treatment-emergent adverseevent	**Summary of clinical EFFICACY:**NCT03355209 was a multicenter, randomized, placebo-controlled, double-blind, phase3 trial to evaluate efficacy and safety of fenfluramine in pts with LGS. Eligibility criteria includedage 2 to 35 years,ESC–confirmed LGS diagnosis, stableASM regimens (≥1 and ≤4 concomitantASMs) and stable 4-week seizure baselinewith ≥2 dropseizures per week of GTC, secondary GTC, tonic, atonic, or tonic-atonicseizure. After a 4-week period to establish baseline seizure frequency, pts wererandomized1:1:1 to receive fenfluramine 0.7mg/kg/day(N=87) or 0.2-mg/kg/day (N=89) (maximum 26mg/day) or placebo (N=87). During the first 2 weeks (= titration period), pts in the 0.7-mg/kg/day fenfluramine group were titrated to thetarget dose, whereas pts in the other groupsstarted at their target dose.Pts remained at their assigned dose for 12 weeks (i.e.maintenanceperiod). Changes in ASMswere not permittedduring the trial. The primary endpoint was the % change frombaselinein ESC–confirmed drop seizuresin the 0.7-mg/kg/day fenfluraminegroup vs the placebo group. Among the 263 randomized pts, 242 completed the trial. Atbaseline, 89%were using 2 to 4 concomitantASMs (the most common were valproate, clobazam, lamotrigine, levetiracetam, andrufinamide). The median % reduction in drop seizure frequencywas 26.5% in the 0.7-mg/kg/day fenfluraminegroup, 14.2% in the 0.2-mg/kg/day fenfluraminegroup, and 7.6% in the placebo group. Pts who received 0.7mg/kg/day of fenfluramine achieved anestimated median difference from placebo of −19.9% (95%CI: −31.0% to −8.7%; P=0.001)in drop seizure frequency comparedwith baseline level.The study met its primary efficacy endpoint. At the end of the maintenance period, eligible patientscould continue to an open-label extension study [4]. **Summary of clinical SAFETY:**Among the 263 randomized pts in NCT03355209 trial, 21 withdrew early from the study, with the most common reason being AEs.Most pts (81%) experienced a TEAE (90% in the 0.7-mg/kg/day fenfluramine group; 78% inthe0.2-mg/kg/day fenfluramine group;75%in the placebo group). More pts in the 0.7-mg/kg/day fenfluramine group compared with the other groupsexperienced ≥1 serious TEAE (11% in the 0.7-mg/kg/day fenfluramine group; 4% in the 0.2-mg/kg/day fenfluramine group; 5% in the placebo group). The most common TEAEsin the 0.7-mg/kg/day fenfluramine group vs 0.2-mg/kg/day fenfluramine group vs placebo group were decreased appetite (36% vs 20% vs 11%, respectively), somnolence (17% vs 10% vs 10%) and fatigue (18% vs 9% vs 10%) [4]. **Ongoing studies:** ● ***For the same indication:***No ● ***For other indications:***Yes **Discontinued studies (for the same indication):**No **References:** 1.https://www.ema.europa.eu/en/documents/product-information/fintepla-epar-product-information_en.pdf 2.https://www.ema.europa.eu/en/medicines/human/summaries-opinion/fintepla-0 3.https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/212102s003lbl.pdf 4.https://pubmed.ncbi.nlm.nih.gov/35499850/ 5.https://gallery.farmadati.it/ 6.Taruscio D (Ed.). Il Registro Nazionale e iRegistriRegionali/interregionalidellemalattierare.Rapporto anno 2011. Roma: IstitutoSuperiorediSanità; 2011 (Rapporti ISTISAN 11/20). 7.https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=IT&Expert=2382 8. https://rarediseases.org/rare-diseases/lennox-gastaut-syndrome/#:~:text=The%20three%20main%20forms%20of,of%20a%20team%20of%20specialists. 9. https://clinicaltrials.gov/	**Cost of therapy:**Considering the maximum dose of 26 mg/day [3,4] and the ex-factory price for a 360 mL oral solution, the monthly cost for the therapy would be 5,517.99€ [5]. **Epidemiology:**LGS was reported to the Italian National Registry for Rare Disease with a frequency of 125 during the 3-year reference period (30/06/2007-30/06/2010) [6].Orphanet reports an estimated prevalence of 15/100.000 [7]. **POSSIBLE PLACE IN THERAPY:**The main therapeutic options for the treatment of LGS are ASMs. However, because pts with LGS have different types of seizures, individual response is highly variable and pts often require therapy with multiple types of ASMs, including clonazepam, sodium valproate, topiramate, lamotrigine, felbamate, clobazam,rufinamide or cannabidiol[8]. Fenfluramine has been authorized for LGS asadd-on therapy to other anti-epileptic medicines[2]. **OTHER INDICATIONS IN DEVELOPMENT:** CDKL5 Deficiency Disorder, Photosensitive Epilepsy[9]. **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT:** - **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:** phase 3: soticlestat, carisbamate; phase 2: clemizole [9]. *Service reorganization: No *Possible off label use: Yes

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