UCB News

# FINTEPLA®▼ (fenfluramine) oral solution approved in Japan for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS)

**Brussels, Belgium – 17 April 2024 – 7:00 AM CET–** UCB's FINTEPLA®▼ (fenfluramine) oral solution has been approved by the Japanese Ministry of Health, Labour, and Welfare (MHLW) for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) as an add-on therapy to other anti-epileptic medicines for patients two years of age and older.[1]

The approval by the MHLW was based on safety and efficacy data from a global, double-blind, placebo-controlled, parallel-group randomized Phase 3 clinical trial (1601 Study Cohort A & B), in 296 patients with LGS (aged 2-35 years), including 33 in Japan. In the Japanese sub-population, adjunctive fenfluramine, at a dose of 0.7 mg/kg/day, provided a greater reduction in the frequency of drop seizures compared to placebo. The most common (≥10%) non-cardiovascular treatment–emergent adverse events (TEAEs) were decreased appetite, somnolence, weight decreased, diarrhea, and nasopharyngitis. No cases of valvular heart disease or pulmonary arterial hypertension were observed.[2]

"We know that the unmet needs in Lennox-Gastaut syndrome are great, and we look forward to bringing this important treatment advancement to people and families impacted by this condition in Japan. We are working to ensure that all patients who need our treatments can access them, and this approval further demonstrates that commitment," said Mike Davis, Head of Global Epilepsy & Rare Syndromes, UCB.

"This approval is an important milestone for UCB, delivering on our mission to bring several innovative new medicines to people living with severe neurological and immunological diseases in Japan this year, "said Kanako Kikuchi, Head of UCB Japan. "We would like to thank our Japanese patients and families for participating in the clinical trials, enabling families and people impacted by Lennox-Gastaut to have this new treatment option."

Lennox-Gastaut syndrome (LGS) is a childhood-onset severe developmental and epileptic encephalopathy (DEE), characterized by multiple types of drug-resistant seizures, and associated with high morbidity and profound effects on the quality of life (QoL) of patients and their families.[3,4] Motor, cognitive, and behavioural abnormalities are lifelong, with serious intellectual disability worsening over time.[5-9] Seizures leading to falls ("drop attacks/seizures") are common in LGS and tonic seizures are a hallmark feature of this syndrome.[3,4] Among the typical seizures associated with a drop, the generalized tonic–clonic seizures (GTCS) are commonly observed and usually occur in later stages of LGS but sometimes may precede core seizure types. In addition to being associated with bodily injury and hospitalizations, GTC seizures are a primary risk factor of sudden unexpected death in epilepsy (SUDEP). Patients with epilepsy with GTC seizures have an approximately 10-fold greater risk for SUDEP than patients with other seizure types.[2]

Inspired by patients.
Driven by science.

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Fenfluramine is marketed in Japan by Nippon Shinyaku Co., Ltd. based on the exclusive sales agreement signed in 2019 between Zogenix Inc., (acquired by UCB in 2022) and Nippon Shinyaku Co., Ltd. UCB is the Marketing Authorization holder.

## About UCB

UCB, Brussels, Belgium (www.ucb.com) is a global biopharmaceutical company focused on the discovery and development of innovative medicines and solutions to transform the lives of people living with severe diseases of the immune system or of the central nervous system. With approximately 9,000 people in approximately 40 countries, the company generated revenue of € 5.3 billion in 2023. UCB is listed on Euronext Brussels (symbol: UCB). Follow us on Twitter: @UCB_news

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**Important Safety Information about FINTEPLA▼ (fenfluramine) in the EU[10]**

Active Ingredient: Oral solution: 2.2 mg fenfluramine (as fenfluramine hydrochloride) per ml.
Indications: Treatment 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.
Dosage and Administration: Please refer to SmPC for full information. Should be initiated and supervised by physicians with experience in the treatment of epilepsy. Fintepla is prescribed and dispensed according to the Fintepla controlled access programme. Dravet syndrome: Patients who are not taking stiripentol: Starting dose is 0.1 mg/kg twice daily (0.2 mg/kg/day). After 7 days, if tolerated, can increase dose to 0.2 mg/kg twice daily (0.4 mg/kg/day). After an additional 7 days, if tolerated and further seizure reduction required, can increase dose to a maximum of 0.35 mg/kg twice daily (0.7 mg/kg/day), which is the recommended maintenance dose. Patients requiring more rapid titration may increase the dose every 4 days. Do not exceed maximum daily dose of 26 mg (13 mg twice daily). Patients who are taking stiripentol: Starting dose is 0.1 mg/kg twice daily (0.2 mg/kg/day). After 7 days, if tolerated, can increase dose to 0.2 mg/kg twice daily (0.4 mg/kg/day), which is the recommended maintenance dose. Patients requiring more rapid titration may increase the dose every 4 days. Do not exceed a total dose of 17 mg (8.6 mg twice daily). Lennox-Gastaut syndrome: Starting dose is 0.1 mg/kg twice daily (0.2 mg/kg/day). After 7 days, the dose should be increased to 0.2 mg/kg twice daily (0.4 mg/kg/day), if tolerated. After an additional 7 days, if tolerated, dose should be increased to 0.35 mg/kg twice daily (0.7 mg/kg/day), which is the recommended maintenance dose. Do not exceed maximum daily dose of 26 mg (13 mg twice daily). Discontinuation: When discontinuing treatment, decrease the dose gradually. As with all anti-epileptic medicines, avoid abrupt discontinuation when possible to minimize the risk of increased seizure frequency and status epilepticus. A final echocardiogram should be conducted 3-6 months after the last dose of treatment with fenfluramine. Renal impairment: Generally, no dose adjustment is recommended when administered to patients with mild to severe renal impairment, however, a slower titration may be considered. If adverse reactions are reported, a dose reduction may be needed. Has not been studied in patients with end-stage renal disease. Not known if fenfluramine or its active metabolite, norfenfluramine, is dialyzable. Hepatic impairment: Hepatic impairment: Generally, no dose adjustment is recommended when Fintepla is administered without concomitant stiripentol to patients with mild and moderate hepatic impairment (Child-Pugh Class A and B). In patients with severe hepatic impairment (Child-Pugh C) not receiving concomitant stiripentol, the maximum dosage is 0.2mg/kg twice daily, and the maximal total daily dose is 17 mg. There are limited clinical data on the use of Fintepla with stiripentol in patients with mild impaired hepatic function. A slower titration may be considered in patients with hepatic



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impairment and a dose reduction may be needed if adverse reactions are reported. No clinical data is available on the use of Fintepla with stiripentol in moderate and severe hepatic impairment, therefore not recommended for use. Elderly: No data available. Paediatric population: Safety and efficacy in children below 2 years of age not yet established. No data available.
Contraindications: Hypersensitivity to active substance or any excipients. Aortic or mitral valvular heart disease and pulmonary arterial hypertension. Within 14 days of the administration of monoamine oxidase inhibitors due to an increased risk of serotonin syndrome.
Warnings and Precautions: Aortic or mitral valvular heart disease and pulmonary arterial hypertension: Prior to starting treatment, patients must undergo an echocardiogram to establish a baseline and exclude any pre-existing valvular heart disease or pulmonary hypertension. Conduct echocardiogram monitoring every 6 months for the first 2 years and annually thereafter. If an echocardiogram indicates pathological valvular changes, consider follow-up earlier to evaluate whether the abnormality is persistent. If pathological abnormalities seen on echocardiogram, evaluate the benefit versus risk of continuing fenfluramine treatment with the prescriber, caregiver and cardiologist. Once treatment is discontinued for any reasons, a final echocardiogram should be conducted 3-6 months after the last dose of treatment with fenfluramine. If echocardiogram findings suggestive of pulmonary arterial hypertension, perform a repeat echocardiogram as soon as possible and within 3 months to confirm these findings. If echocardiogram finding is confirmed suggestive of an increased probability of pulmonary arterial hypertension defined as intermediate probability, conduct a benefit-risk evaluation of continuation of Fintepla by the prescriber, carer and cardiologist. If echocardiogram suggests a high probability, it is recommended fenfluramine treatment should be stopped. Decreased appetite and weight loss: Fenfluramine can cause decreased appetite and weight loss - an additive effect can occur in combination with other anti-epileptic medicines such as stiripentol. Monitor the patient's weight. Undertake risk-benefit evaluation before starting treatment if history of anorexia nervosa or bulimia nervosa. Fintepla controlled access programme: A controlled access programme has been created 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. Somnolence: Fenfluramine can cause somnolence which could be potentiated by other central nervous system depressants. Suicidal behaviour and ideation: Suicidal behaviour and ideation have been reported in patients treated with anti-epileptic medicines in several indications. Advise patients and caregivers to seek medical advice should any signs of suicidal behaviour and ideation emerge. Serotonin syndrome: Serotonin syndrome, a potentially life-threatening condition, may occur with fenfluramine treatment, particularly with concomitant use of other serotonergic agents; with agents that impair metabolism of serotonin such as MAOIs; or with antipsychotics that may affect the serotonergic neurotransmitter systems. Carefully observe the patient, particularly during treatment initiation and dose increases. Increased seizure frequency: A clinically relevant increase in seizure frequency may occur during treatment, which may require adjustment in the dose of fenfluramine and/or concomitant anti-epileptic medicines, or discontinuation of fenfluramine, should the benefit-risk be negative. Cyproheptadine: Cyproheptadine is a potent serotonin receptor antagonist and may therefore decrease the efficacy of fenfluramine. If cyproheptadine is added to treatment with fenfluramine, monitor patient for worsening of seizures. If fenfluramine treatment is initiated in a patient taking cyproheptadine, fenfluramine's efficacy may be reduced. Glaucoma: Fenfluramine can cause mydriasis and can precipitate angle closure glaucoma. Discontinue therapy in patients with acute decreases in visual acuity. Consider discontinuation if ocular pain of unknown origin. Effect of CYP1A2 or CYP2B6 inducers: Co-administration with strong CYP1A2 inducers or CYP2B6 inducers will decrease fenfluramine plasma concentrations, which may lower the efficacy of fenfluramine. If co-administration is considered necessary, the patient should be monitored for reduced efficacy and a dose increase of fenfluramine could be considered provided that it does not exceed twice the maximum daily dose (52 mg/day). If a strong CYP1A2 or CYP2B6 inducer is discontinued during maintenance treatment with fenfluramine, consider gradual reduction of the fenfluramine dosage to the dose administered prior to initiating the inducer. Effect of CYP1A2 or CYP2D6 inhibitors: Initiation of concomitant treatment with a strong CYP1A2 or CYP2D6 inhibitor may result in higher exposure and, therefore, adverse events should be monitored, and a dose reduction may be needed in some patients. Excipients: Contains sodium ethyl para-hydroxybenzoate (E 215) and sodium methyl para-hydroxybenzoate (E 219) - may cause allergic reactions (possibly delayed). It also contains sulfur dioxide (E 220) which may rarely cause severe hypersensitivity reactions and bronchospasm. Patients with rare glucose-galactose malabsorption should not take this medicine. The product contains less than 1 mmol sodium (23 mg) per the maximum daily dose of 12 mL; essentially 'sodium-free'. Contains glucose - may be harmful to teeth. Interactions: Pharmacodynamic interactions with other CNS depressants increase the risk of aggravated central nervous system depression. An increase in dose may be necessary when coadministered with rifampicin or a strong CYP1A2 or CYP2B6 inducer. In in vitro studies co-administration with a strong CYP1A2 or CYP2D6 inhibitor may result in higher exposure (see section 4.4 of the SmPC). Co-administration with CYP2D6 substrates or MATE1 substrates may increase their plasma concentrations. Co-administration with CYP2B6 or CYP3A4 substrates may decrease their plasma concentrations. Pregnancy and lactation: Limited data in pregnant women. As a precaution, avoid use of Fintepla in pregnancy. It is unknown whether fenfluramine/metabolites are excreted in human milk. Animal data have shown excretion of fenfluramine/metabolites in milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Fintepla taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Drive and use machines.: Fintepla has moderate influence on the ability to drive/ use machines as it may cause somnolence and fatigue. Advise patients not to drive or operate machinery until they have sufficient experience to gauge whether it adversely affects their abilities.
Adverse effects: Dravet syndrome: Very common (≥1/10): Upper respiratory tract infection, decreased appetite, somnolence, diarrhoea, pyrexia, fatigue, blood glucose decreased, echocardiogram abnormal (Consisted of trace and mild mitral regurgitation, and trace aortic regurgitation, which are considered physiologic). Common (≥1/100 to <1/10): Bronchitis, abnormal behaviour, aggression,



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agitation, insomnia, mood swings, ataxia, hypotonia, lethargy, seizure, status epilepticus, tremor, constipation, salivary hypersecretion, weight decreased and blood prolactin increased. Not known (cannot be estimated from the available data): Pulmonary arterial hypertension. Lennox-Gastaut syndrome: Very common (≥1/10): Upper respiratory tract infection, decreased appetite, somnolence, diarrhoea, vomiting, fatigue. Common (≥1/100 to <1/10): Bronchitis, influenza, pneumonia, aggression, seizure, status epilepticus, lethargy, tremor, constipation, salivary hypersecretion, blood prolactin increased, weight decreased, fall. Refer to SmPC for other adverse reactions. Pharmaceutical Precautions: Use within 3 months of opening. Do not refrigerate or freeze. Package Quantities and Marketing Authorisation Number: Fintepla is presented in a white bottle with oral syringes included which should be used to administer the prescribed dose. Bottle sizes of 60 mL, 120 mL, 250mL and 360 mL. EU/1/20/1491/001, EU/1/20/1491/002, EU/1/20/1491/003 and EU/1/20/1491/004. Legal Category: POM. Marketing Authorisation Holder: UCB Pharma S.A. Allée de la Recherche 60, B-1070 Bruxelles, Belgium. Date of revision: 27 March 2024.

▼ *This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.*

*FINTEPLA® is a registered trademark of the UCB Group of Companies.*

Refer to the European Summary of Product Characteristics for further safety information and full prescribing information.
https://www.ema.europa.eu/en/documents/product-information/fintepla-epar-product-information_en.pdf

**Forward looking statements**

This press release may contain forward-looking statements including, without limitation, statements containing the words "believes", "anticipates", "expects", "intends", "plans", "seeks", "estimates", "may", "will", "continue" and similar expressions. These forward looking statements are based on current plans, estimates and beliefs of management. All statements, other than statements of historical facts, are statements that could be deemed forward-looking statements, including estimates of revenues, operating margins, capital expenditures, cash, other financial information, expected legal, arbitration, political, regulatory or clinical results or practices and other such estimates and results. By their nature, such forward-looking statements are not guarantees of future performance and are subject to known and unknown risks, uncertainties and assumptions which might cause the actual results, financial condition, performance or achievements of UCB, or industry results, to differ materially from those that may be expressed or implied by such forward-looking statements contained in this press release. Important factors that could result in such differences include: changes in general economic, business and competitive conditions, the inability to obtain necessary regulatory approvals or to obtain them on acceptable terms or within expected timing, costs associated with research and development, changes in the prospects for products in the pipeline or under development by UCB, effects of future judicial decisions or governmental investigations, safety, quality, data integrity or manufacturing issues; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, product liability claims, challenges to patent protection for products or product candidates, competition from other products including biosimilars, changes in laws or regulations, exchange rate fluctuations, changes or uncertainties in tax laws or the administration of such laws, and hiring and retention of its employees. There is no guarantee that new product candidates will be discovered or identified in the pipeline, will progress to product approval or that new indications for existing products will be developed and approved. Movement from concept to commercial product is uncertain; preclinical results do not guarantee safety and efficacy of product candidates in humans. So far, the complexity of the human body cannot be reproduced in computer models, cell culture systems or animal models. The length of the timing to complete clinical trials and to get regulatory approval for product marketing has varied in the past and UCB expects similar unpredictability going forward. Products or potential products, which are the subject of partnerships, joint ventures or licensing collaborations may be subject to differences disputes between the partners or may prove to be not as safe, effective or commercially successful as UCB may have believed at the start of such partnership. UCB's efforts to acquire other products or companies and to integrate the operations of such acquired companies may not be as successful as UCB may have believed at the moment of acquisition. Also, UCB or others could discover safety, side effects or manufacturing problems with its products and/or devices after they are marketed. The discovery of significant problems with a product similar to one of UCB's products that implicate an entire class of products may have a material adverse effect on sales of the entire class of affected products. Moreover, sales may be impacted by international and domestic trends toward managed care and health care cost containment, including pricing pressure, political and public scrutiny, customer and prescriber patterns or practices, and the reimbursement policies imposed by third-party payers as well as legislation affecting biopharmaceutical pricing and reimbursement activities and outcomes. Finally, a breakdown, cyberattack or information security breach could compromise the confidentiality, integrity and availability of UCB's data and systems.

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