UCB News

FINTEPLA®▼ (fenfluramine) oral solution recommended for approval in the EU for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS)

- Recommendation based on Phase 3 study data demonstrating safety and efficacy in the most difficult to treat seizure types, including drop seizures[1,2]
- LGS is a rare severe form of epilepsy that typically starts during childhood and persists into adulthood. It is characterized by multiple types of drug-resistant seizures with high morbidity[3,4] as well as serious impairment of neurodevelopmental, cognitive, and motor functions[4]

Brussels, Belgium – 19 December 2022 – 07:00 AM CET– UCB, a global biopharmaceutical company, today announced that FINTEPLA®▼ (fenfluramine) oral solution has been recommended for marketing authorization in the European Union (EU) for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older. Fenfluramine is already approved in the US for the treatment of seizures associated with Lennox- Gastaut syndrome. In addition, it is also approved for the treatment of seizures associated with Dravet syndrome in the EU*, US, and Japan.[5,6,7]

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency based its positive opinion on safety and efficacy data from a global, randomized, placebo-controlled Phase 3 clinical trial, in 263 patients with LGS (aged 2-35 years), that demonstrated adjunctive fenfluramine at a dose of 0.7/mg/kg/day, provided a significantly greater reduction in the frequency of drop seizures (p=0.001) compared to placebo.[1] The most common treatment-emergent adverse events were decreased appetite, somnolence, fatigue and pyrexia.[1] No cases of valvular heart disease or pulmonary arterial hypertension were observed.[1]

The CHMP's positive opinion on fenfluramine will be referred to the European Commission (EC), which will deliver a final decision in Q1 2023.

"This positive CHMP opinion is a significant regulatory milestone towards providing a new treatment option to individuals – and their families – living with this rare epilepsy in the EU," said Mike Davis, Head of Global Epilepsy & Rare Syndromes, UCB. "We're delighted by this recommendation, highlighting our ongoing commitment to the LGS community by ensuring we bring differentiated medicines to those with unmet needs."

Additional data supporting the safety and efficacy of fenfluramine in LGS in the open label extension (OLE) part of the study was recently published in *Epilepsia* showing fenfluramine, when added to a patient's current anti-epileptic treatment regimen for seizures associated with LGS, was effective in reducing the frequency of multiple seizure types and was generally well tolerated during a median treatment duration of 364 days.[2] Study participants experienced a sustained reduction in the frequency of motor seizures including those that resulted

Date of preparation: December 2022
GL-N-FA-LGS-2200004

in a drop or fall (Generalized Tonic-Clonic Seizures (GTCS), secondary GTCS (SGTC; focal to bilateral tonic-clonic), tonic seizures, atonic seizures, and tonic-atonic seizures).[2] In the OLE phase, the most common treatment-emergent adverse events were decreased appetite, fatigue, nasopharyngitis and seizure. The cardiovascular safety in this study further corroborates the fenfluramine safety profiles observed; no cases of valvular heart disease or pulmonary arterial hypertension were observed. [2]

LGS is a severe childhood-onset developmental and epileptic encephalopathy (DEE) characterized by multiple types of drug-refractory seizures with high morbidity[3,4] as well as serious impairment of neurodevelopmental, cognitive, and motor functions.[4] LGS affects an estimated 2 in 10,000 people in European Union (EU).[8] LGS has far-reaching effects beyond seizures, including issues with developmental communication, psychiatric symptoms, sleep, behavioural challenges, and mobility.[9] Drop seizures are hallmark features of LGS, particularly tonic seizures. Convulsive seizures (eg, generalized tonic-clonic [GTC] seizures) are also 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 GTC seizures have an approximately 10-fold greater risk for SUDEP than patients with other seizure types.[5]

About fenfluramine C-IV in EU

*Fintepla is indicated for the treatment of seizures associated with Dravet syndrome as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older. Fenfluramine is a 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-HT1D, 5-HT2A, and 5-HT2C receptors, and also by acting on the sigma-1 receptor.[5]

Fenfluramine oral solution is available under a controlled access program for Dravet Syndrome to ensure regular cardiac monitoring and to mitigate potential off-label use for weight management.

Please refer to Summary of Product Characteristics (SmPC) before prescribing.

▼*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.*

Key Safety Information about FINTEPLA®▼ in EU[5]

Aortic or mitral valvular heart disease and pulmonary arterial hypertension

Because of reported cases of valvular heart disease that may have been caused by fenfluramine at higher doses used to treat adult obesity, cardiac monitoring must be performed using echocardiography. In the controlled clinical studies of fenfluramine for the treatment of Dravet syndrome, no valvular heart disease was observed. Prior to starting treatment, patients must undergo an echocardiogram to establish a baseline prior to initiating treatment 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. If an echocardiogram indicates pathological valvular changes, a follow-up echocardiogram should be considered at an earlier timeframe to evaluate whether the abnormality is persistent. If pathological abnormalities on the echocardiogram are observed, it is recommended to evaluate the benefit versus risk of continuing fenfluramine treatment with the prescriber, caregiver, and cardiologist. If treatment is stopped because of aortic or mitral valvular heart disease, appropriate monitoring and follow-up should be provided in accordance with local guidelines for the treatment of aortic or mitral valvular heart disease. With past use in higher doses to treat adult obesity, fenfluramine was reported to be associated with pulmonary arterial hypertension. Pulmonary arterial hypertension was not observed in the clinical programme, but because of the low incidence of this disease, the clinical trial experience with fenfluramine is inadequate to

determine if fenfluramine increases the risk for pulmonary arterial hypertension in patients with Dravet syndrome. If echocardiogram findings are suggestive of pulmonary arterial hypertension, a repeat echocardiogram should be performed as soon as possible and within 3 months to confirm these findings. If the echocardiogram finding is confirmed suggestive of an increased probability of pulmonary arterial hypertension defined as "intermediate probability" by the 2015 European Society of Cardiology (ESC) and the European Respiratory Society (ERS) Guidelines, it should lead to a benefit-risk evaluation of continuation of Fintepla by the prescriber, carer, and cardiologist. If the echocardiogram finding, after confirmation, suggests of a high probability of pulmonary arterial hypertension, as defined by the 2015 ESC and ERS Guidelines, it is recommended fenfluramine treatment should be stopped.

Decreased appetite and weight loss
Fenfluramine can cause decreased appetite and weight loss. An additive effect on decreased appetite can occur when fenfluramine is combined with other anti-epileptic medicines, for example stiripentol. The decrease in weight appears to be dose related. Most subjects resumed weight gain over time while continuing treatment. The patient's weight should be monitored. A benefit risk evaluation should be undertaken prior to commencing treatment with fenfluramine in patients with a 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. Other central nervous system depressants, including alcohol, could potentiate the somnolence effect of fenfluramine.

Suicidal behaviour and ideation
Suicidal behaviour and ideation have been reported in patients treated with anti-epileptic medicines in several indications. A meta-analysis of randomised placebo-controlled trials with anti-epileptic medicines that did not include fenfluramine has shown a small increased risk of suicidal behaviour and ideation. The mechanism of this risk is not known, and the available data do not exclude the possibility of an increased risk for fenfluramine. Patients and caregivers of patients should be advised to seek medical advice should any signs of suicidal behaviour and ideation emerge.

Serotonin syndrome
As with other serotonergic agents, serotonin syndrome, a potentially life-threatening condition, may occur with fenfluramine treatment, particularly with concomitant use of other serotonergic agents (including SSRIs, SNRIs, tricyclic antidepressants, or triptans); with agents that impair metabolism of serotonin such as MAOIs; or with antipsychotics that may affect the serotonergic neurotransmitter systems. Serotonin syndrome symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (eg, hyperreflexia, incoordination), and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhoea). If concomitant treatment with fenfluramine and other serotonergic agents that may affect the serotonergic systems is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Increased seizure frequency
As with other anti-epileptic medicines, a clinically relevant increase in seizure frequency may occur during treatment with fenfluramine, 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, patients should be monitored 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 there is ocular pain and another cause cannot be determined.

Strong CYP1A2 or CYP2B6 inducers
Co-administration with strong CYP1A2 inducers or CYP2B6 inducers may decrease fenfluramine plasma concentrations. An increase in fenfluramine dosage should be considered when co-administered with a strong CYP1A2 or CYP2B6 inducer; the maximum daily dose should not be exceeded.

Excipients
This medicinal product contains sodium ethyl para-hydroxybenzoate (E 215) and sodium methyl para hydroxybenzoate (E 219) which 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 medicinal product. This medicinal product contains less than 1 mmol sodium (23 mg) per the maximum daily dose of 12 mL, that is to say essentially 'sodium-free'. This medicinal product contains glucose which may be harmful to the teeth.

For further safety information and full prescribing information visit: Fintepla, INN-fenfluramine (europa.eu)

For further information, contact UCB:

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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 8 600 people in approximately 40 countries, the company generated revenue of € 5.8 billion in 2021. UCB is listed on Euronext Brussels (symbol: UCB). Follow us on Twitter: @UCB_news

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[5] Fintepla EMA SmPC https://www.ema.europa.eu/en/documents/product-information/fintepla-epar-product-information_en.pdf Accessed December 2022

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