UCB News

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

Brussels, Belgium – 8 February 2023 – 7:00 AM CET– UCB's FINTEPLA®▼ (fenfluramine) oral solution has been approved 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 two years of age and older.[1]

The approval by the European Commission (EC) was based 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. The most common treatment-emergent adverse events were decreased appetite, somnolence, fatigue, and pyrexia (fever). No cases of valvular heart disease or pulmonary arterial hypertension were observed.[2]

Professor Rima Nabbout, MD, PhD, Professor of Paediatric Neurology at University Paris cité, APHP, Necker Enfants Malades, Institut Imagine, Paris, France, said: "LGS is a developmental and epileptic encephalopathy where seizures are frequent, inducing high level of trauma injuries and negatively impacting development and quality of life. Seizures are often resistant to currently available medications, making this approval especially important for the individuals affected and their families."

Mike Davis, Head of Global Epilepsy & Rare Syndromes, UCB, said: "With this approval, fenfluramine is now an important additional treatment option for those impacted by this difficult to treat condition in Europe. This approval underscores our commitment to improving treatment outcomes, while addressing the high unmet need for new treatments for people living with LGS and rare epilepsies."

LGS is a severe childhood-onset developmental and epileptic encephalopathy (DEE) characterized by multiple types of drug-resistant seizures with high morbidity, as well as serious impairment of neurodevelopmental, cognitive, and motor functions,[3,4] affecting an estimated 2 in 10,000 people in European Union (EU).[5] Seizures leading to falls ("drop attacks/seizures") are common in LGS and tonic seizures are a hallmark feature of this syndrome.[3,4] In addition, convulsive seizures (e.g., 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.[2]

Additionally, the EC has also adopted the EMA Committee for Orphan Medicinal Products (COMP) recommendation that the orphan designation for fenfluramine be maintained.[6]

Inspired by patients.
Driven by science.

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About fenfluramine C-IV in EU[1]

Fintepla is indicated for the treatment of seizures associated with Lennox-Gastaut and 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. The precise mode of action of fenfluramine in Dravet syndrome and Lennox-Gastaut syndrome is not known.

Fenfluramine oral solution is available under a controlled access program to ensure regular cardiac monitoring and to mitigate potential off-label use

Please refer to Fintepla, INN-fenfluramine (europa.eu) (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[1]

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 and Lennox-Gastaut 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 and Lennox-Gastaut 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.

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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.

Effect of CYP1A2 and 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 of a strong CYP1A2 or CYP2B6 inducer with fenfluramine 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.

Coadministration of a single 0.35 mg/kg dose of fenfluramine with fluvoxamine (a strong CYP1A2 inhibitor) at steady state (50 mg once daily) in healthy volunteers increased the AUC0-t of fenfluramine by a ratio of 2.1-fold and the Cmax by a ratio of 1.2-fold, and decreased the AUC0-t of norfenfluramine by a ratio of 1.3-fold and the Cmax by a ratio of 1.4-fold, as compared to fenfluramine administered alone.

Coadministration of a single 0.35 mg/kg dose of fenfluramine with paroxetine (a strong CYP2D6 inhibitor) at steady state (30 mg once daily) in healthy volunteers increased the AUC0-t of fenfluramine by a ratio of 1.8-fold and the Cmax by a ratio of 1.1-fold, and decreased the AUC0-t of norfenfluramine by a ratio of 1.2-fold and the Cmax by a ratio of 1.3-fold, as compared to fenfluramine administered alone.

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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)

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