UCB News

# FINTEPLA®▼ (fenfluramine) Approved in Japan for the Treatment of Seizures Associated with Dravet Syndrome

- *Approval supported by clinical trial data that showed when added to existing treatment regimens, fenfluramine significantly reduced monthly convulsive seizure frequency compared to placebo*[1]
- *Approval highlights UCB's commitment to expanding global access to fenfluramine; an estimated 3,000 – 6,000 patients live with Dravet syndrome in Japan*[2]

**Brussels (Belgium), 27 September 2022 – 7.00 (CET) –** UCB, a global biopharmaceutical company, today announced that FINTEPLA®▼ (fenfluramine) oral solution has been approved by the Japanese Ministry of Health, Labour and Welfare (MHLW) 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.[3] FINTEPLA® will be available at all Japanese hospitals and pharmacies.

Fenfluramine will be marketed 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 now the Marketing Authorization holder.

"This approval in Japan delivers on our commitment towards expanding access to new treatment options to address unmet needs of those living with refractory epilepsy across the globe," said Charl van Zyl, Executive Vice President, Neurology Solutions, UCB. "We would like to thank our Japanese patients and families for participating in the clinical trial and making this significant milestone happen so that more people with Dravet syndrome can help achieve their treatment goals."

The MHLW approval was based a clinical trial program including data from a multi-national randomized, double-blind, placebo-controlled study of 143 children and young adults (2-18 years) with Dravet syndrome [that included trial participants from Japan], whose seizures were not adequately controlled with existing anti-epileptic medications. The study showed that when added to existing treatment regimens, those treated with 0.7 mg/kg day fenfluramine experienced a greater reduction (64.8%) in mean monthly convulsive seizures compared to placebo (P <.0001). The median age of patients in the study was 9 years (range, 2–18) and the average baseline convulsive seizure frequency across the study groups was approximately 63 seizures per month. Following a 6-week baseline observation

period, patients were randomized to 1 of 3 treatment groups: 0.7 mg/kg per day (n = 49), 0.2 mg/kg per day (n = 46), or placebo (n = 48), in which fenfluramine or placebo was added to each patient's current treatment regimen of anti-epileptic drugs. Patients were titrated to their target dose of fenfluramine over 2 weeks and then remained at that fixed dose for 12 weeks (26-mg maximum daily dose).[1]

The incidence of treatment-emergent adverse events was higher in the treatment groups as compared to the placebo group, with 91.7% (n=44) of patients in the 0.7 mg/kg/day group and 91.3% (n=42) of patients in the 0.2 mg/kg/day group experiencing at least one treatment-emergent adverse event compared to 83.3% (n=40) of patients in the placebo group. The incidence of serious adverse events was similar in all three groups with 6.3% (n=3) of patients in the 0.7 mg/kg/day group and 6.5% (n=3) of patients in the 0.2 mg/kg/day group experiencing at least one treatment-emergent serious adverse event compared to 4.2% (n=2) of patients in the placebo group, including one placebo patient who died due to SUDEP (sudden unexpected death in epilepsy). Prospective cardiac safety monitoring throughout the study showed that no study patients developed valvular heart disease or pulmonary arterial hypertension. [1]

As a condition of regulatory approval in Japan, UCB is required to undertake various post-marketing surveillance programs.

**About Dravet Syndrome**

Dravet syndrome is a rare, devastating and life-long form of developmental and epileptic encephalopathy that generally begins in infancy and is marked by frequent, treatment-resistant seizures, significant developmental, motor, and behavioral impairments, and an increased risk of mortality and sudden unexpected death in epilepsy (SUDEP). Most patients follow a course of developmental delay with cognitive, motor and behavioral deficits that persist into adulthood. Dravet syndrome severely impacts quality of life for patients, families, and caregivers due to the high physical, emotional, caregiving, and financial burden associated with the disease.[4,5,6]

**About fenfluramine C-IV**

Fenfluramine oral solution is a prescription medication used to treat seizures associated with Dravet syndrome in patients two years of age and older. Fenfluramine and the metabolite, norfenfluramine, increase extracellular levels of serotonin through interaction with serotonin transporter proteins, and exhibit agonist activity at serotonin 5HT-2 receptors. [7,8]

**Key Safety Information about FINTEPLA®▼ in EU[7]**

*Aortic or mitral valvular heart disease and pulmonary arterial hypertension*

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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.

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*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)

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**Key Safety Information about FINTEPLA®▼ in Japan[3]**

The administration of fenfluramine, the active ingredient of FINTEPLA, has been reported to be associated with valvular heart disease and pulmonary arterial hypertension. The following monitoring should be performed in collaboration with a cardiologist.

Before starting FINTEPLA treatment, the presence or absence of cardiac diseases should be confirmed by echocardiography, etc.

During the FINTEPLA treatment period, echocardiography and also adequate observation (e.g., physical findings such as auscultation, chest X-ray, electrocardiogram, etc.) should be performed periodically.

If echocardiography reveals any valvular abnormalities, additional echocardiography should be performed to make sure the abnormality does not persist. If echocardiography reveals findings indicative of valvular heart disease or pulmonary arterial hypertension, a decision on whether FINTEPLA can be administered should be reached based on a careful consideration of the risks and benefits for initiating or continuing treatment.

FINTEPLA can cause decreased appetite. Patients and their caregivers should be thoroughly informed in advance and instructed to visit their physicians if necessary. Since weight loss may occur, patients should be carefully monitored during treatment with this product, including periodic weigh-ins, and if weight loss is observed, a dosage reduction should be considered.

Since FINTEPLA may cause drowsiness and impaired attention, concentration, and reflex-motor skills, advise patients and caregiver should be cautioned that patients taking FINTEPLA should not drive a car or operate other hazardous machineries.

Fenfluramine can cause mydriasis and can precipitate angle closure glaucoma. Consider discontinuing treatment with FINTEPLA in patients with acute decreases in visual acuity or ocular pain.

When discontinuing FINTEPLA, the dose should be reduced gradually to minimize the risk of increased seizure frequency and status epilepticus.

For further safety information and full Japanese prescribing information visit: フィンテプラ内用液 2.2mg/mL (pmda.go.jp)

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*▼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.*

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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 more than 7 600 people in approximately 40 countries, the company generated revenue of €5.3 billion in 2020. UCB is listed on Euronext Brussels (symbol: UCB). Follow us on Twitter: @UCB_news

**Forward looking statements**

This press release contains 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 but not limited to, the ability of UCB to successfully integrate the operations of Zogenix as planned or at all, 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: the global spread and impact of COVID-19, 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, 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 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' 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

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outcomes. Finally, a breakdown, cyberattack or information security breach could compromise the confidentiality, integrity and availability of UCB's data and systems.

Given these uncertainties, you should not place undue reliance on any of such forward-looking statements. There can be no guarantee that the investigational or approved products described in this press release will be submitted or approved for sale or for any additional indications or labelling in any market, or at any particular time, nor can there be any guarantee that such products will be or will continue to be commercially successful in the future.

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## References

1. UCB Data on File. Sullivan, J. AES. 2020. Poster 853.
2. Yamada M, Suzuki K, Matsui D, Inoue Y, Ohtsuka Y. Long-term safety and effectiveness of stiripentol in patients with Dravet syndrome: Interim report of a post-marketing surveillance study in Japan. Epilepsy Res. 2021;170:106535.
3. Fintepla Japan PI. September 2022. フィンテプラ内用液2.2mg/mL (pmda.go.jp). Accessed September 2022
4. Dravet C. The Core Dravet Syndrome Phenotype. Epilepsia. 2011 Apr;52 Suppl 2:3-9.
5. Dravet C. Dravet syndrome history. Dev Med Child Neurol. 2011 Apr;53 Suppl 2:1-6.
6. Wu YW, Sullivan J, McDaniel SS, et al. Incidence of Dravet Syndrome in the US Population. Pediatrics. 2015 Nov;136(5):e1310-1315.
7. Fintepla EMEA SmPC.https://www.ema.europa.eu/en/documents/product-information/fintepla-epar-product-information_en.pdf. Accessed September 2022
8. Fintepla® US PI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212102s000lbl.pdf. Accessed September 2022

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