UCB News

UCB Showcases Strength of Broad Neurology Portfolio at 74th American Academy of Neurology (AAN) Annual Meeting

- Scientific presentations illustrate UCB's commitment to addressing unmet needs of people living with a broad range of serious neurological diseases
- New data focused on epilepsy and Parkinson's disease (PD), including real-world use of BRIVIACT® (brivaracetam) CV, long-term use of FINTEPLA® ▼ (fenfluramine) CIV [Lennox Gastaut syndrome indication in the US only] early use of NAYZILAM® (midazolam) CIV [FDA approved only] and pre-clinical evaluation of an investigational treatment for Parkinson's disease (UCB0599)
- UCB will also host an industry sponsored therapeutic update session 'MG: What lies beneath?' on April 4 to contribute to improved understanding about Myasthenia Gravis

Brussels (Belgium), 01 April 2022 – 07:00 (CET) – UCB today announced that new data from its expansive and innovative neurology portfolio will be presented at the 74th American Academy of Neurology (AAN) Annual Meeting, from 2-7 April 2022.

Twelve scientific abstracts have been accepted including data from UCB's epilepsy portfolio and Parkinson's disease development program.

"At UCB, we are inspired to develop new solutions that help transform the lives of people living with severe neurological disorders. Our world-class scientists make this ambition possible; advancing our understanding of human biology and driving breakthroughs in areas of science," said Charl van Zyl, Executive Vice President Neurology & Head of Europe/International Markets at UCB. "We are excited to showcase the scale and passion of our commitment at AAN, building on our legacy and expertise in epilepsy, myasthenia gravis and Parkinson's disease."

Epilepsy

At the congress, UCB will be reporting data from several significant clinical epilepsy studies from its broad epilepsy portfolio. Notably, these data include real-world retrospective interim evidence evaluating the effectiveness and tolerability of brivaracetam*, for adult patients with partial-onset seizures, in routine clinical practice in a large multicenter international patient population, as well as prospective US RWE data. In the U.S., brivaracetam* is approved for the treatment of partial onset seizures in patients 1 month of age and older.[2]

Additionally, presented data will evaluate dose-response relationships for the impact of fenfluramine on everyday executive function in patients, as captured using the Behavior Rating Inventory of Executive Function (BRIEF®). In the US, fenfluramine* is indicated for the treatment of seizures associated with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) in patients 2 years of age and older.[1]

Data will also summarize the early use of midazolam nasal spray in patients with seizure clusters. In the U.S., midazolam nasal spray is indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 12 years of age and older.[5] Please see IMPORTANT SAFETY INFORMATION, including Boxed Warning, below.

Two podium presentations will also be taking place during the congress, highlighting the long-term evidence of the cardiovascular safety profile of fenfluramine. **Please note that fenfluramine is available only through the REMS Program due to the risk of valvular heart disease and pulmonary arterial hypertension. Please see IMPORTANT SAFETY INFORMATION, including Boxed Warning, below.[1]**

- **Interim Analysis of Long-Term Safety and Efficacy of FINTEPLA® (fenfluramine) in Patients with Lennox-Gastaut Syndrome** Knupp K, Scheffer I, Ceulemans B, et al.
  Session S13: Epilepsy/Clinical Neurophysiology (EEG): Antiseizure Medications
  Authors available: Monday, April 4 2022, at 2:48 PM PT

- **Long-Term Cardiovascular Safety of Fenfluramine for Lennox-Gastaut Syndrome: Interim Analysis of Open-Label Safety Study** Agarwal A, Farfel G, Gammaitoni A, et al.
  Session S24: Epilepsy/Clinical Neurophysiology (EEG): Clinical Epilepsy
  Authors available: Tuesday, April 5 2022, at 4:18 PM PT

An additional presentation will take place to summarize a real-world study of brivaracetam in the United States.

- **Real-world Study of Brivaracetam in the United States.** Dave H, French JA, Altalib HH, Henninger H, Porter RJ, Gelfand M, Martin MS, Dongre P, Elmoufti S, Schulz AL, Sperling MR
  Session S13 Epilepsy/clinical Neurophysiology (EEG) antiseizure medications
  Authors available: Monday, April 4 at 1:00 PM PT

*Licenses may vary by country. Please always refer to the Prescribing Information available in your country

Myasthenia Gravis

UCB will be hosting an Industry Therapeutic Update titled 'MG: What lies beneath? The MG pathophysiology forum', Monday, 4 April, 19:00-20:15 PT (Leonesa Ballroom III, Grand Hyatt Seattle). An esteemed faculty will explore how advances in understanding of the pathogenic mechanisms of generalized myasthenia gravis are a catalyst for innovation in disease management. UCB is excited to be progressing knowledge, understanding and discussion about disease management and the potential benefits of targeted therapies in this rare neuro-muscular disease, and is very proud to be part of the rapidly evolving MG community alongside patients, clinicians, caregivers and healthcare providers.

Parkinson's disease

In Parkinson's disease, UCB's long-term ambition is to transform the treatment landscape from the management of symptoms, to treatments that can slow or stop the progression of disease. At AAN UCB has a podium presentation on the data evaluating the preclinical effects of chronic dosing of its investigational molecule currently in development with Novartis, (UCB0599), in α-synuclein transgenic mice. An additional study reviewed the extent to which legacy patient-reported outcome instruments are fit for purpose for use in trials involving people with early-stage Parkinson's disease.

- **Preclinical In Vivo Characterization of UCB0599, an Orally Available, Small Molecule Inhibitor of a-Synuclein Misfolding in Development for Parkinson's Disease.** Price D, Khan A, Angers R, Cardenas A, Key-Prato M, Citron M, Bonhaus D, Biere A
  S36/ Movement Disorders: clinical and pathologic characterization of neurodegenerative movement disorders

Poster presentations

The following is a guide to the UCB-sponsored poster presentations at the 74th American Academy of Neurology Annual Meeting:

<u>Brivaracetam</u>

- **12-month effectiveness and tolerability of brivaracetam in the real-world: interim analysis of the international, non-interventional EXPERIENCE study.** Villanueva V, D'Souza W, Faught E, Klein P, Reuber M, Rosenow F, Salas-Puig J, Strzelczyk A, Szaflarski J, Ricchetti-Masterson K, Laloyaux C, Sendersky V, Zhou S, Floricel F, Daniels T, Steinhoff B

- **Effectiveness and Tolerability of Brivaracetam by Reason for Initiation in Adults with Focal Seizures: Post-hoc Analysis of a Real-world, US Study.** Henninger H, Sperling MR, Altalib HH, Dave H, Gelfand M, Porter RJ, Martin MS, Elmoufti S, Schulz AL, Dongre P, French JA

- **Patient-reported Outcomes in Mood, Fatigue, Sleep Disturbance, and Disability While on Brivaracetam Treatment: a Prospective Observational Study.** Altalib HH, French JA, Sperling MR, Henninger H, Dave H, Gelfand M, Schulz AL, Elmoufti S, Dongre P, Martin MS

- **Time-course of Treatment-emergent Adverse Events Potentially Associated with Behavioral Disorders during Adjunctive Brivaracetam Treatment of Adults with Focal Seizures.** Meador KJ, Dimova S, Laloyaux C, Nondonfaz X, Floricel F, Elmoufti S, Klein P

- **Cognitive and Behavioral Effects and Tolerability of Adjunctive Brivaracetam in Children and Adolescents with Focal Seizures: Pooled Interim Analysis.** Elshoff JP, Fleyshman S, De La Loge C, Nondonfaz X, Reichel C, Floricel F, Smeyers P

Fenfluramine oral solution [Lennox Gastaut syndrome indication in the US only]

Fenfluramine Improves Everyday Executive Functioning in Patients With Lennox-Gastaut Syndrome: Analysis of Phase 3 Data

Bishop K, Isquith P, Giola G, Knupp K, Sullivan J, Nabbout R, Farfel G, Galer B, Gammaitoni A

Midazolam nasal spray [FDA approved only]

- **Early Intervention With Midazolam Nasal Spray and Efficacy in Patients With Seizure Clusters: Post-hoc Analysis of an Open-label Extension Trial.** Wheless JW, Brunnert M, Floricel F, Dimova S, Fannon B

Parkinson's disease

- **Outcome assessment in early-stage Parkinson's disease (PD) clinical trials: Are legacy patient-reported outcome (PRO) instruments 'fit for purpose'?** Morel T, Cleanthous S, Andrejack J, Barker RA, Blavat G, Boroojerdi B, Brooks W, Burns P, Cano S, Gallagher C, Gosden L, Siu C, Slagle AF, Trenam K, Ratcliffe N, Schroeder K

About BRIVIACT® (brivaracetam)

About BRIVIACT® (brivaracetam) CV in the U.S.[2]

- BRIVIACT was approved in the U.S. in 2016 as an add-on therapy for adult patients with partial-onset seizures. BRIVIACT was approved as monotherapy for adults in September 2017, and as monotherapy or adjunctive therapy in patients four years of age and older with partial-onset seizures in 2018. In August 2021, BRIVIACT was approved for the treatment of partial-onset seizures in patients as young as one month of age. BRIVIACT is available in three formulations: oral tablets, oral solution, and intravenous (IV) injection. More information is available at Drugs@FDA: FDA-Approved Drugs.

UCB News

BRIVIACT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Suicidal Behavior and Ideation:** Antiepileptic drugs, including BRIVIACT, increase the risk of suicidal behavior and ideation. Monitor patients taking BRIVIACT for the emergence or worsening of depression; unusual changes in mood or behavior; or suicidal thoughts, behavior, or self-harm. Advise patients, their caregivers, and/or families to be alert for these behavioral changes and report them immediately to a healthcare provider.
- **Neurological Adverse Reactions:** BRIVIACT causes somnolence, fatigue, dizziness, and disturbance in coordination. Monitor patients for these signs and symptoms and advise them not to drive or operate machinery until they have gained sufficient experience on BRIVIACT.
- **Psychiatric Adverse Reactions:** BRIVIACT causes psychiatric adverse reactions, including non-psychotic and psychotic symptoms in adult and pediatric patients. Advise patients to report these symptoms immediately to a healthcare provider.
- **Hypersensitivity:** BRIVIACT can cause hypersensitivity reactions. Bronchospasm and angioedema have been reported. Discontinue BRIVIACT if a patient develops a hypersensitivity reaction after treatment. BRIVIACT is contraindicated in patients with a prior hypersensitivity reaction to brivaracetam or any of the inactive ingredients.
- **Withdrawal of Antiepileptic Drugs:** As with all antiepileptic drugs, BRIVIACT should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus.

ADVERSE REACTIONS

In adult adjunctive therapy placebo-controlled clinical trials, the most common adverse reactions (at least 5% for BRIVIACT and at least 2% more frequently than placebo) were somnolence and sedation, dizziness, fatigue, and nausea and vomiting symptoms. Adverse reactions reported in clinical studies of pediatric patients were generally similar to those in adult patients. Adverse reactions with BRIVIACT injection in adult and pediatric patients were generally similar to those observed with BRIVIACT tablets. Other adverse events that occurred in adult patients who received BRIVIACT injection included dysgeusia, euphoric mood, feeling drunk, and infusion site pain.

BRIVIACT is a Schedule V controlled substance.

Please refer to the full US Prescribing Information and visit www.BRIVIACThcp.com.

Important Safety Information about BRIVIACT® in the EU and EEA[3]

BRIVIACT® (brivaracetam) is indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 2 years of age with epilepsy. **Contraindications** Hypersensitivity to the active substance, other pyrrolidone derivatives or any of the excipients. **Special warnings and precautions for use** Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic drugs (AEDs) in several indications, including BRIVIACT®. Patients should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and caregivers) should be advised to seek medical advice should any signs of suicidal ideation or behaviour emerge. BRIVIACT® film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take BRIVIACT®. Brivaracetam film-coated tablets, solution for injection/infusion and oral solution contain less than 1 mmol sodium (23mg) per tablet/vial/ml respectively, that is to say essentially 'sodium free'. The oral solution contains 168 mg sorbitol (E420) in each ml. Patients with hereditary fructose intolerance (HFI) should not take this medicinal product. The oral solution contains methyl parahydroxybenzoate (E218), which may cause allergic reactions (possibly delayed). Brivaracetam oral solution contains propylene glycol (E1520). **Posology** No dose adjustment is needed in adults with impaired renal function. Based on data in adults, no dose adjustment is necessary neither in paediatric patients with impaired renal function. No clinical data are available in paediatric patients with renal impairment. In patients with hepatic impairment, the following adjusted doses, administered in 2 divided doses, approximately 12 hours apart, are recommended for all stages of hepatic impairment: In adults, adolescents and children weighing ≥50 kg, a 50 mg/day starting dose is recommended, with a maximum daily dose of 150 mg/day. For adolescents and children weighing from 20 kg to <50 kg, a 1 mg/kg/day starting dose is recommended, with a maximum daily dose of 3 mg/kg/day. For children weighing from 10 kg to <20 kg, a 1 mg/kg/day starting dose is recommended, with a maximum daily dose of 4 mg/kg/day. No clinical data are available in paediatric patients with hepatic impairment.

Interaction with other medicinal products and other forms of interaction. With co-administration of BRIVIACT® 200 mg single dose and ethanol 0.6 g/L continuous infusion in healthy subjects there was no pharmacokinetic interaction, but the effect of alcohol on psychomotor function, attention and memory was doubled. Intake of BRIVIACT® with alcohol is not recommended. Limited clinical data are available implying that coadministration of cannabidiol may increase the plasma exposure of brivaracetam, possibly through CYP2C19 inhibition, but the clinical relevance is uncertain. In healthy subjects, co-administration with rifampicin, a strong enzyme-inducer (600 mg/day for 5 days), decreased BRIVIACT® area under the plasma concentration curve (AUC) by 45%. Prescribers should consider adjusting the dose of BRIVIACT® for patients starting or ending treatment with rifampicin. Other strong enzyme-inducers (such as St John´s wort [Hypericum perforatum]) may also decrease the systemic exposure of BRIVIACT®. Therefore, starting or ending treatment with St John's wort should be done with caution. *In vitro* studies have shown that brivaracetam exhibits little or no inhibition of CYP450 isoforms except for CYP2C19. Brivaracetam

may increase plasma concentrations of medicinal products metabolised by CYP2C19 (e.g., lansoprazole, omeprazole, diazepam). CYP2B6 induction has not been investigated in vivo and BRIVIACT® may decrease plasma concentrations of medicinal products metabolised by CYP2B6 (e.g. efavirenz). In vitro studies have also shown that BRIVIACT® has inhibitory effects on OAT3. BRIVIACT® 200 mg/day may increase plasma concentrations of medicinal products transported by OAT3. BRIVIACT® plasma concentrations are decreased when co-administered with strong enzyme inducing antiepileptic drugs (carbamazepine, phenobarbital, phenytoin) but no dose adjustment is required. **Effects on ability to drive and use machines** BRIVIACT®, has minor or moderate influence on the ability to drive and use machines. Patients should be advised not to drive a car or to operate other potentially hazardous machines until they are familiar with the effects of BRIVIACT®, on their ability to perform such activities. **Undesirable effects.** The most frequently reported adverse reactions with BRIVIACT® (reported by >10% of patients) were somnolence (14.3%) and dizziness (11.0%). They were usually mild to moderate in intensity. Somnolence and fatigue were reported at higher incidences with increasing dose. Very common adverse reactions (≥1% to <10%) were influenza, decreased appetite, depression, anxiety, insomnia, irritability, convulsion, vertigo, upper respiratory tract infections, cough, nausea, vomiting, constipation and fatigue. Neutropenia has been reported in 0.5% (6/1,099) BRIVIACT® patients and 0% (0/459) placebo-treated patients. Four of these patients had decreased neutrophil counts at baseline, and experienced additional decrease in neutrophil counts after initiation of BRIVIACT®. None of the six cases were severe, required any specific treatment, led to BRIVIACT® discontinuation or had associated infections. Suicidal ideation was reported in 0.3 % (3/1099) of BRIVIACT® treated patients and 0.7 % (3/459) of placebo-treated patients. In short-term clinical studies of BRIVIACT® in patients with epilepsy, there were no cases of completed suicide and suicide attempt, however both were reported in the long-term open-label extension studies. Reactions suggestive of immediate (Type I) hypersensitivity have been reported in a small number of BRIVIACT® patients (9/3022) during clinical development. The safety profile of brivaracetam observed in children from 1 month of age was consistent with the safety profile observed in adults. In the open label, uncontrolled, long-term studies suicidal ideation was reported in 4.7 % of paediatric patients assessed from 6 years onwards (more common in adolescents) compared with 2.4 % of adults and behavioural disorders were reported in 24.8 % of paediatric patients compared with 15.1 % of adults. The majority of events were mild or moderate in intensity, were non-serious, and did not lead to discontinuation of study drug. An additional adverse reaction reported in children was psychomotor hyperactivity (4.7 %). No specific pattern of adverse event (AE) was identified in children from 1 month to < 4 years of age when compared to older paediatric age groups. No significant safety information was identified indicating the increasing incidence of a particular AE in this age group. As data available in children younger than 2 years of age are limited, brivaracetam is not indicated in this age range. No clinical data are available in neonates. **Overdose** There is limited clinical experience with BRIVIACT® overdose in humans. Somnolence and dizziness were reported in a healthy subject taking a single dose of 1,400 mg of BRIVIACT®. The following adverse reactions were reported with brivaracetam overdose: nausea, vertigo, balance disorder, anxiety, fatigue, irritability, aggression, insomnia, depression, and suicidal ideation in the post-marketing experience. In general, the adverse reactions associated with brivaracetam overdose were consistent with the known adverse reactions. There is no specific antidote. Treatment of an overdose should include general supportive measures. Since less than

10% of BRIVIACT® is excreted in urine, haemodialysis is not expected to significantly enhance BRIVIACT® clearance.

Refer to the European Summary of Product Characteristics for other adverse reactions and full prescribing information. Date of revision: 24 February 2022

http://www.ema.europa.eu/

About FINTEPLA® (fenfluramine)

Important Safety Information about FINTEPLA® (fenfluramine) oral solution, CIV in the US[1]

INDICATIONS AND USAGE

FINTEPLA is indicated for the treatment of seizures associated with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) in patients 2 years of age and older.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: VALVULAR HEART DISEASE and PULMONARY ARTERIAL HYPERTENSION

- **There is an association between serotonergic drugs with 5-HT2B receptor agonist activity, including fenfluramine (the active ingredient in FINTEPLA), and valvular heart disease and pulmonary arterial hypertension.**
- **Echocardiogram assessments are required before, during, and after treatment with FINTEPLA.**
- **FINTEPLA is available only through a restricted program called the FINTEPLA REMS.**

CONTRAINDICATIONS

FINTEPLA is contraindicated in patients with hypersensitivity to fenfluramine or any of the excipients in FINTEPLA and with concomitant use, or within 14 days of the administration of monoamine oxidase inhibitors because of an increased risk of serotonin syndrome.

WARNINGS AND PRECAUTIONS

Valvular Heart Disease and Pulmonary Arterial Hypertension (see Boxed Warning): Because of the association between serotonergic drugs with 5-HT2B receptor agonist activity, including fenfluramine (the active ingredient in FINTEPLA), and valvular heart disease (VHD) and pulmonary arterial hypertension (PAH), cardiac monitoring via echocardiogram is required prior to starting treatment, during treatment, and after treatment with FINTEPLA concludes. Cardiac

monitoring via echocardiogram can aid in early detection of these conditions. In clinical trials for DS and LGS of up to 3 years in duration, no patient receiving FINTEPLA developed VHD or PAH.

Monitoring: Prior to starting treatment, patients must undergo an echocardiogram to evaluate for VHD and PAH. Echocardiograms should be repeated every 6 months, and once at 3-6 months post treatment with FINTEPLA.

The prescriber must consider the benefits versus the risks of initiating or continuing treatment with FINTEPLA if any of the following signs are observed via echocardiogram: valvular abnormality or new abnormality; VHD indicated by mild or greater aortic regurgitation or moderate or greater mitral regurgitation, with additional characteristics of VHD (eg, valve thickening or restrictive valve motion); PAH indicated by elevated right heart/pulmonary artery pressure (PASP >35mmHg).

FINTEPLA REMS Program (see Boxed Warning): FINTEPLA is available only through a restricted distribution program called the FINTEPLA Risk Evaluation and Mitigation Strategy (REMS) Program. Prescribers must be certified by enrolling in the FINTEPLA REMS. Prescribers must counsel patients receiving FINTEPLA about the risk of valvular heart disease and pulmonary arterial hypertension, how to recognize signs and symptoms of valvular heart disease and pulmonary arterial hypertension, the need for baseline (pretreatment) and periodic cardiac monitoring via echocardiogram during FINTEPLA treatment, and cardiac monitoring after FINTEPLA treatment. Patients must enroll in the FINTEPLA REMS and comply with ongoing monitoring requirements. The pharmacy must be certified by enrolling in the FINTEPLA REMS and must only dispense to patients who are authorized to receive FINTEPLA. Wholesalers and distributors must only distribute to certified pharmacies. Further information is available at www.FinteplaREMS.com or by telephone at 1-877-964-3649.

Decreased Appetite and Decreased Weight: FINTEPLA can cause decreases in appetite and weight. Decreases in weight appear to be dose related. Approximately half of the patients with LGS and most patients with DS resumed the expected measured increases in weight during the open-label extension studies. Weight should be monitored regularly during treatment with FINTEPLA, and dose modifications should be considered if a decrease in weight is observed.

Somnolence, Sedation, and Lethargy: FINTEPLA can cause somnolence, sedation, and lethargy. Other central nervous system (CNS) depressants, including alcohol, could potentiate these effects of FINTEPLA. Prescribers should monitor patients for somnolence and sedation and should advise patients not to drive or operate machinery until they have gained sufficient experience on FINTEPLA to gauge whether it adversely affects their ability to drive or operate machinery.

Suicidal Behavior and Ideation: Antiepileptic drugs (AEDs), including FINTEPLA, increase the risk of suicidal thoughts or behaviors in patients taking these drugs for any indication. Patients treated with an AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviors, or any unusual changes in mood or behavior.

Anyone considering prescribing FINTEPLA or any other AED must balance the risk of suicidal thoughts or behaviors with the risks of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviors. Should suicidal thoughts and behaviors emerge during treatment,

consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Withdrawal of Antiepileptic Drugs: As with most AEDs, FINTEPLA should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus. If withdrawal is needed because of a serious adverse reaction, rapid discontinuation can be considered.

Serotonin Syndrome: Serotonin syndrome, a potentially life-threatening condition, may occur with FINTEPLA, particularly during concomitant administration of FINTEPLA with other serotonergic drugs, including, but not limited to, selective serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), bupropion, triptans, dietary supplements (eg, St. John's Wort, tryptophan), drugs that impair metabolism of serotonin (including monoamine oxidase inhibitors [MAOIs], which are contraindicated with FINTEPLA), dextromethorphan, lithium, tramadol, and antipsychotics with serotonergic agonist activity. Patients should be monitored for the emergence of signs and symptoms of serotonin syndrome, which include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular signs (eg, hyperreflexia, incoordination), and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). If serotonin syndrome is suspected, treatment with FINTEPLA should be stopped immediately and symptomatic treatment should be started.

Increase in Blood Pressure: FINTEPLA can cause an increase in blood pressure. Rare cases of significant elevation in blood pressure, including hypertensive crisis, has been reported in adult patients treated with fenfluramine, including patients without a history of hypertension. In clinical trials for DS and LGS of up to 3 years in duration, no pediatric or adult patient receiving FINTEPLA developed hypertensive crisis. Monitor blood pressure in patients treated with FINTEPLA.

Glaucoma: 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.

ADVERSE REACTIONS

The most common adverse reactions observed in DS studies (incidence at least 10% and greater than placebo) were decreased appetite; somnolence, sedation, lethargy; diarrhea; constipation; abnormal echocardiogram; fatigue, malaise, asthenia; ataxia, balance disorder, gait disturbance; blood pressure increased; drooling, salivary hypersecretion; pyrexia; upper respiratory tract infection; vomiting; decreased weight; fall; status epilepticus.

The most common adverse reactions observed in the LGS study (incidence at least 10% and greater than placebo) were diarrhea; decreased appetite; fatigue; somnolence; vomiting.

DRUG INTERACTIONS

Strong CYP1A2, CYP2B6, or CYP3A Inducers: Coadministration with strong CYP1A2, CYP2B6, or CYP3A inducers will decrease fenfluramine plasma concentrations. If coadministration of a strong CYP1A2, CYP2B6, or CYP3A inducer with FINTEPLA is necessary, monitor the patient for reduced efficacy and consider increasing the dosage of FINTEPLA as needed. If a strong CYP1A2, CYP2B6, or CYP3A inducer is discontinued during maintenance treatment with FINTEPLA, consider gradual reduction in the FINTEPLA dosage to the dose administered prior to initiating the inducer.

Strong CYP1A2 or CYP2D6 Inhibitors: Coadministration with strong CYP1A2 or CYP2D6 inhibitors will increase fenfluramine plasma concentrations. If FINTEPLA is coadministered with strong CYP1A2 or CYP2D6 inhibitors, the maximum daily dosage of FINTEPLA is 20 mg. If a strong CYP1A2 or CYP2D6 inhibitor is discontinued during maintenance treatment with FINTEPLA, consider gradual increase in the FINTEPLA dosage to the dose recommended without CYP1A2 or CYP2D6 inhibitors. If FINTEPLA is coadministered with stiripentol and a strong CYP1A2 or CYP2D6 inhibitor, the maximum daily dosage of FINTEPLA is 17 mg.

USE IN SPECIFIC POPULATIONS

Administration to patients with hepatic impairment is not recommended.

To report SUSPECTED ADVERSE REACTIONS, contact Zogenix Inc. at 1-866-964-3649 (1-866-Zogenix) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see full Prescribing Information, including Boxed Warning, for additional important information on FINTEPLA.

Important Safety Information about FINTEPLA® ▼ in the EU and EEA[4]

Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6.1. Aortic or mitral valvular heart disease. Pulmonary arterial hypertension. 4 Within 14 days of the administration of monoamine oxidase inhibitors due to an increased risk of serotonin syndrome

Special warnings and precautions for use

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 (see section 4.3) 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 (see section 4.8). 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 (see sections 4.5 and 4.7).

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 (see sections 4.3 and 4.5).

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 (see section 4.5).

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.

Refer to the European Summary of Product Characteristics for other adverse reactions and full prescribing information. Date of revision: 04 Nov 2021.

https://www.ema.europa.eu/en/documents/product-information/fintepla-epar-product-information_en.pdf

▼ *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.*

About NAYZILAM® (midazolam) nasal spray, CIV in the U.S.[5]

NAYZILAM is a benzodiazepine indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 12 years of age and older.

NAYZILAM IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

NAYZILAM is contraindicated in patients with acute narrow-angle glaucoma.

RISKS FROM CONCOMITANT USE WITH OPIOIDS

Concomitant use of benzodiazepines, including NAYZILAM, and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for patients for whom alternative treatment options are

inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.

ABUSE, MISUSE, AND ADDICTION

The use of benzodiazepines, including NAYZILAM, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes. Before prescribing NAYZILAM and throughout treatment, assess each patient's risk for abuse, misuse, and addiction.

DEPENDENCE AND WITHDRAWAL REACTIONS AFTER USE OF NAYZILAM MORE FREQUENTLY THAN RECOMMENDED

The continued use of benzodiazepines may lead to clinically significant physical dependence. The risks of dependence and withdrawal increase with longer treatment duration and higher daily dose. Although NAYZILAM is indicated only for intermittent use, if used more frequently than recommended, abrupt discontinuation or rapid dosage reduction of NAYZILAM may precipitate acute withdrawal reactions, which can be life-threatening. For patients using NAYZILAM more frequently than recommended, to reduce the risk of withdrawal reactions, use a gradual taper to discontinue NAYZILAM.

Risks of Cardiorespiratory Adverse Reactions

Serious cardiorespiratory adverse reactions have occurred after administration of midazolam. Warn patients and caregivers about the risks of respiratory depression, cardiac and respiratory arrest.

Respiratory depression was observed with the administration of NAYZILAM during clinical trials. Cardiac or respiratory arrest caused by NAYZILAM was not reported during clinical trials.

Central Nervous System Depression from Concomitant Use with Other Central Nervous System Depressants, or Moderate or Strong CYP3A4 Inhibitors

Drug products containing midazolam, including NAYZILAM, have a central nervous system (CNS) depressant effect.

Risks from Concomitant Use with Other CNS Depressants

NAYZILAM may cause an increased CNS-depressant effect when used with alcohol or other CNS depressants (e.g., opioids). Warn patients and caregivers that the use of NAYZILAM in combination with alcohol or other CNS depressant drugs may increase the risk of hypoventilation, airway obstruction, desaturation, or apnea and may contribute to profound and/or prolonged drug effect.

Risks from Concomitant Use with Moderate or Strong CYP3A4 Inhibitors

Concomitant use of NAYZILAM with moderate or strong CYP3A4 enzyme inhibitors may result in prolonged sedation because of a decrease in plasma clearance of midazolam. Caution patients against engaging in hazardous occupations requiring mental alertness, such as operating machinery, driving a motor vehicle or riding a bicycle until they have completely returned to their level of baseline functioning.

Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including NAYZILAM, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Monitor patients treated with NAYZILAM for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Advise patients and caregivers to be alert for these behavioral changes and to immediately report them to the healthcare provider.

Impaired Cognitive Function

Midazolam, including NAYZILAM, is associated with a high incidence of partial or complete impairment of recall for several hours following an administered dose. Counsel patients on when they can engage in activities requiring complete mental alertness, operate hazardous machinery, or drive a motor vehicle after taking NAYZILAM.

Glaucoma

Benzodiazepines, including NAYZILAM, can increase intraocular pressure in patients with glaucoma. NAYZILAM may be used in patients with open-angle glaucoma only if they are receiving appropriate therapy. NAYZILAM is contraindicated in patients with narrow-angle glaucoma.

ADVERSE REACTIONS

In the randomized, double-blind, placebo-controlled trial, the most common adverse reactions (≥5% in any NAYZILAM treatment group) were somnolence, headache, nasal discomfort, throat irritation, and rhinorrhea.

NAYZILAM is a Schedule IV controlled substance.

Please refer to the full Prescribing Information.

For additional medical information about NAYZILAM, patient assistance, or any other information please visit our website or call UCBCares® at 1-844-599-2273.

About UCB0599

UCB0599 is an orally administered, brain penetrant, small molecule inhibitor of ASYN misfolding under investigation for the potential use as a disease-modifying treatment to slow the progression of PD.[6,7] UCB0599 was discovered by NeuroPore and was licenced to UCB in 2014 for further development.[6] In 2021, UCB entered into a global co-development and co-commercialization agreement with Novartis covering UCB0599.[8]

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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.

Forward looking statements UCB

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 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, 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 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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