UCB News

UCB to present data at the American Epilepsy Society 76th Annual Meeting 2022 supporting a decades-long commitment to transforming epilepsy care

- 21 scientific presentations, including 7 late breakers, showcase the breadth of UCB's portfolio, reinforcing commitment to improving the lives of people living with epilepsy
- New data include insights into the efficacy and safety profile of BRIVIACT® (brivaracetam) CV, FINTEPLA® (fenfluramine) CIV, and VIMPAT® (lacosamide) CV as well as into the utilization of NAYZILAM® (midazolam) nasal spray CIV
- Studies include focus on the treatment of epileptic seizures in real-world settings, elderly and pediatric patients, health equity, and behavior and cognition in rare epilepsy syndromes

Brussels (Belgium) - December 1, 2022, 07:00 a.m. (CET): – UCB, a global biopharmaceutical company, today announced that data from its anti-seizure medication portfolio (brivaracetam, fenfluramine, lacosamide, and midazolam nasal spray) will be presented at the 76th American Epilepsy Society (AES) Annual Meeting (Nashville, Tennessee), December 2-6.

"UCB has been at the forefront of epilepsy research for over three decades and we look forward to continuing to advance the science and understanding of the epilepsies, particularly rare epilepsies and those with high unmet needs," said Konrad Werhahn, MD PhD, Global Epilepsy Medical Affairs at UCB. "The data presented this year at the American Epilepsy Society annual meeting continue to further reinforce our commitment to redefining the future of epilepsy care, designing meaningful, patient-focused treatment outcomes for people impacted by epileptic seizures."

Data highlights

Key data being presented at AES include a wealth of insights from the international EXPERIENCE study assessing brivaracetam effectiveness and tolerability in multiple sub-populations, including pediatrics and the elderly with focal seizures, as well as the efficacy and safety of fenfluramine on seizures for those living with Dravet and/or Lennox-Gastaut syndromes, and its impact on non-seizure parameters, including everyday executive functioning. Presented data featured in the company's scientific exhibit, "UCB: Leading with science for epilepsy and rare epilepsy syndromes" (December 5, 9:00 a.m. – 12:00 p.m. ET, in 207 A/B, Floor 2, Music City Center), provides attending healthcare professionals an opportunity to engage in discussions around UCB's epilepsy research, real-world updates and latest clinical data.

Symposium focus on key issues of real-world evidence and health equity

Complementary to the poster presentations, UCB will facilitate two satellite symposia for registered delegates at AES.

Inspired by patients.
Driven by science.

GL-N-BR-EPOS-2200014
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- Building on our commitment to taking action to bridge gaps and facilitate healthy equity, the first symposium – entitled "Exploring Health Disparities, Inequities, and Barriers to Care for Black Patients Living with Epilepsy" (December 2, 7:00 – 9:30 p.m. ET, Davidson Ballroom A, Floor 1M, Music City Center) – will discuss the opportunities to move toward solutions to provide more equitable care, enhance patient-provider communication, address medical mistrust, and improve outcomes for Black people living with epilepsy.
- The second symposium – entitled "How Does Clinical Experience Become Real-World Evidence? Expert Perspectives on BRIVIACT® (brivaracetam) CV Long-Term Treatment Outcomes" (December 4, 7:00 – 9:00 p.m. ET, Davidson Ballroom A, Floor 1M, Music City Center) – will focus on the need for and challenges with delivering high-quality real-world evidence, exploring the link between clinical evidence and real-world experience.

Brad Chapman, Head of U.S. Epilepsy & Rare Syndromes at UCB, comments: "As UCB continues to expand our portfolio of medicines for epilepsy, rare epilepsy syndromes, and seizure rescue, we are committed to building trust with communities by continuing to listen, learn, and evolve in how we care for and find solutions for patients."

Poster presentations
The following is a guide to the UCB-sponsored poster presentations at the 76th American Epilepsy Society (AES 2022) Annual Meeting:

Brivaracetam Posters

- **Treatment Outcomes During Brivaracetam Treatment by Seizure Freedom Status: Post hoc Analysis of a Real-world, US Study.** Hina Dave et al. December 3, 2022, 12:00 PM - 2:00 PM. Poster Session Number: 1.309

- **12-Month Effectiveness and Tolerability of Brivaracetam by Number of Prior Antiseizure Medications and Mono vs Polytherapy: Subgroup Data From International EXPERIENCE Pooled Analysis.** Cédric Laloyaux et al. December 3, 2022, 12:00 PM - 2:00 PM. Poster Session Number: 1.300

- **12-Month Effectiveness and Tolerability of Brivaracetam in Patients With Epilepsy Aged ≥65 years Vs ≥16–<65 years in the Real-World: Subgroup Data From the International EXPERIENCE Pooled Analysis.** Edward Faught et al. December 3, 2022, 12:00 PM - 2:00 PM. Poster Session Number: 1.299

- **12-Month Effectiveness and Tolerability of Brivaracetam in the Real-World: The International EXPERIENCE Pooled Analysis.** Vicente Villanueva et al. December 3, 2022, 12:00 PM - 2:00 PM. Poster Session Number: 1.298

- **12-Month Effectiveness and Tolerability of Brivaracetam in Pediatric Patients in the Real-World: Subgroup Data From the EXPERIENCE Analysis.** Victor Soto Insuga et al. December 3, 2022, 12:00 PM - 2:00 PM. Poster Session Number: 1.301

- **Cognitive and Behavioral Effects of Adjunctive Brivaracetam in Children and Adolescents with Focal Seizures: Final Data From an Open-label Follow-up Trial.** Jan-Peer Elshoff et al. December 5, 2022, 12:00 PM - 1:45 PM. Poster Session Number: 3.284

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- **Long-term Safety and Efficacy of Adjunctive Brivaracetam in Pediatric Patients with Epilepsy: An Open-label, Follow-up Trial.** Kerstin Alexandra Klotz et al. December 3, 2022, 12:00 PM - 2:00 PM. Poster Session Number: 1.284

- **Effectiveness and Tolerability of Brivaracetam by Number of Lifetime Antiseizure Medications in Adults with Focal Onset Seizures: Pooled Data From Two Real-world Studies.** Melinda S Martin et al. December 3, 2022, 12:00 PM - 2:00 PM. Poster Session Number: 1.305

- **Effectiveness and Tolerability of Brivaracetam in Patients Aged <65 and ≥65 Years With Focal Onset Seizures: Pooled Data From Two Real-world Studies.** Allison Little et al. December 3, 2022, 12:00 PM - 2:00 PM. Poster Session Number: 1.308

- **Real-world Outcomes in Patients on Concomitant Levetiracetam at Brivaracetam Initiation: Post Hoc Analysis by Levetiracetam Discontinuation Status.** Michael A. Gelfand et al. December 5, 2022, 12:00 PM - 1:45 PM. Poster Session Number: 3.304

Fenfluramine Posters

- **Fenfluramine Treatment Is Associated With Improvement in Everyday Executive Function in Adults With Lennox-Gastaut Syndrome: Post-Hoc Analysis of Dose Effects From a Phase 3 Trial Rationale.** Kim I. Bishop et al. December 5, 2022, 12:00 PM - 1:45 PM. Poster Session Number: 3.411

- **Interim Safety Analysis of an Ongoing Open-Label Extension Study of Fenfluramine for Dravet Syndrome.** Ingrid Scheffer et al. December 5, 2022, 12:00 PM - 1:45 PM. Poster Session Number: 3.412

- **Effect of Fenfluramine on Generalized Tonic-Clonic Seizures in Developmental and Epileptic Encephalopathies: A Review of Published Studies.** J Helen Cross et al. December 5, 2022, 12:00 PM - 1:45 PM. Poster Session Number: 3.416

- **Real-World Analysis of Fenfluramine Discontinuation Rates in Dravet Syndrome and Lennox-Gastaut Syndrome.** Shikha Polega et al. December 5, 2022, 12:00 PM - 1:45 PM. Poster Session Number: 3.417

- **Impact of Fenfluramine in Patients With Lennox-Gastaut Syndrome: Subgroup Analysis of Dose-Capping on Drop Seizure Frequency Reduction in the Open-Label Extension Data.** Kelly G. Knupp et al. December 5, 2022, 12:00 PM - 1:45 PM. Poster Session Number: 3.418

- **Time-to-Event Analysis to Measure Treatment Effect of Fenfluramine Therapy: Pooled Analysis of Two Phase 3 Studies in Dravet Syndrome.** Joseph Sullivan et al. December 4, 2022, 12:00 PM – 2:00 PM. Poster Session Number: 2.434

- **Balancing seizure management with broader needs in the Dravet Syndrome patient: a qualitative study of the lived experience of patients and families.** Judith Luker et al. December 4, 2022, 12:00 PM – 2:00 PM. Poster Session Number: 2.466

Lacosamide Posters

- **Pharmacokinetics, Safety, and Tolerability of Lacosamide in Neonates with Seizures: Interim Analysis of a Phase 2/3, Open-label, Randomized, Active Comparator Trial.** Anuj Jayakar et al. December 4, 2022, 12:00 PM – 2:00 PM. Poster Session Number: 2.477

Midazolam nasal spray [FDA Approved Only] Posters

- **Baseline Characteristics and Antiseizure Medication Use of Patients with Epilepsy in the Year Prior to Initiating Midazolam Nasal Spray, Diazepam Rectal Gel, or Diazepam Nasal Spray.** Angela Ting et al. December 4, 2022, 12:00 PM – 2:00 PM. Poster Session Number: 2.253

General Epilepsy Posters

- **Development of a Self-Management Intervention for People with New-Onset Seizures and Epilepsy using Patient Activation Theory and the Adult Epilepsy Self-Management Measurement Instrument**. Wendy R. Trueblood Miller et al. December 4, 2022, 12:00 PM – 2:00 PM. Poster Session Number: 2.358

- **Epilepsy Management in US Nursing Homes**. Ilo E. Leppik et al. December 3, 2022, 12:00 PM – 2:00 PM. Poster Session Number: 1.223

About Epilepsy[1-3]

Epilepsy is a common neurological condition worldwide and affects approximately 50 million people.[1] Epilepsy and seizures can develop in any person at any age,[2] and is usually diagnosed after a person has had at least two seizures (or after one seizure with a high risk for more) that were not caused by some known medical condition.[3]

About UCB in Epilepsy

UCB has a rich heritage in epilepsy with thirty years of experience in the research and development of anti-seizure medications. As a company with a long-term commitment to epilepsy research, our goal is to address unmet medical needs. Our scientists are proud to contribute to advances in the understanding of epilepsy and its treatment. We partner and create super-networks with world-leading scientists and clinicians in academic institutions, pharmaceutical companies, and other organizations who share our goals. At UCB, we are inspired by patients, and driven by science in our commitment to support patients with epilepsy.

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

GL-N-BR-EPOS-2200014
Date of preparation: November 2022

About BRIVIACT® (brivaracetam)

Important Safety Information about BRIVIACT® in the EU[4]

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**

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

About BRIVIACT® (brivaracetam) CV in the U.S.[5]
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.

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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 Prescribing Information and visit www.BRIVIACThcp.com.

About FINTEPLA® (fenfluramine) C-IV[6]
FINTEPLA® (fenfluramine) oral solution is a prescription medication approved in the US for the treatment of seizures associated with Dravet syndrome in patients two years of age and older. FINTEPLA is also approved in the U.S. for the treatment of seizures associated with Lennox-Gastaut syndrome in patients two years of age and older.

In the United States, FINTEPLA is available only through a restricted distribution program called the FINTEPLA REMS program. FINTEPLA is available in Europe under a controlled access program requested by the EMA to prevent off-label use for weight management and to confirm that prescribing physicians have been informed

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of the need for periodic cardiac monitoring in patients taking FINTEPLA. Further information is available at www.FinteplaREMS.com or by telephone at +1 877 964 3649.

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

Key Safety Information about FINTEPLA in the U.S.

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, 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

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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,

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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 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

Stiripentol Plus Clobazam: Coadministration of FINTEPLA with stiripentol plus clobazam, with or without valproate, increases fenfluramine plasma concentrations. If FINTEPLA is coadministered with stiripentol plus clobazam, the maximum daily dosage of FINTEPLA is 0.2 mg/kg twice daily (maximum daily dosage of 17 mg).

Strong CYP1A2, CYP2B6, or CYP3A Inducers: Coadministration of FINTEPLA with strong CYP1A2, CYP2B6, or CYP3A inducers will decrease fenfluramine plasma concentrations, which may lower the efficacy of FINTEPLA. It is recommended to avoid coadministration of strong CYP1A2, CYP2B6 or CYP3A inducers. 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; however, do not exceed the maximum daily dosage of FINTEPLA. 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 of FINTEPLA 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; however, do not exceed the maximum daily dosage of FINTEPLA. If FINTEPLA is coadministered with stiripentol and a strong CYP1A2 or CYP2D6 inhibitor, do not exceed the maximum daily dosage of FINTEPLA of 17 mg.

USE IN SPECIFIC POPULATIONS

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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.

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

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

GL-N-BR-EPOS-2200014
Date of preparation: November 2022

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.

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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.

Refer to the European Summary of Product Characteristics for other adverse reactions and full prescribing information.

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 VIMPAT® (lacosamide)

Important Safety Information about VIMPAT® in the EU and EEA[8]

VIMPAT® is indicated as monotherapy in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 2 years of age with epilepsy. VIMPAT® 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 and in the treatment of primary generalised tonic-clonic seizures in adults, adolescents and children from 4 years of age with idiopathic generalised epilepsy. Lacosamide therapy can be initiated with either oral administration (either tablets or syrup) or IV administration (solution for infusion). The physician should prescribe the most appropriate formulation and strength according to weight and dose. A loading dose may be initiated in patients in situations when the physician determines that rapid attainment of lacosamide steady state plasma concentration and therapeutic effect is warranted. It should be administered under medical supervision with consideration of the potential for increased incidence of serious cardiac arrhythmia and Central Nervous System (CNS) adverse reactions. Administration of a loading dose has not been studied in acute conditions such as status epilepticus. Administration of a loading dose has not been studied in children. Use of a loading dose is not recommended in adolescents and children weighing less than 50 kg. No dose adjustment is necessary in mildly and moderately renally impaired adult and paediatric patients (CLCR > 30 ml/min). In paediatric patients weighing 50 kg or more and in adult patients with mild or moderate

renal impairment, a loading dose of 200 mg may be considered, but further dose titration (>200 mg daily) should be performed with caution. In paediatric patients weighing 50 kg or more and in adult patients with severe renal impairment (CLCR ≤ 30 ml/min) or with end-stage renal disease, a maximum dose of 250 mg/day is recommended and the dose titration should be performed with caution. In paediatric patients weighing less than 50 kg with severe renal impairment (CLCR ≤ 30 ml/min) and in those with end-stage renal disease, a reduction of 25 % of the maximum dose is recommended. A maximum dose of 300 mg/day is recommended for paediatric patients weighing 50 kg or more and for adult patients with mild to moderate hepatic impairment. Based on data in adults, in paediatric patients weighing less than 50 kg with mild to moderate hepatic impairment, a reduction of 25 % of the maximum dose should be applied. Lacosamide should be administered to adult and paediatric patients with severe hepatic impairment only when the expected therapeutic benefits are anticipated to outweigh the possible risks. The dose may need to be adjusted while carefully observing disease activity and potential side effects in the patient. In adolescents and adults weighing 50 kg or more with mild to moderate hepatic impairment a loading dose of 200mg may be considered, but further dose titration (>200 mg daily) should be performed with caution. Lacosamide is not recommended for use in children below the age of 4 years in the treatment of primary generalized tonic-clonic seizures and below the age of 2 years in the treatment of partial-onset seizures as there are limited data on safety and efficacy in these age groups. Contraindications: Hypersensitivity to the active substance or any of the excipients; known second- or third-degree atrioventricular (AV) block. Special warnings and precautions for use: Suicidal ideation and behaviour have been reported in patients treated with antiepileptic medicinal products in several indications. Therefore, patients should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge. Dose-related prolongations in PR interval with lacosamide have been observed in clinical studies. Lacosamide should be used with caution in patients with underlying proarrhythmic conditions such as known cardiac conduction problems or severe cardiac diseases (e.g. myocardial ischaemia/infarction, heart failure, structural heart disease or cardiac sodium channelopathies) or patients treated with medicinal products affecting cardiac conduction, including antiarrhythmics and sodium channel blocking antiepileptic medicinal products, as well as in elderly patients. In these patients it should be considered to perform an electrocardiogram (ECG) before a lacosamide dose increase above 400mg/day and after lacosamide is titrated to steady-state. In the placebo-controlled clinical studies of lacosamide in epilepsy patients, atrial fibrillation or flutter were not reported; however both have been reported in open-label epilepsy studies and in post-marketing experience. In post-marketing experience, AV block (including second degree or higher AV block) has been reported. In patients with proarrhythmic conditions, ventricular tachyarrhythmia has been reported. In rare cases, these events have led to asystole, cardiac arrest and death in patients with underlying proarrhythmic conditions. Patients should be made aware of the symptoms of cardiac arrhythmia (e.g. slow, rapid or irregular pulse, palpitations, shortness of breath, feeling lightheaded, fainting). Patients should be counselled to seek immediate medical advice if these symptoms occur. Treatment with lacosamide has been associated with dizziness which could increase the occurrence of accidental injury or falls. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicine. New onset or worsening of myoclonic seizures has been reported in both adult and paediatric patients with primary generalized tonic-clonic seizures (PGTCS), in particular during titration. In patients with more than one seizure type, the observed benefit of control for one seizure type should be weighed against any observed worsening in another seizure type. The safety and efficacy of lacosamide in paediatric patients with epilepsy syndromes in which focal and generalised seizures may coexist have not been determined. VIMPAT® syrup contains sodium methyl parahydroxybenzoate (E219) which may cause allergic reactions (possibly delayed). Vimpat Syrup contains sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take this medicine. Sorbitol may cause gastrointestinal discomfort and mild laxative effect. The syrup contains aspartame

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(E951), a source of phenylalanine, which may be harmful for people with phenylketonuria. Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age. Vimpat syrup contains propylene glycol (E1520). VIMPAT® syrup contains 1.42 mg sodium per ml, equivalent to 0.07 % of the WHO recommended maximum daily intake of 2 g sodium for an adult. VIMPAT® solution for infusion contains 59.8 mg sodium per vial, equivalent to 3% of the WHO recommended maximum daily intake of 2 g sodium for an adult. Effects on ability to drive and use machines: Lacosamide may have minor to moderate influence on the ability to drive and use machines. Lacosamide treatment has been associated with dizziness or blurred vision. Accordingly, patients should be advised not to drive a car or to operate other potentially hazardous machinery until they are familiar with the effects of lacosamide on their ability to perform such activities. Undesirable effects: The most frequently reported adverse reactions (≥10%) are dizziness, headache, nausea and diplopia. They were usually mild to moderate in intensity. Some were dose-related and could be alleviated by reducing the dose. Incidence and severity of CNS and gastrointestinal (GI) adverse reactions usually decreased over time. Incidence of CNS adverse reactions such as dizziness may be higher after a loading dose. Other common adverse reactions (≥1% - <10%) are depression, confusional state, insomnia, balance disorder, myoclonic seizures, ataxia, memory impairment, cognitive disorder, somnolence, tremor, nystagmus, hypoesthesia, dysarthria, disturbance in attention, paraesthesia, vision blurred, vertigo, tinnitus, vomiting, constipation, flatulence, dyspepsia, dry mouth, diarrhoea, pruritus, rash, muscle spasms, gait disturbance, asthenia, fatigue, irritability, feeling drunk, injection site pain or discomfort (local adverse events associated with intravenous administration), irritation (local adverse events associated with intravenous administration), fall, and skin laceration and contusion. The use of lacosamide is associated with dose-related increase in the PR interval. Adverse reactions associated with PR interval prolongation (e.g. atrioventricular block, syncope, bradycardia) may occur. Multiorgan Hypersensitivity Reactions: Multiorgan hypersensitivity reactions (also known as Drug Reaction with Eosinophilia and Systemic Symptoms, DRESS) have been reported in patients treated with some antiepileptic medicinal products. These reactions are variable in expression but typically present with fever and rash and can be associated with involvement of different organ systems. If multiorgan hypersensitivity reaction is suspected, lacosamide should be discontinued. The safety profile of lacosamide in adjunctive therapy in paediatric patients with partial- onset seizures was consistent with the safety profile observed in adults. The additional adverse reactions observed in the paediatric population were pyrexia, nasopharyngitis, pharyngitis, decreased appetite, abnormal behaviour and lethargy. Somnolence was reported more frequently in the paediatric population (≥ 1/10) compared to the adult population (≥ 1/100 to < 1/10).Refer to the European Summary of Product Characteristics for other adverse reactions and full prescribing information. Date of revision: October 2022. https://www.ema.europa.eu/en/documents/product-information/vimpat-epar-product-information_en.pdf

About VIMPAT (lacosamide) CV in the U.S[9]

VIMPAT® was approved in the U.S. in 2008 as an add-on therapy for the treatment of partial-onset seizures in adult patients with epilepsy. VIMPAT was approved as monotherapy for adults in August 2014, and as monotherapy or adjunctive therapy in patients four years of age and older with partial-onset seizures in 2017. In 2020, it was approved adjunctive therapy in the treatment of primary generalized tonic-clonic seizures (PGTCS) in patients four years of age and older and VIMPAT injection for intravenous use in children four years of age and older. In October 2021, VIMPAT received an expanded indication to treat partial-onset seizures in patients as young as one month of age. VIMPAT is available in three formulations: oral tablets, oral solution, and intravenous (IV) injection.

VIMPAT IMPORTANT SAFETY INFORMATION

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Date of preparation: November 2022

VIMPAT® is indicated for the treatment of partial-onset seizures in patients 1 month of age and older. VIMPAT is indicated as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in patients 4 years of age and older.

VIMPAT is associated with important warnings and precautions including suicidal behavior and ideation, dizziness and ataxia, cardiac rhythm and conduction abnormalities, syncope, and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multi-organ hypersensitivity.

Partial-Onset Seizures
In the adult adjunctive placebo-controlled trials for partial-onset seizures, the most common adverse reactions (≥10% and greater than placebo) were dizziness, headache, nausea, and diplopia. In the adult monotherapy clinical trial, adverse reactions were generally similar to those observed and attributed to drug in adjunctive placebo-controlled trials, with the exception of insomnia (observed at a higher rate of ≥2%).

Primary Generalized Tonic-Clonic Seizures
In the adjunctive therapy placebo-controlled trial for primary generalized tonic-clonic seizures, the adverse reactions were generally similar to those that occurred in the partial-onset seizures trials. The adverse reactions most commonly reported were dizziness, somnolence, headache, and nausea.

Pediatric Patients
Adverse reactions reported in clinical studies for partial-onset seizures in patients 1 month to less than 17 years of age and for primary generalized tonic-clonic seizures for patients 4 to less than 17 years of age were similar to those seen in adult patients.

Injection
In adult adjunctive therapy clinical trials for partial-onset seizures, adverse reactions with intravenous administration generally were similar to those that occurred with the oral formulation, although intravenous administration was associated with local adverse reactions such as injection site pain or discomfort (2.5%), irritation (1%), and erythema (0.5%). When administering a loading dose, the incidence of CNS adverse reactions, such as dizziness, somnolence, and paresthesia, may be higher with 15-minute administration than over a 30- to 60-minute period. The adverse reactions associated with VIMPAT injection in adult patients with primary generalized tonic-clonic seizures are expected to be similar to those seen in adults with partial- onset seizures. The adverse reactions associated with VIMPAT injection in pediatric patients are expected to be similar to those noted in adults. Infusion times less than 30 minutes were not adequately studied in pediatric patients.

VIMPAT is a Schedule V controlled substance.
Please refer to the full Prescribing Information and visit www.VIMPAThcp.com.

About NAYZILAM® (midazolam) nasal spray, CIV in the U.S.[10]
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 [FDA Approved Only]

CONTRAINDICATIONS

GL-N-BR-EPOS-2200014
Date of preparation: November 2022

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

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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.

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