



UCB presents latest research at 2018 American Epilepsy Society Annual Meeting demonstrating neurology commitment and leadership

- **20 scientific presentations illustrate and reinforce dedication to improving patient value in epilepsy**
- **Data covers licensed medicines, pipeline assets and non-product specific topics, providing a platform to share and reinforce UCB's patient value driven approach for people with epilepsy.**

Brussels (Belgium) & Atlanta, Georgia (USA), November 30 2018, 07:00 (CET): UCB is excited to be presenting 20 abstracts at this year's American Epilepsy Society Meeting, taking place between November 30 and December 4 in New Orleans, Louisiana.

Posters further describing VIMPAT® (lacosamide) CV and BRIVIACT® (brivaracetam) CV clinical data, alongside preliminary data on UCB's developmental drug candidate for epilepsy, padsevonil*, are scheduled for presentation during the meeting.

In collaboration with Proximagen, UCB will be sharing 2 posters describing long term safety and efficacy of Midazolam Nasal Spray, a developmental medicine currently being reviewed by the FDA for the treatment of Seizure Clusters*. UCB acquired Midazolam Nasal Spray from Proximagen in June 2018.

Additionally, UCB will share data about non-product specific research alongside our commitments to innovation in the field of epilepsy. These include posters describing UCB's eliprio™ suite of

predictive analytics tools which aim to support the epilepsy community in harnessing data and machine learning to help identify patients who are at high risk of failing through multiple AED treatments and to support improved AED treatment selection.

UCB will also be organising a 'Commitment to Epilepsy Care' scientific exhibit during AES, where there will also be a clinical trial information desk. This will provide attending healthcare professionals and researchers an opportunity to learn more about UCB's epilepsy research, clinical studies currently recruiting, and the company's unique *Inspired by Patients, Driven by Science* approach to medicines development and discovery.

"We're pleased to be presenting a wide range of data at this year's American Epilepsy Society meeting, demonstrating our commitment to finding solutions for people with epilepsy, that are driven by science, and aim to help them live their best lives," explained Mike Davis, Head of US Neurology, UCB. *"Our commitment to delivering what patients with epilepsy value is demonstrated through our continuing innovation, exploration of new technologies and solutions, and programs to support patients on their unique journey."*

The AES annual meeting is the largest gathering in the world focusing on epilepsy. The meeting brings together professionals in academia, clinical practice, industry, and advocacy to exchange ideas, learn about clinical information and to focus on supporting patients with epilepsy and seizure disorders.

"Throughout UCB's 90-year journey, innovation and agile entrepreneurship have always been essential components in our company's DNA. In this mindset, we continue to progress patient centric, innovative advances for the treatment of epilepsy," explained Jeff Wren, Executive Vice-President, Head of UCB's Neurology Patient Value Unit. *"It's an honor and a privilege to be able to share our research with the Global epilepsy community. By engaging with patients and stakeholders, and listening to their comments, feedback and first-hand experiences, we're confident we can make a real difference to the millions of people around the world looking for support in managing their epilepsy."*

The UCB congress exhibit will also be open throughout the AES congress and is located within the main exhibition hall from November 30 – December 4, Booth 709.

The UCB scientific exhibit 'Commitment to Epilepsy' will take place Monday, December 3 8:00 AM – 5:00 PM in the Convention Center, Room 282, Second Floor.

The following UCB abstracts have been accepted for presentation at AES 2018:

Lacosamide related abstracts:

1. Efficacy and tolerability of lacosamide and controlled-release carbamazepine monotherapy in patients with cerebrovascular epilepsy etiology: post hoc analysis of a randomized double-blind trial. Authors: Reetta Kälviäinen, Ali Bozorg, Svetlana Dimova, Ying Zhang, Björn Steiniger-Brach, Bruno Ferrò, Felix Rosenow. Poster # 1.290 -Poster session 1, Saturday December 1, 2018.

2. Long-term safety and efficacy of lacosamide and controlled-release carbamazepine monotherapy in patients with newly diagnosed epilepsy. Authors: Elinor Ben-Menachem, Hans Peter Grebe, Kiyohito Terada, Lori Jensen, Ting Li, Marc De Backer, Teresa Gasalla, Melissa Brock, Victor Biton. Poster # 1.291 -Poster session 1, Saturday December 1, 2018.

3. Healthcare resource utilization and cost before and after adding lacosamide as adjunctive therapy among patients diagnosed with epilepsy: a retrospective US claims analysis. Authors: David M Labiner, Barbara Johnson, Melinda Martin, Jesse Fishman, Carolyn Lew. Poster # 2.258 - Poster session 2, Sunday December 2, 2018.

Brivaracetam related abstracts:

4. Long-term retention on adjunctive brivaracetam in adults with focal seizures previously exposed to carbamazepine, lamotrigine, levetiracetam, or topiramate: a post hoc analysis. Authors: Melinda Martin, Svetlana Dimova, Sami Elmoufti, Cédric Laloyaux, Steve Chung. Poster # 1.294 -Poster Session 1, Saturday December 1, 2018.

5. Behavioral and cognitive effects of long-term adjunctive brivaracetam in children with epilepsy. Authors: Lieven Lagae, Teresa Gasalla, Simon Borghs, Melinda Martin, Jody M Cleveland, Vincent Badalamenti, Jan-Peer Elshoff, Jesus Pina-Garza. Poster # 1.292 -Poster session 1, Saturday December 1, 2018.

6. Long-term effectiveness of adjunctive brivaracetam in children with epilepsy: pooled analysis of data from two open-label trials. Authors: Teresa Gasalla, Melinda Martin, Sami

Elmoufti, Vincent Badalamenti, Jan-Peer Elshoff, Anup Patel. Poster # 1.293 -Poster session 1, Saturday December 1, 2018.

7. Efficacy and safety of IV brivaracetam as a treatment for increased seizure activity in an Epilepsy Monitoring Unit. Authors: Jerzy Szaflarski, Ahmed Sadek, Bernhard Greve, Paulette Williams, Julie Varner, Brian Moseley. Late breaking abstract, Abstract ID: 2.464 – Poster session 2, Sunday December 2, 2018.

Non-product specific abstracts:

8. Longitudinal predictors of healthcare use in adults with epilepsy. Authors: Jesse Fishman, Boris Vabson, Andrew Wilner. Poster # 1.331-Poster Session 1, Saturday December 1, 2018.

9. Predictors of epilepsy among the young. Authors: Boris Vabson, Hyunmi Kim, Jesse Fishman. Poster # 1.328 -Poster session 1, Saturday December 1, 2018.

Eliprio™ related abstracts:

10. Treatment decision support systems (TDSS) in epilepsy –exploring proxy validity and overall clinical outcome success related to TDSS-predicted antiepileptic drug (AED) choices. Authors: Edward Han-Burgess, Ali Bozorg, John D Hixson, Bosny Pierre-Louis, Shweta Joshi, Stephen Yates. Poster # 1.323 -Poster session 1, Saturday December 1, 2018.

11. Adequacy of patient information in electronic medical records and claims sources –an exploratory, retrospective record review to guide development of an antiepileptic drug treatment decision support system (TDSS). Authors: John D Hixson, Stephen Yates, Bosny Pierre-Louis, Robert Warnock, Edward Han-Burgess, Shweta Joshi, Jonathan Williams, Marla Gorges, Steven Vandamme, Joseph Robertson, Ali Bozorg. Poster # 1.324 -Poster session 1, Saturday December 1, 2018.

12. Predicting drug-resistant epilepsy (DRE) –use of big data from administrative claims and machine-learning models. Authors: Cynthia Dilley, Brandon Westover, Joseph Robertson, Jeffrey N Valdez, Sungtae An, Edward Han-Burgess. Poster # 1.325 -Poster session 1, Saturday December 1, 2018.

13. A machine learning approach for developing antiepileptic drug treatment decision support systems (TDSS). Authors: Joseph Robertson, Edward Han-Burgess, Cynthia Dilley, Chris Clark, Jeffrey N Valdez. Poster # 1.326 -Poster session 1, Saturday December 1, 2018.

14. Impact of psychiatric and substance use disorder comorbidity on treatment success among patients with epilepsy –retrospective analysis of claims data. Authors: Jon Duke, Eun Jung Choi, Edward Han-Burgess. Poster # 1.327 -Poster session 1, Saturday December 1, 2018.

Padsevonil* related abstracts:

15. Padsevonil differs from brivaracetam and levetiracetam in its interaction with the synaptic vesicle 2A (SV2A) protein. Authors: Martyn Wood, Michel Gillard. Poster # 2.225 -Poster session 2, Sunday December 2, 2018.

16. Protective effects of padsevonil in chronic models of focal and generalized epilepsies with spontaneous recurrent seizures. Authors: Rafal M Kaminski, Karine Leclercq. Poster # 2.224 -Poster session 2, Sunday December 2, 2018.

17. No impact of P-glycoprotein on the brain distribution of padsevonil. Authors: Hugues Chanteux, Hélène Chapy, Judith Van Asperen, Kenneth Saunders, Rafal M Kaminski, David Sciberras. Poster # 2.226 -Poster session 2, Sunday December 2, 2018.

18. Dissecting the heterogeneous clinical response to padsevonil in adults with drug-resistant focal seizures: post hoc responder analysis of a proof-of-concept trial. Authors: Wim Van Paesschen, Manuel Toledo, Christian Brandt, Bernhard J Steinhoff, Marian Majoie, Paul Boon, Elizabeth Webster, Steven De Bruyn, Konrad J Werhahn, Pierandrea Muglia, Andreja Avbersek, Christian Otoul. Poster # 1.289 -Poster session 1, Saturday December 1, 2018.

** Padsevonil is an investigational drug candidate for epilepsy currently in clinical development.*

Additionally, the following posters describing Midazolam Nasal Spray* will be presented by Proximagen at the 2018 AES Meeting:

19. Long-term efficacy experience of Nayzilam® (USL261; Midazolam Nasal Spray) for outpatient treatment of seizure clusters: efficacy results from the open-label, Phase III

extension study ARTEMIS-2. Authors: Tze-Chiang Meng, David J. Sequeira, Peter J. Van Ess, William E. Pullman. Poster # 2.235, Poster Session 2, Sunday December 2, 2018.

20. Long-term safety experience of Nayzilam® (USL261; Midazolam Nasal Spray) in subjects with seizure clusters: safety results from the open-label, Phase III extension study ARTEMIS-2. Authors: David J. Sequeira, Tze-Chiang Meng, William E. Pullman, Peter J. Van Ess. . Poster # 2.236, Poster Session 2, Sunday December 2, 2018.

** Midazolam Nasal Spray has not been approved by the FDA. These statements solely reflect the opinions of the authors.*

About VIMPAT® (lacosamide): ^{21,22}

In the U.S., VIMPAT® is indicated for the treatment of partial-onset seizures in patients 4 years of age and older. As the safety of VIMPAT® injection in pediatric patients has not been established, VIMPAT® injection is indicated for the treatment of partial-onset seizures only in adult patients (17 years of age and older). VIMPAT® was approved in the U.S. in 2008 as an add-on therapy for adult patients. 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. VIMPAT® is available in three formulations: oral tablets, oral solution, and intravenous (IV) injection. Important safety information about VIMPAT® in the U.S. is available below.

VIMPAT® (lacosamide) was first launched in the European Union in September 2008, as adjunctive therapy for the treatment of partial-onset seizures with or without secondary generalisation in adult and adolescent (16-18 years) patients with epilepsy. In September 2017 the use of VIMPAT® was expanded in the EU to adolescents and children from 4 years of age. In countries of the EU, VIMPAT® is available as film-coated tablets, syrup and solution for infusion. VIMPAT® solution for infusion is an alternative for patients when oral administration is temporarily not feasible. The availability of the oral tablets, oral syrup, and intravenous (IV) injection allows for consistent patient treatment.

In Asia, VIMPAT® is available in Hong Kong, Malaysia, Philippines and Thailand, and was approved for use in Japan in 2016, where the product will be jointly commercialised by Daiichi Sankyo.

VIMPAT® is not approved in China.

Important safety information about VIMPAT® is available below:

VIMPAT® (lacosamide) CV U.S. Indication and Important Safety Information

INDICATION

VIMPAT® is indicated for the treatment of partial-onset seizures in patients 4 years of age and older.

As the safety of VIMPAT injection in pediatric patients has not been established, VIMPAT injection is indicated for the treatment of partial-onset seizures only in adult patients (17 years of age and older).

WARNINGS AND PRECAUTIONS

- **Suicidal Behavior and Ideation:** Antiepileptic drugs (AEDs), including VIMPAT, increase the risk of suicidal behavior and ideation. Monitor patients taking VIMPAT 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.
- **Dizziness and Ataxia:** VIMPAT may cause dizziness and ataxia. In adult clinical trials, the onset of dizziness and ataxia was most commonly observed during titration. Advise patients not to drive, operate complex machinery, or engage in other hazardous activities until they are familiar with the effects of VIMPAT on their ability to perform such activities. Dizziness and ataxia were also observed in pediatric clinical trials.
- **Cardiac Rhythm and Conduction Abnormalities**
PR Interval Prolongation, Atrioventricular Block, and Ventricular Tachyarrhythmia
Dose-dependent prolongations in PR interval with VIMPAT have been observed in clinical studies in adult patients and in healthy volunteers. When VIMPAT is given with other drugs that prolong the PR interval, further PR prolongation is possible.

In the postmarketing setting, there have been reports of cardiac arrhythmias in patients treated with VIMPAT, including bradycardia, AV block, and ventricular tachyarrhythmia, which have rarely resulted in asystole, cardiac arrest, and death. Most, although not all, cases have occurred in patients with underlying proarrhythmic conditions, or in those taking concomitant medications that affect cardiac conduction or prolong the PR interval. These events have

occurred with both oral and intravenous routes of administration and at prescribed doses as well as in the setting of overdose.

Vimpat should be used with caution in patients with underlying proarrhythmic conditions such as known cardiac conduction problems (e.g., marked first-degree AV block, second-degree or higher AV block and sick sinus syndrome without pacemaker), severe cardiac disease (such as myocardial ischemia or heart failure, or structural heart disease), and cardiac sodium channelopathies (e.g., Brugada Syndrome).

VIMPAT should also be used with caution in patients on concomitant medications that affect cardiac conduction, including sodium channel blockers, beta-blockers, calcium channel blockers, potassium channel blockers, and medications that prolong the PR interval. In such patients, obtaining an ECG before beginning VIMPAT, and after VIMPAT is titrated to steady-state maintenance dose, is recommended. In addition, these patients should be closely monitored if they are administered VIMPAT through the intravenous route. Patients should be made aware of and report cardiac signs or symptoms to their healthcare provider right away.

Atrial Fibrillation and Atrial Flutter

VIMPAT administration may predispose to atrial arrhythmias (atrial fibrillation or flutter), especially in patients with diabetic neuropathy and/or cardiovascular disease.

- **Syncope:** VIMPAT may cause syncope in adult and pediatric patients.
- **Withdrawal of Antiepileptic Drugs:** Gradually withdraw VIMPAT (over a minimum of 1 week) to minimize the potential of increased seizure frequency.
- **Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS):** Also known as multi-organ hypersensitivity, has been reported with antiepileptic drugs, including VIMPAT. Some of these events have been fatal or life-threatening. If signs or symptoms are present, immediately evaluate the patient. Discontinue VIMPAT if an alternative etiology for the signs and symptoms cannot be established.

- **Risks in Patients with Phenylketonuria:** VIMPAT oral solution contains aspartame, a source of phenylalanine which can be harmful in patients with phenylketonuria (PKU). A 200 mg dose of VIMPAT oral solution (equivalent to 20 mL) contains 0.32 mg of phenylalanine.

Adverse Reactions

- **Adjunctive therapy:** In the adult placebo-controlled clinical trials, the most frequently seen adverse reaction with VIMPAT was dizziness (31% vs 8% placebo). Other common adverse reactions occurring in ≥ 10 percent of VIMPAT-treated patients, and greater than placebo, were headache, nausea, and diplopia.
- **Monotherapy:** In the adult clinical trial, adverse reactions were generally similar to those observed and attributed to drug in adjunctive placebo-controlled trials, with the exception of insomnia (occurred at a higher rate of $\geq 2\%$).
- **Pediatric patients:** Adverse reactions reported in clinical studies of pediatric patients 4 to less than 17 years of age were similar to those seen in adult patients.
- **Injection:** In adult adjunctive therapy clinical trials, 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.

Dosing Considerations

VIMPAT injection is for intravenous and adult use only when oral administration is temporarily not feasible. The loading dose for adult patients should be administered with medical supervision considering the VIMPAT pharmacokinetics and increased incidence of CNS adverse reactions. The safety of VIMPAT injection and the use of a loading dose in pediatric patients have not been studied. Dosage adjustments are recommended for patients with mild or moderate hepatic impairment or severe renal impairment. Use in patients with severe hepatic impairment is not recommended. Perform dose titration with caution in all patients with renal and/or hepatic impairment.

VIMPAT is a Schedule V controlled substance.

Please refer to full Prescribing Information available at www.VIMPATHCP.com.

Important Safety Information about VIMPAT® in the EU and EEA

VIMPAT® is indicated as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 4 years of age with epilepsy. VIMPAT® therapy can be initiated with either oral or IV administration. For the paediatric population, the physician should prescribe the most appropriate formulation and strength according to weight and dose. A single 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 CNS adverse reactions. Administration of a loading dose has not been studied in acute conditions such as status epilepticus. Use of a loading dose is not recommended in adolescents and children weighing less than 50 kg. Administration of a loading dose has not been studied in children. A maximum dose of 300 mg/day is recommended for paediatric patients with mild to moderate hepatic impairment weighing 50 kg or more and for adult patients with mild to moderate hepatic impairment as well. 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. 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. 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: Treatment with VIMPAT® 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. Dose-related prolongations in PR interval with VIMPAT® have been observed in clinical studies. Cases with second- and third-degree AV block associated with VIMPAT® treatment have been reported in post-marketing experience. VIMPAT® should be used with caution in patients with known conduction problems, severe cardiac disease (e.g. history of myocardial infarction or heart failure), in elderly patients, or when VIMPAT® is used in combination with products known to be associated with PR prolongation. In these patients it should be considered to perform an ECG before a Vimpat dose increase above 400mg/day and after Vimpat is titrated to steady-state. In the placebo-controlled trials of VIMPAT® in epilepsy patients, atrial fibrillation or flutter were not reported; however both have been reported in open-label epilepsy trials and in post-marketing experience. Patients should be made aware of the symptoms of second-degree or higher AV block (e.g. slow or irregular pulse, feeling of lightheaded and fainting) and of the symptoms of atrial fibrillation and flutter (e.g. palpitations, rapid or irregular pulse, shortness of breath). Patients should be counseled to seek medical advice should any of these symptoms occur. 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 behaviours 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. 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. The syrup contains aspartame (E951), a source of phenylalanine, which may be harmful for people with phenylketonuria. VIMPAT® syrup and the solution for infusion contain sodium, which should be taken into consideration for patients on a controlled sodium diet. Effects on ability to drive and use machines: VIMPAT® may have minor to moderate influence on the ability to drive and use machines. VIMPAT® 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 VIMPAT® on their ability to perform such activities. Undesirable effects: The most common adverse reactions ($\geq 10\%$) are dizziness, headache, diplopia, and nausea. 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 ($\geq 1\%$ - $< 10\%$) are depression, confusional state, insomnia, balance disorder, coordination abnormal, 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, contusion. The use of VIMPAT® 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. The safety profile of lacosamide in placebo-controlled and in open-label studies (n=408) in adjunctive therapy in children from 4 years of age was consistent with the safety profile observed in adults although the frequency of some adverse reactions (somnolence, vomiting and convulsion) was increased and additional adverse reactions (nasopharyngitis, pyrexia, pharyngitis, decreased appetite, lethargy and abnormal behaviour) have been reported in paediatric patients: nasopharyngitis (15.7 %), vomiting (14.7 %), somnolence (14.0 %), dizziness (13.5 %), pyrexia (13.0 %), convulsion (7.8 %), decreased appetite (5.9 %), pharyngitis (4.7 %), lethargy (2.7 %) and abnormal behaviour (1.7 %). Laboratory abnormalities: Abnormalities in liver function tests have been observed in controlled trials with VIMPAT® in adult patients with partial-onset seizures who were taking 1-3 concomitant antiepileptic medicinal products. Elevations of ALT to ≥ 3 XULN occurred in 0.7% (7/935) of VIMPAT® patients and 0% (0/356) of placebo patients. 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, VIMPAT® should be discontinued.

Refer to the European Summary of Product Characteristics for other adverse reactions and full prescribing information. Date of revision: 26 July 2018 <http://www.ema.europa.eu/>

About BRIVIACT® (brivaracetam) ^{23,24}

BRIVIACT (brivaracetam) is a new molecular entity that was rationally designed and developed by UCB. It was first approved in the EU and U.S. in 2016.

Brivaracetam displays a high and selective affinity for synaptic vesicle protein 2A (SV2A) in the brain, which may contribute to the anticonvulsant effect. However, the precise mechanism of action by which brivaracetam exerts its anticonvulsant activity is not known.

In the U.S., BRIVIACT® (brivaracetam) CV is indicated for the treatment of partial-onset seizures in patients 4 years of age and older. As the safety of BRIVIACT injection in pediatric patients has not been established, BRIVIACT injection is indicated for the treatment of partial-onset seizures only in adult patients (16 years of age and older).

In the European Union, 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 4 years of age with epilepsy.

The European Medicines Agency has different regulatory requirements from FDA for approval of monotherapy indications.

Important safety information about BRIVIACT® is available below.

BRIVIACT® (brivaracetam) CV U.S. Indication and Important Safety Information

INDICATION

BRIVIACT is indicated for the treatment of partial-onset seizures in patients 4 years of age and older. As the safety of BRIVIACT injection in pediatric patients has not been established, BRIVIACT injection is indicated for the treatment of partial-onset seizures only in adult patients (16 years of age and older).

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. Somnolence and fatigue-related adverse reactions were reported in 25% of adult patients taking at least 50 mg per day of BRIVIACT compared to 14% of adult patients taking placebo. Dizziness and disturbance in gait and coordination were reported in 16% of adult patients taking at least 50 mg per day of BRIVIACT compared to 10% of adult patients taking placebo. The risk is greatest early in treatment but can occur at any time. 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. These events were reported in approximately 13% of adult patients taking at least 50 mg per day of BRIVIACT compared to 8% of adult patients taking placebo. A total of 1.7% of adult patients taking BRIVIACT discontinued treatment due to psychiatric reactions compared to 1.3% of patients taking placebo. Psychiatric adverse reactions were also observed in open-label pediatric trials and were generally similar to those observed in adults. 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.

DOSING CONSIDERATIONS

- Dose adjustments are recommended for patients with all stages of hepatic impairment. When BRIVIACT is co-administered with rifampin, an increase in the BRIVIACT dose is recommended.

IMPORTANT SAFETY INFORMATION

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 4 years to less than 16 years of age were generally similar to those in adult patients.

BRIVIACT is a Schedule V controlled substance.

Please refer to full Prescribing Information available at www.BRIVIACTHCP.com.

Important Safety Information about BRIVIACT® in the EU and EEA

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 4 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.

Posology Based on data in adults, no dose adjustment is necessary in paediatric patients with impaired renal function. In adults with hepatic impairment, a 50 mg/day starting dose should be considered. In children and adolescents weighing 50 kg or greater, a 50 mg/day starting dose is recommended. A maximum daily dose of 150 mg administered in 2 divided doses is recommended for all stages of hepatic impairment. In children and adolescents weighing less than 50 kg, a 1 mg/kg/day starting dose is recommended. The maximum dose should not exceed 3 mg/kg/day. No clinical data are available in paediatric patients with hepatic impairment. BRIVIACT® film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take BRIVIACT®. Both the solution for injection/infusion and the oral solution contain sodium – to be taken into consideration for patients on a controlled sodium diet. The oral solution contains sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take this medicine. The oral solution contains methyl parahydroxybenzoate (E218), which may cause allergic reactions (possibly delayed).

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. 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 (8.2 %) were reported at higher incidences with increasing dose. Other common adverse reactions ($\geq 1\%$ to $< 10\%$) were influenza, decreased appetite, depression, anxiety, insomnia, irritability, convulsion, vertigo, upper respiratory tract infections, cough, nausea, vomiting and constipation. 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. In patients who were followed up in the open-label extension studies for up to 8 years, the safety profile was similar to that observed in the short-term, placebo-controlled 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 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 (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 %). There are limited safety data from open-label studies in children from 1 month to <4 years of age. Limited data are available on neurodevelopment in children <4 years of age. 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®. 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: 11 July 2018.

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

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About UCB in Epilepsy:

UCB has a rich heritage in epilepsy with over 20 years of experience in the research and development of antiepileptic drugs. 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.

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Moreover, sales may be impacted by international and domestic trends toward managed care and health care cost containment and the reimbursement policies imposed by third-party payers as well as legislation affecting biopharmaceutical pricing and reimbursement.

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