



UCB's anti-epileptic drug VIMPAT® (lacosamide) receives EU CHMP positive opinion for both monotherapy and adjunctive therapy in children aged 4 years and older with epilepsy

- Paediatric focal-onset seizures (FOS) account for around 60% of all epileptic seizures in children,¹ which if uncontrolled can lead to life-long cognitive, emotional and physical consequences.
- UCB awaits decision from the European Commission (EC) on the potential approval of this new VIMPAT® license extension in the European Union.

Brussels (Belgium), 24th July 2017 – 06:30 (CEST): UCB today announced that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has adopted a positive opinion on a new license extension for its anti-epileptic drug (AED) VIMPAT® (lacosamide) for use as monotherapy and adjunctive therapy in the treatment of focal-onset seizures (FOS, also known as partial-onset seizures (POS) according to ILAE terminology^{2,3}) in children from 4 to 16 years of age.⁴

The positive opinion is based on the principle of extrapolation of VIMPAT® efficacy data from adults to children, and is supported by safety and pharmacokinetics data collected in children.

The European Commission's (EC) approval decision is expected in the third quarter of 2017, which would further broaden the clinical application of VIMPAT®, and make a new treatment option available to aid the management of childhood epilepsy.

Epilepsy is the most common serious, neurological disorder among children and young adults, with the prevalence of paediatric epilepsy in Europe ranging from 3.2 – 5.1 per 1,000.⁵ Childhood epilepsy is a chronic condition and paediatric focal seizure prevalence increases with age.^{6,7,8,9} Repeated seizures in childhood may result in important neuro-development delay as well as direct physical injury. Approximately 10 – 29% of paediatric patients have inadequate seizure control with currently available AEDs.^{10,11} Paediatric patients may suffer from adverse events with currently available AEDs.¹² As such, there is a need for additional treatment options that may provide seizure control with a low side effect profile.

“The management of paediatric epilepsy is challenging and poor seizure control can be a great burden of stress for children and their families,” said Jeff Wren, Head of UCB’s Neurology Patient Value Unit. “UCB is proud to play a part in improving the lives of children with epilepsy and we look forward to making this therapy available to this patient population in the EU, pending EC approval.”

The established efficacy, safety and tolerability of adjunctive VIMPAT[®] therapy in adults with focal seizures was previously demonstrated by three primary double-blind, placebo-controlled studies (SP0667, SP0754, and SP0755)^{13,14,15} and three open-label extension studies (SP0615, SP0756, and SP0774).^{16,17,18} The efficacy, safety and tolerability profile of first-line VIMPAT[®] monotherapy has been demonstrated in a phase 3, double-blind, active comparator trial (SP0993) and the related open-label extension study (SP0994).¹⁹ VIMPAT[®] has over 1,056,500 patient-years of exposure.²⁰

“Non-adherence to AEDs is a common problem for children with epilepsy, in particular those with newly diagnosed epilepsy. Non-adherence is a potentially remediable cause of poor seizure control; continued seizures can be devastating and lead to long-term physical, behavioural and psychological consequences for children,” said Professor Helen Cross, Honorary Consultant in Paediatric Neurology at UCL Institute of Child Health. “There are currently few AEDs which are licensed for the treatment of younger children with focal onset seizures, especially as monotherapy. As such, the availability of lacosamide would provide an additional treatment option to support healthcare professionals in the management of childhood epilepsy.”

The EMA has established that focal epilepsies in children of 4 years of age have a similar clinical expression to focal epilepsies in adolescents and adults.²¹ The Food and Drug Administration (FDA) and EMA allow extension of indication to paediatric populations using extrapolated data provided the dose is established and the safety is demonstrated. The EMA states that, from the safety viewpoint, a minimum of 100 children treated by the study drug should be followed for at least one year.²² The Paediatric Epilepsy Academic Consortium for Extrapolation (PEACE) has shown that AED concentrations at approved doses lead to similarity of exposure between adult and paediatric patients.^{22,23}

Currently VIMPAT[®] is approved in 72 countries worldwide. In the EU it is approved as monotherapy and adjunctive therapy for the treatment of POS with or without secondary generalisation in adults and adolescents (16-18 years) with epilepsy.²⁴ In the US, VIMPAT[®] is approved as monotherapy or adjunctive therapy for the treatment of POS in adults with epilepsy (ages \geq 17 years).²⁵

About VIMPAT[®]

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 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. VIMPAT[®] tablets and injection were launched in the U.S. in May 2009 as an add-on therapy for the treatment of partial-onset seizures in people with epilepsy who are aged 17 years and older. VIMPAT[®] injection is a short-term replacement when oral administration is not feasible in these patients. VIMPAT[®] oral solution was launched in the US in June 2010. The availability of the oral tablets, oral solution, and intravenous (IV) injection allows for consistent patient treatment. In Asia, VIMPAT[®] is available in Korea, Hong Kong, Malaysia, Philippines and Thailand, and was recently approved for use in Japan, where the product will be jointly commercialised by Daiichi Sankyo. VIMPAT[®] is not approved in China. Important safety information about VIMPAT[®] is available below.

About Epilepsy^{26,27}

Epilepsy is a disease of the brain affecting approximately 65 million people worldwide. It is defined as either the occurrence of two or more unprovoked seizures >24 hours apart or one unprovoked (or reflex) seizure and a probability of further seizures occurring over the next 10 years that is similar to the general recurrence risk (at least 60%) after two unprovoked seizures or diagnosis of an epilepsy syndrome. Although epilepsy may be linked to factors such as health conditions, race and age, it can develop in anyone at any age, and approximately 1 in 26 people will develop epilepsy in their lifetime.

About UCB in Epilepsy

UCB has a longstanding commitment to improving the lives of people with epilepsy around the world. With over 20 years of experience in the research and development of antiepileptic drugs, our goal is to become a preferred partner for the global epilepsy community, improving knowledge about and access to effective solutions to help patients better manage their individual epilepsy journeys. We strive to 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 people 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 7500 people in approximately 40 countries, the company generated revenue of €4.2 billion in 2016. UCB is listed on Euronext Brussels (symbol: UCB). Follow us on Twitter: @UCB_news

Important Safety Information about VIMPAT® in the EU and EEA

VIMPAT® (lacosamide) is indicated as monotherapy and adjunctive therapy in the treatment of focal-onset seizures with or without secondary generalization in adult and adolescent (16-18 years) patients with epilepsy. VIMPAT® therapy can be initiated with either oral or IV administration. 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. A maximum dose of 300 mg/day is recommended for patients with mild to moderate hepatic impairment. Lacosamide should be administered to 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 patients with severe renal impairment (CLCR ≤30 ml/min) and in patients with endstage renal disease, a maximum maintenance dose of 250 mg/day 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 anti-epileptic agents 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. VIMPAT® syrup contains sodium methyl parahydroxybenzoate (E219) which may cause allergic reactions (possibly delayed). It contains 3.7 g sorbitol (E420) per dose (200 mg lacosamide), corresponding to a calorific value of 9.7 kcal. 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 (≥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 (≥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. Laboratory abnormalities: Abnormalities in liver function tests have been observed in controlled trials with VIMPAT® in adult patients with focal-onset seizures who were taking 1-3 concomitant antiepileptic drugs. Elevations of ALT to ≥3XULN 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 agents. 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: 3 May 2017. <http://www.ema.europa.eu/>

Forward looking statements

This press release contains forward-looking statements based on current plans, estimates and beliefs of management. All statements, other than statements of historical fact, are statements that could be deemed forward-looking statements, including estimates of revenues, operating margins, capital expenditures, cash, other financial information, expected legal, political, regulatory or clinical results and other such estimates and results. By their nature, such forward-looking statements are not guarantees of future performance and are subject to risks, uncertainties and assumptions which could cause actual results to differ materially from those that may be implied by such forward-looking statements contained in this press release. Important factors that could result in such differences include: changes in general economic, business and competitive conditions, the inability to obtain necessary regulatory approvals or to obtain them on acceptable terms, costs associated with research and development, changes in the prospects for products in the pipeline or under development by UCB, effects of future judicial decisions or governmental investigations, product liability claims, challenges to patent protection for products or product candidates, changes in laws or regulations, exchange rate fluctuations, changes or uncertainties in tax laws or the administration of such laws and hiring and retention of its employees. UCB is providing this information as of the date of this press release and expressly disclaims any duty to update any information contained in this press release, either to confirm the actual results or to report a change in its expectations.

There is no guarantee that new product candidates in the pipeline will progress to product approval or that new indications for existing products will be developed and approved. Products or potential products which are the subject of partnerships, joint ventures or licensing collaborations may be subject to differences between the partners. Also, UCB or others could discover safety, side effects or manufacturing problems with its products after they are marketed.

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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References

¹ Camfield, P., Camfield, C. Incidence, prevalence and aetiology of seizures and epilepsy in children. *Epileptic Disord.* 2015;17(2):117-123.

² Fisher, R.S., Cross, H.J., French, J.A., *et al.* Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia.* 2017;58(4):522-530.

³ Berg, A.T., *et al.* Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009. *Epilepsia.* 2010;51:676-85.

⁴ European Medicines Agency Committee for Medicinal Products for Human Use (CHMP), 20th July 2017:

http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/000863/WC500231716.pdf

⁵ Pugliatti, M., Beghi, E., Forsgren, L., Ekman, M., Sobocki, P. Estimating the cost of epilepsy in Europe: A review with economic modelling. *Epilepsia.* 2007;48(12):2224–2233.

⁶ Kurtz, Z., Tookey, P., Ross, E. Epilepsy in young people: 23 year follow up of the British national child development study. *BMJ.* 1998;316(7128):339-342.

⁷ Sidenvall, R., Forsgren, L., Heijbel, J. Prevalence and characteristics of epilepsy in children in northern Sweden. *Seizure.* 1996;5(2):139-146.

⁸ Eriksson, K., Koivikko, M. Prevalence, classification, and severity of epilepsy and epileptic syndromes in children. *Epilepsia.* 1997;38(12):1275-1282.

⁹ Endziniene, M., Pauza, V., Miseviciene, I. Prevalence of childhood epilepsy in Kaunas, Lithuania. *Brain Dev.* 1997;19(6):379-387.

¹⁰ Ohtsuka Y, Yoshinaga H, Kobayashi K. Refractory childhood epilepsy and factors related to refractoriness. *Epilepsia.* 2000;41(Suppl 9):14-17.

¹¹ Berg, A., Shinnar, S., Levy, S., Testa, F., Smith-Rapaport, S., Beckerman, B. Early development of intractable epilepsy in children: a prospective study. *Neurology.* 2001;56(11):1445-1452.

¹² Guerrini, R., Zaccara, G., la Marca, G., Rosati, A. Safety and Tolerability of Antiepileptic Drug Treatment in Children with Epilepsy. *Drug Saf.* 2012;35(7):519-533.

- ¹³ Ben-Menachem, E., Biton, V., Jatuzis, D., Abou-Khalil, B., Doty, P., Rudd, G.D. Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures. *Epilepsia*. 2007;48(7):1308-1317.
- ¹⁴ Chung, S., Sperling, M.R., Biton, V., Krauss, G., Hebert, D., Rudd, G.D., Doty, P. Lacosamide as adjunctive therapy for partial-onset seizures: A randomized controlled trial. *Epilepsia*. 2010;51(6):958-967.
- ¹⁵ Halász, P., Kälviäinen, R., Mazurkiewicz-Beldzinska, M., Rosenow, F., Doty, P., Hebert, D., Sullivan, T. Adjunctive lacosamide for partial-onset seizures: Efficacy and safety results from a randomized controlled trial. *Epilepsia*. 2009;50(3):443-453.
- ¹⁶ Rosenfeld, W., Fountain, N.B., Kaubrys, G., *et al.* Safety and efficacy of adjunctive lacosamide among patients with partial-onset seizures in a long-term open-label extension trial of up to 8 years. *Epilepsy Behav*. 2014;41:164-170.
- ¹⁷ Husain, A., Chung, S., Faught, E., Isojarvi, J., McShea, C., Doty, P. Long-term safety and efficacy in patients with uncontrolled partial-onset seizures treated with adjunctive lacosamide: results from a Phase III open-label extension trial. *Epilepsia*. 2012;53(3):521-528.
- ¹⁸ Rosenow, F., Kelemen, A., Ben-Menachem, E., *et al.* Long-term adjunctive lacosamide treatment in patients with partial-onset seizures. *Acta Neurol Scand*. 2016;133(2):136-144.
- ¹⁹ Baulac, M., Rosenow, F., Toledo, M., Terada, K., Li, T., de Backer, M., Werhahn, K.J., Borck, M. Efficacy, safety, and tolerability of lacosamide monotherapy versus controlled-release carbamazepine in patients with newly diagnosed epilepsy: a phase 3, randomised, double-blind, non-inferiority trial. *Lancet Neurology*. 2017;16(1):43-54.
- ²⁰ Periodic Safety Update Report data lock point Dec 15th 2016.
- ²¹ European Medicines Agency. Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders. 2010. Accessed July 2017 from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070043.pdf
- ²² Pellock, J.M., Carman, W.J., Thyagarajan, V., Daniels, T., Morris, D.L., D'Cruz, O. Efficacy of antiepileptic drugs in adults predicts efficacy in children: a systematic review. *Neurology*. 2012;79:1482-1489.
- ²³ U.S. Food and Drug Administration. Assessing quality and quantity of data to establish exposure-response similarity between adults and pediatric patients: PEACE Initiative. Presentation at the CERSI Workshop on the Use of Exposure Matching and Exposure Response for Extrapolation of Efficacy in Pediatric Drug Development. 2015.
- ²⁴ European Medicines Agency. VIMPAT® (lacosamide). Accessed July 2017 from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000863/human_med_001139.jsp&mid=WC0b01ac058001d124.
- ²⁵ U.S. Food and Drug Administration. VIMPAT® (lacosamide) Prescribing Information. Accessed July 2017 from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022255s026s027_022254s019s020_022255s012s013lbl.pdf.
- ²⁶ The Epilepsy Foundation of America. Who gets epilepsy? Accessed July 2017 from: <http://www.epilepsy.com/learn/epilepsy-101/who-gets-epilepsy>.
- ²⁷ Fisher, R.S., *et al.*, ILAE Official Report: A practical clinical definition of epilepsy. *Epilepsia*. 2014;55(4):475-482.