UCB News

New indication for VIMPAT® (lacosamide): UCB's anti-epileptic drug approved by FDA as monotherapy in the treatment of patients with partial-onset seizures

- VIMPAT® (lacosamide) C-V approved in the U.S. as monotherapy in the treatment of partial-onset seizures in adults with epilepsy[1]
- FDA also approved new single loading dose administration option for all formulations of VIMPAT®[1]
- New indication and administration options broaden the clinical application of VIMPAT®, making it available to more adults in the U.S. living with partial-onset seizures

Brussels (Belgium), 1st September, 2014 – 0700 (CEST) – regulated information – UCB announced today that the U.S. Food and Drug Administration (FDA) has approved a supplemental new drug application (sNDA) for VIMPAT® (lacosamide) C-V as monotherapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older.[1] This is a new indication for VIMPAT® which is already approved in the U.S. as adjunctive treatment for partial-onset seizures in patients in this age group.[1] This new indication means that adults with partial-onset seizures can be initiated on VIMPAT® monotherapy, and patients already on an anti-epileptic drug can be converted to VIMPAT® monotherapy.

UCB also announced today that the FDA has approved a new single loading dose administration option for all formulations of VIMPAT®, when used as monotherapy or adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older.[1]

"People living with epilepsy have individual needs. It's our aim at UCB to provide as many patients as possible with various options to reduce their seizures. Now, physicians and epilepsy patients in the U.S. have more VIMPAT® options to treat partial-onset seizures – VIMPAT® as an initial monotherapy, converting to VIMPAT® monotherapy and VIMPAT® as an adjunctive therapy. In addition, based on individual patients' needs, physicians can choose between VIMPAT® formulations - tablets, oral solution or injection. Also, initiation of VIMPAT® as a single loading dose provides

physicians with an alternative administration option to the standard titration schedule," said Professor Dr. Iris Loew Friedrich, Chief Medical Officer and Executive Vice President, UCB.

VIMPAT® Monotherapy

The new U.S. monotherapy approval for VIMPAT® is based on a Phase 3 historical-control conversion to lacosamide monotherapy study in adult epilepsy patients with partial-onset seizures.[1] The study met its primary endpoint, demonstrating that the exit percentage, defined as the estimated percentage of patients meeting pre-defined exit criteria, for patients converting to lacosamide 400 mg/day was significantly lower than the historical control exit percentage, used as a comparator. Lacosamide 300 mg/day also met the pre-specified criteria for efficacy.[1]

The most common adverse reactions in the monotherapy study were similar to those seen in adjunctive therapy studies; however, one adverse reaction, insomnia, was observed at a rate of ≥2% and was not reported at a similar rate in previous studies. Insomnia has also been observed in postmarketing experience. Because this study did not include a placebo control group, causality could not be established. In adjunctive therapy studies, the most common adverse reactions (≥10% and greater than placebo) were dizziness, headache, nausea and diplopia. Additional important safety information for VIMPAT® in the U.S. is available below.[1]

VIMPAT® Single Loading Dose

The new single loading dose administration option for VIMPAT® as monotherapy or adjunctive treatment of partial-onset seizures in adults with epilepsy allows the initiation of VIMPAT® as a single loading dose of 200 mg (oral or injection), followed approximately 12 hours later by a 100 mg twice daily dose (200 mg/day). The most common loading dose adverse events (≥5%) were dizziness, headache, paraesthesia and gait disturbance. The loading dose should be administered with medical supervision considering the VIMPAT® pharmacokinetics and increased incidence of CNS adverse reactions.[1]

VIMPAT® in the European Union

In the European Union, VIMPAT® is approved as adjunctive therapy for the treatment of partial-onset seizures with or without secondary generalization in adult and adolescent (16-18 years) patients with epilepsy. VIMPAT® may also be initiated with a single loading dose of 200 mg, followed

approximately 12 hours later by a 100 mg twice daily (200 mg/day) maintenance dose regimen. Additional important information on VIMPAT® loading dose in the European Union is available below. VIMPAT® is not approved in the European Union as monotherapy.[3]

A non-inferiority monotherapy study is underway to support the potential monotherapy filing with the European Medicines Agency. The study aims to compare the efficacy and safety of lacosamide to carbamazepine controlled-release as monotherapy in newly or recently newly diagnosed patients (≥ 16 years) with partial-onset seizures.[4]

Notes to editors

About the Phase 3 conversion to lacosamide monotherapy study[1,2,5]

The Phase 3 study was a historical-control, multicenter, randomized study that evaluated the efficacy and safety of conversion to lacosamide 400 mg/day monotherapy in adult epilepsy patients with partial-onset seizures. The study enrolled 425 patients, aged 16–70 years, on stable doses of 1-2 AEDs and experiencing 2-40 partial-onset seizures per 28 days during the 8 week prospective baseline. Patients taking 2 AEDs must have been taking ≤50% of the minimum recommended maintenance dose for 1 of the 2 AEDs, per U.S. product label.

Patients were randomized to lacosamide 400 or 300 mg/day (3:1 ratio), starting at 200 mg/day (100 mg/day twice daily) and titrated over 3 weeks (100 mg/day each week) to the randomized dose. Patients then entered the 16-week lacosamide maintenance phase, which included a 6-week background AED withdrawal phase and a 10-week lacosamide monotherapy phase. Patients were evaluated from the first day of tapering of the background AEDs and required to discontinue the study if they experienced any of the predefined exit events defined by an increase in seizure frequency, duration or severity.

The primary efficacy assessment was the percentage of patients receiving lacosamide 400 mg/day who met one or more of the pre-defined exit criteria by day 112 (end of lacosamide maintenance phase) compared with the historical control. The historical control consisted of a pooled analysis of the control groups from 8 studies of similar design, which utilized a sub-therapeutic dose of an AED as a control. For the lacosamide 400 mg/day group, the estimated percentage of patients meeting at least one exit criterion by day 112 was 30.0% (95% Confidence Interval [CI]: 24.6%, 35.5%).

The upper limit of the 2-sided 95% CI (35.5%) was below the threshold of 65.3% derived from the historical control data, meeting the pre-specified criteria for efficacy.

In the monotherapy trial, 16% of patients randomized to receive lacosamide at the recommended doses of 300 and 400 mg/day discontinued from the trial as a result of an adverse event. The adverse reaction most commonly (≥1% on lacosamide) leading to discontinuation was dizziness. Adverse reactions observed in this study were generally similar to those observed and attributed to drug in adjunctive placebo-controlled studies. Dizziness, headache, nausea, somnolence, and fatigue were all reported at lower incidences during the AED withdrawal phase and monotherapy phase, compared with the titration phase.

About Epilepsy[6,7,8,9,10]

Epilepsy is a chronic neurological disorder affecting approximately 65 million people worldwide and more than 2 million people in the U.S. It is the fourth most common neurological disorder in the U.S. Anyone can develop epilepsy; it occurs across all ages, races and genders and is defined as two or more unprovoked seizures that occur at least 24 hours apart. Anti-epileptic drug monotherapy is in general the initial management approach in epilepsy care, since many patients may be successfully managed with the first or second monotherapy utilized.

About VIMPAT®[1,3]

VIMPAT® is approved in the U.S. as tablets, injection and oral solution as monotherapy or adjunctive therapy in the treatment of partial-onset seizures in people with epilepsy ages 17 years and older. VIMPAT® injection is a short-term replacement when oral administration is not feasible in these patients. The availability of the oral tablets, oral solution, and intravenous (IV) injection formulations permits flexibility in administration.

A single loading dose administration option is also approved in the U.S. for all formulations of VIMPAT® when used as monotherapy or adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older.

Since the initial launch of VIMPAT® tablets and injection in May 2009, there have been more than 200,000* VIMPAT® patient exposures in the U.S.

In the European Union, VIMPAT® (film-coated tablets, syrup and solution for infusion) is approved as adjunctive therapy for the treatment of partial-onset seizures with or without secondary generalization in adult and adolescent (16-18 years) patients with epilepsy. VIMPAT® is also approved in the European Union for initiation as a single loading dose of 200 mg, followed approximately 12 hours later by a 100 mg twice-daily maintenance dose regimen.

Important safety information about VIMPAT® in the U.S. and the European Union is available below.

IMPORTANT SAFETY INFORMATION ABOUT VIMPAT® IN THE U.S.

Warnings and Precautions

- **Suicidal Behavior and Ideation**: Antiepileptic drugs (AEDs), including VIMPAT®, increase the risk of suicidal behavior and ideation. Patients taking VIMPAT® should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Patients and caregivers should also be advised 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. Accordingly, patients should be advised not to drive a car or to operate other complex machinery until they are familiar with the effects of VIMPAT® on their ability to perform such activities.
- **Cardiac Rhythm and Conduction Abnormalities**:

  PR interval prolongation

  Dose-dependent prolongations in PR interval with VIMPAT® have been observed in clinical studies in patients and in healthy volunteers. Second degree and complete AV block have been reported in patients in pain studies and in patients with seizures. When VIMPAT® is given with other drugs that prolong the PR interval, further PR prolongation is possible.

  VIMPAT® should be used with caution in patients with known cardiac conduction problems (e.g., marked first-degree AV block, second-degree or higher AV block and sick sinus syndrome without pacemaker), sodium channelopathies (e.g., Brugada Syndrome), or with severe cardiac disease such as myocardial ischemia or heart failure, or structural heart disease. VIMPAT® should be used with caution in patients on concomitant medications that prolong PR interval, because of a risk of AV block or bradycardia, e.g., beta-blockers and calcium channel blockers. In such patients, obtaining an ECG before beginning VIMPAT®, and after VIMPAT® is titrated to steady-state, is recommended. In addition, these patients should be closely monitored if they are administered VIMPAT® through the intravenous route.

  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**: Patients should be advised that VIMPAT® may cause syncope.
- **Withdrawal of Antiepileptic Drugs**: VIMPAT® should be gradually withdrawn (over a minimum of 1 week) to minimize the potential of increased seizure frequency.
- **Multiorgan Hypersensitivity Reactions**: Multiorgan hypersensitivity reactions (also known as Drug Reaction with Eosinophilia and Systemic Symptoms, or DRESS) have been reported with antiepileptic drugs. If this reaction is suspected, VIMPAT® should be discontinued and alternative treatment started.
- **Phenylketonurics**: VIMPAT® oral solution contains aspartame, a source of phenylalanine. A 200 mg dose of VIMPAT® oral solution (equivalent to 20 mL) contains 0.32 mg of phenylalanine.

Adverse Reactions

- **Adjunctive therapy**: In the 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 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%).
- **Injection**: In adjunctive therapy clinical trials, adverse reactions with intravenous administration generally were similar to those observed with the oral formulation, although intravenous administration was associated with local adverse events 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

The loading dose should be administered with medical supervision considering the VIMPAT® pharmacokinetics and increased incidence of CNS adverse reactions.

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. Dose titration should be performed with caution in all patients with renal and/or hepatic impairment.

VIMPAT® is a Schedule V controlled substance.

Please refer to full Prescribing Information provided by the sales representative and visit VIMPAT®.com/hcp.

For more information on VIMPAT® contact 844-599-CARE (2273).

VIMPAT® is a registered trademark used under license from Harris FRC Corporation.

IMPORTANT SAFETY INFORMATION ABOUT VIMPAT® IN THE EU AND EEA[3]

VIMPAT® (lacosamide) is indicated as adjunctive therapy in the treatment of partial-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. 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. 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 or severe cardiac disease such as a history of

myocardial infarction or heart failure. Caution should especially be exerted when treating elderly patients as they may be at an increased risk of cardiac disorders or when VIMPAT® is used in combination with products known to be associated with PR prolongation. 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 partial-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: 25th April 2014. http://www.ema.europa.eu/

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About UCB

UCB, Brussels, Belgium (www.ucb.com) is a global biopharmaceutical company focused on the discovery and development of innovative medicines and solutions to transform the lives of people living with severe diseases of the immune system or of the central nervous system. With more than 8500 people in approximately 40 countries, the company generated revenue of € 3.4 billion in 2013. UCB is listed on Euronext Brussels (symbol: UCB). Follow us on Twitter: @UCB_news

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.