UCB News

UCB files BRIVIACT® (brivaracetam) CV in the U.S. as monotherapy treatment for adult epilepsy patients with partial-onset seizures

- **Application follows recent FDA General Advice Letter supporting use of extrapolated data to assess monotherapy use of drugs already approved as adjunctive therapy**

Brussels (Belgium), Atlanta (Georgia, USA), 19 January 2017 – 18:30 (CET): UCB has today announced the filing of a supplemental New Drug Application (sNDA) to the U.S. Food and Drug Administration (FDA) for BRIVIACT® (brivaracetam) CV as monotherapy in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy within the U.S.

BRIVIACT® is currently approved in the U.S. as adjunctive therapy in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy[i]. The most common adverse reactions (at least 5% for BRIVIACT® and at least 2% more frequently than placebo) in adjunctive therapy clinical trials were somnolence and sedation, dizziness, fatigue, and nausea and vomiting symptoms. Please see additional BRIVIACT® Important Safety information below. Brivaracetam is not currently approved as monotherapy.

UCB submitted its supplemental application taking into account a recent General Advice Letter issued by the FDA[ii] which stated that it is "*acceptable to extrapolate the efficacy and safety of drugs approved as adjunctive therapy for the treatment of partial onset seizures (POS) to their use as monotherapy for the treatment of POS*". The communication stipulates that, to support extrapolation, proposed dosages of a drug when used as monotherapy should result in exposures similar to those demonstrated to be safe and effective when the drug is used as adjunctive therapy and that adequate pharmacokinetic information must be provided *"to demonstrate such similarity, taking into consideration possible drug-drug interactions (inhibition or induction) that may alter the metabolism of*

the drug". UCB has included this information within its BRIVIACT® monotherapy supplemental application.

"We are very pleased to be able to submit a label change for brivaracetam to the FDA, to include its use as monotherapy for partial-onset seizures. The FDA's agreement to the principle of extrapolation from existing data in their assessment of antiepileptic drugs has enabled us to base this submission on the existing wealth of brivaracetam data, less than a year after its launch as an adjunctive therapy in the U.S., and could improve patient access to the medicine if approved," said Professor Dr. Iris Loew-Friedrich, UCB's Chief Medical Officer. *"This submission, under the FDA's extrapolation principle, allows us to use the strength of our brivaracetam clinical trials data, involving more than 2,400 adult patients with partial-onset seizures, and reinforces our longstanding commitment to develop and make available meaningful treatment solutions to improve the lives of people living with epilepsy."*

While the supplemental application of BRIVIACT® as monotherapy in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy in the U.S. has been accepted by the FDA, acceptance of this submission does not necessarily mean BRIVIACT® will be approved for this indication.

About Epilepsy[iii],[iv]

Epilepsy is a chronic neurological disorder of the brain. It is the fourth most common neurological condition worldwide and affects approximately 65 million people. In the U.S., 3 million people have epilepsy. Anyone can develop epilepsy; it occurs across all ages, races and genders, and is defined as one or more unprovoked seizures with a risk of further seizures. One third of patients with epilepsy live with uncontrolled seizures.

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.

About BRIVIACT® [i,v]

BRIVIACT® is a new molecular entity that was rationally designed and developed by UCB. 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 BRIVIACT® exerts its anticonvulsant activity is not known. In the U.S. and European Union, BRIVIACT® is approved as adjunctive therapy (a therapy used together with primary treatment) in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy. BRIVIACT® is available in three formulations (film-coated tablets, oral solution, and injection).

Important Safety Information about BRIVIACT® in the U.S.[i]

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 patients taking at least 50 mg per day of BRIVIACT® compared to 14% of patients taking placebo. Dizziness and disturbance in gait and coordination were reported in 16% of patients taking at least 50 mg per day of BRIVIACT® compared to 10% of 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 nonpsychotic and psychotic symptoms. These events were reported in approximately 13% of patients taking at least 50 mg per day of BRIVIACT® compared to 8% of 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. 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

The most common adverse reactions (at least 5% for BRIVIACT® and at least 2% more frequently than placebo) are somnolence and sedation, dizziness, fatigue, and nausea and vomiting symptoms.

BRIVIACT is a Schedule V controlled substance.

Please refer to full Prescribing Information at http://www.briviact.com/briviact-PI.pdf.

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

BRIVIACT® is a registered trademark of the UCB Group of Companies.

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

BRIVIACT® (brivaracetam) is indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adult and adolescent patients from 16 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. Dose adjustments are recommended for patients with hepatic impairment (50 mg/day starting dose should be considered, up to maximum daily dose of 150 mg administered in 2 divided doses). 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 interaction studies have shown that BRIVIACT® can inhibit CYP2C19, therefore BRIVIACT® may increase plasma concentrations of medicinal products metabolised by CYP2C19 (e.g., lanzoprazole, 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 (≥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. **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: 05 December 2016. 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 7 700 people in approximately 40 countries, the company generated revenue of € 3.9 billion in 2015. UCB is listed on Euronext Brussels (symbol: UCB). Follow us on Twitter: @UCB_news

Forward looking statements - UCB

This press release contains forward-looking statements 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.

References:

[i] Briviact® U.S. Prescribing Information. Brussels, Belgium: UCB, 2016. https://www.briviact.com/briviact-PI.pdf accessed January 10th 2017.

[ii] Data on File (FDA General Advice Letter, dated 09/13/2016)

[iii] The Epilepsy Foundation of America. About Epilepsy Basics http://www.epilepsy.com/learn/about-epilepsy-basics accessed January 10th 2017.

[iv] The Epilepsy Foundation of America. What is Epilepsy? http://www.epilepsy.com/learn/epilepsy-101/what-epilepsy accessed January 10th 2017.

[v] Briviact® EU Prescribing Information. Brussels, Belgium: UCB, 2016. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003898/WC500200206.pdf accessed January 10th 2017.