UCB News

UCB's epilepsy drug BRIVIACT®(brivaracetam)[1] approved in Japan for treatment of focal onset seizures

- **Brivaracetam will offer increased treatment choice to physicians and patients in Japan living with epilepsy**
- **Approval is supported by positive results from a Phase 3 clinical study which evaluated the efficacy and safety of adjunctive brivaracetam in participants with focal-onset seizures across the Asia-Pacific region**
- **The fourth approval of brivaracetam in the Asia-Pacific region reinforces UCB's commitment to bringing treatment options to the global epilepsy community[2]**

Brussels (Belgium), 26th June – 7:00 am (CET) – UCB, a global biopharmaceutical company, today announced that the Japanese Ministry of Health, Labor and Welfare (MHLW) has granted marketing authorization for BRIVIACT® (brivaracetam) as monotherapy and adjunctive therapy in the treatment of partial onset seizures of epilepsy patients with or without secondary generalization in adult patients with epilepsy.[3] Brivaracetam treatment is initiated without titration, meaning patients receive a therapeutic dose from the first day of treatment.[3]

This announcement marks the fourth approval for brivaracetam in the Asia-Pacific region, which is already approved in Taiwan as monotherapy and adjunctive therapy for focal-onset seizures in patients aged ≥4 years and in Hong Kong and the Republic of Korea as adjunctive therapy for focal-onset seizures in patients aged ≥16 years (BRV not launched in the Republic of Korea).[2]

"Today's approval from the Japanese Ministry of Health, Labor and Welfare is exciting news for those in Japan who are living with epilepsy and need alternative treatment options," said Kanako Kikuchi, Head of UCB Japan. "One of UCB's key ambitions is improving the lives of people with epilepsy around the world, and we are thrilled to bring brivaracetam to patients in Japan."

Epilepsy is a chronic neurological disorder affecting around 710,000–930,000 people in Japan.[4] Despite currently available treatments, many patients with epilepsy still experience seizures regardless of using or having used at least one antiseizure medication.[4]

"There is an unmet need for epilepsy medicines that effectively and rapidly control seizures and are also well tolerated by patients," said Konrad Werhahn, Global Head of Medical Affairs, Epilepsy & Rare Syndromes, UCB. "We remain committed to transforming epilepsy care, designing meaningful, patient-focused treatment outcomes for people impacted by epileptic seizures."

The approval in Japan is based on clinical data from a Phase III, randomized, double-blind, placebo-controlled study of brivaracetam published in *Epilepsia Open* involving 449 patients aged ≥16–80 years with epilepsy and focal-onset seizures in the Asia-Pacific region.[2] The study included 97 Japanese patients, n=97 received ≥1 dose of brivaracetam. The study met its primary endpoint as brivaracetam demonstrated statistically significant reductions over placebo in partial-onset seizure frequency per 28 days (percent reduction over placebo in 28-day adjusted focal seizure frequency was 24.5% and 33.4% with brivaracetam 50 mg/day and 200 mg/day, respectively, (P=0.0005 and p<0.0001).[2] The proportion of patients showing a 50% responder rate was 19.0%, 41.1%, and 49.3% with placebo, brivaracetam 50 mg/day, and brivaracetam 200 mg/day, respectively (p<0.0001 for both BRV groups vs. placebo), meaning the study met its secondary endpoint.[2]

Brivaracetam was generally well tolerated by patients. Incidences of treatment-emergent adverse events were similar between patients on placebo (58.4%) and all patients receiving brivaracetam (58.5%).[2] Overall, the most common (≥10%) TEAEs by preferred term in all patients receiving BRV were somnolence (14.4%) and dizziness (12.7%); incidences of somnolence and dizziness in patients receiving placebo were 8.1% and 4.0%, respectively and 4.7% of patients on placebo and 3.0% of all patients on BRV discontinued due to TEAEs.[2] The efficacy, safety, and tolerability profiles were consistent with brivaracetam studies in predominantly non-Asian populations, demonstrating that adjunctive brivaracetam was efficacious and generally well-tolerated in adult Asian patients with focal-onset seizures.[2]

For further information, contact UCB:
Global Communications
Nick Francis
T +44 7769 307745
email nick.francis@ucb.com

Corporate Communications, Media Relations
Laurent Schots
T +32 2 559 92 64
email Laurent.schots@ucb.com

Investor Relations
Antje Witte
T +32 2 559 94 14
email antje.witte@ucb.com

About Epilepsy

Epilepsy is a chronic neurological disorder affecting approximately 65 million people worldwide. It is considered to be a disease of the brain defined by any of the following conditions: (1) at least two unprovoked (or reflex) seizures occurring >24 hours apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; or (3) diagnosis of an epilepsy syndrome. [6]

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. Partial seizures begin with an electrical discharge in one area of the brain. Different things can cause partial seizures, for example, head injury, brain infection, stroke, tumour, and changes in the way an area of the brain was formed before birth, called cortical dysplasia. Many times, no known cause is found, but genetic factors may be important in some partial seizures.[7,8]

About BRIVIACT® (brivaracetam)

Important Safety Information about BRIVIACT® in the EU and EEA[1]

BRIVIACT® (brivaracetam) is indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 2 years of age with epilepsy.
Contraindications Hypersensitivity to the active substance, other pyrrolidone derivatives or any of the excipients. **Special warnings and precautions for use** Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic drugs (AEDs), including BRIVIACT®, in several indications. A meta-analysis of randomized placebo controlled clinical studies of AEDs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for BRIVIACT®. 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 any signs of suicidal ideation or behaviour emerge. There are limited clinical data on the use of BRIVIACT® in patients with pre-existing hepatic impairment. BRIVIACT® film-coated tablets contain lactose. Patients with rare hereditary problems of galactose

intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine. BRIVIACT® film-coated tablets contain less than 1 mmol sodium (23mg) per tablet, that is to say essentially 'sodium free'. **Posology** The recommended starting dose is either 50 mg/day or 100 mg/day based on physician's assessment of required seizure reduction versus potential side effects. Based on individual patient response and tolerability, the dose may be adjusted in the effective dose range of 50 mg/day to 200 mg/day. In adults, adolescents and children weighing ≥50 kg, the recommended starting dose is 50 mg/day. BRIVIACT® may also be initiated at 100 mg/day based on physician's assessment of need for seizure control. The recommended maintenance dose is 100 mg/day. Based on individual patient response, the dose may be adjusted in the effective dose range of 50 mg/day to 200 mg/day. For adolescents and children weighing from 20 kg to <50 kg, the recommended starting dose is 1 mg/kg/day. BRIVIACT® may also be initiated at doses up to 2 mg/kg/day based on physician's assessment of need for seizure control. The recommended maintenance dose is 2 mg/kg/day. Based on individual patient response, the dose may be adjusted in the effective dose range of 1 mg/kg/day to 4 mg/kg/day. For children weighing from 10 kg to <20 kg, the recommended starting dose is 1 mg/kg/day. BRIVIACT® may also be initiated at doses up to 2.5 mg/kg/day based on physician's assessment of need for seizure control. The recommended maintenance dose is 2.5 mg/kg/day. Based on individual patient response, the dose may be adjusted in the effective dose range of 1 mg/kg/day to 5 mg/kg/day. BRIVIACT® is not recommended in end-stage renal disease patients undergoing dialysis due to lack of data. Based on data in adults, no dose adjustment is necessary in paediatric patients with impaired renal function. No clinical data are available in paediatric patients with renal impairment. Exposure to BRIVIACT® was increased in adult patients with chronic liver disease. In patients with hepatic impairment, the following adjusted doses, administered in 2 divided doses, approximately 12 hours apart, are recommended for all stages of hepatic impairment: In adults, adolescents and children weighing ≥50 kg, a 50 mg/day starting dose is recommended, with a maximum daily dose of 150 mg/day. For adolescents and children weighing from 20 kg to <50 kg, a 1 mg/kg/day starting dose is recommended, with a maximum daily dose of 3 mg/kg/day. For children weighing from 10 kg to <20 kg, a 1 mg/kg/day starting dose is recommended, with a maximum daily dose of 4 mg/kg/day. No clinical data are available in paediatric patients with hepatic impairment. **Interaction with other medicinal products and other forms of interaction.** In the clinical studies, although the numbers were limited, there was no observed benefit of BRIVIACT® versus placebo in patients taking levetiracetam concurrently. In a pharmacokinetic and pharmacodynamic interaction study between BRIVIACT® 200 mg single dose and ethanol 0.6 g/L continuous infusion in healthy subjects, there was no pharmacokinetic interaction, but BRIVIACT® approximately doubled the effect of alcohol on psychomotor function, attention and memory. Intake of brivaracetam with alcohol is not recommended. BRIVIACT® plasma concentrations may increase when coadministered with CYP2C19 strong inhibitors s (e.g. fluconazole, fluvoxamine), but the risk of a clinically relevant CYP2C19-mediated interaction is considered to be low. Limited clinical data are available implying that coadministration of cannabidiol may increase the plasma exposure of BRIVIACT®, possibly through CYP2C19 inhibition, but the clinical relevance is uncertain. In healthy subjects, coadministration with the strong enzyme inducer rifampicin (600 mg/day for 5 days), decreased BRIVIACT® area under the plasma concentration curve (AUC) by 45 %. Prescribers should consider adjusting the brivaracetam dose in patients starting or ending treatment with rifampicin. BRIVIACT® plasma concentrations are decreased when coadministered with strong enzyme inducing AEDs (carbamazepine, phenobarbital, phenytoin) but no dose adjustment is required. 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. lanzoprazole, omeprazole, diazepam). When tested in vitro BRIVIACT® did not induce CYP1A1/2 but induced CYP3A4 and CYP2B6. No CYP3A4 induction was found in vivo (see midazolam above). CYP2B6 induction has not been investigated in vivo and brivaracetam may decrease plasma concentrations of medicinal products metabolised by CYP2B6 (e.g. efavirenz). In vitro, interaction studies to determine the potential inhibitory effects on transporters concluded that there were no clinically relevant effects, except for OAT3. In vitro, BRIVIACT® inhibits OAT3 with a half maximal inhibitory concentration 42-fold higher than the Cmax at the highest clinical dose. BRIVIACT® 200mg/day may increase plasma concentrations of medicinal products transported by OAT3. BRIVIACT® is a moderate reversible inhibitor of epoxide hydrolase resulting in an increased concentration of carbamazepine epoxide, an active metabolite of carbamazepine. In controlled clinical studies, the carbamazepine epoxide plasma concentration increased by a mean of 37 %, 62 % and 98 % with little variability at BRIVIACT® doses of 50 mg/day, 100 mg/day and 200 mg/day respectively. No safety risks were observed. There was no additive effect of BRIVIACT® and valproate on the AUC of carbamazepine epoxide. Co-administration of BRIVIACT® (100 mg/day) with an oral contraceptive containing ethinylestradiol (0.03 mg) and levonorgestrel (0.15 mg)

did not influence the pharmacokinetics of either substance. **Fertility, pregnancy and lactation** Physicians should discuss family planning and contraception with women of childbearing potential taking brivaracetam. If a woman decides to become pregnant, the use of BRIVIACT®, should be carefully re-evaluated. There is a limited amount of data from the use of BRIVIACT® in pregnant women. There is no data on placental transfer in humans, but BRIVIACT® was shown to readily cross the placenta in rats. The potential risk for humans is unknown. Animal studies did not detect any teratogenic potential of BRIVIACT®. In clinical studies, BRIVIACT® was used as adjunctive therapy and when it was used with carbamazepine, it induced a dose-related increase in the concentration of the active metabolite, carbamazepine-epoxide. There is insufficient data to determine the clinical significance of this effect in pregnancy. As a precautionary measure, BRIVIACT® should not be used during pregnancy unless clinically necessary. BRIVIACT® is excreted in human breast milk. A decision should be made whether to discontinue breastfeeding or to discontinue brivaracetam, taking into account the benefit of the medicinal product to the mother. In case of co-administration of BRIVIACT® and carbamazepine, the amount of carbamazepine-epoxide excreted in breast milk could increase. There is insufficient data to determine the clinical significance. No human data on the effect of brivaracetam on fertility are available. In rats, there was no effect on fertility with BRIVIACT®. **Effects on ability to drive and use machines** BRIVIACT®, has minor or moderate influence on the ability to drive and use machines. Due to possible differences in individual sensitivity some patients might experience somnolence, dizziness, and other central nervous system (CNS) related symptoms. Patients should be advised not to drive a car or to operate other potentially hazardous machines until they are familiar with the effects of BRIVIACT® on their ability to perform such activities. **Undesirable effects.** The most frequently reported adverse reactions with BRIVIACT® (reported by >10% of patients) were somnolence (14.3%) and dizziness (11.0%). They were usually mild to moderate in intensity. Somnolence and fatigue were reported at higher incidences with increasing dose. Very common adverse reactions (≥1% to <10%) were influenza, decreased appetite, depression, anxiety, insomnia, irritability, convulsion, vertigo, upper respiratory tract infections, cough, nausea, vomiting, constipation and fatigue. Neutropenia has been reported in 0.5% (6/1,099) BRIVIACT® patients and 0% (0/459) placebo-treated patients. Four of these patients had decreased neutrophil counts at baseline, and experienced additional decrease in neutrophil counts after initiation of BRIVIACT®. None of the six cases were severe, required any specific treatment, led to discontinuation of BRIVIACT® and none had associated infections. Suicidal ideation was reported in 0.3 % (3/1099) of BRIVIACT® treated patients and 0.7 % (3/459) of placebo-treated patients. In short-term clinical studies of BRIVIACT® in patients with epilepsy, there were no cases of completed suicide and suicide attempt, however both were reported in the long-term open-label extension studies. Reactions suggestive of immediate (Type I) hypersensitivity have been reported in a small number of BRIVIACT® patients (9/3022) during clinical development. The safety profile of BRIVIACT® observed in children from 1 month of age was consistent with the safety profile observed in adults. In the open label, uncontrolled, long-term studies suicidal ideation was reported in 4.7 % of paediatric patients assessed from 6 years onwards (more common in adolescents) compared with 2.4 % of adults and behavioural disorders were reported in 24.8 % of paediatric patients compared with 15.1 % of adults. The majority of events were mild or moderate in intensity, were non-serious, and did not lead to discontinuation of study drug. An additional adverse reaction reported in children was psychomotor hyperactivity (4.7 %). No specific pattern of adverse event (AE) was identified in children from 1 month to < 4 years of age when compared to older paediatric age groups. No significant safety information was identified indicating the increasing incidence of a particular AE in this age group. As data available in children younger than 2 years of age are limited, BRIVIACT® is not indicated in this age range. Limited clinical data are available in neonates. **Overdose** There is limited clinical experience with BRIVIACT® overdose in humans. Somnolence and dizziness were reported in a healthy subject taking a single dose of 1,400 mg of BRIVIACT®. The following adverse reactions were reported with BRIVIACT® overdose: nausea, vertigo, balance disorder, anxiety, fatigue, irritability, aggression, insomnia, depression, and suicidal ideation in the post-marketing experience. In general, the adverse reactions associated with BRIVIACT® overdose were consistent with the known adverse reactions. There is no specific antidote. Treatment of an overdose should include general supportive measures. Since less than 10% of BRIVIACT® is excreted in urine, haemodialysis is not expected to significantly enhance BRIVIACT® clearance.

Refer to the European Summary of Product Characteristics for other adverse reactions and full prescribing information. https://www.ema.europa.eu/en/documents/product-information/briviact-epar-product-information_en.pdf

About 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 approximately 8,600 people in approximately 40 countries, the company generated revenue of €5.3 billion in 2023. UCB is listed on Euronext Brussels (symbol: UCB). Follow us on Twitter: @UCB_news.

Forward looking statements

This press release may contain forward-looking statements including, without limitation, statements containing the words "believes", "anticipates", "expects", "intends", "plans", "seeks", "estimates", "may", "will", "continue" and similar expressions. These forward-looking statements are based on current plans, estimates and beliefs of management. All statements, other than statements of historical facts, are statements that could be deemed forward-looking statements, including estimates of revenues, operating margins, capital expenditures, cash, other financial information, expected legal, arbitration, political, regulatory or clinical results or practices and other such estimates and results. By their nature, such forward-looking statements are not guarantees of future performance and are subject to known and unknown risks, uncertainties and assumptions which might cause the actual results, financial condition, performance or achievements of UCB, or industry results, to differ materially from those that may be expressed or implied by such forward-looking statements contained in this press release. Important factors that could result in such differences include: the global spread and impact of COVID-19, changes in general economic, business and competitive conditions, the inability to obtain necessary regulatory approvals or to obtain them on acceptable terms or within expected timing, 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, safety, quality, data integrity or manufacturing issues; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, product liability claims, challenges to patent protection for products or product candidates, competition from other products including biosimilars, 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. There is no guarantee that new product candidates will be discovered or identified in the pipeline, will progress to product approval or that new indications for existing products will be developed and approved. Movement from concept to commercial product is uncertain; preclinical results do not guarantee safety and efficacy of product candidates in humans. So far, the complexity of the human body cannot be reproduced in computer models, cell culture systems or animal models. The length of the timing to complete clinical trials and to get regulatory approval for product marketing has varied in the past and UCB expects similar unpredictability going forward. Products or potential products, which are the subject of partnerships, joint ventures or licensing collaborations may be subject to differences disputes between the partners or may prove to be not as safe, effective or commercially successful as UCB may have believed at the start of such partnership. UCB's efforts to acquire other products or companies and to integrate the operations of such acquired companies may not be as successful as UCB may have believed at the moment of acquisition. Also, UCB or others could discover safety, side effects or manufacturing problems with its products and/or devices after they are marketed. The discovery of significant problems with a product similar to one of UCB's products that implicate an entire class of products may have a material adverse effect on sales of the entire class of affected products. Moreover, sales may be impacted by international and domestic trends toward managed care and health care cost containment, including pricing pressure, political and public scrutiny, customer and prescriber patterns or practices, and the reimbursement policies imposed by third-party payers as well as legislation affecting biopharmaceutical pricing and reimbursement activities and outcomes. Finally, a breakdown, cyberattack or information security breach could compromise the confidentiality, integrity and availability of UCB's data and systems.

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