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Corporate Release

Lundbeck and Otsuka announce FDA acceptance of sNDA filing for brexpiprazole in combination with sertraline for the treatment of adults with post-traumatic stress disorder (PTSD)

- *The supplemental new drug application (sNDA) for brexpiprazole in combination with sertraline for the treatment of adults with post-traumatic stress disorder (PTSD) has been accepted and filed by the FDA*
- *The FDA target date (PDUFA date) for completion of the review is 8 February 2025*
- *If approved, brexpiprazole and sertraline combination treatment would be the first FDA-approved pharmacological treatment for PTSD in more than 20 years*

Valby, Denmark, 25 June 2024 – H. Lundbeck A/S (Lundbeck) and Otsuka Pharmaceutical Co., Ltd. (Otsuka) announce the U.S. Food and Drug Administration (FDA) has determined that the supplemental New Drug Application (sNDA) for brexpiprazole in combination with sertraline for the treatment of adults with post-traumatic stress disorder (PTSD) is sufficiently complete to permit a substantive review. The FDA has assigned the application for a Prescription Drug User Fee Act (PDUFA) target action date of 8 February 2025.

The sNDA submission is based on data from three randomized clinical trials evaluating the safety and efficacy of brexpiprazole in combination with sertraline in adult patients with PTSD[1,2].

The primary endpoint for all three trials was the change from Week 1 to Week 10 in the Clinician-Administered PTSD Scale (CAPS-5) total score for brexpiprazole and sertraline combination therapy versus sertraline plus placebo in patients diagnosed with PTSD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)[1].

The trials were randomized, double blind, active-controlled, and Trial 061 (phase II) and 071 (phase III) were flexible dose trials, while Trial 072 (phase III) was a fixed dose trial[1]. In Trial 061 and 071, brexpiprazole in combination with sertraline was associated with a statistically significant reduction ($p<0.05$) in PTSD symptoms compared to sertraline plus placebo, as measured by the change in the CAPS-5 total score from Week 1 to Week 10 (primary endpoint). In Trial 072, while the primary endpoint was not met, reductions in PTSD symptom severity with brexpiprazole in combination with sertraline were consistent with Trials 061 and 071. Improvements were consistently observed across the Clinical Global Impression Severity (CGI-S) scale and the four CAPS-5 clusters of re-experiencing, avoidance, negative cognition/mood and arousal/reactivity symptoms in Trials 061 and 071[1,3].

Across the three randomized trials, the combination of brexpiprazole and sertraline in adult patients with PTSD were generally well-tolerated, and no new safety observations were identified. The safety and

tolerability results were consistent with the known profile of brexpiprazole in its approved indications and what has been observed in other clinical trials. The overall incidence of treatment-emergent adverse events (TEAEs) across the three trials was 55.5 percent with brexpiprazole plus sertraline, and 56.2 percent with sertraline plus placebo[2].

"*Post-traumatic stress disorder is one of the most common mental health disorders in the United States. Approximately 13 million adults in the U.S. have PTSD during a given year and between seven to eight out of every 100 will experience PTSD at some point in their lives*[4-9]", said John Kraus, M.D., Ph.D., executive vice president and chief medical officer, Otsuka. "*This is a significant development, and we look forward to continuing our efforts to provide a treatment option that may benefit the millions of patients and caregivers who are impacted by the debilitating effects of PTSD.*"

"*Brexpiprazole in combination with sertraline could represent an important advancement over current standard of care, and we look forward to working with the FDA, in the process of seeking approval of this combination*," said Johan Luthman, Ph.D., executive vice president, Lundbeck Research & Development. "*We are grateful to the patients and caregivers who participated in these important trials*".

About the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)

The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) is a structured interview designed to assess PTSD diagnostic status and symptoms severity as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). The interview consists of 30 items, with a higher score indicating a worse outcome.

About Post-Traumatic Stress Disorder

PTSD is one of the most common mental health disorders in the United States, with approximately five percent of the population affected during a given year[6-10]. It may occur in people who have experienced or witnessed a traumatic event, series of events or set of circumstances. An individual may experience this as emotionally or physically harmful or life-threatening and may affect mental, physical, social, and/or spiritual well-being. Examples include physical/sexual assault, natural disasters, serious accidents, terrorist acts, war/combat, historical trauma, intimate partner violence and bullying[11,12].

Symptoms of PTSD are generally grouped into four types: intrusion (re-experiencing), avoidance, negative cognitions and mood, and marked alterations in arousal and reactivity[6,12]. Symptoms can vary over time or vary from person to person[12]. Symptoms usually begin within 3 months of the traumatic incident, but they sometimes emerge later. To meet the criteria for PTSD diagnosis, symptoms must last longer than one month, and they must be severe enough to interfere with aspects of daily life, such as relationships or work. Symptoms also must not be due to medications, substance use, or a medical condition[6]. Guideline recommended first-line treatment includes psychotherapy (e.g., cognitive behavioral therapy) and first line pharmacotherapy options include certain antidepressants[13].

About brexpiprazole

Brexpiprazole was approved in the U.S. in 2015, as an adjunctive therapy to antidepressants in adults with MDD and as a treatment for schizophrenia in adults. Most recently, brexpiprazole was approved in the U.S. for the treatment of agitation associated with dementia due to Alzheimer's disease, in May 2023. Brexpiprazole was also approved by Health Canada for schizophrenia and adjunctive treatment of MDD in

2017 and 2019, respectively, and for agitation associated with Alzheimer's dementia in 2024. It was approved by the Ministry of Health, Labour and Welfare in Japan and by the European Medicines Agency in 2018 for the treatment of schizophrenia.

Brexpiprazole was discovered by Otsuka and is being co-developed by Otsuka and Lundbeck. The mechanism of action of brexpiprazole is unknown, however the efficacy of brexpiprazole may be mediated through a combination of partial agonist activity at serotonin 5-HT1A and dopamine D2 receptors, antagonist activity at serotonin 5-HT2A receptors, as well as antagonism of alpha 1B/2C receptors.

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About H. Lundbeck A/S

Lundbeck is a biopharmaceutical company focused exclusively on neuroscience, with more than 70 years of experience in improving the lives of people with neurological and psychiatric diseases.

As a focused innovator, we strive for our research and development programs to tackle some of the most complex challenges. We develop transformative medicines targeting people for whom there are few, if any, treatment options.

Our goal is to create long term value and make a positive contribution to people and societies, everywhere we operate. We are committed to fighting stigma and discrimination, and we act to improve health equity for the people we serve and the communities we are part of.

About Otsuka

Otsuka Pharmaceutical Co., Ltd. is a global healthcare company with the corporate philosophy: Otsuka–people creating new products for better health worldwide. Otsuka researches, develops, manufactures, and markets innovative products, with a focus on pharmaceutical products to meet unmet medical needs and nutraceutical products for the maintenance of everyday health.

In pharmaceuticals, Otsuka is a leader in the challenging areas of mental, renal, and cardiovascular health and has additional research programs in oncology and on several under-addressed diseases

including tuberculosis, a significant global public health issue. These commitments illustrate how Otsuka is a “big venture” company at heart, applying a youthful spirit of creativity in everything it does.

Otsuka established a presence in the U.S. in 1973 and today its U.S. affiliates include Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) and Otsuka America Pharmaceutical, Inc. (OAPI). These two companies’ 2,250 employees in the U.S. develop and commercialize medicines in the areas of mental health and nephrology, using cutting-edge technology to address unmet healthcare needs.

OPDC and OAPI are indirect subsidiaries of Otsuka Pharmaceutical Co., Ltd., which is a subsidiary of Otsuka Holdings Co., Ltd. headquartered in Tokyo, Japan. The Otsuka group of companies employed 34,400 people worldwide and had consolidated sales of approximately USD 14.2 billion in 2023.

All Otsuka stories start by taking the road less traveled. Learn more about Otsuka in the U.S. at www.otsuka-us.com and connect with us on LinkedIn and Twitter at @OtsukaUS. Otsuka Pharmaceutical Co., Ltd.’s global website is accessible at https://www.otsuka.co.jp/en/.

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