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Otsuka and Lundbeck 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 February 8, 2025.*
- *If approved, brexpiprazole and sertraline combination treatment would be the first FDA-approved pharmacological option for PTSD in more than 20 years.*

Otsuka Pharmaceutical, Co. Ltd. (Otsuka) and H. Lundbeck A/S (Lundbeck) 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 February 8, 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 randomization (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 randomization (Week 1) to Week 10 (primary endpoint). In Trial 072, while the primary endpoint was not met, reductions in PTSD symptoms 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 was 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,"[4-10] 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 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 clusters: intrusion (re-experiencing), avoidance, negative cognitions and mood, and marked alterations in arousal and reactivity.[7,12] 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.[7] Guideline recommended first-line treatment includes psychotherapy (e.g., cognitive behavioral therapy) and first line pharmacotherapy options include certain antidepressants.[13]

About REXULTI (brexpiprazole)

Brexpiprazole was approved in the U.S. in 2015, as an adjunctive therapy to antidepressants in adults with major depressive disorder (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 dementia due to Alzheimer's disease in 2024. It was approved by the European Medicines Agency in 2018 for the treatment of schizophrenia and the Ministry of Health, Labour and Welfare in Japan for the treatment of schizophrenia and MDD in 2018 and 2023, respectively.[14]

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-HT_{1A} and dopamine D_2 receptors, antagonist activity at serotonin 5-HT_{2A} receptors, as well as antagonism of alpha 1B/2C receptors.[14-16]

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