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Otsuka and Lundbeck Announce Results of Brexpiprazole on Symptoms of Agitation Related to Alzheimer's-type Dementia

Tokyo, Japan, May 2, 2017 - Otsuka Pharmaceutical Co., Ltd. (Otsuka) and H. Lundbeck A/S (Lundbeck) announce top-line results from two phase III clinical trials evaluating the efficacy, safety and tolerability of brexpiprazole in the treatment of agitation in patients with dementia of the Alzheimer's type.

The primary endpoint of both trials was change from baseline in the Cohen-Mansfield Agitation Inventory (CMAI) total score, a 29-item scale to systematically assess the symptoms of agitation.[1] The key secondary endpoint was the change from baseline in the Clinical Global Impression-Severity of Illness (CGI-S) score, a 7-point scale assessing overall severity of the patient's agitation.[1] These studies were conducted in multiple countries in North America and Europe, and in the Russian Federation.

In both studies, patients treated with brexpiprazole showed improvements in symptoms of agitation relative to placebo. In the first study, the improvement in the primary endpoint of CMAI for 2 mg brexpiprazole was statistically better than placebo ($p<0.05$) and appeared more robust than the improvements on the key secondary endpoint of CGI-S ($p>0.05$). In the second study, the improvements in the primary endpoint of CMAI ($p>0.05$) appeared less robust than improvements observed on the key secondary endpoint of CGI-S ($p<0.05$). In both studies, there was variability in the data from different countries, perhaps associated with differing standards of care; the data from Russian sites showed especially poor separation between placebo and drug.

Regarding safety and tolerability, both studies confirmed the profile of brexpiprazole as observed in the clinical trials for schizophrenia and for adjunctive treatment of major depressive disorder (MDD). The most common adverse events in patients receiving brexpiprazole versus placebo (incidence >3% and greater than placebo) were insomnia (4.7% vs. 3.3%), agitation (3.5% vs. 2.9%), and somnolence (3.3% vs. 2.2%). Overall mortality during the studies was 0.86% and none of the deaths were considered to be related to treatment.

About the studies

Both trials were randomized, double-blind, placebo-controlled phase III studies that enrolled a combined total of approximately 700 participants. Trial participants were between 51 and 90 years of age with a diagnosis of probable Alzheimer's disease and symptoms of agitation. Both outpatients and patients living in institutionalcare settings were included in the trials. One of the trials studied fixed doses of either 1 or 2 mg per day of brexpiprazole or placebo, while the other trial studied a flexible-dose range of 0.5 mg, 1 mg or 2 mg per day of brexpiprazole, or placebo. Both trials were 12-weeks in duration.

The companies plan to meet with the FDA to discuss the results of the studies. The results will be presented in scientific congresses over the next year.

About Alzheimer's disease and related agitation

Alzheimer's disease is estimated to account for between 60% and 80% of the estimated 5.5 million people in the U.S. with dementia.[2] Behavioral symptoms develop in the majority of people with Alzheimer's disease and many of these symptoms are clinically diagnosed as "agitation," including restlessness, significant emotional distress, aggressive behaviors, and irritability. Symptoms of agitation place a serious burden on the people afflicted with the disease and their caregivers, significantly affecting the quality of life for all concerned. Agitation is often a determining factor in the decision to place patients in high-level residential care facilities, contributing to the roughly USD 259 billion cost burden of Alzheimer's disease in the U.S. for 2017.[2] It is estimated that agitation symptoms affect nearly 50% or more of patients with Alzheimer's disease observed over a multiyear period.[3]

About brexpiprazole

Brexpiprazole was approved by the U.S. Food and Drug Administration in July 2015 to treat patients with schizophrenia and as an adjunctive treatment for patients with MDD. Brexpiprazole was also approved in February 2017 by Health Canada for the treatment of schizophrenia. In both countries brexpiprazole is distributed and marketed under the brand name REXULTI®.

Brexpiprazole was discovered by Otsuka and is being co-developed by Otsuka and Lundbeck. The mechanism of action for brexpiprazole in the adjunctive treatment of major depressive disorder or schizophrenia 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, and antagonist activity at serotonin 5-HT_{2A} receptors. Brexpiprazole exhibits high affinity (sub-nanomolar) for these receptors as well as for noradrenaline alpha1B/2C receptors.

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[1] Garriga M., Pacchiarotti, I., Kasper, S., Zeller S. et al. Assessment and management of agitation in psychiatry: Expert consensus. World J Biological Psychiatry 2016;17,(2):93

[2] Alzheimer's Association. 2017 Alzheimer's disease facts and figures. 2017;13:325-373

[3] Bergh, S.and Selbæk, G. The prevalence and the course of neuropsychiatric symptoms in patients with dementia. Norsk Epidemiologi 2012; 22 (2): 225-232.