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.

INDICATION AND IMPORTANT SAFETY INFORMATION for REXULTI® (brexpiprazole)

INDICATIONS

REXULTI is indicated for:

- Use as an adjunctive therapy to antidepressants in adults with major depressive disorder
- Treatment of schizophrenia in adults

IMPORTANT SAFETY INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. REXULTI is not approved for the treatment of patients with dementia-related psychosis.

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

Antidepressants increase the risk of suicidal thoughts and behaviors in patients aged 24 years and younger. Monitor for clinical worsening and emergence of suicidal thoughts and behaviors. The safety and effectiveness of REXULTI have not been established in pediatric patients.

Contraindication: In patients with known hypersensitivity reaction to brexpiprazole or any of its components. Reactions have included: rash, facial swelling, urticaria and anaphylaxis.

Cerebrovascular Adverse Events, Including Stroke: In clinical trials, elderly patients with dementia randomized to risperidone, aripiprazole, and olanzapine had a higher incidence of stroke and transient ischemic attack, including fatal stroke. REXULTI is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS): NMS is a potentially fatal symptom complex reported in association with administration of antipsychotic drugs. Clinical signs of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability. Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Manage NMS with immediate discontinuation of REXULTI, intensive symptomatic treatment, and monitoring.

Tardive Dyskinesia (TD): Risk of TD, and the potential to become irreversible, are believed to increase with duration of treatment and total cumulative dose of antipsychotic drugs. TD can develop after a relatively brief treatment period, even at low doses, or after discontinuation of treatment. For chronic treatment, use the lowest dose and shortest duration of REXULTI needed to produce a clinical response. If signs and symptoms of TD appear, drug discontinuation should be considered.

Metabolic Changes: Atypical antipsychotic drugs have caused metabolic changes including:

- **Hyperglycemia/Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assess fasting plasma glucose before or soon after initiation of antipsychotic medication, and monitor periodically during long-term treatment.
- **Dyslipidemia:** Atypical antipsychotics cause adverse alterations in lipids. Before or soon after initiation of antipsychotic medication, obtain a fasting lipid profile at baseline and monitor periodically during treatment.
- **Weight Gain:** Weight gain has been observed in patients treated with REXULTI. Monitor weight at baseline and frequently thereafter.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia and neutropenia have been reported with antipsychotics. Agranulocytosis (including fatal cases) has been reported with other agents in this class. Monitor complete blood count in patients with pre-existing low white blood cell count (WBC)/absolute neutrophil count or history of drug-induced leukopenia/neutropenia. Discontinue REXULTI at the first sign of a clinically significant decline in WBC and in severely neutropenic patients.

Orthostatic Hypotension and Syncope: Atypical antipsychotics cause orthostatic hypotension and syncope.

Generally, the risk is greatest during initial dose titration and when increasing the dose. Monitor in patients vulnerable to hypotension, and those with cardiovascular and cerebrovascular diseases.

Falls: Antipsychotics may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls causing fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating treatment and recurrently during therapy.

Seizures: REXULTI may cause seizures and should be used with caution in patients with a history of seizures or with conditions that lower the seizure threshold.

Body Temperature Dysregulation: Use REXULTI with caution in patients who may experience conditions that increase body temperature (e.g., strenuous exercise, extreme heat, dehydration, or concomitant use with anticholinergics).

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotics. including REXULTI, and should be used with caution in patients at risk for aspiration.

Potential for Cognitive and Motor Impairment: REXULTI has the potential to impair judgment, thinking, or motor skills. Patients should not drive or operate hazardous machinery until they are reasonably certain REXULTI does not affect them adversely.

Concomitant Medication: Dosage adjustments are recommended in patients who are known cytochrome P450 (CYP) 2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers.

Most commonly observed adverse reactions: In clinical trials, the most common adverse reactions were:

- **Major Depressive Disorder (MDD)** (adjunctive treatment to antidepressant therapy; ≥5% incidence and at least twice the rate of placebo for REXULTI vs. placebo, respectively): akathisia (9% vs. 2%) and weight increase (7% vs. 2%)
- **Schizophrenia** (≥4% incidence and twice incidence of placebo for REXULTI vs. placebo, respectively): weight increased (4% vs. 2%)

Dystonia: Symptoms of dystonia may occur in susceptible individuals during the first days of treatment and at low doses.

Pregnancy: Adequate and well-controlled studies to assess the risks of REXULTI during pregnancy have not been conducted. REXULTI should be used during pregnancy only if the benefit justifies the risk to the fetus.

Lactation: It is not known if REXULTI is excreted in human breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

To report SUSPECTED ADVERSE REACTIONS, contact Otsuka America Pharmaceutical, Inc. at 1-800- 438-9927 or FDA at 1-800-FDA-1088 (www.fda.gov/medwatch).

Please see accompanying FULL PRESCRIBING INFORMATION, including **BOXED WARNING**.

About Otsuka Pharmaceutical Co., Ltd.

Otsuka Pharmaceutical 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 for the treatment of diseases and nutraceutical products for the maintenance of everyday health.

In pharmaceuticals, Otsuka is a leader in the challenging area of mental health and also has research programs 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 Pharmaceutical is a subsidiary of Otsuka Holdings Co., Ltd. headquartered in Tokyo, Japan. The Otsuka group of companies employed 45,000 people worldwide and had consolidated sales of approximately USD 11 billion (€ 9.9 billion) in 2016.

All Otsuka stories start by taking the road less travelled. Learn more about Otsuka Pharmaceutical Company on its global website at https://www.otsuka.co.jp/en. Learn more about Otsuka in the U.S. at www.otsuka-us.com and connect with us on Twitter at @OtsukaUS.

About Lundbeck

H. Lundbeck A/S (LUN.CO, LUN DC, HLUYY) is a global pharmaceutical company specialized in psychiatric and neurological disorders. For more than 70 years, we have been at the forefront of research within neuroscience. Our key areas of focus are Alzheimer's disease, depression, Parkinson's disease and schizophrenia.

Our approximately 5,000 employees in 55 countries are engaged in the entire value chain throughout research, development, manufacturing, marketing and sales. Our pipeline consists of several late-stage development programmes and our products are available in more than 100 countries. We have production facilities in Denmark, France and Italy. Lundbeck generated revenue of DKK 15.6 billion in 2016 (EUR 2.1 billion; USD 2.2 billion).

For additional information, we encourage you to visit our corporate site www.lundbeck.com and connect with us on Twitter at @Lundbeck.

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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.