Otsuka and Lundbeck to Start Third Phase 3 Trial in June to Evaluate Brexpiprazole in the Treatment of Agitation in Patients with Alzheimer's Disease

Tokyo, Japan and Deerfield, Ill., U.S., May 23, 2018 - Otsuka Pharmaceutical Company, Ltd. (Otsuka) and Lundbeck announce that the two companies' third clinical Phase 3 study of brexpiprazole in the treatment of agitation in patients with dementia of the Alzheimer's type will commence in June.

Approximately 300 patients are expected to be enrolled in this 12-week, randomized, double-blind, placebo-controlled trial. Additional information about the trial will be available in the near future at clinicaltrials.gov and will be updated periodically following initiation of the study.

The decision to initiate a third trial follows discussions with the U.S. Food and Drug Administration (FDA) regarding two Phase 3 clinical trials for the agitation in Alzheimer's disease indication that were completed by Otsuka and Lundbeck in 2017. Results for the two completed trials were announced in May of last year and presented in poster sessions at the American Association for Geriatric Psychiatry annual meeting in March of this year.

About Alzheimer's Disease and Related Agitation
Of the approximately 5.5 million people in the U.S. with dementia, it is estimated that 60-80 percent have Alzheimer's disease.[1,2] Behavioral symptoms develop in the majority of people with Alzheimer's disease and many of these symptoms are clinically diagnosed as agitation, including wandering, restlessness, significant emotional distress, aggressive behaviors, and irritability. It is estimated that agitation symptoms affect nearly 50 percent or more of patients with Alzheimer's disease observed over a multiyear period.[3]

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.[1]

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 major depressive disorder. Brexpiprazole was subsequently approved in Canada, Australia and Japan for the treatment of schizophrenia. In all four countries brexpiprazole is distributed and marketed under the brand name REXULTI®. Brexpiprazole is not approved for use in treating agitation associated with Alzheimer's disease.

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 not fully understood. 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 $alpha_{1B/2C}$ receptors.

INDICATIONS 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.

Pathological Gambling and Other Compulsive Behaviors: Intense urges, particularly for gambling, and the inability to control these urges have been reported while taking REXULTI. Other compulsive urges have been reported less frequently. Prescribers should ask patients or their caregivers about the development of new or intense compulsive urges. Consider dose reduction or stopping REXULTI if such urges develop.

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): akathisia and weight increase
- **Schizophrenia** (≥4% incidence and at least twice the rate of placebo for REXULTI vs. placebo): weight increased

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 FULL PRESCRIBING INFORMATION, including **BOXED WARNING**.

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 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 Company is a subsidiary of Otsuka Holdings Co., Ltd. headquartered in Tokyo, Japan. The Otsuka group of companies employed 46,000 people worldwide and had consolidated sales of approximately USD 11.1 billion in 2017.

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

Lundbeck 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 research focus are depression, schizophrenia, Parkinson's disease and Alzheimer's disease.

An estimated 700 million people worldwide are living with psychiatric and neurological disorders and far too many suffer due to inadequate treatment, discrimination, a reduced number of working days, early retirement and other unnecessary consequences. Every day, we strive for improved treatment and a better life for people living with psychiatric and neurological disorders — we call this Progress in Mind.

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 programs and our products are available in more than 100 countries. We have production facilities in Denmark, France and Italy.

In the U.S., Lundbeck employs nearly 1,000 people focused solely on accelerating therapies for brain disorders. With a special commitment to the lives of patients, families and caregivers, Lundbeck U.S. actively engages in hundreds of initiatives each year that support our patient communities. For additional information, we encourage you to visit our corporate site at www.lundbeckus.com and connect with us on Twitter at @LundbeckUS.

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

[2] Alzheimer’s Disease International, The world Alzheimer’s report 2015; 30

[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.