



DATA DEMONSTRATE SAFETY AND EFFICACY OF BREXPIPIRAZOLE IN PATIENTS WITH SCHIZOPHRENIA EXPERIENCING SEVERE PSYCHOTIC SYMPTOMS

The Severity of Schizophrenia Symptoms Can Be a Significant Predictor of Poor Treatment Outcomes

(Orlando, Fla., October 26, 2018) – Otsuka Pharmaceutical Co., Ltd. (Otsuka) and H. Lundbeck A/S (Lundbeck) announced study results on the safety and efficacy of brexpiprazole in the treatment of patients with schizophrenia experiencing severe psychotic symptoms during an acute episode. The data will be presented at the upcoming Psych Congress, held in Orlando from October 25-28, 2018.

The *post hoc*, pooled analysis focused on three short-term studies, Vector [[NCT01396421](#)], Beacon [[NCT01393613](#)], and Lighthouse [[NCT01810380](#)], evaluating brexpiprazole in subgroups of patients with severe psychotic symptoms. Patients with severe psychotic symptoms were defined based on the total scores of the Positive and Negative Syndrome Scale (PANSS), a scale used to rate the symptoms of schizophrenia. Patients with severe psychotic symptoms were specified by having PANSS total scores of greater than 95, which was the median score of the full patient population at baseline.

The 681 patients included in the analysis exhibited an average baseline PANSS total score of 106 with 427 patients given a dose of 2-4 mg of brexpiprazole and 254 given placebo. The study demonstrated that patients receiving brexpiprazole showed a mean improvement in PANSS Total score of 24.03 vs. 17.27 for patients receiving placebo (placebo-adjusted difference of 6.76, $p < 0.0001$). Response rates (defined as change from baseline greater than or equal to 30% in PANSS Total Score or CGI-I score of 1 or 2 at Week 6 of the study) were greater for those patients treated with brexpiprazole versus placebo (46.9% and 27.3%, respectively, $p < 0.0001$). Similar results were observed for patients with less severe symptoms (i.e. patients with baseline PANSS score less than 95). The most common treatment emergent adverse events (occurring in greater than or equal to 5% of patients in any group) included insomnia, headache and akathisia and were similar between patients with more or less severe psychotic symptoms.

“Schizophrenia is a chronic, disabling and progressive disease, impacting approximately three million Americans, that is often challenging to treat, and the severity of schizophrenia symptoms can be a significant predictor of poor treatment outcomes,” said Nicole Meade, PhD, Senior Medical Science Liaison, Otsuka. “These results underscore the potential of brexpiprazole as an effective treatment option with a safety profile that can provide physicians the confidence to prescribe it to patients with schizophrenia with a broad range of symptoms, including those with more severe psychotic symptoms.”

About brexpiprazole

Brexpiprazole is a molecule discovered by Otsuka and 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 D₂ receptors, and antagonist activity at serotonin 5-HT_{2A} receptors. Brexpiprazole exhibits high affinity (subnanomolar) for these receptors as well as for noradrenaline alpha1B/2C receptors. The drug was approved in the U.S. on July 10, 2015, as an adjunctive therapy to antidepressants in adults with major depressive disorder and as a treatment in adults with schizophrenia. Brexpiprazole is currently marketed as REXULTI®.

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; $\geq 5\%$ incidence and at least twice the rate of placebo for REXULTI vs. placebo): akathisia and weight increase
- **Schizophrenia** ($\geq 4\%$ 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 accompanying [FULL PRESCRIBING INFORMATION](#), including **BOXED WARNING**.

Otsuka Pharmaceutical Development & Commercialization, Inc.

Otsuka Pharmaceutical Company 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 Development & Commercialization, Inc. (OPDC) is dedicated to clinical development of promising drug candidates in mental health, oncology, cardio-renal, and nephrology. Other activities include strategic planning for drug approval, marketing, and lifecycle management to maximize a product’s full potential.

OPDC is an indirect subsidiary of Otsuka Pharmaceutical Company, Ltd., which 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 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 www.otsuka.co.jp/en/.

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 depression, schizophrenia, Parkinson's disease and Alzheimer's disease.

An estimated 700 million people worldwide are living with brain disease 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 brain disease – we call this Progress in Mind. Read more at www.lundbeck.com/global/about-us/progress-in-mind.

Our approximately 5,000 employees in more than 50 countries are engaged in the entire value chain throughout research, development, production, marketing and sales. Our pipeline consists of several late-stage development programmes and our products are available in more than 100 countries. Our research centre is based in Denmark and our production facilities are located in Denmark, France and Italy. Lundbeck generated revenue of DKK 17.2 billion in 2017 (EUR 2.3 billion; USD 2.6 billion).

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

Lundbeck in the U.S.

In the U.S., Lundbeck employs more than 800 people focused solely on accelerating therapies for brain diseases. With a special commitment to the lives of patients, families and caregivers, Lundbeck US actively engages in hundreds of initiatives each year that support our patient communities. To learn more, visit us at <http://www.LundbeckUS.com> and connect with us on Twitter at @LundbeckUS.

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