



U.S. FDA ACCEPTS FOR REVIEW OTSUKA AND LUNDBECK'S sNDA FILING FOR LABELING UPDATE OF REXULTI® (BREXPIPIRAZOLE) FOR MAINTENANCE TREATMENT OF SCHIZOPHRENIA

- The safety and efficacy of REXULTI (brexpiprazole) as maintenance treatment in adults with schizophrenia aged 18 to 65 years was demonstrated in a 52-week randomized withdrawal trial.
- The anticipated date for the FDA to complete its review of the proposed expanded labeling is September 23, 2016. REXULTI was approved by the U.S. FDA in July 2015 as a treatment for adults with schizophrenia and as an adjunctive treatment for adults with major depressive disorder.
- There are approximately 2.4 million adults in the US with schizophrenia and around 75% of patients experience relapses where their symptoms come back or in some cases, worsen.

Princeton, New Jersey and Valby, Denmark – February 8, 2016 – Otsuka Pharmaceutical Co., Ltd. (Otsuka) and H. Lundbeck A/S (Lundbeck) announced today that the U.S. Food and Drug Administration (FDA) has accepted for review a supplemental New Drug Application (sNDA) for the proposed labeling update of REXULTI (brexpiprazole) for the maintenance treatment of adults with schizophrenia. Under the Prescription Drug User Fee Act (PDUFA), the PDUFA date is September 23, 2016.

The sNDA is supported by results from a 52-week randomized withdrawal trial in adults with schizophrenia aged 18 to 65 years. In the trial, patients were stabilized on REXULTI and were then randomized to continued therapy with REXULTI (n=96) or placebo (n=104). The primary endpoint of the study was time from randomization to relapse. At a pre-specified interim analysis, the study demonstrated a statistically significantly longer time to relapse in patients randomized to the REXULTI group (1 mg/day to 4 mg/day) compared to placebo-treated patients and the trial was terminated early because maintenance of efficacy had been demonstrated (p < 0.0001, final analysis). During the randomized maintenance phase, adverse reactions were similar to those reported in the short-term schizophrenia trials.

About REXULTI® (brexpiprazole)

REXULTI is a molecule discovered by Otsuka and co-developed by Otsuka and Lundbeck. The mechanism of action for REXULTI in the adjunctive treatment of major depressive disorder or schizophrenia is unknown. However, the efficacy of REXULTI 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. REXULTI exhibits high affinity (subnanomolar) for these receptors as well as for noradrenaline alpha_{1B/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.

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

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs 2.6%, respectively). Although the causes of death were varied, most of the deaths appeared to be cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. REXULTI is not approved for the treatment of patients with dementia-related psychosis.

Suicidal Thoughts and Behaviors

Antidepressants increased the risk compared to placebo of suicidal thoughts and behavior in patients aged 24 years and younger in short-term studies. All antidepressant-treated patients should be monitored for clinical worsening, and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy and at times of dosage changes. Families and caregivers should be advised of the need for close observation for changes in behavior and to alert the healthcare provider. The safety and efficacy of REXULTI has not been established in pediatric patients with depression.

See Full Prescribing Information for complete Boxed WARNING

Contraindication: Known hypersensitivity reaction to REXULTI or any of its components. Reactions have included: rash, facial swelling, urticaria and anaphylaxis.

Cerebrovascular Adverse Events, Including Stroke: In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks), including fatalities, compared to placebo-treated patients.

Neuroleptic Malignant Syndrome (NMS): A potentially fatal complex sometimes referred to as NMS has been associated with the administration of antipsychotic drugs. NMS can cause hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Management should include immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems.

Tardive Dyskinesia (TD): The risk of developing TD and the potential for it to become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic increase. The syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Prescribing should be consistent with the need to minimize TD. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that include:

- **Hyperglycemia/Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics. There have been reports of hyperglycemia in patients treated with REXULTI. Patients with diabetes should be regularly monitored for worsening of glucose control; those with risk factors for diabetes should undergo baseline and periodic fasting blood glucose testing. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the atypical antipsychotic drug.
- **Dyslipidemia:** Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.
- **Weight Gain:** Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia, neutropenia, and agranulocytosis have been reported temporally related to atypical antipsychotics. Patients with history of a clinically significant low white blood cell (WBC) count or drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of REXULTI should be considered at the first sign of a clinically significant decline in WBC count in the absence of other causative factors.

Orthostatic Hypotension and Syncope: REXULTI may be associated with orthostatic hypotension and should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions which would predispose them to hypotension.

Seizures: As with other antipsychotic drugs, REXULTI should be used with caution in patients with a history of seizures or with conditions that lower the seizure threshold.

Body Temperature Dysregulation: Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotics. Appropriate care is advised for patients who may exercise strenuously, be exposed to extreme heat, receive concomitant medication with anticholinergic activity, or be subject to dehydration.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. REXULTI should be used with caution in patients at risk for aspiration pneumonia.

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

Alcohol: Physicians should advise patients to avoid alcohol while taking REXULTI.

Concomitant Medication: Administer half the dose of REXULTI with strong CYP2D6 or CYP3A4 inhibitors. Administer a quarter of the dose with strong/moderate CYP2D6 inhibitors or known CYP2D6 poor metabolizers taken with strong/moderate CYP3A4 inhibitors. Double the dose with strong CYP3A4 inducers over 1 to 2 weeks.

In clinical trials examining the adjunctive use of REXULTI in the treatment of MDD, dosage was not adjusted for strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine). CYP considerations were already factored into general dosing recommendations for MDD. Thus, REXULTI may be administered without dosage adjustment in these patients.

Most commonly observed adverse reactions: Adult patients with major depressive disorder (adjunctive treatment to antidepressant therapy; $\geq 5\%$ incidence and twice incidence of placebo for REXULTI vs. placebo, respectively): akathisia (9% vs. 2%) and weight increase (7% vs. 2%). Adult patients with schizophrenia ($\geq 4\%$ 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: Non-Teratogenic Effects – Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. These complications have varied in severity, from being self-limited to requiring prolonged hospitalization. REXULTI should be used during pregnancy only if the potential benefit justifies the potential 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.

Please see [FULL PRESCRIBING INFORMATION](#), including **Boxed WARNING**, for REXULTI (brexpiprazole).

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)

About Otsuka America Pharmaceutical, Inc.

Otsuka America Pharmaceutical, Inc. (OAPI) is an innovative, fast-growing healthcare company that commercializes Otsuka-discovered and in-licensed products in the U.S., with a strong focus on neuroscience, oncology, cardio-renal, and medical devices. For more information, visit www.otsuka-us.com. OAPI is a subsidiary of Otsuka America, Inc. (OAI), a holding company established in the U.S. in 1989. OAI is wholly owned by Otsuka Pharmaceutical Co., Ltd., a global healthcare company with the corporate philosophy: 'Otsuka-people creating new products for better health worldwide.' Otsuka Pharmaceutical is a leading firm in the challenging area of mental

health and also has products and research programs for several under-addressed diseases including tuberculosis, a significant global public health issue. These commitments illustrate more powerfully than words how Otsuka is a “big venture” company at heart, applying a youthful spirit of creativity in everything it does. Otsuka Pharmaceutical and its affiliates employ approximately 30,000 people globally, and the company welcomes you to visit its global website at: <http://www.otsuka.co.jp/en/index.php>.

About Lundbeck

Lundbeck is a global pharmaceutical company specialized in brain diseases. For more than 70 years, we have been at the forefront of research within neuroscience. The key areas of focus are Alzheimer's disease, depression, Parkinson's disease and psychosis.

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.

Our approximately 5,500 employees in 57 countries are engaged in the entire value chain throughout research, development, production, marketing and sales. Our pipeline consists of several late-stage development programs and our products are available in more than 100 countries. We have research centres in China and Denmark and production facilities in China, Denmark, France and Italy. Lundbeck generated core revenue of DKK 13.5 billion in 2014 (EUR 1.8 billion; USD 2.4 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 www.LundbeckUS.com and connect with us on Twitter at @LundbeckUS.

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