



## H. Lundbeck A/S

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## Corporate Release

### US FDA approves labeling update of Rexulti® (brexpiprazole) for maintenance treatment of schizophrenia

- *Labeling update includes clinical data on use of Rexulti in adult patients with schizophrenia in the maintenance phase of treatment*
- *Approval was based on Rexulti demonstrating efficacy and safety in a long-term randomized withdrawal trial*
- *The trial demonstrated a statistically significant, longer time to relapse in patients treated with Rexulti compared to placebo-treated patients*

**Valby, Denmark and Princeton, New Jersey, 23 September 2016** - H. Lundbeck A/S (Lundbeck) and Otsuka Pharmaceutical Development & Commercialization, Inc. (Otsuka) announced today that the US Food and Drug Administration (FDA) approved the labeling update of Rexulti® (brexpiprazole) to reflect clinical data for maintenance treatment of schizophrenia. The approval was based on results from a long-term randomized withdrawal trial in adults with schizophrenia aged 18 to 65 years.

*“There are approximately 2.4 million adults in the US with schizophrenia<sup>i</sup> and 75% of patients experience relapses where their symptoms return or worsen<sup>ii</sup>,”* said Dr. Christoph U. Correll, Professor of Psychiatry, Hofstra Northwell School of Medicine and medical director, Recognition and Prevention Program (RAP), The Zucker Hillside Hospital, both in New York. *“These data, as included in the product labeling, confirm the utility of Rexulti in the maintenance treatment of patients with schizophrenia in order to help delay the time to relapse, giving patients and their physicians new data to consider when selecting an antipsychotic.”*

#### **Clinical Trial Results<sup>iii</sup>**

The safety and efficacy of Rexulti as maintenance treatment in adults with schizophrenia aged 18 to 65 years were demonstrated in a long-term randomized withdrawal trial. After cross-titration from a prior antipsychotic to Rexulti and a 12 to 36-week, single-blind Rexulti stabilization phase, patients who had been symptomatically stable on Rexulti for 12 consecutive weeks in the stabilization phase were randomized in a double-blind treatment phase to either Rexulti (n=97) or placebo (n=105). Impending relapse during the double-blind phase was determined if patients met any of the following pre-specified criteria: worsening symptoms defined by changes in PANSS or CGI-I scores; hospitalization for worsening psychotic symptoms; suicidal behavior or; violent/aggressive behavior.



A pre-specified interim analysis conducted after about 50% of the expected relapses (in order to minimize continued exposure to placebo) demonstrated a statistically significant longer time to relapse in patients randomized to Rexulti compared to placebo. The trial was subsequently terminated early because maintenance of efficacy had been demonstrated. The final analysis demonstrated a statistically significant longer time to relapse (hazard ratio: 0.292,  $p < 0.0001$ ) in patients randomized to Rexulti (1 mg/day to 4 mg/day) compared to placebo. The key secondary endpoint, the proportion of subjects who met the criteria for impending relapse, was statistically significantly lower in Rexulti-treated patients compared with placebo group.

### **Brexpiprazole in Europe**

Lundbeck and Otsuka anticipate submitting a Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) for the use of brexpiprazole in the treatment of adult patients with schizophrenia.

### **About Rexulti (brexpiprazole)**

Rexulti is 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<sub>1A</sub> and dopamine D<sub>2</sub> receptors, and antagonist activity at serotonin 5-HT<sub>2A</sub> receptors. Rexulti exhibits high affinity (sub-nanomolar) for these receptors as well as for noradrenaline alpha<sub>1B/2C</sub> receptors. The drug was approved in the US in July 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**

##### **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):** 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 with immediate discontinuation, 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. TD can develop after a relatively brief treatment period, even at low doses, or after discontinuation of treatment. If signs and symptoms of TD appear, drug discontinuation should be considered.

**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 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:** 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:** 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, respectively): akathisia (9% vs. 2%) and weight increase (7% vs. 2%)
- 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:** 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](http://www.fda.gov/medwatch)).

Please see accompanying FULL PRESCRIBING INFORMATION, including BOXED WARNING.

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### About H. Lundbeck A/S

H. Lundbeck A/S (LUN.CO, LUN DC, HLUY) 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 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 programmes 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 14.6 billion in 2015 (EUR 2 billion; USD 2.2 billion).

For additional information, we encourage you to visit our corporate site [www.lundbeck.com](http://www.lundbeck.com) and connect with us on Twitter at @Lundbeck.

### About Otsuka Pharmaceutical Development & Commercialization, Inc.

Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) is an innovative, fast-growing healthcare company that discovers and develops new compounds that address unanswered medical needs and advance human health. With a focus on neuroscience, oncology, and cardio-renal treatments, OPDC is dedicated to improving the health and quality of human life. For more information, visit [www.otsuka-us.com](http://www.otsuka-us.com) and follow Otsuka on Twitter at @OtsukaUS.

OPDC 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. The Otsuka Group employs approximately



42,000 people globally and its products are available in more than 80 countries worldwide. Otsuka welcomes you to visit its global website at <http://www.otsuka.co.jp/en/index.php>.

### **Safe Harbor/Forward-Looking Statements**

The above information contains forward-looking statements that provide our expectations or forecasts of future events such as new product introductions, product approvals and financial performance.

Such forward-looking statements are subject to risks, uncertainties and inaccurate assumptions. This may cause actual results to differ materially from expectations and it may cause any or all of our forward-looking statements here or in other publications to be wrong. Factors that may affect future results include interest rate and currency exchange rate fluctuations, delay or failure of development projects, production problems, unexpected contract breaches or terminations, government-mandated or market-driven price decreases for Lundbeck's products, introduction of competing products, Lundbeck's ability to successfully market both new and existing products, exposure to product liability and other lawsuits, changes in reimbursement rules and governmental laws and related interpretation thereof, and unexpected growth in costs and expenses.

Certain assumptions made by Lundbeck are required by Danish Securities Law for full disclosure of material corporate information. Some assumptions, including assumptions relating to sales associated with product that is prescribed for unapproved uses, are made taking into account past performances of other similar drugs for similar disease states or past performance of the same drug in other regions where the product is currently marketed. It is important to note that although physicians may, as part of their freedom to practice medicine in the US, prescribe approved drugs for any use they deem appropriate, including unapproved uses, at Lundbeck, promotion of unapproved uses is strictly prohibited.

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<sup>i</sup> The National Alliance of Mental Illness, Mental Illness Facts and Numbers. March 2013. Available at:

[http://www2.nami.org/factsheets/mentalillness\\_factsheet.pdf](http://www2.nami.org/factsheets/mentalillness_factsheet.pdf)

<sup>ii</sup> British Medical Journal of Clinical Evidence. Schizophrenia (maintenance treatment). April 2009.

<http://www.ncbi.nlm.nih.gov/pubmed/19445748>

<sup>iii</sup> Clinical Trials ID: NCT01668797