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Corporate Release

FDA approves Rexulti® (brexpiprazole) as adjunctive treatment for adults with major depressive disorder and as a treatment for adults with schizophrenia

- *There are approximately 15 million adults in the US with major depressive disorder (MDD), and many of them have an inadequate response to monotherapy with antidepressants^{i, ii}. There are 2.4 million adults with schizophrenia in the US, many of whom continue to need effective treatmentsⁱ*
- *The US approval of Rexulti is based on a clinical program in which Rexulti showed improvement vs. placebo in symptoms when used as an adjunctive therapy in MDD and as monotherapy in schizophrenia*
- *Rexulti will become available to patients in the US in early August 2015*

Valby, Denmark and Tokyo, Japan – 11 July 2015 - H. Lundbeck A/S (Lundbeck) and Otsuka Pharmaceutical Co., Ltd. (Otsuka) announced today that the US Food and Drug Administration (FDA) approved Rexulti® (brexpiprazole) as an adjunctive therapy for the treatment of adults with major depressive disorder (MDD) and as a treatment for adults with schizophrenia. Rexulti was discovered by Otsuka and co-developed with Lundbeck. It will be co-marketed by the two companies and is expected to become available to patients in the US in early August 2015.

The mechanism of action of Rexulti in the treatment of MDD 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. In addition, Rexulti exhibits high affinity (subnanomolar) for these receptors, as well as for noradrenaline alpha_{1B/2C} receptorsⁱⁱⁱ.

Rexulti was studied in more than 4,300 subjects in phase II and III clinical trials, and the approval was supported by four completed placebo-controlled clinical phase III studies in the now-approved indications – two studies as adjunctive therapy to antidepressants in MDD and two studies in schizophrenia.



Rexulti as MDD adjunctive treatment in adults

“For some patients with MDD, antidepressant monotherapy is not enough, and these patients continue to suffer from unresolved symptoms,” said Michael E. Thase, MD, Professor of Psychiatry, Director, Mood and Anxiety Program, University of Pennsylvania School of Medicine and study investigator. *“In the clinical trials that led to the FDA’s approval, adding brexpiprazole to ongoing antidepressant therapy helped MDD patients improve unresolved symptoms of MDD.”*

As adjunctive therapy for MDD, the efficacy of Rexulti was evaluated in two, 6-week, placebo-controlled clinical trials of adult patients. Patients met the DSM-IV-TR criteria for MDD, with or without symptoms of anxiety, and previously failed to reach an adequate response during one to three treatment attempts with antidepressant therapy (ADT), and further failed to reach adequate response in a single-blind ADT phase for 8 weeks. The primary endpoint for both studies was change in MADRS (Montgomery–Åsberg Depression Rating Scale). Data from the clinical trials showed:

- Rexulti + ADT at 2 mg and 3 mg was superior to placebo; the mean baseline MADRS score decreased from 27 at randomization by 8.36 (2 mg) and 8.29 (3 mg), compared to placebo + ADT reductions of 5.15 and 6.33 in the respective studies; the 1 mg dose was not superior to placebo.
- Discontinuation due to adverse reactions was 3% for Rexulti + ADT compared with 1% for placebo + ADT. The most common adverse reactions for the pooled doses of adjunctive Rexulti + ADT (at least 5% and with twice the incidence of placebo), included akathisia (9% vs. 2% for placebo), and weight increase (7% vs. 2% for placebo).

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.

Rexulti as schizophrenia treatment in adults

“One key priority for physicians is to find medications that help improve symptoms and are tolerable for patients,” said Dr. Christoph U. Correll, Professor of Psychiatry, Hofstra North Shore LIJ School of Medicine and Medical Director, Recognition and Prevention Program (RAP), The Zucker Hillside Hospital, both in New York, and lead author of one of the study reports. *“In the Rexulti clinical trials for schizophrenia, we saw a combination of efficacy and symptom improvement within a tight target dose range with one adverse event, weight increase, occurring in at least 4% of patients and with twice the incidence of placebo.”*

The efficacy of Rexulti was established in two, 6-week, phase III randomized, placebo-controlled clinical trials with fixed doses of Rexulti vs. placebo. Clinical trial data showed:

- Rexulti, at an adequate dose for 6 weeks, demonstrated statistically significant efficacy for the primary endpoint of PANSS (Positive and Negative Syndrome Scale)
- In one trial, change from baseline in PANSS total score for Rexulti at both 2 mg/day and 4 mg/day (-20.73 and -19.65) was superior to placebo (-12.01); in a second trial, the change from baseline in PANSS total score at a dose of 4 mg/day (-20.00 vs. -13.53, respectively) was superior to placebo (2 mg was not superior to placebo in this trial)



- The most common adverse reactions (incidence of 4% or greater, and twice the incidence of placebo) from the pooled safety data associated with Rexulti at 1, 2 and 4 mg vs. placebo, included weight gain (4% vs. 2%, respectively)
- The incidence of somnolence (also including sedation and hypersomnia) in all patients with schizophrenia who received Rexulti (n=1,256) was 4.9% compared to 3.2% for patients receiving placebo (n=463).

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.

"Psychiatric diseases remain a challenging therapeutic area where many people are unsatisfied with their treatments," noted Tatsuo Higuchi, President and Representative Director, Otsuka Pharmaceutical, Co., Ltd. *"Today's approval of Rexulti is another example of Otsuka and Lundbeck's commitment to bringing new therapeutic alternatives to the mental health community."*

"All treatment options require healthcare providers, patients and caregivers to balance efficacy and tolerability in managing their diseases," said Kåre Schultz, President and CEO, Lundbeck. *"We are proud to introduce Rexulti to help adult patients living with MDD and schizophrenia."*

Rexulti will become available to patients in the US in early August 2015. It is given in a once-daily oral dose with a well-defined titration schedule that can be taken with or without food.

- MDD: Initiate treatment at 0.5 g or 1 mg once daily. Titrate at weekly intervals to 1 mg once daily, then up to the target dosage of 2 mg once daily based on the patient's clinical response and tolerability
- Schizophrenia: Initiate treatment at 1 mg once daily for the first 4 days. Titrate to 2 mg once daily on Day 5 through Day 7, then to 4 mg on Day 8 based on the patient's clinical response and tolerability
- Specific dosage adjustments for inhibitors and inducers of the metabolism of Rexulti are described in the USPI

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 or 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 accompanying 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)

Financial guidance

The content of this release will have no influence on the Lundbeck Group's financial guidance for 2015, which was provided on 5 February 2015.

Lundbeck is obliged to make a milestone payment to Otsuka of USD 200 million upon approval.

About Rexulti® (brexpiprazole)

Rexulti is a new molecule (i.e., not a metabolite or isomer) discovered by Otsuka and co-developed by Otsuka and Lundbeck. The mechanism of action for Rexulti in the 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. In addition, Rexulti exhibits high affinity (subnanomolar) for these receptors as well as for noradrenaline $\alpha_{1B/2C}$ receptors.ⁱⁱⁱ The drug was approved in the US on 10 July, as an adjunctive therapy to antidepressants in adults with major depressive disorder and as a treatment in adults with schizophrenia.



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About Lundbeck

H. Lundbeck A/S (LUN.CO, LUN DC, HLUYY) is a global pharmaceutical company specialized in brain diseases. For more than 70 years, we have been at the forefront of research within neuroscience. Our key areas of focus are alcohol dependence, Alzheimer's disease, bipolar disorder, depression/anxiety, epilepsy, Huntington's disease, Parkinson's disease, schizophrenia and symptomatic neurogenic orthostatic hypotension (NOH).

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.



Lundbeck has approximately 6,000 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 100 countries. We have research centers in China, Denmark and the United States and production facilities in China, Denmark, France and Italy. Lundbeck generated revenue of approximately DKK 13.5 billion in 2014 (EUR 1.8 billion; USD 2.4 billion).

Lundbeck's shares are listed on the stock exchange in Copenhagen under the symbol "LUN". Lundbeck has a sponsored Level 1 ADR program listed in the US (OTC) under the symbol "HLUYY".

For additional information, we encourage you to visit our corporate site www.lundbeck.com.

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 and original 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, which employs approximately 28,700 people worldwide, is a wholly owned subsidiary of Otsuka Holdings Co., Ltd., the holding company for the Otsuka Group that is headquartered in Tokyo, Japan. The Otsuka Group has business operations in 26 countries and regions around the world, with consolidated sales of approximately USD 10.2 billion in fiscal year 2014, a nine-month period (4/1/2014-12/31/2014) due to the company's change to a calendar year reporting cycle. Otsuka welcomes you to visit its global website at <https://www.otsuka.co.jp/en>.

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.

ⁱ The National Alliance of Mental Illness, Mental Illness Facts and Numbers. March 2013. Available at: http://www2.nami.org/factsheets/mentalillness_factsheet.pdf

ⁱⁱ Rush, J. et al. Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report.

ⁱⁱⁱ Maeda, K. et al. Pharmacological Profile of Brexpiprazole (OPC-2471234712): a Novel Serotonin-Dopamine Activity Modulator. Poster presentation at American Psychiatric Association annual meeting, 3-7 May 2014