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Company name Otsuka Holdings Co., Ltd.
Representative Tatsuo Higuchi
President and Representative Director, CEO
Code number 4578 First Section , Tokyo Stock Exchange
Inquiries Yuji Kogure
Director, Investors Relations Department

U.S. FDA APPROVES OTSUKA AND LUNDBECK'S REXULTI® (BREXPIRAZOLE) AS ADJUNCTIVE TREATMENT FOR ADULTS WITH MAJOR DEPRESSIVE DISORDER AND AS A TREATMENT FOR ADULTS WITH SCHIZOPHRENIA

Otsuka Pharmaceutical Co., Ltd., a wholly-owned subsidiary of Otsuka Holdings Co. Ltd., and H. Lundbeck A/S today announced that the U.S. Food and Drug Administration (FDA) approved REXULTI® (brexpirazole) on July 10, 2015 as an adjunctive therapy for the treatment of adults with major depressive disorder (MDD) and as a treatment for adults with schizophrenia.

- There are approximately 15 million adults in the U.S. with major depressive disorder (MDD), and many of them have an inadequate response to monotherapy with antidepressants.^{1,2} There are 2.4 million adults with schizophrenia in the U.S., many of whom continue to need effective treatments.³
- The 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 U.S. in early August 2015.

Tokyo, Japan and Valby, Denmark – July 11, 2015(JST) – Otsuka Pharmaceutical Co., Ltd. (Otsuka) and H. Lundbeck A/S (Lundbeck) announced today that the U.S. Food and Drug Administration (FDA) approved REXULTI® (brexpirazole) 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 U.S. 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 $\alpha_{1B/2C}$ receptors.³

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 U.S. 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 mg 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)

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.³ 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.

¹ The National Alliance of Mental Illness, Mental Illness Facts and Numbers. March 2013. Available at: http://www2.nami.org/factsheets/mentalillness_factsheet.pdf

² Rush, J. et al. Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report.

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