



## **U.S. FDA APPROVES OTSUKA AND LUNDBECK'S REXULTI® (BREXPIPIRAZOLE) 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 U.S. with major depressive disorder (MDD), and many of them have an inadequate response to monotherapy with antidepressants.<sup>1,2</sup> There are 2.4 million adults with schizophrenia in the U.S., many of whom continue to need effective treatments.<sup>1</sup>
- 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** – Otsuka Pharmaceutical Co., Ltd. (Otsuka) and H. Lundbeck A/S (Lundbeck) announced today that the U.S. 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 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<sub>1A</sub> and dopamine D<sub>2</sub> receptors, and antagonist activity at serotonin 5-HT<sub>2A</sub> receptors. In addition, REXULTI exhibits high affinity (subnanomolar) for these receptors, as well as for noradrenaline alpha<sub>1B/2C</sub> receptors.<sup>3</sup>

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.

### **About REXULTI<sup>®</sup> (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<sub>1A</sub> and dopamine D<sub>2</sub> receptors, and antagonist activity at serotonin 5-HT<sub>2A</sub> receptors. In addition, REXULTI exhibits high affinity (subnanomolar) for these receptors as well as for noradrenaline alpha<sub>1B/2C</sub> receptors.<sup>3</sup> 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.

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<sup>1</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>2</sup> Rush, J. et al. Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR\*D Report.

<sup>3</sup> 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