



## **FDA Accepts a Supplemental New Drug Application for Review of Brintellix<sup>®</sup> (vortioxetine) Clinical Trial Data That Assessed Cognitive Function in Patients with Major Depressive Disorder**

**Osaka, Japan, August 10, 2015 and Valby, Denmark, August 10, 2015** – Takeda Pharmaceutical Company Limited (Takeda) and H. Lundbeck A/S (Lundbeck) announced today the U.S. Food and Drug Administration (FDA) has accepted a supplemental New Drug Application (sNDA) for review to add clinical data regarding the effect of Brintellix (vortioxetine) on certain aspects of cognitive function in adults with Major Depressive Disorder (MDD) to the current product label. Brintellix is currently approved and available in the U.S. for the treatment of MDD in adults. The FDA is expected to take action on this filing by March 28, 2016.

Depression includes a range of symptoms including cognitive ones.<sup>i</sup> The cognitive symptoms of depression may go unrecognized by both healthcare providers and patients. Common cognitive complaints include difficulty concentrating, indecisiveness, trouble thinking and forgetfulness.<sup>ii</sup> These symptoms are common and many of them often persist between major depressive episodes.<sup>iii</sup> According to a three-year prospective study of people treated for depression, cognitive symptoms (defined as diminished ability to think or concentrate and/or indecisiveness) were reported 94 percent of the time during major depressive episodes and 44 percent of the time between major depressive episodes (or during periods of partial remission).<sup>ii</sup>

“Cognitive symptoms are often present in patients suffering from MDD and reducing these symptoms can be challenging,” explains John Zajecka, M.D., Associate Professor of Psychiatry, Rush University Medical Center, in Chicago. “Many patients continue to experience certain cognitive and other symptoms even after improvement in their MDD.”

The sNDA is primarily based on the FOCUS and CONNECT studies, which were specifically designed to assess the effect of Brintellix on certain aspects of cognitive function in adult patients with MDD utilizing objective measures of cognitive function.<sup>iii,iv</sup> These two 8-week, randomized, double-blind, placebo-controlled studies of Brintellix 10 and 20 mg/day used a well-established neuropsychological test (the Digit Symbol Substitution Test or DSST).<sup>iii,iv</sup> The DSST performance measurement involves executive function, processing speed and attention.<sup>iii,iv</sup>

“If approved by the FDA, Brintellix would be the first treatment for MDD to include clinical trial data showing an effect on certain aspects of cognitive function in the U.S. label. We look forward to working with the Agency as it considers this important need for patients with MDD,” said Charlie Baum, M.D., Vice President, U.S. Medical Affairs, Takeda.

“The rigorous studies we have conducted with Brintellix evaluating the effects on certain aspects of cognitive functioning in patients with MDD are examples of the commitment our companies have to assessing prevalent cognitive symptoms in patients with MDD - in particular, a core set of symptoms that remain problematic for many people with depression,” said Staffan Schuberg, President, Lundbeck U.S. “We look forward to contributing to this emerging area of clinical understanding with the hopes of increasing the awareness of the burden of this disorder.”

The FDA approved Brintellix on September 30, 2013 for the treatment of MDD in adults.

Patients can visit [www.brintellix.com](http://www.brintellix.com) to sign up for additional information about this treatment option.

### **About Brintellix (vortioxetine)**

The mechanism of the antidepressant effect of Brintellix is not fully understood. It is an inhibitor of serotonin (5-HT) reuptake and that is thought to be a mechanism of its action. It is also an agonist at 5-HT<sub>1A</sub> receptors, a partial agonist at 5-HT<sub>1B</sub> receptors and an antagonist at 5-HT<sub>3</sub>, 5-HT<sub>1D</sub> and 5-HT<sub>7</sub> receptors. The contribution of each of these activities to Brintellix's antidepressant effect has not been established. It is considered to be the first and only compound with this combination of pharmacodynamic activity. The clinical relevance of this is unknown.

Brintellix was discovered by Lundbeck researchers in Copenhagen, Denmark. The clinical trial program in the U.S. was conducted jointly by Lundbeck and Takeda, and Takeda holds the new drug application for the U.S. market. Brintellix is a trademark of H. Lundbeck A/S and is used under license by Takeda Pharmaceuticals U.S.A., Inc.

The World Health Organization has issued an Anatomical Therapeutic Chemical (ATC) code for Brintellix that places it in the category of "Other" antidepressants.

The most commonly observed adverse events in MDD patients treated with Brintellix in 6-8 week placebo-controlled studies (incidence greater than or equal to 5 percent and at least twice the rate of placebo) were nausea, constipation and vomiting. Overall, 5 to 8 percent of the patients who received Brintellix 5 to 20 mg/day in short-term trials discontinued treatment due to an adverse reaction, the most common being nausea, compared with 4 percent of placebo-treated patients in these studies. Brintellix and other antidepressants may cause serious side effects. See Important Safety Information below.

In clinical studies, Brintellix had no significant effect on body weight as measured by the mean change from baseline in 6-8 week placebo-controlled studies. In the 6-month, double-blind, placebo-controlled phase of a long-term study in patients who had responded to Brintellix during the initial 12-week, open-label phase, there was no significant effect on body weight between Brintellix and placebo-treated patients. Brintellix has not been associated with any clinically significant effects on vital signs, including systolic and diastolic blood pressure and heart rate, as measured in placebo-controlled studies.

The recommended starting dose of Brintellix is 10 mg once daily without regard to meals. The dose should then be increased to 20 mg/day, as tolerated, because higher doses demonstrated better treatment effects in trials conducted in the U.S. A dose decrease down to 5 mg/day may be considered for patients who do not tolerate higher doses. The available doses provide important flexibility for physicians to help address the variability of patient needs.

Brintellix is available as 5 mg, 10 mg and 20 mg tablets.

### **IMPORTANT SAFETY INFORMATION**

#### **Suicidal Thoughts and Actions and Antidepressant Drugs**

**Antidepressants may increase suicidal thoughts or actions in some children, teens or young adults within the first few months of treatment or when the dose is changed. Depression or other serious mental illnesses are the most important causes of suicidal thoughts or actions. People who have (or have a family history of) bipolar illness, or suicidal thoughts or actions may have a particularly high risk. Pay close attention to any changes, especially sudden changes in mood, behavior, thoughts or feelings. Call your healthcare provider right away if symptoms such as anxiety, irritability, impulsivity, trouble sleeping, aggressive behavior or suicidal thoughts are new, worse or worry you. BRINTELLIX has not been evaluated for use in patients under 18.**

**Do not take BRINTELLIX if you:**

- Are allergic to vortioxetine or any of the ingredients in BRINTELLIX
- Take a Monoamine Oxidase Inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI, including the antibiotic linezolid; do not take an MAOI within 21 days of stopping BRINTELLIX; do not start BRINTELLIX if you stopped taking an MAOI in the last 14 days

**BRINTELLIX may cause serious side effects including:**

**Serotonin Syndrome:** A potentially life-threatening problem that can happen when medicines such as BRINTELLIX are taken with certain other medicines. Symptoms may include agitation, hallucinations, coma or other changes in mental status; problems controlling movements or muscle twitching, stiffness or tightness; fast heartbeat, high or low blood pressure; sweating or fever; nausea, vomiting or diarrhea.

**Abnormal bleeding or bruising:** BRINTELLIX and other serotonergic antidepressant medicines may increase your risk of bleeding or bruising, especially if you take the blood thinner warfarin (Coumadin®, Jantoven®), a non-steroidal anti-inflammatory drug (NSAID), or aspirin.

**Manic episode:** Symptoms may include greatly increased energy; severe trouble sleeping; racing thoughts; reckless behavior; unusually grand ideas; excessive happiness or irritability; talking more or faster than usual.

**Visual problems:** May include eye pain, changes in vision, swelling or redness in or around the eye. Only some people are at risk for these problems. You may want to undergo an eye examination to see if you are at risk and receive preventative treatment if you are.

**Low salt (sodium) levels in the blood:** Symptoms may include headache; difficulty concentrating, memory changes or confusion; weakness and unsteadiness on your feet; and in severe or sudden cases hallucinations, fainting, seizures or coma. If not treated, severe low sodium levels can cause death.

**Before starting BRINTELLIX, tell your healthcare provider if** you have or had liver problems, seizures or convulsions, bipolar disorder (manic depression) or mania, low salt (sodium) levels in your blood, bleeding problems, drink alcohol, have any other medical conditions or if you are pregnant, nursing, plan to become pregnant, or plan to nurse.

**BRINTELLIX and some medicines may interact with each other, may not work as well, or may cause serious side effects when taken together.** Tell your healthcare provider if you plan on or are taking any other prescription and non-prescription medicines, vitamins and herbal supplements including medicines for migraine headaches, such as triptans; medicines used to treat mood, anxiety, psychotic or thought disorders such as tricyclics, lithium, SSRIs, SNRIs, bupropion, buspirone or antipsychotics; MAOIs including linezolid (a specific antibiotic); over-the-counter supplements such as tryptophan or St. John's wort; and the following medicines: aspirin, NSAIDs, warfarin (Coumadin®, Jantoven®), diuretics, rifampicin, carbamazepine, phenytoin, quinidine, tramadol or fentanyl.

**Common side effects of BRINTELLIX include:** nausea, constipation or vomiting. These are not all the possible side effects of BRINTELLIX.

**Do not start or stop taking BRINTELLIX without talking to your healthcare provider first.** Suddenly stopping BRINTELLIX when you take higher doses may cause you to have side effects including headache, stiff muscles, mood swings, sudden outbursts of anger, dizziness or feeling lightheaded, or runny nose.

Until you know how BRINTELLIX affects you, do not drive, operate heavy machinery or engage in other dangerous activities.

Avoid drinking alcohol while taking BRINTELLIX.

Talk to your healthcare provider.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or call 1-800-FDA-1088.

### **Indication for BRINTELLIX**

BRINTELLIX is a prescription medicine used to treat Major Depressive Disorder (MDD) in adults.

Please see full [Prescribing Information](#), including [Medication Guide](#) for BRINTELLIX.

### **About Takeda Pharmaceutical Company Limited**

Located in Osaka, Japan, Takeda ([TSE: 4502](#)) is a research-based global company with its main focus on pharmaceuticals. As the largest pharmaceutical company in Japan and one of the global leaders of the industry, Takeda is committed to strive towards better health for people worldwide through leading innovation in medicine.

Additional information about Takeda is available through its corporate website, [www.takeda.com](http://www.takeda.com).

### **About Takeda Pharmaceuticals U.S.A., Inc. and Takeda Development Center Americas, Inc.**

Based in Deerfield, Ill., Takeda Pharmaceuticals U.S.A., Inc. and Takeda Development Center Americas, Inc. are subsidiaries of Takeda Pharmaceutical Company Limited, the largest pharmaceutical company in Japan. The respective companies currently market oral diabetes, CNS, rheumatology, gastroenterology and cardiovascular disease treatments and seek to bring innovative products to people through a pipeline that includes compounds in development for diabetes, gastroenterology, neurology and other conditions. To learn more about these Takeda companies, visit [www.takeda.us](http://www.takeda.us).

### **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. 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](http://www.lundbeck.com/global/about-us/progress-in-mind).

In 2015, Lundbeck can celebrate its 100th anniversary. During the past century, millions of people have been treated with our therapies. It is complex and challenging to develop improved treatments for brain disease, but we keep our focus: There is still so much we need to achieve in the next 100 years to ensure a better life for people living with brain disease.

Lundbeck has approximately 6,000 employees in 57 countries who are engaged in the entire value chain throughout research, development, production, 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, Denmark and the United States 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).

#### *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](http://www.LundbeckUS.com) and connect with us on Twitter at @LundbeckUS.

*This press release contains forward-looking statements. Forward-looking statements include statements regarding Takeda's plans, outlook, strategies, results for the future, and other statements that are not descriptions of historical facts. Forward-looking statements may be identified by the use of forward-looking words such as "may," "believe," "will," "expect," "project," "estimate," "should," "anticipate," "plan," "assume," "continue," "seek," "pro forma," "potential," "target," "forecast," "guidance," "outlook" or "intend" or other similar words or expressions of the negative thereof. Forward-looking statements are based on estimates and assumptions made by management that are believed to be reasonable, though they are inherently uncertain and difficult to predict. Investors are cautioned not to unduly rely on such forward-looking statements.*

*Forward-looking statements involve risks and uncertainties that could cause actual results or experience to differ materially from that expressed or implied by the forward-looking statements. Some of these risks and uncertainties include, but are not limited to, (1) the economic circumstances surrounding Takeda's business, including general economic conditions in Japan, the United States and worldwide; (2) competitive pressures and developments; (3) applicable laws and regulations; (4) the success or failure of product development programs; (5) actions of regulatory authorities and the timing thereof; (6) changes in exchange rates; (7) claims or concerns regarding the safety or efficacy of marketed products or product candidates in development; and (8) integration activities with acquired companies.*

*The forward-looking statements contained in this press release speak only as of the date of this press release, and Takeda undertakes no obligation to revise or update any forward-looking statements to reflect new information, future events or circumstances after the date of the forward-looking statement. If Takeda does update or correct one or more of these statements, investors and others should not conclude that Takeda will make additional updates or corrections.*

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#### **Takeda Pharmaceutical Company Limited Contacts**

##### **Japanese media**

Nanako Nakamura

Tel: +81-3-3278-2339

Email: [nanako.nakamura@takeda.com](mailto:nanako.nakamura@takeda.com)

##### **Media outside Japan**

Roseanne Durril

Tel: +1-224-554-1474

Email: [roseanne.durril@takeda.com](mailto:roseanne.durril@takeda.com)

#### **H. Lundbeck A/S Contacts**

##### **Investors:**

Palle Holm Olesen

Chief Specialist, Head of Investor Relations

[palo@lundbeck.com](mailto:palo@lundbeck.com)

+45 36 43 24 26

##### **Media:**

##### **EUROPE**

Mads Kronborg

Media Relations Manager

[mavk@lundbeck.com](mailto:mavk@lundbeck.com)

+45 36 43 30 30

##### **U.S.**

Ashleigh Duchene

Public Affairs

Lundbeck US

+1 847 282 1164

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<sup>1</sup> Diagnostic and Statistical Manual of Mental Disorders (DSM-5). (5th ed., 155-188). America Psychiatric Association, 2013.

<sup>ii</sup> Conradi, H., Ormel, J., & De Jonge, P. (2011). Presence of individual (residual) symptoms during depressive episodes and periods of remission: A 3-year prospective study. *Psychological Medicine*, 41(06), 1165-1174.

<sup>iii</sup> McIntyre R.S., Olsen K. (2014). A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *Int J Neuropsychopharm.*17, 1557-1567.

<sup>iv</sup> Mahableshwarkar A.R., Zajecka J., Jacobson W., et al. (2015). A Randomized, Placebo-Controlled, Active-Reference, Double-Blind, Flexible-Dose Study of the Efficacy of Vortioxetine on Cognitive Function in Major Depressive Disorder. *Neuropsychopharm.* 40, 2025-2037.