



Takeda and Lundbeck Receive Complete Response Letter for Brintellix[®] (vortioxetine) sNDA

Osaka, Japan, March 29, 2016 and Valby, Denmark, March 29, 2016 – Takeda Pharmaceutical Company Limited (Takeda) and H. Lundbeck A/S (Lundbeck) today announced that the U.S. Food and Drug Administration (FDA) issued a complete response letter (CRL) for the supplemental new drug application (sNDA) to include new data in the clinical trials section of the U.S. label of Brintellix[®] (vortioxetine) for treating certain aspects of cognitive dysfunction in adults with major depressive disorder (MDD). The FDA approved Brintellix on September 30, 2013 for the treatment of MDD in adults. The CRL does not apply to the use of Brintellix in MDD.

Takeda and Lundbeck are disappointed with the response given that the U.S. FDA Psychopharmacologic Drugs Advisory Committee (PDAC) voted 8 to 2 that Takeda and Lundbeck presented substantial evidence to support a claim of effectiveness for Brintellix in treating certain aspects of cognitive dysfunction in adults with MDD.¹ However, the companies were pleased that FDA recognized the importance of cognitive dysfunction in MDD and view it as a legitimate target for drug development.

Takeda and Lundbeck look forward to reviewing the contents of the letter with the FDA to determine the appropriate path forward.

We remain committed to the depression community and Brintellix as a treatment option for patients with MDD.

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_{1A} receptors, a partial agonist at 5-HT_{1B} receptors and an antagonist at 5-HT₃, 5-HT_{1D} and 5-HT₇ 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

USD/VOR/16/0053

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 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.

About Lundbeck

Lundbeck is a global pharmaceutical company specialized in brain diseases. For more than 70 years, we have been at the forefront of a research within neuroscience. The key areas of focus are Alzheimer's disease, depression, Parkinson's disease and psychosis.

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.

Our approximately 5,500 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 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 and connect with us on Twitter at @Lundbeck.

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 and connect with us on Twitter at @LundbeckUS.

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ⁱ U.S. Food and Drug Administration (FDA). (2016, February 3). *Summary Minutes Meeting of the Psychopharmacologic Drugs Advisory Committee*. Retrieved from: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM491913.pdf>.