New Data Added to TRINTELLIX® (vortioxetine) Labeling Demonstrated Superiority Over Escitalopram in Improving SSRI-Induced Sexual Dysfunction in Patients with Major Depressive Disorder

- TRINTELLIX is the first antidepressant to include head-to-head data in its labeling that showed improvement in treatment-emergent sexual dysfunction in patients with MDD who switched from certain SSRI treatments.
- This is the second time this year the FDA has approved a TRINTELLIX labeling update.

Deerfield, IL, October 22, 2018 – Takeda Pharmaceuticals U.S.A., Inc. (“Takeda”) and Lundbeck today announced that the U.S. Food and Drug Administration (FDA) approved a supplemental new drug application (sNDA) for TRINTELLIX® (vortioxetine), a prescription medication used for adults with major depressive disorder (MDD), also known as depression.

The TRINTELLIX U.S. prescribing information now includes head-to-head clinical study data that demonstrated superiority to a commonly-used selective serotonin reuptake inhibitor (SSRI), Lexapro® (escitalopram) in improving treatment-emergent sexual dysfunction (TESD). In the study, patients with well-treated depression who were experiencing TESD while taking an SSRI (paroxetine, sertraline or citalopram) were switched to TRINTELLIX or escitalopram. This is the first time an antidepressant has included data of this type in its labeling. These data build upon the voluntary and prospective reports of sexual dysfunction with TRINTELLIX in clinical trials.

“Sexual dysfunction is one of the most common and bothersome side effects patients with depression struggle with when prescribed an SSRI,” said lead study investigator, Dr. Anita Clayton, Chair, Department of Psychiatry & Neurobehavioral Sciences, University of Virginia School of Medicine. “We designed the study to specifically look at these troublesome side effects. Changing to a medication with potentially fewer sexual side effects, while not losing progress in treating depression, provides an important option for patients with depression.”

TESD can affect any aspect of the sexual response cycle including desire, arousal and orgasm.

In an eight-week head-to-head, randomized, double-blind study, well-treated adult MDD patients with TESD (N=447) were switched to TRINTELLIX (N=225) or escitalopram (N=222), from citalopram, paroxetine, or sertraline, due to SSRI-induced sexual dysfunction. For both TRINTELLIX and escitalopram, patients were started on 10 mg, increased to 20 mg at week one, followed by flexible dosing (10 mg or 20 mg). TRINTELLIX demonstrated statistically significant improvement vs. escitalopram from baseline to week eight as measured by mean Change in Sexual Functioning Questionnaire Short Form (CSFQ-14) Total Score (8.8 vs. 6.6, p=0.013). Both drugs maintained prior improvement in depression based on overall score on standardized depression rating scale.

“There remains a need for effective antidepressants that may have less impact on sexual function. We are pleased with the FDA’s decision to approve the addition of this meaningful comparative data in the U.S. labeling of TRINTELLIX,” said Dr. Louis Mini, Medical Head, Neuroscience, U.S. Medical Office, Takeda.

“One of our key priorities is to develop treatment options for depression that address what matters to patients. We aim to find ways patients can get the most benefit from therapy and this news is a step forward with that goal,” said Doug Williamson, Chief Medical Officer and Vice President, U.S. Medical, Lundbeck.

In the five years since FDA approval on September 30, 2013, more than 845,000 patients have been prescribed TRINTELLIX. Vortioxetine is approved in 77 countries and available in more than 60 countries to date. This is the second time this year FDA has approved an sNDA for TRINTELLIX to add new data to the TRINTELLIX U.S. labeling.
About Major Depressive Disorder (MDD)
MDD is a complex mental health illness that affects approximately 16 million people annually. Also known as clinical depression, MDD is the leading cause of disability worldwide and a major contributor to the overall global burden of disease. MDD may trigger emotional, cognitive and physical symptoms, which includes depressed mood, loss of interest or pleasure, significant weight loss or gain or change in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive guilt, diminished ability to think or concentrate, or indecisiveness, and recurrent suicidal ideation.

About TRINTELLIX (vortioxetine)
The mechanism of the antidepressant effect of TRINTELLIX 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-HT1A receptors, a partial agonist at 5-HT1B receptors and an antagonist at 5-HT3, 5-HT1D and 5-HT7 receptors. The contribution of each of these activities to TRINTELLIX’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.

The most commonly observed adverse events in MDD patients treated with TRINTELLIX 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 TRINTELLIX 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. TRINTELLIX and other antidepressants may cause serious side effects. See Important Safety Information below.

Voluntary reports of sexual dysfunction with TRINTELLIX in 6-8 week controlled trials were \( \leq 5\% \). Because voluntary reports of sexual dysfunction are known to be underreported, a separate, self-rated questionnaire was provided to patients prospectively in TRINTELLIX clinical studies. When assessed proactively in patients without sexual dysfunction at baseline, reports of treatment emergent sexual dysfunction across doses 5 mg, 10mg, 20 mg were 16%, 20%, 29% in males (N=212) respectively and females 22%, 23% and 34% (N=226) respectively, compared to 14% (N=162) and 20% (N=135), respectively, in placebo.

In clinical studies, TRINTELLIX 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 TRINTELLIX during the initial 12-week, open-label phase, there was no significant effect on body weight between TRINTELLIX and placebo-treated patients. Some reports of weight gain have been received since product approval. TRINTELLIX 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.

TRINTELLIX 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. TRINTELLIX is a trademark of H. Lundbeck A/S and is used under license by Takeda Pharmaceuticals U.S.A., Inc. For more information, visit www.Trintellix.com.

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

The recommended starting dose of TRINTELLIX 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.

TRINTELLIX 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. TRINTELLIX has not been evaluated for use in patients under 18.

Do not take TRINTELLIX if you:

- Are allergic to vortioxetine or any of the ingredients in TRINTELLIX
- 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 TRINTELLIX; do not start TRINTELLIX if you stopped taking an MAOI in the last 14 days

TRINTELLIX may cause serious side effects including:

Serotonin Syndrome: A potentially life-threatening problem that can happen when medicines such as TRINTELLIX 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: TRINTELLIX 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 TRINTELLIX, 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.

TRINTELLIX 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, rifampin, carbamazepine, phenytoin, quinidine, tramadol or fentanyl.

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

Do not start or stop taking TRINTELLIX without talking to your healthcare provider first. Suddenly stopping TRINTELLIX 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.

Talk to your healthcare provider.

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

Indication for TRINTELLIX

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

Please see accompanying Prescribing Information, including Medication Guide for TRINTELLIX.

About Takeda Pharmaceutical Company Limited

Takeda Pharmaceutical Company Limited (TSE: 4502) is a global, research and development-driven pharmaceutical company committed to bringing better health and a brighter future to patients by translating science into life-changing medicines. Takeda focuses its R&D efforts on oncology, gastroenterology and neuroscience therapeutic areas plus vaccines. Takeda conducts R&D both internally and with partners to stay at the leading edge of innovation. Innovative products, especially in oncology and gastroenterology, as well as Takeda’s presence in emerging markets, are currently fueling the growth of Takeda. Around 30,000 Takeda employees are committed to improving quality of life for patients, working with Takeda’s partners in health care in more than 70 countries. For more information, visit https://www.takeda.com/newsroom/.

Takeda Pharmaceuticals U.S.A., Inc. is located in Deerfield, Ill., and is the U.S. marketing and sales organization of Takeda Pharmaceutical Company Limited.

Additional information about Takeda is available through its corporate website, www.takeda.com, and additional information about Takeda Pharmaceuticals U.S.A., Inc. is available through its website, www.takeda.us.

About Takeda Neuroscience

Neuroscience is a core therapeutic area for Takeda. Our mission is to bring innovative medicines to patients suffering from neurologic and psychiatric diseases for whom there are no treatments available. We identify targets either genetically linked with specific neurologic or psychiatric disorders or with high association to the disease pathophysiology, design and operationalize clinical trials in novel ways in an effort to overcome historical challenges, and collaborate with patients, academic institutions, pharmaceutical and biotechnology partners, payors, regulators and prescribers to integrate their unique expertise and perspective. The current Takeda Neuroscience global portfolio consists of five approved medicines, which treat adults with Major Depressive Disorder, Alzheimer’s-type dementia, insomnia, multiple sclerosis, and Parkinson’s disease. In addition, there are many assets in clinical development for targeted patient populations.
About H. Lundbeck A/S
H. Lundbeck A/S (LUN.CO, LUN DC, HLUYY) is a global pharmaceutical company specialized in psychiatric and neurological disorders. For more than 70 years, we have been at the forefront of research within neuroscience. Our key areas of focus are Alzheimer's disease, depression, Parkinson's disease and schizophrenia.

Our approximately 5,000 employees in 55 countries are engaged in the entire value chain throughout research, development, manufacturing, marketing and sales. Our pipeline consists of several late-stage development programs and our products are available in more than 100 countries. We have production facilities in Denmark, France and Italy. Lundbeck generated revenue of DKK 17.2 billion in 2017 (EUR 2.3 billion; USD 2.6 billion).

For additional information, visit www.lundbeck.com and connect 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 disorders. With a special commitment to the lives of patients, families and caregivers, Lundbeck U.S. actively engages in hundreds of initiatives each year that support our patient communities.

For additional information, visit www.lundbeckus.com and connect on Twitter at @LundbeckUS.

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