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Corporate Release

FDA updates Trintellix® (vortioxetine) label to include data showing improvement in processing speed, an important aspect of cognitive function in acute Major Depressive Disorder (MDD)

- *Trintellix® (vortioxetine) is the first FDA-approved treatment for MDD to have data in the U.S. Prescribing Information showing a positive effect on processing speed, an aspect of cognitive function that is impaired in many patients with MDD*
- *Depression is the leading cause of disability worldwide, and is a major contributor to the overall global burden of disease*[i]

Valby, Denmark, 2 May 2018 - H. Lundbeck A/S (Lundbeck) today announced the U.S. Food and Drug Administration (FDA) approved a supplemental new drug application for Trintellix® (vortioxetine). The clinical trials section of the U.S. label now includes data from the largest replicated clinical studies on an important aspect of cognitive function in acute major depressive disorder (MDD, depression). The *FOCUS* and *CONNECT* studies show Trintellix has a positive effect on processing speed, an important aspect of cognitive function observed in some patients with MDD.

Depression is a complex disorder that is more than just sadness. This condition has a wide range of symptoms, including depressed mood or loss of interest, physical symptoms such as sleep deprivation, and cognitive symptoms, like difficulty concentrating, slowed thinking or trouble thinking[ii]. Cognitive impairment is highly prevalent in depression[iii].

"*Many of my MDD patients recognize the mood and physical attributes of depression, but do not often recognize that their cognitive symptoms may also be part of their depression. As part of a comprehensive treatment approach, it's important for clinicians to talk to patients about all symptoms associated with depression. This updated Trintellix labelling regarding improvements in processing speed provides important information to improve discussions between healthcare providers and patients about their depression*," said Dr. Gregory Mattingly, Associate Clinical Professor, Department of Psychiatry, Washington University School of Medicine.

"*With my depression, I felt like my thoughts slowed down. It was as if my brain just couldn't keep up. After speaking with my doctor, I was surprised to learn that this could be part of my depression*," said David, a patient who spoke about his experience with depression at a FDA Advisory Committee meeting in 2016.

The new data in the label are from the *FOCUS* and *CONNECT* studies, which were specifically designed to assess the effect of Trintellix on certain aspects of cognitive dysfunction in adult patients (18-65 years) with depression[iv,v]. These two eight-week, randomized, double-blind, placebo-controlled studies of Trintellix 10 and 20 mg/day used a neuropsychological measure, known as the Digit Symbol Substitution Test (DSST). The DSST is a neuropsychological test that most specifically measures processing speed, an aspect of cognitive function that may be impaired in MDD. The effects observed on DSST may reflect improvements in depression. Comparative studies have not been conducted to demonstrate a therapeutic advantage over other antidepressants on the DSST.

The FDA approved Trintellix on 30 September 2013 for the treatment of MDD in adults. Vortioxetine is furthermore approved in 77 countries (including Europe, Canada, Chile, China, Mexico, Argentina, South Korea, Turkey, Australia, Hong Kong, Singapore and South Africa). It is available in more than 60 countries to date. Outside North America, vortioxetine is recognized as Brintellix®.

About Major Depressive Disorder (MDD)

MDD is a complex mental health illness that affects approximately 14 million people annually[vi]. Depression is the leading cause of disability worldwide, and is a major contributor to the overall global burden of disease[i]. 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. Despite treatment, many symptoms of depression may not be addressed.[vii]

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-HT_{1A} receptors, a partial agonist at 5-HT_{1B} receptors and an antagonist at 5-HT_3, 5-HT_{1D} and 5-HT_7 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.

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.

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

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.

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. 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.

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, rifampicin, 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.

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

Avoid drinking alcohol while taking TRINTELLIX.

Talk to your healthcare provider.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit http://www.fda.gov/Safety/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 Prescribing Information, including Medication Guide for TRINTELLIX.

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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 programmes 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, we encourage you to visit our corporate site www.lundbeck.com and connect with us on Twitter at @Lundbeck.

Safe Harbor/Forward-Looking Statements

The above information contains forward-looking statements that provide our expectations or forecasts of future events such as new product introductions, product approvals and financial performance.

Such forward-looking statements are subject to risks, uncertainties and inaccurate assumptions. This may cause actual results to differ materially from expectations and it may cause any or all of our forward-looking statements here or in other publications to be wrong. Factors that may affect future results include interest rate and currency exchange rate fluctuations, delay or failure of development projects, production problems, unexpected contract breaches or terminations, government-mandated or market-driven price decreases for Lundbeck's products, introduction of competing products, Lundbeck's ability to successfully market both new and

existing products, exposure to product liability and other lawsuits, changes in reimbursement rules and governmental laws and related interpretation thereof, and unexpected growth in costs and expenses.

Certain assumptions made by Lundbeck are required by Danish Securities Law for full disclosure of material corporate information. Some assumptions, including assumptions relating to sales associated with product that is prescribed for unapproved uses, are made taking into account past performances of other similar drugs for similar disease states or past performance of the same drug in other regions where the product is currently marketed. It is important to note that although physicians may, as part of their freedom to practice medicine in the US, prescribe approved drugs for any use they deem appropriate, including unapproved uses, at Lundbeck, promotion of unapproved uses is strictly prohibited.

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[i] World Health Organization; http://www.who.int/mediacentre/factsheets/fs369/en/

[ii] *Diagnostic and Statistical Manual of Mental Disorders (DSM-5). (5th ed., 155-188). America Psychiatric Association, 2013.*

[iii] McClintock SM, Husain MM, Wisniewski SR, et al. Residual symptoms in depressed outpatients who respond by 50% but do not remit to antidepressant medication. J Clin Psychopharmacol. 2011;31(2):180-186.

[iv] 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.

[v] Mahableshwarkar A.R., Zajecka J., Jacobson W., et al. (2015). A Randomized, Placebo-Controlled, Active-Reference, Double-Blind, Flexible-Doze Study of the Efficacy of Vortioxetine on Cognitive Function in Major Depressive Disorder. Neuropsychopharm. 40, 2025-2037.

[vi] Kessler, R., Berglund, P., Demler, O., et al. The Epidemiology of Major Depressive Disorder. JAMA. 2005;289(23):3095-105

[vii] Nierenberg AA, Husain MM, Trivedi MH, et al. Psychol Med. 2010;40:41-50.