

OSAKA, Japan and COPENHAGEN, Denmark, Sept. 30, 2013 /PRNewswire/ -- Takeda Pharmaceutical Company Limited (Takeda) and H. Lundbeck A/S (Lundbeck) jointly announced today that the U.S. Food and Drug Administration (FDA) has approved Brintellix (vortioxetine) for the treatment of adults with major depressive disorder (MDD), a debilitating mental health illness affecting approximately 14 million adult Americans in a given year.

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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.

"MDD is a multifaceted disorder that encompasses emotional, physical and cognitive symptoms that may make it challenging to treat," said Michael Thase, M.D., professor of Psychiatry at the Perelman School of Medicine at the University of Pennsylvania

. "Because patients respond to treatments differently, it is important to have additional new options available to help address the overall symptoms of major depression."

The efficacy and safety of Brintellix were established across a comprehensive global clinical trial program, including six positive 6-8 week short-term studies – one of which was a dedicated study in the elderly – that demonstrated statistically significant improvements in overall symptoms of depression. The primary efficacy measure was the mean change from baseline to endpoint in the Hamilton Depression Scale (HAM-D-24) total score in two short-term studies, including the elderly study, and the Montgomery-Asberg Depression Rating Scale (MADRS) total score in the other studies. In addition, the clinical trial program included a positive 24-64 week long-term maintenance study in which Brintellix treatment resulted in a statistically significant longer time to recurrence of depressive episodes (defined as a MADRS total score $\geq$ 22 or as judged by the investigator) compared to placebo. Studies evaluated for safety

included more than 4,700 patients aged 18 to 88 years. It is expected that Brintellix will be available to patients by year end 2013.

"We are pleased that the FDA has approved Brintellix for the treatment of MDD, a serious and complex condition," said Charlie Baum, M.D., vice president and head, U.S. Medical and Scientific Affairs at Takeda Pharmaceuticals International. "Together with our partner Lundbeck, we have been committed to applying our collective expertise to develop new medicines that may help people with depression."

According to The World Health Organization, fewer than half of people with depression worldwide are receiving treatment, and the burden of depression is expected to continue to rise globally. For those who do seek treatment, discontinuation is not uncommon. MDD is a heterogeneous disorder that does not consistently respond to therapy; thus it's important for patients to work with a healthcare provider to help find a treatment plan that works for them.

"There are very few new antidepressant drugs currently in development even though so many patients still struggle with depression. We are excited about the approval of Brintellix and being able to offer a new option for patients," said Anders Gersel Pedersen, executive vice president and head, Research and Development at Lundbeck. "This approval continues our six-decade history of innovation in research and treatments for brain disorders, and underscores the commitment of the Takeda and Lundbeck partnership to bring forward new treatments for depression."

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 America, Inc.

The World Health Organization has issued a new Anatomical Therapeutic Chemical (ATC) code for Brintellix to be implemented in 2014.

The most commonly observed adverse events in MDD patients treated with Brintellix in 6-8 week placebo-controlled studies (incidence $\geq$ 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 20mg/day, as tolerated, because higher doses demonstrated better treatment effects in trials conducted in the U.S. The available doses provide important flexibility for physicians to help address the variability of patient needs.

Brintellix will be available as 5 mg, 10 mg and 20 mg tablets.

IMPORTANT SAFETY INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a trend

towards reduced risk with antidepressant use in patients aged 65 and older.

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber.

BRINTELLIX has not been evaluated for use in pediatric patients.

CONTRAINDICATIONS**Hypersensitivity:** Hypersensitivity to vortioxetine or any components of the BRINTELLIX formulation. Angioedema has been reported in patients treated with BRINTELLIX.

Monoamine Oxidase Inhibitors (MAOIs): Due to an increased risk of serotonin syndrome, do not use MAOIs intended to treat psychiatric disorders with BRINTELLIX or within 21 days of stopping treatment with BRINTELLIX. Do not use BRINTELLIX within 14 days of stopping an MAOI intended to treat psychiatric disorders. Do not start BRINTELLIX in a patient who is being treated with linezolid or intravenous methylene blue.

WARNINGS AND PRECAUTIONS**Clinical Worsening and Suicide Risk:** All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality (anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania), especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Families and caregivers of patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients daily.

Serotonin Syndrome: The development of a potentially life-threatening serotonin syndrome has been reported with serotonergic antidepressants (SNRIs, SSRIs, and others), including BRINTELLIX, when used alone but more often when used concomitantly with other serotonergic

drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort), and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue). Serotonin syndrome symptoms may include mental status changes (eg, agitation, hallucinations, delirium, and coma), autonomic instability (eg, tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (eg, tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). If such symptoms occur, discontinue BRINTELLIX and any concomitant serotonergic agents, and initiate supportive symptomatic treatment. If concomitant use of BRINTELLIX is clinically warranted, patients should be made aware of and monitored for potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

Abnormal Bleeding: Treatment with serotonergic antidepressants (SSRIs, SNRIs, and others) may increase the risk of abnormal bleeding. Patients should be cautioned about the increased risk of bleeding when BRINTELLIX is coadministered with NSAIDs, aspirin, or other drugs that affect coagulation.

Activation of Mania/Hypomania: Activation of mania/hypomania can occur with antidepressant treatment. Prior to initiating treatment with an antidepressant, screen patients for bipolar disorder. As with all antidepressants, use BRINTELLIX cautiously in patients with a history or family history of bipolar disorder, mania, or hypomania.

Hyponatremia: Hyponatremia has occurred as a result of serotonergic drugs and in many cases, appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Elderly patients and patients taking diuretics or who are otherwise volume-depleted can be at greater risk. More severe or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death. Discontinue BRINTELLIX in patients with symptomatic hyponatremia and initiate appropriate medical intervention.

Adverse Reactions: The most commonly observed adverse reactions for BRINTELLIX in 6- to 8-week placebo-controlled studies (incidence $\geq$ 5% and at least twice the rate of placebo) were by dose (5 mg, 10 mg, 15 mg, 20 mg) vs placebo: nausea (21%, 26%, 32%, 32% vs 9%), constipation (3%, 5%, 6%, 6% vs 3%) and vomiting (3%, 5%, 6%, 6% vs 1%).

Drug Interactions: Concomitant administration of BRINTELLIX and strong CYP2D6 inhibitors

or strong CYP inducers may require a dose adjustment of BRINTELLIX.

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

The Science of Major Depression The monoamine-deficiency theory posits that the underlying pathophysiological basis of depression is a depletion of serotonin, norepinephrine or dopamine in the central nervous system. The exact cause of MDD is unknown. Research suggests that there are multiple serotonin receptors that may be important in MDD and may influence many biologic and neurologic processes. The release of bio-chemicals, such as serotonin, dopamine and norepinephrine enables impulses to be passed from one cell to another in the nervous system.

Takeda and Lundbeck Alliance In September 2007, Lundbeck and Takeda Pharmaceutical Company Limited formed a strategic alliance for the exclusive co-development and co-commercialization in the U.S. and Japan of several compounds in Lundbeck's pipeline for the treatment of mood and anxiety disorders. The companies plan to co-promote Brintellix in the U.S. for the commercial launch of the product. The Lundbeck–Takeda alliance in the U.S. will benefit from the synergy of Lundbeck's longstanding expertise and knowledge of psychiatry and Takeda's understanding and established presence in the very important primary care environment.

About Lundbeck H. Lundbeck A/S (LUN.CO, LUN DC, HLUY) is a global pharmaceutical company specialized in brain diseases. For more than 50 years, we have been at the forefront of research within neuroscience. Our development and distribution of pioneering treatments continues to make a difference to people living with brain diseases. Our key areas of focus are alcohol dependence, Alzheimer's disease, depression/anxiety, epilepsy, Huntington's disease, Parkinson's disease, schizophrenia and stroke. Lundbeck's U.S. business is based in Deerfield, Illinois

. To learn more about Lundbeck in the U.S., visit www.lundbeckus.com.

Our 5,800 employees in 57 countries are engaged in the entire value chain throughout research, development, production, marketing and sales, and are committed to improving the quality of life of people living with brain diseases. Our pipeline consists of several late-stage development programs and our products are available in more than 100 countries. We have

research centers in China, Denmark and the United States, and production facilities in China, Denmark

,
France

,
Italy
and
Mexico

. Lundbeck generated revenue of approximately
DKK15 billion
in 2012 (
EUR 2 billion
;
USD 2.6 billion
).

Lundbeck's shares are listed on the stock exchange in Copenhagen under the symbol "LUN."
Lundbeck has a sponsored Level 1 ADR program listed in the US (OTC) under the symbol
"HLUYY." For additional information, we encourage you to visit our corporate site
www.lundbeck.com

About Takeda Pharmaceutical Company Limited Located in Osaka, Japan, Takeda 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 patients worldwide through leading innovation in medicine. Additional information
about Takeda is available through its corporate website,
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, insomnia, 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

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,

he 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 and Lundbeck Announce FDA Approval of Brintellix™ (vortioxetine) for Treatment of Adults with

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¹ As estimated by the National Comorbidity Survey Replication (NCS-R), conducted from February 2001

to

December 2002

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