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Press release

Valby, 05 March 2015

European CHMP issues positive opinion for a label update of Brintellix® (vortioxetine) to reflect its effect on certain aspects of cognitive function in patients with depression

This will be the first label (summary of the product characteristics) of an antidepressant to include an effect on certain aspects of cognitive function in patients with depression in Europe.

H. Lundbeck A/S (Lundbeck) today announced that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive opinion for a Type-II Variation related to the update of the European summary of the product characteristics (SmPC) for Brintellix.

The update of the SmPC provides physicians with new Brintellix data related to its effect on certain aspects of cognitive function and patient functioning in general, as measured by cognitive performance assessment (neuropsychological test such as Digit Symbol Substitution Test (DSST)) and by functional capacity assessment (University of San Diego Performance-Based Skills Assessment (UPSA)) in patients with major depression, commonly referred to as depression. Patients with depression have cognitive symptoms 94% of the timeⁱ. Cognitive symptoms encompass a wide variety of signs, including attention and concentration difficulties, problems with thinking speed and difficulty making decisions.ⁱⁱ

The CHMP positive opinion was reached after a review of comprehensive data from the international clinical program comprised of five studies assessing the safety and efficacy of Brintellix including its effect on cognitive performance and function. The application was based primarily on data from one recently completed clinical study (CONNECT) in addition to four clinical studies that were previously submitted as part of the original approval process, as well as a newly completed clinical pharmacology functional magnetic resonance imaging (fMRI) studyⁱⁱⁱ in remitted patients with depression. The application, known as a Type II Variation, was submitted to the European Medicines Agency (EMA) in September 2014.

“We are delighted that Brintellix has received this positive opinion from the CHMP, particularly given the role cognitive deficits play in impacting treatment outcomes for many patients” said Anders Gersel Pedersen, Executive Vice President and Head of R&D at Lundbeck. *“The encouraging data we have seen on Brintellix when addressing cognitive dysfunction reinforces our belief that Brintellix has the potential to help many patients with their treatment of depression”.*

The variation will be implemented upon finalization of the linguistic review process by EMA, expected end of March.

Lundbeck announces publication of CONNECT study results

The peer-reviewed journal *Neuropsychopharmacology* has published the CONNECT trial results.^{iv} The article “A Randomized, Placebo-Controlled, Active-Reference, Double-Blind, Flexible-Dose Study of the Efficacy of Vortioxetine on Cognitive Function in Major Depressive Disorder” is available online at <http://www.ncbi.nlm.nih.gov/pubmed/25687662>

In the publication, the authors conclude that “Brintellix is an efficacious and well-tolerated treatment for patients suffering from depression. In this study of adults with MDD and self-reported cognitive dysfunction, Brintellix was statistically significantly superior to placebo on the predefined primary analysis, an objective measure of cognitive functioning, and on both predefined key secondary endpoints of global clinical status and patient-reported cognitive functioning. Brintellix was also significantly superior to placebo in the treatment of depressive symptoms and in the improvement of functional capacity.”

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About the CONNECT study^{iv}

In the CONNECT study (NCT01564862), a total of 602 subjects were randomized (198 on Brintellix, 210 on duloxetine, and 194 on placebo). Adults (18-65 years) with MDD, MADRS \geq 26 and self-reported cognitive dysfunction were enrolled. The primary endpoint was change from baseline to Week 8 on the Digit Symbol Substitution Test (DSST). Key secondary endpoints, patient-reported Perceived Deficits Questionnaire (PDQ) and Clinical Global Impression — Global Improvement (CGI—I) Scale at Week 8 were analyzed in a pre-specified testing sequence using the full-analysis set (FAS). Additional endpoints included the objective performance-based University of San Diego Performance-Based Skills Assessment (UPSA) to measure functional capacity, the Montgomery-Åsberg Depression Rating Scale (MADRS) to assess efficacy in depression, and a pre-specified path-analysis to detect direct vs indirect effects of Brintellix on cognitive function.

Brintellix was statistically superior to placebo on the primary endpoint (the Digit Symbol Substitution Test or DSST) ($p < 0.05$) and the two key secondary endpoints — patient-reported Perceived Deficits Questionnaire (PDQ) ($p = 0.001$) and CGI-I ($p < 0.05$). Brintellix was statistically superior to placebo on the MADRS ($p < 0.05$) and UPSA ($p < 0.001$) change from baseline at Week 8. A pre-specified path-analysis to detect direct vs. indirect effects of treatment on cognitive functioning, as measured by the DSST performance showed that the improvement observed with Brintellix could be mainly attributed to a direct effect and not only due to alleviation of overall depressive symptoms.

Duloxetine was included in the study as an active reference to demonstrate assay sensitivity for depression. Duloxetine was not statistically significantly different from placebo on the primary study

endpoint (DSST) or UPISA, and it was statistically significantly different on the 2 key secondary endpoints PDQ, CGI-I as well as MADRS, the latter validating the study.

Common adverse events ($\leq 5\%$) for Brintellix were nausea, headache, and diarrhea.

About cognitive function in major depression

Cognitive dysfunction is well-documented in the different phases of major depression, and plays an important role in functional recovery from major depression^v. A general assumption is that cognitive dysfunction is restored as mood symptoms of depression improve^{vi}. However, studies have shown that daily life functioning, including work and family life often remain impaired even in remission^{vii}.

Research suggests that different factors may explain why improvement in depression-related symptoms is not followed by improvement in daily life functioning. These associated factors include residual symptoms, comorbidity, misdiagnosis and long-lasting cognitive impairment^{viii}.

Cognition is defined as the mental action or process of acquiring knowledge and understanding through thought, experience and the senses. It can be seen as comprised of several domains such as for example attention, memory, producing and understanding language, learning, reasoning, problem solving, and decision making. Cognition is generally impacted in major depression, and focus is often on four of the domains, executive function, attention, speed of processing and memory.

About Brintellix® (vortioxetine)

Brintellix is an inhibitor of serotonin (5-HT) reuptake and 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. Brintellix is considered to be the first and only compound with this combination of pharmacodynamic activity, although the mechanism of the antidepressant effect of Brintellix is not fully understood and has not been established.

Brintellix (vortioxetine) was discovered by Lundbeck researchers in Copenhagen, Denmark. The clinical trial program in the US was conducted jointly by Lundbeck and Takeda, and Takeda holds marketing authorization for the US market. Brintellix is a trademark of H. Lundbeck A/S and is used under license by Takeda Pharmaceuticals America, Inc.

Brintellix is approved in the United- States, Europe, Canada, Chile, South Korea, Turkey, Australia, Hong Kong, Singapore and South Africa.

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

About Lundbeck

H. Lundbeck A/S (LUN.CO, LUN DC, HLUYY) 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 <http://www.lundbeck.com/fr/a-propos-de-lundbeck/progress-in-mind>

In 2015, Lundbeck celebrates 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.

Our approximately 6,000 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 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).

For additional information, we encourage you to visit our corporate www.lundbeck.com

ⁱ Conradi HJ *et al.* *Psychol Med* 2011

ⁱⁱ European Depression Association, Ipsos Healthcare. *IDEA: Impact of Depression at Work in Europe Audit* 2012; Biringier E *et al.* *Curr Psychiatry Rev* 2009; Hammar Å, Årdal G. *Front Hum Neurosci* 2009 ; Lee RS *et al.* *J Affect Disord* 2012; Marazziti D *et al.* *Eur J Pharmacol* 2010 ; Rock PL *et al.* *Psychol Med* 2013

ⁱⁱⁱ Positive data from the fMRI study was described in poster presentations at the Annual Meeting of the American College of Neuropsychopharmacology (ACNP) in December 2014 (Browning *et al.*; Dawson *et al.*).

^{iv} Atul R Mahableshwarkar, John Zajecka, William Jacobson, Yinzhong Chen, Richard SE Keefe, A Randomized, Placebo-Controlled, Active-Reference, Double-Blind, Flexible-Dose Study of the Efficacy of Vortioxetine on Cognitive Function in Major Depressive Disorder, *Neuropsychopharmacology* accepted article preview 17 February 2015; doi: 10.1038/npp.2015.52.

^v Jaeger J., Berns S., Uzelac S., Davis-Conway S. (2006). Neurocognitive deficits and disability in major depressive disorder, *Psychiatry Research*; 145(1):39-48.

^{vi} Hammar, A., Ardal, G. (2009). Cognitive Functioning in Major Depression — A Summary. *Frontiers in Human Neuroscience*; 3:26.

^{vii} Angermeyer MC., Holzinger A., Matschinger H., Stengler-Wenzke K. (2002). Depression and quality of life: results of a follow-up study, *International Journal Social Psychiatry*; 48(3):189-99.

^{viii} Kennedy N., Foy K., Sherazi R., McDonough M., McKeon P. (2007). Review Long-term social functioning after depression treated by psychiatrists: a review, *Bipolar Disorders*; 9(1-2):25-37.