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# Janssen Submits European Marketing Authorisation Application for Esketamine Nasal Spray for Treatment-Resistant Depression

*Data from five pivotal Phase 3 studies submitted as the basis for Marketing Authorisation Application for esketamine nasal spray*

**BEERSE, BELGIUM, 10 October, 2018** – The Janssen Pharmaceutical Companies of Johnson & Johnson announced today the submission of a Marketing Authorisation Application (MAA) to the European Medicines Agency (EMA) seeking approval for esketamine nasal spray, a glutamate receptor modulator, for treatment-resistant depression (TRD) in adults with Major Depressive Disorder (MDD) who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode.

Esketamine nasal spray is an investigational product for the treatment of TRD that is being studied as part of a global development programme. As a glutamate receptor modulator, esketamine nasal spray is a rapidly-acting antidepressant that is thought to help restore synaptic connections in brain cells in people with TRD – a novel mechanism of action, meaning it works differently than currently available therapies for depression.

"Major Depressive Disorder affects approximately 40 million people across Europe, and is the leading cause of disability worldwide.[1,2] Of these people, about one-third do not respond to currently available treatments.[3] Janssen is committed to improving the outcomes for patients with treatment-resistant depression, and we look forward to working with the EMA to provide a new targeted treatment option for these patients," said Mathai Mammen, M.D., Ph.D., Global Head, Janssen Research & Development.

The MAA is based on five pivotal Phase 3 studies of esketamine nasal spray in patients with TRD: three short-term studies, one randomised withdrawal and maintenance of effect study, and one long-term safety study. Data from these Phase 3 studies demonstrated that treatment with esketamine nasal spray plus a newly initiated oral antidepressant, compared to an active comparator (newly initiated antidepressant plus placebo nasal spray), was associated with rapid reduction of depressive symptoms, as early as day 2, and reduced the risk of relapse by 51% in stable remitters.[4,5] The long-term safety study showed that the esketamine nasal spray doses studied were generally tolerated, with no new safety signals in dosing up to 52 weeks, comparable to the data from the short-term esketamine nasal spray studies.[6]

The safety of esketamine nasal spray was also evaluated in the five Phase 3 studies (three short-term and two long-term studies) and one Phase 2 study. These data provide insights related to the safety profile of esketamine nasal spray in patients with TRD over the long-term and show that esketamine nasal spray may be beneficial in terms of extending time to relapse in a patient population that is challenging to treat. The most commonly observed adverse reactions with esketamine nasal spray (≥10% of patients) were dissociation, anxiety, dysgeusia, dizziness, sedation, hypoaesthesia, headache, vertigo, nausea, vomiting and increased blood pressure.[4–9]

“The results from our Phase 3 studies reinforce the potential of esketamine nasal spray as a novel treatment to help patients who haven’t responded to available therapies,” said Husseini K. Manji, M.D., Global Head, Neuroscience Therapeutic Area, Janssen Research & Development, LLC. “We look forward to bringing a new treatment option to people who need it most.”

A New Drug Application (NDA) has also been submitted to the U.S. Food and Drug Administration (FDA) for esketamine nasal spray for TRD.[10]

Janssen acknowledges and supports World Mental Health Day, 10th October, a day which drives greater awareness for the 1 in 4 people worldwide affected by a mental health disorder. The heritage and dedication that Janssen has demonstrated in the field of psychiatry spans 60 years this year, and the company is proud to mark this important milestone today in the hope of bringing a new treatment option to patients.

#ENDS#

**About Esketamine**

Esketamine nasal spray is an investigational compound being studied by Janssen Research & Development, LLC as part of a global development programme. Esketamine is a glutamate receptor modulator, which is thought to help restore synaptic connections in brain cells in people with treatment-resistant depression (TRD) – a novel mechanism of action, meaning it works differently from currently available therapies for depression.

Esketamine nasal spray received two breakthrough therapy designations from the U.S. Food and Drug Administration (FDA) in November 2013 for TRD and in August 2016 for the indication of MDD with imminent risk for suicide.[11] If approved by regulatory authorities esketamine nasal spray would provide the first new mode of action to treat TRD seen in the last 30 years. Esketamine nasal spray will be self-administered and patients should be observed under the supervision of a healthcare professional for as long as clinically necessary.

**About Major Depressive Disorder**

MDD affects nearly 300 million people of all ages globally and is the leading cause of disability worldwide.[2] Individuals with depression, including MDD, experience continuous suffering from a serious, biologically-based disease which has a significant negative impact on all aspects of life, including quality of life and function. Although currently available antidepressants are effective for many patients, about one-third of patients do not respond to treatment and are considered to have TRD.[3] Janssen studies of esketamine nasal spray defined TRD as no response to two or more currently available antidepressants of adequate dose and duration in the current moderate to severe episode of depression.

**About the Janssen Pharmaceutical Companies of Johnson & Johnson**
At the Janssen Pharmaceutical Companies of Johnson & Johnson, we are working to create a world without disease. Transforming lives by finding new and better ways to prevent, intercept, treat and cure disease inspires us. We bring together the best minds and pursue the most promising science.

We are Janssen. We collaborate with the world for the health of everyone in it. Learn more at www.janssen.com/emea. Follow us at www.twitter.com/JanssenEMEA. Janssen Research & Development, LLC and Janssen-Cilag International NV are part of the Janssen Pharmaceutical Companies of Johnson & Johnson.

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*Cautions Concerning Forward-Looking Statements*

*This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding product development of esketamine. The reader is cautioned not to rely on these forward-looking statements. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or known or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of Janssen Cilag International NV, any of the other Janssen Pharmaceutical Companies and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in product research and development, including the uncertainty of clinical success and of obtaining regulatory approvals; uncertainty of commercial success; manufacturing difficulties and delays; competition, including technological advances, new products and patents attained by competitors; challenges to patents; product efficacy or safety concerns resulting in product recalls or regulatory action; changes in behavior and spending patterns of purchasers of health care products and services; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and descriptions of these risks, uncertainties and other factors can be found in Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended December 31, 2017, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," in the company's most recently filed Quarterly Report on Form 10-Q, and in the company's subsequent filings with the Securities and Exchange Commission. Copies of these filings are available online at* www.sec.gov, www.jnj.com *or on request from Johnson & Johnson. Neither the Janssen Pharmaceutical Companies nor Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.*

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1 World Health Organization. Depression and Other Common Mental Health Disorders: Global Health Estimates, 2017. Available at: http://www.who.int/mental_health/management/depression/prevalence_global_health_estimates/en/. Last accessed October 2018.

2 World Health Organization. Depression Fact Sheet, 2018. Available at: http://www.who.int/news-room/fact-sheets/detail/depression. Last accessed October 2018.

3 Ionescu D, *et al*. "Pharmacological Approaches to the Challenge of Treatment-Resistant Depression". *Dialogues Clin Neurosci*. 2015; 17(2):111–26. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4518696/. Last accessed October 2018.

4 Popova V, *et al*. "Randomized, double-blind study of flexibly dosed intranasal esketamine plus oral antidepressant vs active control in treatment-resistant depression". Poster PS068 presented at CINP 2018, 16–19 June, Vienna, Austria.

5 Daly E, *et al*. "A Randomized Withdrawal, Double-Blind Study of Flexibly-Dosed Intranasal Esketamine Plus Oral Antidepressants for Relapse prevention in Treatment-Resistant Depression." Poster W68 presented at ASCP 2018, 29 May–01 Jun, Miami, Florida.

6 Wajs E, *et al*. "Long-Term Safety of Intranasal Esketamine Plus Oral Antidepressant in Patients with Treatment-Resistant Depression: Phase 3, Open-Label, Safety and Efficacy Study". Poster PS074 presented at CINP 2018, 16–19 June, Vienna, Austria.

7 Ochs-Ross R, *et al*. "Efficacy and safety of esketamine nasal spray plus an oral antidepressant in elderly patients with treatment-resistant depression". Poster PS066 presented at CINP 2018, 16–19 June, Vienna, Austria.

8 Fedgchin M, *et al*. "Randomized, Double-Blind Study of Fixed-Dosed Intranasal Esketamine Plus Oral Antidepressant vs. Active Control in Treatment-Resistant Depression". Poster 18 presented at ISAD 2018, 20-22 Sep, Houston, Texas.

9 Daly E, *et al*. "Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA Psychiatry 2018 Feb; 75(2):139–148.

10 Johnson & Johnson Press Release. Janssen Submits Esketamine Nasal Spray New Drug Application to U.S. FDA for Treatment-Resistant Depression. Available at: https://www.prnewswire.com/news-releases/janssen-



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[11] Johnson & Johnson Press Release. Esketamine Receives Breakthrough Therapy Designation from U.S. Food and Drug Administration for Major Depressive Disorder with Imminent Risk for Suicide. Available at: https://www.jnj.com/media-center/press-releases/esketamine-recieves-breakthrough-therapy-designation-from-us-food-and-drug-administration-for-major-depressive-disorder-with-imminent-risk-of-suicide. Last accessed October 2018.