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SPRAVATO®▼ (Esketamine) Nasal Spray Approved in Europe for Adults with Treatment-Resistant Major Depressive Disorder

- *Esketamine nasal spray offers the first new mechanism of action for an antidepressant in 30 years*
- *EC approval is based on data from a clinical trial programme in adult patients with treatment-resistant major depressive disorder, including five Phase 3 trials*
- *Treatment with esketamine nasal spray plus a newly initiated oral antidepressant was associated with a significant reduction in depressive symptoms, with the onset of efficacy as early as Day 2, with approximately half of all treated patients achieving remission after four weeks of treatment*

BEERSE, BELGIUM, DECEMBER 19, 2019 – The Janssen Pharmaceutical Companies of Johnson & Johnson announced today that the European Commission (EC) has approved SPRAVATO®▼ (esketamine) nasal spray, in combination with a selective serotonin reuptake inhibitor (SSRI) or serotonin and norepinephrine reuptake inhibitor (SNRI), for adults living with treatment-resistant major depressive disorder (TRD). According to the approval, patients are considered to have TRD if they have not responded to at least two different treatments with antidepressants in the current moderate-to-severe depressive episode.[1]

"The EC approval of esketamine nasal spray provides a new way to manage treatment-resistant major depressive disorder with a novel mechanism of action," says Husseini K. Manji, MD, Global Head, Neuroscience Therapeutic Area, Janssen Research & Development, LLC. "Janssen is committed to reducing the devastating burden caused by

serious mental illnesses, and we are proud to be introducing a new and innovative treatment option, which will help to address a significant unmet need."

Major depressive disorder (MDD) affects approximately 40 million people across Europe and is the leading cause of disability worldwide.[2,3] For these patients, the main goal of treatment is to relieve the symptoms of depression, and ultimately achieve remission, with few, if any, symptoms of depression remaining.[4] However, about one third of patients with MDD do not respond to currently available treatments.[5]

The approval of esketamine is based on data from a clinical trial programme in patients with TRD, including over 1,600 patients treated with esketamine. The five Phase 3 trials included three short-term studies, one randomised withdrawal and maintenance of effect study, and one long-term safety study.[6,7,8,9,10]* These data demonstrated that treatment with esketamine nasal spray plus a newly initiated oral antidepressant was associated with a greater reduction in depressive symptoms compared to a newly initiated oral antidepressant plus placebo nasal spray, in adult patients (18-64 years), with the onset of efficacy as early as Day 2.[6] Approximately 70 percent of esketamine-treated patients responded to treatment, with a ≥50 percent symptom reduction. Furthermore, approximately half of all treated patients achieved remission at the end of the 4 week studies.[1] Continued treatment with esketamine nasal spray plus oral antidepressant reduced the risk of relapse by 70 percent among patients with stable response and by 51 percent in patients in stable remission, compared to continuing treatment with oral antidepressant alone.[9]

Across the five Phase 3 and one Phase 2 clinical trials, esketamine nasal spray demonstrated a favourable benefit-risk profile, with sustained efficacy and no new safety concerns were observed over a period of up to one year.[6,7,8,9,10,11] The most commonly observed adverse events in TRD patients treated with esketamine were dizziness, nausea, dissociation, headache, somnolence, vertigo, dysgeusia, hypoaesthesia, and vomiting.[1] These side effects were generally mild-to-moderate, transient (typically resolving within 2 hours) and occurred on the day of dosing.

"MDD is a debilitating illness that can have a profound impact on patients and their loved ones," said Professor Siegfried Kasper,† President of the International College of Neuropsychopharmacology (CINP), former Head of the Department of Psychiatry and Psychotherapy at the Medical University of Vienna. "I have seen patients who have been suffering from MDD for a really long time and have tried multiple different treatments, which often take between four to six weeks to take effect.[12] The fast-acting nature of

esketamine nasal spray and the high remission rates seen in the pivotal trials makes it a welcome treatment option for individuals who need it most."

Esketamine is an antagonist of the N-methyl-D-aspartate (NMDA) glutamate receptor, and is understood to work differently than other currently available therapies for MDD.[13,14] It is thought to help restore synaptic connections between brain cells in people with TRD, allowing for more activity and communication between specific regions of the brain. Based on results from clinical trials, this increase in activity and communication is thought to help improve the symptoms of depression.[13,14]

A risk management plan (RMP) will detail the measures to be undertaken to prevent or minimise risks associated with the use of the medicine in patients.

EC approval is valid in all 28 member states of the European Union as well as the European Economic Area countries (Norway, Iceland and Liechtenstein).

#ENDS#

* The analysis used to calculate the primary efficacy endpoint in the acute Phase 3 clinical trial publications is the Mixed Model for Repeated Measurements (MMRM) analysis. As per the request of the European Medicines Agency (EMA), the European SPRAVATO®▼ Summary of Product Characteristics (SmPC) uses an analysis of covariance – best observation carried forward (AVCOVA BOCF). Both the MMRM and the AVCOVA BOCF are appropriate methods for analysing the change in depressive symptoms from baseline on the Montgomery–Åsberg Depression Rating Scale (MADRS). The methods yield slightly different results, but do not change the statistical significance of the study results. In addition, response and remission rates at Day 28 in the publications were calculated using patients who completed the double blind induction period; response and remission rates in the SmPC were calculated using all patients who were randomised.

† Professor Siegfried Kasper is a paid consultant for Janssen. He has not been compensated for any media work.

About SPRAVATO®▼

As an antagonist of the N-methyl-D-aspartate (NMDA) glutamate receptor, SPRAVATO®▼ (esketamine) nasal spray offers the first new mechanism of action in 30 years to treat major depressive disorder (MDD).[13,14]

Esketamine nasal spray is self-administered through a single-use nasal spray device, offering a novel mode of drug administration for the treatment of major depressive disorder (MDD).[1] It must be administered in conjunction with a selective serotonin reuptake inhibitor (SSRI) or serotonin and noradrenaline reuptake inhibitor (SNRI) and

the decision to prescribe esketamine nasal spray should be determined by a psychiatrist.[1]

Esketamine nasal spray is also approved for use, in conjunction with an oral antidepressant, for adults living with treatment-resistant major depressive disorder (TRD) in the US by the Food and Drug Administration (FDA), and marketing authorisation application procedures are currently ongoing in a number of other countries worldwide.[15]

About Major Depressive Disorder

Major depressive disorder (MDD) affects nearly 40 million people of all ages in Europe and is the leading cause of disability worldwide.[2,3] 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, their onset of effect takes between four to six weeks.[12] Furthermore, about one third of patients do not respond to currently available treatments, and are considered to have treatment-resistant depression or 'TRD'.[1,5] Per the esketamine nasal spray license, TRD is defined as non-response to at least two different treatments with antidepressants in the current moderate-to-severe depressive episode.[1]

About the Janssen Pharmaceutical Companies of Johnson & Johnson

At Janssen, we're creating a future where disease is a thing of the past. We're the Pharmaceutical Companies of Johnson & Johnson, working tirelessly to make that future a reality for patients everywhere by fighting sickness with science, improving access with ingenuity, and healing hopelessness with heart. We focus on areas of medicine where we can make the biggest difference: Cardiovascular & Metabolism, Immunology, Infectious Diseases & Vaccines, Neuroscience, Oncology, and Pulmonary Hypertension.

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 SPRAVATO®▼. 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 materialise, 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 behaviour and spending patterns of purchasers of healthcare products and services; changes to applicable laws and regulations, including global healthcare reforms; and trends toward healthcare 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 30, 2018, 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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