FOR UK CONSUMER HEALTH MEDIA ONLY

News Release

Media contact:
Jennifer White
Mobile: +44 (0)7824 545660
Email: jwhite34@its.jnj.com

Investor contacts:
Christopher DelOrefice
Johnson & Johnson
Office: +1 732 524 2955

Lesley Fishman
Johnson & Johnson
Office: +1 732 524 3922

JANSSEN'S NOVEL ANTIDEPRESSANT SPRAVATO® ▼ (ESKETAMINE) NASAL SPRAY RECEIVES EUROPEAN MARKETING AUTHORISATION

Authorised for patients who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode and in combination with a Selective Serotonin Reuptake Inhibitor (SSRI) or Serotonin and Norepinephrine Reuptake Inhibitor (SNRI)

Esketamine nasal spray is the first antidepressant medicine with a new mechanism of action in 30 years for adults with treatment-resistant major depressive disorder

HIGH WYCOMBE, UK, 19 December 2019 – The Janssen Pharmaceutical Companies of Johnson & Johnson today announced that the European Commission (EC) has granted authorisation for 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), who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode.[1]

"This new treatment represents an exciting new therapeutic option for a common,

debilitating and difficult to treat condition," says Professor Allan Young, Chair of Mood Disorders and Director of the Centre for Affective Disorders, King's College London.[*] *"I believe both clinicians and patients will welcome this treatment option for this often-devastating illness."*

MDD affects approximately 40 million people across Europe and around 1.8 million adults in England.[2—4] It is a major health condition, recognised as the most common mental health condition in Europe, and can cause significant ill-health, disability and suffering for patients and their families.[5,6] People with MDD can suffer with episodes for many months or even years before being diagnosed and the effects go beyond the psychiatric and physical symptoms.[7] It may also affect employment and education, relationships, health and overall quality of life.[8] One-third of people in Europe living with MDD are considered to have TRD, that can cause significantly lower health-related quality of life, reduced productivity at work and increased absenteeism.[9,10]

"*The marketing authorisation of esketamine nasal spray is a testament to Janssen's dedication to improving outcomes for people struggling to overcome the devastating effects of treatment-resistant major depressive disorder,"* said Bernardo Soares, Medical Director UK, Janssen-Cilag Ltd. "*We are proud to be introducing this innovative treatment option, which we hope will help to address a significant unmet need.*"

The European marketing authorisation was based on evidence from five Phase 3 clinical trials in patients with TRD, which included more than 1,600 esketamine-treated patients.[11—15] The five Phase III trials included three short-term studies, one randomised withdrawal and maintenance of effect study, and one long-term safety study.[11—15]

The short-term (one-month) flexible dosing study in adults under 65 years of age demonstrated statistically significant reductions in depressive symptoms at 28 days for esketamine nasal spray and oral antidepressant compared to oral antidepressant and placebo nasal spray. Approximately 70 percent of esketamine nasal spray-treated patients responded to treatment, with a ≥50 percent symptom reduction. Furthermore, approximately half of all esketamine nasal spray-treated patients achieved remission at the end of the 4-week study.[†11]

The short-term (one-month) fixed dosing study in adults under 65 years of age demonstrated clinically meaningful (not statistically significant) reductions in depressive symptoms at 28 days for either 54 mg or 84 mg esketamine nasal spray and oral antidepressant compared to oral antidepressant and placebo nasal spray. Approximately 54 percent and 53 percent of patients treated with 56 mg and 84 mg esketamine nasal spray, respectively, responded to treatment. Approximately 36 percent and 38 percent of patients treated with 56 mg and 84 mg esketamine nasal

spray, respectively, achieved remission at the end of the 4-week study.[†13]

The short-term (one-month) flexible dosing study in elderly adults over 65 years of age demonstrated clinically meaningful (not statistically significant) reductions in depressive symptoms at 28 days for esketamine nasal spray and oral antidepressant compared to oral antidepressant and placebo nasal spray. Of all esketamine nasal spray-treated patients, 27 percent responded to treatment and approximately 17 percent achieved remission at the end of the 4-week study.[†12]

Continued treatment with esketamine nasal spray plus an 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 an oral antidepressant alone.[†14]

The safety profile of esketamine nasal spray was also evaluated across all Phase 3 studies and one Phase 2 study. [11—16] The most commonly observed adverse reactions in TRD patients treated with esketamine nasal spray were dizziness, nausea, dissociation, headache, somnolence, vertigo, dysgeusia, hypoaesthesia, and vomiting.[11-17] These side effects were generally mild-to-moderate, transient (resolving within 2 hours) and happened on the day of dosing.

Esketamine nasal spray is a controlled drug which is intended to be self-administered by the patient under the direct supervision of a healthcare professional. Risk of harm and abuse is minimised through; safe storage, a single-use disposable nasal spray device, which prevents multi-use and safeguards against more than one dose of the drug being delivered in a single administration, and patient risk for abuse or misuse is assessed before administration. A treatment session consists of nasal administration of esketamine nasal spray and a post-administration observation period. Both administration and post-administration observation of esketamine nasal spray should be carried out in an appropriate clinical setting.

###

[†]*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.[17]

[*]Professor Allan Young is a paid consultant for Janssen. He has not been compensated for any media work.

About SPRAVATO® (esketamine) nasal spray

Esketamine is a glutamate receptor modulator which works on the N- methyl-D-aspartate (NMDA) ionotropic glutamate receptor. It is thought that, by acting on the NMDA receptor, esketamine nasal spray increases signaling between certain cells in the brain, which may contribute to the restoration of synaptic function in these brain regions involved with the regulation of mood and emotional behaviour.[18–21] Based on these differences in pharmacology, esketamine nasal spray has been appraised by the European Medicines Agency (EMA) as a distinct active substance.

The European Commission (EC) authorisation follows the positive opinion from the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) on 18 October 2019.[22]

On 5 March 2019, esketamine nasal spray was granted US marketing authorisation by the Food & Drug Administration (FDA) under the brand name SPRAVATO® for use in conjunction with an oral antidepressant in adults with TRD.[19]

Adverse events should be reported. ▼This medicinal product is subject to additional monitoring and it is therefore important to report any suspected adverse events related to this medicinal product. Reporting forms and information can be found at www.yellowcard.mhra.gov.uk or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Janssen-Cilag Limited on 01494 567447 or at dsafety@its.jnj.com.

About Major Depressive Disorder (MDD) and Treatment Resistant Depression (TRD)

Major depressive disorder (MDD) is a severe and chronic mood disorder that can have a profound and devastating impact on those affected as well as their carers, families and loved ones around them.[23,24] It causes severe and persistent symptoms of depression which can affect almost every aspect of a person's life.[23] Treatment-resistant depression (TRD) is defined as an inadequate response to two or more currently available treatments with antidepressants in a single, current episode of moderate-to-severe depression. A third of people who suffer from MDD do not respond to treatment and are considered to have TRD.[25]

According to the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders 5th edition, American Psychiatric Association, 2013) MDD is diagnosed when at least 5 symptoms of depression, which must include depressed mood and/or loss of interest or pleasure in activities, cause clinically significant distress or impaired functioning almost every day for at least a 2-week period.[23] Other symptoms may also include: irritability, disturbances in sleep, appetite or sexual desire, constipation, suicidal thoughts and slowing of speech and action.[23,26]

Although MDD is diagnosed when symptoms are present for at least 2 weeks, episodes usually last significantly longer – months or even years, so people living with MDD may delay seeking help.

The impact of Major Depressive Disorder (MDD) and Treatment Resistant Depression (TRD)

Depression, including MDD, and TRD represent a substantial burden both for patients and the wider society. Research suggests patients with TRD are impacted by multiple negative health outcomes including poorer health-related quality of life, higher work productivity loss and increased healthcare use including hospitalisations, compared to the general population.[27,28]

In addition, this critical unmet health need carries a significant societal and economical burden. In 2007, the estimated cost of MDD in England was £1.7 billion, and this is projected to reach £3 billion by 2026.[29,30] It is believed that TRD may add up to 68% in societal costs.[31]

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/uk. Follow us at www.twitter.com/JanssenUK.

Cautions Concerning Forward-Looking Statements

This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding marketing authorisation of SPRAVATO® (esketamine) nasal spray. 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 31, 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.*

# # #

[1] European Commission. Union Register. Available at: https://ec.europa.eu/health/documents/community-register_en/. Accessed December 2019.
[2] Dwight LE, *et al.* (2017) Depression and other common mental disorders: global health estimates. Available at: www.who.int/mental_health/management/depression/prevalence_global_health_estimates/en/. Accessed December 2019.
[3] McManus S, *et al.* (2016) Mental Health and Wellbeing in England: Adult Psychiatric Morbidity Survey 2014. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/556596/apms-2014-full-rpt.pdf. Accessed December 2019.
[4] Office for National Statistics (2018) Population estimates for the UK, England and Wales, Scotland and Northern Ireland: mid-2017. Available at: www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/previousReleases. Accessed December 2019.
[5] Alonso, J *et al*. (2004) Prevalence of mental disorders in Europe: results from the European study of the epidemiology of mental disorders (ESEMeD) project. *Acta Psychiatr Scand*;109:21-7.
[6] Blumenthal JA, *et al.* (2007) Exercise and pharmacotherapy in the treatment of major depressive disorder. *Psychosom Med*;69(7):587-96.
[7] Üstün, T., & Kessler, R. (2002) Global burden of depressive disorders: The issue of duration. *British Journal of Psychiatry*;181(3):181-183.
[8] Trivedi MH, *et al.* (2004) The Link Between Depression and Physical Symptoms. *Prim Care Companion J Clin Psychiatry*;6(Suppl 1):12-16.
[9] Brown J, Johnson & Johnson. (2018). 4 things we now know about Treatment-Resistant Depression. Available at: www.jnj.com/health-and-wellness/4-facts-about-treatment-resistant-depression. Accessed December 2019.
[10] Woo J, *et al.* (2011) Impact of depression on work productivity and its improvement after outpatient treatment with antidepressants. *Value Health*;14(4):475-82.
[11] Popova V, *et al.* (2019) Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study. *Am J Psychiatry*;176(6):428-43.
[12] Ochs-Ross R, Daly E, Zhang Y, *et al.* Efficacy and safety of esketamine nasal spray plus an oral antidepressant in elderly patients with treatment-resistant depression. Poster W27 presented at ASCP 2018, 19 May–01 June,

Miami, Florida.
[13] Fedgchin M, *et al.* (2019) Efficacy and Safety of Fixed-Dose Esketamine Nasal Spray Combined With a New Oral Antidepressant in Treatment-Resistant Depression: Results of a Randomized, Double-Blind, Active-Controlled Study (TRANSFORM-1). *Int J neuropsychopharmacol*;22(10):616-630.
[14] Daly E *et al.* (2019) Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients With Treatment-Resistant Depression: A Randomized Clinical Trial. *JAMA Psychiatry*. doi: 10.1001/jamapsychiatry.2019.1189. [Epub ahead of print].
[15] Wajs E, *et al*. (2018) Poster T67 - Long-Term Safety of Esketamine Nasal Spray Plus Oral Antidepressant in Patients with Treatment-Resistant Depression: Phase 3, Open-Label, Safety and Efficacy Study (SUSTAIN-2). Presented at the 2018 Annual Meeting of the American Society of Clinical Psychopharmacology, 29 May–1 June 2018, Miami, US.
[16] Daly E, Singh J, Fedgchin M *et al.* (2018) Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression. *JAMA Psychiatry*; 75 (2): 139-148.
[17] Summary of Product Characteristics Spravato 28 mg nasal spray. Janssen-Cilag International.
[18] Lener MS, Kadriu B and Zarate Jr C. (2017) Ketamine and Beyond: Investigations into the potential of glutamatergic agents to treat depression. *Drugs*; 77:381-401.
[19] Johnson & Johnson Ltd. Press release on February 2019. FDA advisory committee recommends approval of SPRAVATOTM (esketamine) nasal spray CIII for adults with treatment-resistant depression. Available at: https://www.jnj.com/fda-advisory-committee-recommends-approval-of-spravatotm-esketamine-nasal-spray-ciii-for-adults-with-treatment-resistant-depression. Accessed December 2019.
[20] Duman R, (2018) Ketamine and rapid-acting antidepressants: a new era in the battle against depression and suicide. *F1000 Research*; 7:659.
[21] Duman R, (2014) Pathophysiology of depression and innovative treatments: remodeling glutamatergic synaptic connections. *Dialogues Clin Neurosci*;16(1):11-27.
[22] European Medicines Agency. Spravato. Available at: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/spravato. Accessed December 2019.
[23] American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). *Arlington, VA: American Psychiatric Publishing.*
[24] Shah AJ, *et al.* (2010) Psychological Distress in Carers of People with Mental Disorders. *BJMP*;3(3):a327.
[25] Al-Harbi KS. (2012) Treatment-resistant depression: therapeutic trends, challenges and future directions. *Patient Pref Adherence*;6:369–388.
[26] Habert J *et al.* (2016) Functional Recovery in Major Depressive Disorder: Focus on Early Optimized Treatment*. Prim Care Companion CNS Disord*; 18(5).
[27] Knoth RL et al. (2010) Effect of inadequate response to treatment in patients with depression. *Am J Manag Care*;16;e188-96
[28] Johnston K *et al*. (2019) The burden of treatment-resistant depression: A systematic review of the economic and quality of life literature. *J Affect Disord*;242:195-210.
[29] Department of Health. (2011) No health without mental health: a cross-government mental health outcomes strategy for people of all ages. Supporting document –the economic case for improving efficiency and quality in mental health. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/138253/dh_124058.pdf. Accessed December 2019.
[30] McCrone P, *et al.* (2008) Paying the price. The cost of Mental health care in England to 2026. Available at: www.kingsfund.org.uk/sites/default/files/Paying-the-Price-the-cost-of-mental-health-care-England-2026-McCrone-Dhanasiri-Patel-Knapp-Lawton-Smith-Kings-Fund-May-2008_0.pdf. Accessed December 2019.
[31] Mrazek, D *et al.* (2014) A Review of the Clinical, Economic, and Societal Burden of Treatment-Resistant Depression: 1996–2013. *Psychiatr Serv*;65(8):977-87.