



**News Release**

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**SPRAVATO®▼ (ESKETAMINE) NASAL SPRAY AUTHORISED IN EUROPE  
FOR ADULTS WITH TREATMENT-RESISTANT MAJOR DEPRESSIVE  
DISORDER**

*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 offers the first new mechanism of action in 30 years to treat major depressive disorder (MDD)*

*European Commission (EC) authorisation is based on data from a robust clinical trial programme in adult patients with treatment-resistant major depressive disorder (TRD), including five phase III trials*

**HIGH WYCOMBE, UK, 19 DECEMBER 2019** – The Janssen Pharmaceutical Companies of Johnson & Johnson today announced that the European Commission (EC) has authorised 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.<sup>1</sup>

*"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 1.8 million adults in England alone.<sup>2-4</sup> It is a major health condition that is recognised as the most common mental health condition in Europe that causes significant ill-health, disability and suffering for patients and their families.<sup>5,6</sup> 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.<sup>7</sup> It may also affect employment and education, relationships, health and overall quality of life.<sup>8</sup> 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.<sup>9,10</sup>

*"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 data from a robust clinical trial programme in patients with TRD, including over 1,600 patients treated with esketamine nasal spray. The five phase III trials included three short-term studies, one randomised withdrawal and maintenance of effect study, and one long-term safety study.<sup>11-15</sup>

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  $\geq 50$  percent symptom reduction. Furthermore, approximately half of all esketamine nasal spray-treated patients achieved remission at the end of the 4-week study.<sup>+11</sup>

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.<sup>†13</sup>

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.<sup>†12</sup>

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.<sup>†14</sup>

Across the five phase III and one phase II clinical trials, esketamine nasal spray demonstrated a favourable benefit-risk profile, with sustained efficacy and no new safety concerns when observed over a period of up to 52 weeks.<sup>11–15</sup> The most commonly observed adverse events in TRD patients treated with esketamine nasal spray were dizziness, nausea, dissociation, headache, somnolence, vertigo, dysgeusia, hypoaesthesia, and vomiting.<sup>11–16</sup> These side effects were generally mild-to-moderate, transient (resolving within 2 hours) and occurred 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.

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*†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.<sup>16</sup>*

*\*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 signalling 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.<sup>17–20</sup> Based on its 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 EMA Committee for Medicinal Products for Human Use (CHMP) on 18 October 2019.<sup>21</sup>

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.<sup>18</sup>

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](http://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](mailto: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.<sup>22,23</sup> It causes severe and persistent symptoms of depression which can affect almost every aspect of a person's life.<sup>22</sup> 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.<sup>24</sup>

According to the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders 5<sup>th</sup> 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.<sup>22</sup> Other symptoms may also include: irritability, disturbances in sleep, appetite or sexual desire, constipation, suicidal thoughts and slowing of speech and action.<sup>22,25</sup>

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.<sup>26,27</sup>

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.<sup>28,29</sup> It is believed that TRD may add up to 68% in societal costs.<sup>30</sup>

### **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](http://www.janssen.com/uk). Follow us at [www.twitter.com/JanssenUK](https://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](http://www.sec.gov), [www.jnj.com](http://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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