ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Spravato 28 mg nasal spray, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each nasal spray device contains esketamine hydrochloride corresponding to 28 mg esketamine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Nasal spray, solution.
Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Spravato, in combination with a SSRI or SNRI, is indicated for adults with treatment-resistant Major Depressive Disorder, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode.

Spravato, co-administered with oral antidepressant therapy, is indicated in adults with a moderate to severe episode of Major Depressive Disorder, as acute short-term treatment, for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency.

See section 5.1 for a description of the populations studied.

4.2 Posology and method of administration

The decision to prescribe Spravato should be determined by a psychiatrist.

Spravato is intended to be self-administered by the patient under the direct supervision of a healthcare professional.

A treatment session consists of nasal administration of Spravato and a post-administration observation period. Both administration and post-administration observation of Spravato should be carried out in an appropriate clinical setting.

<u>Assessment before treatment</u>

Prior to dosing with Spravato blood pressure should be assessed.

If baseline blood pressure is elevated the risks of short-term increases in blood pressure and benefit of Spravato treatment should be considered (see section 4.4). Spravato should not be administered if an increase in blood pressure or intracranial pressure poses a serious risk (see section 4.3).

Patients with clinically significant or unstable cardiovascular or respiratory conditions require additional precautions. In these patients, Spravato should be administered in a setting where appropriate resuscitation equipment and healthcare professionals with training in cardiopulmonary resuscitation are available (see section 4.4).

Post-administration observation

After dosing with Spravato, blood pressure should be reassessed at approximately 40 minutes and subsequently as clinically warranted (see section 4.4).

Because of the possibility of sedation, dissociation and elevated blood pressure, patients must be monitored by a healthcare professional until the patient is considered clinically stable and ready to leave the healthcare setting (see section 4.4).

Posology

Treatment-resistant Major Depressive Disorder
The dose recommendations for Spravato for treatment-resistant Major Depressive Disorder are shown in Table 1 and Table 2 (adults ≥65 years). It is recommended to maintain the dose the patient receives at the end of the induction phase in the maintenance phase. Dose adjustments should be made based on efficacy and tolerability to the previous dose. During the maintenance phase, Spravato dosing should be individualised to the lowest frequency to maintain remission/response.

Table 1: Recommended dosing for Spravato in adults <65 years with treatment-resistant Major Depressive Disorder	
Induction phase	**Maintenance phase**
Weeks 1-4: Starting day 1 dose: 56 mg Subsequent doses: 56 mg or 84 mg twice a week	**Weeks 5-8**: 56 mg or 84 mg once weekly **From Week 9:** 56 mg or 84 mg every 2 weeks or once weekly
Evidence of therapeutic benefit should be evaluated at the end of induction phase to determine need for continued treatment.	The need for continued treatment should be re-examined periodically.

Table 2: Recommended dosing for Spravato in adults ≥65 years with treatment-resistant Major Depressive Disorder	
Induction phase	**Maintenance phase**
Weeks 1-4: Starting day 1 dose: 28 mg Subsequent doses: 28 mg, 56 mg or 84 mg twice a week, all dose changes should be in 28 mg increments	**Weeks 5-8**: 28 mg, 56 mg or 84 mg once weekly, all dose changes should be in 28 mg increments **From Week 9:** 28 mg, 56 mg or 84 mg every 2 weeks or once weekly, all dose changes should be in 28 mg increments
Evidence of therapeutic benefit should be evaluated at the end of induction phase to determine need for continued treatment.	The need for continued treatment should be re-examined periodically.

After depressive symptoms improve, treatment is recommended for at least 6 months.

Acute short-term treatment of psychiatric emergency due to Major Depressive Disorder
The recommended dosage of Spravato for adult patients (<65 years) is 84 mg twice per week for 4 weeks. Dosage reduction to 56 mg should be made based on tolerability. After 4 weeks of treatment with Spravato, the oral antidepressant (AD) therapy should be continued, per clinical judgement.

In these patients, treatment with Spravato should be part of the comprehensive clinical care plan.

Food and liquid intake recommendations prior to administration
Since some patients may experience nausea and vomiting after administration of Spravato, patients should be advised not to eat for at least 2 hours before administration and not to drink liquids at least 30 minutes prior to administration (see section 4.8).

Nasal corticosteroid or nasal decongestant
Patients who require a nasal corticosteroid or nasal decongestant on a dosing day should be advised not to administer these medicinal products within 1 hour before Spravato administration.

Missed treatment session(s)
Patients who have missed treatment session(s) during the first 4 weeks of treatment should continue with their current dosing schedule.

For patients with treatment-resistant Major Depressive Disorder who miss treatment session(s) during maintenance phase and have worsening of depression symptoms, per clinical judgement, consider returning to the previous dosing schedule (see Tables 1 and 2).

Special populations

Elderly (65 years of age and older)
In elderly patients the initial Spravato dose for treatment-resistant Major Depressive Disorder is 28 mg esketamine (day 1, starting dose, see Table 2 above). Subsequent doses should be increased in increments of 28 mg up to 56 mg or 84 mg, based on efficacy and tolerability.

Spravato has not been studied in elderly patients as acute short-term treatment of psychiatric emergency due to Major Depressive Disorder.

Hepatic impairment
No dose adjustment is necessary in patients with mild (Child Pugh class A) or moderate (Child Pugh class B) hepatic impairment. However, the maximum dose of 84 mg should be used with caution in patients with moderate hepatic impairment.

Spravato has not been studied in patients with severe hepatic impairment (Child-Pugh class C). Use in this population is not recommended (see sections 4.4 and 5.2).

Renal impairment
No dose adjustment is necessary in patients with mild to severe renal impairment. Patients on dialysis were not studied.

Japanese and Chinese patients with treatment-resistant Major Depressive Disorder
Efficacy of Spravato in Japanese and Chinese patients has been studied, but not established (see section 5.1).

Paediatric population
The safety and efficacy of Spravato in paediatric patients aged 17 years and younger have not been established. No data are available. There is no relevant use of Spravato in children less than 7 years of age.

Method of administration

Spravato is for nasal use only. The nasal spray device is a single-use device that delivers a total of 28 mg of esketamine, in two sprays (one spray per nostril). To prevent loss of medicinal product, the device should not be primed before use. It is intended for administration by the patient under the

supervision of a healthcare professional, using 1 device (for a 28 mg dose), 2 devices (for a 56 mg dose) or 3 devices (for an 84 mg dose), with a 5-minute rest between use of each device.

Sneezing after administration
If sneezing occurs immediately after administration, a replacement device should not be used.

Use of the same nostril for 2 consecutive sprays
If administration in the same nostril occurs, a replacement device should not be used.

Treatment discontinuation with Spravato does not require tapering off; based on data from clinical trials the risk of withdrawal symptoms is low.

4.3 Contraindications

- Hypersensitivity to the active substance, ketamine, or to any of the excipients listed in section 6.1.
- Patients for whom an increase in blood pressure or intracranial pressure poses a serious risk (see section 4.8):
  - Patients with aneurysmal vascular disease (including intracranial, thoracic, or abdominal aorta, or peripheral arterial vessels).
  - Patients with history of intracerebral haemorrhage.
  - Recent (within 6 weeks) cardiovascular event, including myocardial infarction (MI).

4.4 Special warnings and precautions for use

Suicide/suicidal thoughts or clinical worsening

The effectiveness of Spravato in preventing suicide or in reducing suicidal ideation or behaviour has not been demonstrated (see section 5.1). Use of Spravato does not preclude the need for hospitalisation if clinically warranted, even if patients experience improvement after an initial dose of Spravato.

Close supervision of patients and in particular those at high risk should accompany treatment especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted to the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs, therefore, patients should be closely monitored. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts and should receive careful monitoring during treatment.

Neuropsychiatric and motor impairments

Spravato has been reported to cause somnolence, sedation, dissociative symptoms, perception disturbances, dizziness, vertigo and anxiety during the clinical trials (see section 4.8). These effects may impair attention, judgment, thinking, reaction speed and motor skills. At each treatment session, patients should be monitored under the supervision of a healthcare professional to assess when the patient is considered stable based on clinical judgement (see section 4.7).

Respiratory depression

Respiratory depression may occur at high doses following rapid intravenous injection of esketamine or ketamine when used for anaesthesia. No case of respiratory depression was observed in clinical trials with esketamine nasal spray (Spravato); rare cases of deep sedation have been reported. Concomitant use of Spravato with CNS depressants may increase the risk for sedation (see section 4.5). During post-marketing use, rare cases of respiratory depression have been observed. The majority of these cases have been reported with concomitant use of CNS depressants or in patients with comorbidities such as obesity, anxiety, cardiovascular and respiratory conditions. These events were transient in nature and resolved after verbal/tactile stimulation or supplemental oxygen. Close monitoring is required for sedation and respiratory depression.

Effect on blood pressure

Spravato can cause transient increases in systolic and/or diastolic blood pressure which peak at approximately 40 minutes after administration of the medicinal product and last approximately 1-2 hours (see section 4.8). A substantial increase in blood pressure could occur after any treatment session. Spravato is contraindicated in patients for whom an increase in blood pressure or intracranial pressure poses a serious risk (see section 4.3). Before prescribing Spravato, patients with other cardiovascular and cerebrovascular conditions should be carefully assessed to determine whether the potential benefits of Spravato outweigh its risks.

In patients whose blood pressure prior to dose administration is judged to be elevated (as a general guide: >140/90 mmHg for patients <65 years of age and >150/90 mmHg for patients ≥65 years of age), it is appropriate to adjust lifestyle and/or pharmacologic therapies to reduce blood pressure before starting treatment with Spravato. If blood pressure is elevated prior to Spravato administration a decision to delay Spravato therapy should take into account the balance of benefit and risk in individual patients.

Blood pressure should be monitored after dose administration. Blood pressure should be measured around 40 minutes post-dose and subsequently as clinically warranted until values decline. If blood pressure remains elevated for a prolonged period of time, assistance should promptly be sought from practitioners experienced in blood pressure management. Patients who experience symptoms of a hypertensive crisis should be referred immediately for emergency care.

Patients with clinically significant or unstable cardiovascular or respiratory conditions

Only initiate treatment with Spravato in patients with clinically significant or unstable cardiovascular or respiratory conditions if the benefit outweighs the risk. In these patients, Spravato should be administered in a setting where appropriate resuscitation equipment and healthcare professionals with training in cardiopulmonary resuscitation are available. Examples of conditions which should be considered include, but are not limited to:

- Significant pulmonary insufficiency, including COPD;
- Sleep apnoea with morbid obesity (BMI ≥35);
- Patients with uncontrolled brady- or tachyarrhythmias that lead to haemodynamic instability;
- Patients with a history of an MI. These patients should be clinically stable and cardiac symptom free prior to administration;
- Haemodynamically significant valvular heart disease or heart failure (NYHA Class III-IV).

Drug abuse, dependence, withdrawal

Individuals with a history of drug abuse or dependence may be at greater risk for abuse and misuse of Spravato. Prior to prescribing Spravato, each patient's risk for abuse or misuse should be assessed and patients receiving esketamine should be monitored for the development of behaviours or conditions of abuse or misuse, including drug seeking behaviour, while on therapy.

Dependence and tolerance have been reported with prolonged use of ketamine. In individuals who were dependent on ketamine, withdrawal symptoms of cravings, anxiety, shaking, sweating and palpitations have been reported upon discontinuing ketamine.

Ketamine, the racemic mixture of arketamine and esketamine, is a medicinal product that has been reported to be abused. The potential for abuse, misuse and diversion of Spravato is minimised due to the administration taking place under the direct supervision of a healthcare professional. Spravato contains esketamine and may be subject to abuse and diversion.

Other populations at risk

Spravato should be used with caution in patients with the following conditions. These patients should be carefully assessed before prescribing Spravato and treatment initiated only if the benefit outweighs the risk:

- Presence or history of psychosis;
- Presence or history of mania or bipolar disorder;
- Hyperthyroidism that has not been sufficiently treated;
- History of brain injury, hypertensive encephalopathy, intrathecal therapy with ventricular shunts, or any other condition associated with increased intracranial pressure.

Elderly (65 years of age and older)

Elderly patients treated with Spravato may have a greater risk of falling once mobilised, therefore, these patients should be carefully monitored.

Severe hepatic impairment

Due to expected increase in exposure and lack of clinical experience, Spravato is not recommended in patients with Child-Pugh class C (severe) hepatic impairment.

Hepatotoxicity has been reported with chronic ketamine use, therefore, the potential for such an effect due to long-term use of Spravato cannot be excluded.

Urinary tract symptoms

Urinary tract and bladder symptoms have been reported with Spravato use (see section 4.8). It is recommended to monitor for urinary tract and bladder symptoms during the course of treatment and refer to an appropriate healthcare provider when symptoms persist.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of Spravato with CNS depressants (e.g., benzodiazepines, opioids, alcohol) may increase sedation, which therefore should be closely monitored.

Blood pressure should be closely monitored when Spravato is used concomitantly with psychostimulants (e.g., amphetamines, methylphenidate, modafinil, armodafinil) or other medicinal products that may increase blood pressure (e.g. xanthine derivatives, ergometrine, thyroid hormones, vasopressin, or MAOIs, such as, tranylcypromine, selegiline, phenelzine).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Spravato is not recommended during pregnancy and in women of childbearing potential not using contraception.

Pregnancy

There are no or limited data on the use of esketamine in pregnant women. Animal studies have shown that ketamine, the racemic mixture of arketamine and esketamine, induces neurotoxicity in developing foetuses (see section 5.3). A similar risk with esketamine cannot be excluded.

If a woman becomes pregnant while being treated with Spravato, treatment should be discontinued, and the patient should be counselled about the potential risk to the foetus and clinical/therapeutic options as soon as possible.

Breast-feeding

It is unknown whether esketamine is excreted in human milk. Data in animals have shown excretion of esketamine in milk. A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Spravato therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Animal studies showed that fertility and reproductive capacities were not adversely affected by esketamine.

4.7 Effects on ability to drive and use machines

Spravato has a major influence on the ability to drive and use machines. In clinical studies, Spravato has been reported to cause somnolence, sedation, dissociative symptoms, perception disturbances, dizziness, vertigo and anxiety (see section 4.8). Before Spravato administration, patients should be instructed not to engage in potentially hazardous activities requiring complete mental alertness and motor coordination, such as driving a vehicle or operating machinery, until the next day following a restful sleep (see section 4.4).

4.8 Undesirable effects

Summary of the safety profile

The most commonly observed adverse reactions in patients treated with Spravato were dizziness (31%), dissociation (27%), nausea (27%), headache (23%), somnolence (18%), dysgeusia (18%), vertigo (16%), hypoaesthesia (11%), vomiting (11%), and blood pressure increased (10%).

Tabulated list of adverse reactions

Adverse reactions reported with esketamine are listed in Table 3. Within the designated system organ classes, adverse reactions are listed under headings of frequency, using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Table 3: List of adverse reactions				
System Organ Class	**Adverse Drug Reaction**			
	Frequency			
	Very common	**Common**	**Uncommon**	**Rare**
Psychiatric disorders	dissociation	anxiety, euphoric mood, confusional state, derealisation, irritability, hallucination including visual hallucination, agitation, illusion, panic attack, time perception altered	psychomotor retardation, emotional distress, dysphoria	
Nervous system disorders	dizziness, headache, somnolence, dysgeusia, hypoaesthesia	paraesthesia, sedation, tremor, mental impairment, lethargy, dysarthria, disturbance in attention	nystagmus, psychomotor hyperactivity	
Eye disorders		vision blurred		
Ear and labyrinth disorders	vertigo	tinnitus, hyperacusis		
Cardiac disorders		tachycardia		
Vascular disorders		hypertension		
Respiratory, thoracic and mediastinal disorders		nasal discomfort, throat irritation, oropharyngeal pain, nasal dryness including nasal crusting, nasal pruritus		respiratory depression
Gastrointestinal disorders	nausea, vomiting	hypoaesthesia oral, dry mouth	salivary hypersecretion	
Skin and subcutaneous tissue disorders		hyperhidrosis	cold sweat	
Renal and urinary disorders		pollakiuria, dysuria, micturition urgency		
General disorders and administration site conditions		feeling abnormal, feeling drunk, asthenia, crying, feeling of body temperature change	gait disturbance	
Investigations	blood pressure increased			

Description of selected adverse reactions

Dissociation
Dissociation (27%) was one of the most common psychological effects of esketamine. Other related terms included derealisation (2.2%), depersonalisation (2.2%), illusions (1.3%), and distortion of time (1.2%). These adverse reactions were reported as transient and self-limited and occurred on the day of dosing. Dissociation was reported as severe in intensity at the incidence of less than 4% across studies. Dissociation symptoms typically resolved by 1.5 hours post-dose and the severity tended to reduce over time with repeated treatments.

Sedation/somnolence/respiratory depression
In clinical trials, adverse reactions of sedation (9.3%) and somnolence (18.2%) were primarily mild or moderate in severity, occurred on the day of dosing and resolved spontaneously the same day. Sedative effects typically resolved by 1.5 hours post-dose. Rates of somnolence were relatively stable over time during long-term treatment. In the cases of sedation, no symptoms of respiratory distress were observed, and haemodynamic parameters (including vital signs and oxygen saturation) remained within normal ranges. During post-marketing use, rare cases of respiratory depression have been observed (see section 4.4).

Changes in blood pressure
In clinical trials for treatment-resistant Major Depressive Disorder, increases in systolic and diastolic blood pressure (SBP and DBP) over time were about 7 to 9 mmHg in SBP and 4 to 6 mmHg in DBP at 40 minutes post-dose and 2 to 5 mmHg in SBP and 1 to 3 mmHg in DBP at 1.5 hours post-dose in patients receiving Spravato plus oral antidepressants (see section 4.4). The frequency of markedly abnormal blood pressure elevations of SBP (≥40 mmHg increase) ranged from 8% (<65 years) to 17% (≥65 years) and DBP (≥25 mmHg increase) ranged from 13% (<65 years) to 14% (≥65 years) in patients receiving esketamine plus oral antidepressant. The incidence of increased SBP (≥ 180 mmHg) was 3% and DBP (≥ 110 mmHg) was 4%.

Cognitive and memory impairment
Cognitive and memory impairment have been reported with long-term ketamine use or drug abuse. These effects did not increase over time and were reversible after discontinuing ketamine. In long-term clinical trials, the effect of esketamine nasal spray on cognitive functioning was evaluated over time and performance remained stable.

Urinary tract symptoms
Cases of interstitial cystitis have been reported with daily and long-term ketamine use at high doses. In clinical studies with esketamine, there were no cases of interstitial cystitis, however a higher rate of lower urinary tract symptoms was observed (pollakiuria, dysuria, micturition urgency, nocturia, and cystitis) in esketamine-treated patients compared with placebo-treated patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The potential for overdose of Spravato by the patient is minimised due to the product's design and the administration taking place under the supervision of a healthcare professional (see section 4.2).

Symptoms

The maximum single esketamine nasal spray dose tested in healthy volunteers was 112 mg which showed no evidence of toxicity and/or adverse clinical outcomes. However, compared to the recommended dose range, the 112 mg esketamine nasal spray dose was associated with higher rates of

adverse reactions, including dizziness, hyperhidrosis, somnolence, hypoaesthesia, feeling abnormal, nausea and vomiting.

Life-threatening symptoms are expected based on experience with ketamine given at 25-fold the usual anaesthetic dose. Clinical symptoms are described as convulsions, cardiac arrhythmias, and respiratory arrest. Administration of a comparable supratherapeutic dose of esketamine by the intranasal route is unlikely to be feasible.

Management

There is no specific antidote for esketamine overdose. In the case of overdose, the possibility of multiple medicinal products involvement should be considered. Management of Spravato overdose should consist of treating clinical symptoms and relevant monitoring. Close supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psychoanaleptics; Other antidepressants, ATC code: N06AX27.

Mechanism of action

Esketamine is the S-enantiomer of racemic ketamine. It is a non-selective, non-competitive, antagonist of the *N*-methyl-*D*-aspartate (NMDA) receptor, an ionotropic glutamate receptor. Through NMDA receptor antagonism, esketamine produces a transient increase in glutamate release leading to increases in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) stimulation and subsequently to increases in neurotrophic signalling which may contribute to the restoration of synaptic function in these brain regions involved with the regulation of mood and emotional behaviour. Restoration of dopaminergic neurotransmission in brain regions involved in the reward and motivation, and decreased stimulation of brain regions involved in anhedonia, may contribute to the rapid response.

Pharmacodynamic effects

Abuse potential
In a study of abuse potential conducted in recreational polydrug users (n=41), single doses of esketamine nasal spray (84 mg and 112 mg) and the positive control drug intravenous ketamine (0.5 mg/kg infused over 40 minutes) produced significantly greater scores than placebo on subjective ratings of "drug liking" and on other measures of subjective drug effects.

Clinical efficacy and safety

The efficacy and safety of Spravato nasal spray was investigated in five Phase 3 clinical studies in adult patients (18 to 86 years) with treatment-resistant depression (TRD) who met DSM-5 criteria for major depressive disorder and were non-responders to at least two oral antidepressants (ADs) treatments, of adequate dosage and duration, in the current major depressive episode. 1,833 adult patients were enrolled, of which 1,601 patients were exposed to Spravato.

The efficacy and safety of Spravato nasal spray was investigated in two Phase 3 clinical studies in adult patients (18 to 64 years) with moderate to severe MDD (MADRS total score >28) who had affirmative responses to Mini International Neuropsychiatric Interview (MINI) questions B3 ("Think [even momentarily] about harming or of hurting or of injuring yourself: with at least some intent or awareness that you might die as a result; or think about suicide [i.e., about killing yourself]?") and B10 ("Intend to act on thoughts of killing yourself in the past 24 hours?"). 456 adult patients were enrolled, of which 227 patients were exposed to Spravato.

Treatment-resistant depression – Short-term studies

Spravato was evaluated in three Phase 3 short-term (4-week) randomised, double-blind, active-controlled studies in patients with TRD. Studies TRANSFORM-1 (TRD3001) and TRANSFORM-2 (TRD3002) were conducted in adults (18 to < 65 years) and Study TRANSFORM-3 (TRD3005) was conducted in adults ≥ 65 years of age. Patients in TRD3001 and TRD3002 initiated treatment with Spravato 56 mg plus a newly initiated daily oral AD or a newly initiated daily oral AD plus placebo nasal spray on day 1. Spravato dosages were then maintained on 56 mg or titrated to 84 mg or matching placebo nasal spray administered twice-weekly during a 4-week double-blind induction phase. Spravato doses of 56 mg or 84 mg were fixed in Study TRD3001 and flexible in Study TRD3002. In Study TRD3005, patients (≥ 65 years) initiated treatment with Spravato 28 mg plus a newly initiated daily oral AD or a newly initiated daily oral AD plus placebo nasal spray (day 1). Spravato dosages were titrated to 56 mg or 84 mg or matching placebo nasal spray administered twice-weekly during a 4-week double-blind induction phase. In the flexible dose studies, TRD3002 and TRD3005, up titration of Spravato dose was based on clinical judgement and dose could be down titrated based on tolerability. A newly initiated open-label oral AD (SNRI: duloxetine, venlafaxine extended release; SSRI: escitalopram, sertraline) was initiated on day 1 in all studies. The selection of the newly initiated oral AD was determined by the investigator based on the patient's prior treatment history. In all short-term studies, the primary efficacy endpoint was change in MADRS total score from baseline to day 28.

Baseline demographic and disease characteristics for patient in TRD3002, TRD3001, and TRD3005 are presented in Table 4.

Table 4: Baseline demographic characteristics for TRD3002, TRD3001, and TRD3005 (full analysis sets)

	Study TRD3002 (N=223)	**Study TRD3001 (N=342)**	**Study TRD3005 (N=137)**
Age, years			
Median (Range)	47.0 (19; 64)	47.0 (18; 64)	69.0 (65; 86)
Sex, n (%)			
Male	85 (38.1%)	101 (29.5%)	52 (38.0%)
Female	138 (61.9%)	241 (70.5%)	85 (62.0%)
Race, n (%)			
White	208 (93.3%)	262 (76.6%)	130 (94.9%)
Black or African American	11 (4.9%)	19 (5.6%)	--
Prior oral antidepressants with nonresponse (i.e., failed antidepressants)			
Number of specific antidepressants, n (%)			
2	136 (61.0%)	167 (48.8%)	68 (49.6%)
3 or more	82 (36.8%)	167 (48.8%)	58 (42.3%)
Newly initiated oral antidepressant medication initiated at randomisation, n (%)			
SNRI	152 (68.2%)	196 (57.3%)	61 (44.5%)
SSRI	71 (31.8%)	146 (42.7%)	76 (55.5%)
Withdrawn from study (for any reason), n/N (%)	30/227 (13.2%)	31/346 (9.0%)	16/138 (11.6%)

In the flexible dose study TRD3002, at day 28, 67% of the patients randomised to Spravato were on 84 mg. In study TRD3002, esketamine plus a newly initiated oral AD demonstrated clinically meaningful and statistical superiority compared to a newly initiated oral AD (SNRI: duloxetine, venlafaxine extended release; SSRI: escitalopram, sertraline) plus placebo nasal spray (Table 5), and symptom reduction was observed as early as 24 hours post-dose.

In study TRD3001, a clinically meaningful treatment effect in change in MADRS total scores from baseline at the end of the 4-week induction phase was observed favouring Spravato plus newly initiated oral AD compared with a newly initiated oral AD (SNRI: duloxetine, venlafaxine extended

release; SSRI: escitalopram, sertraline) plus placebo nasal spray (Table 5). In Study TRD3001, the treatment effect for the Spravato 84 mg plus oral AD group compared with oral AD plus placebo was not statistically significant.

In study TRD3005, at day 28, 64% of the patients randomised to Spravato were on 84 mg, 25% on 56 mg, and 10% on 28 mg. In study TRD3005, a clinically meaningful but not statistically significant treatment effect in change in MADRS total scores from baseline at the end of the 4-week induction phase was observed favouring Spravato plus newly initiated oral AD compared with a newly initiated oral AD (SNRI: duloxetine, venlafaxine extended release; SSRI: escitalopram, sertraline) plus placebo nasal spray (Table 5). Subgroup analyses suggest limited efficacy in the population over 75 years old.

Table 5: Primary efficacy results for change in MADRS total score for 4-week clinical trials (ANCOVA BOCF[*])

Study no.	Treatment group[§]	Number of patients	Mean baseline score (SD)	LS mean change from baseline to end of week 4 (SE)	LS mean difference (95% CI)†
TRD3001	Spravato 56 mg + oral AD	115	37.4 (4.8)	-18.9 (1.3)	-4.3 (-7.8, -0.8)[#]
	Spravato 84 mg + oral AD	114	37.8 (5.6)	-16.2 (1.3)	-1.2 (-4.7, 2.3)[#]
	Oral AD + placebo nasal spray	113	37.5 (6.2)	-14.7 (1.3)	
TRD3002	Spravato (56 mg or 84 mg) + oral AD	114	37.0 (5.7)	-17.7 (1.3)	-3.5 (-6.7, -0.3)‡
	Oral AD + placebo nasal spray	109	37.3 (5.7)	-14.3 (1.3)	
TRD3005 (≥ 65 years)	Spravato (28 mg, 56 mg or 84 mg) + oral AD	72	35.5 (5.9)	-10.1 (1.7)	-2.9 (-6.5, 0.6)[#]
	Oral AD + placebo nasal spray	65	34.8 (6.4)	-6.8 (1.7)	

SD = standard deviation; SE = standard error; LS Mean = least-squares mean; CI = confidence interval; AD = antidepressant

[*] ANCOVA analysis using Baseline Observation Carried Forward, which means that for a patient who discontinues from treatment, it is assumed that the depression level returns to the baseline level (i.e. the depression level is the same as before start of treatment)

[§] Nasally administered esketamine or placebo; oral AD = a newly initiated AD (SNRI: duloxetine, venlafaxine extended release; SSRI: escitalopram, sertraline)

† Difference (Spravato + oral AD minus Oral AD + placebo nasal spray) in least-squares mean change from baseline

‡ Treatment group that was statistically significantly superior to Oral AD + placebo nasal spray

[#] Median unbiased estimate (i.e., weighted combination of the LS means of the difference from Oral AD + placebo nasal spray), and 95% flexible confidence interval

Response and remission rates

Response was defined as ≥ 50% reduction in the MADRS total score from baseline of the induction phase. Based on the reduction in MADRS total score from baseline, the proportion of patients in Studies TRD3001, TRD3002 and TRD3005 who demonstrated response to Spravato plus oral AD treatment was greater than for oral AD plus placebo nasal spray throughout the 4-week double-blind induction phase (Table 6).

Remission was defined as a MADRS total score ≤ 12. In all three studies, a greater proportion of patients treated with Spravato plus oral AD were in remission at the end of the 4-week double-blind induction phase than for oral AD plus placebo nasal spray (Table 6).

Table 6: Response and remission rates in 4-week clinical trials based on BOCF* data							
		Number of patients (%)					
		Response rate†					Remission rate‡
Study No.	Treatment group§	24 hours	Week 1	Week 2	Week 3	Week 4	Week 4
TRD3001	Spravato 56 mg + oral AD	20 (17.4%)	21 (18.3%)	29 (25.2%)	52 (45.2%)	61 (53.0%)	40 (34.8%)
	Spravato 84 mg + oral AD	17 (14.9%)#	16 (14.0%)	25 (21.9%)	33 (28.9%)	52 (45.6%)	38 (33.3%)
	Oral AD + placebo nasal spray	8 (7.1%)	5 (4.4%)	15 (13.3%)	25 (22.1%)	42 (37.2%)	33 (29.2%)
TRD3002	Spravato 56 mg or 84 mg + oral AD	18 (15.8%)	15 (13.2%)	29 (25.4%)	54 (47.4%)	70 (61.4%)	53 (46.5%)
	Oral AD + placebo nasal spray	11 (10.1%)	13 (11.9%)	23 (21.1%)	35 (32.1%)	52 (47.7%)	31 (28.4%)
TRD3005 (≥ 65 years)	Spravato 28 mg, 56 mg or 84 mg + oral AD	NA	4 (5.6%)	4 (5.6%)	9 (12.5%)	17 (23.6%)	11 (15.3%)
	Oral AD + placebo nasal spray	NA	3 (4.6%)	8 (12.3%)	8 (12.3%)	8 (12.3%)	4 (6.2%)

AD = antidepressant; NA = not available

* Baseline Observation Carried Forward, which means that for a patient who discontinues from treatment, it is assumed that the depression level returns to the baseline level (i.e. the depression level is the same as before start of treatment).

§ Nasally administered Spravato or placebo; oral AD = a newly initiated AD (SNRI: duloxetine, venlafaxine extended release; SSRI: escitalopram, sertraline)

† Response was defined as ≥ 50% reduction in the MADRS total score from baseline

‡ Remission was defined as MADRS total score ≤ 12

First dose was Spravato 56 mg + oral AD

Treatment-resistant depression – Long-term studies

Relapse-prevention study

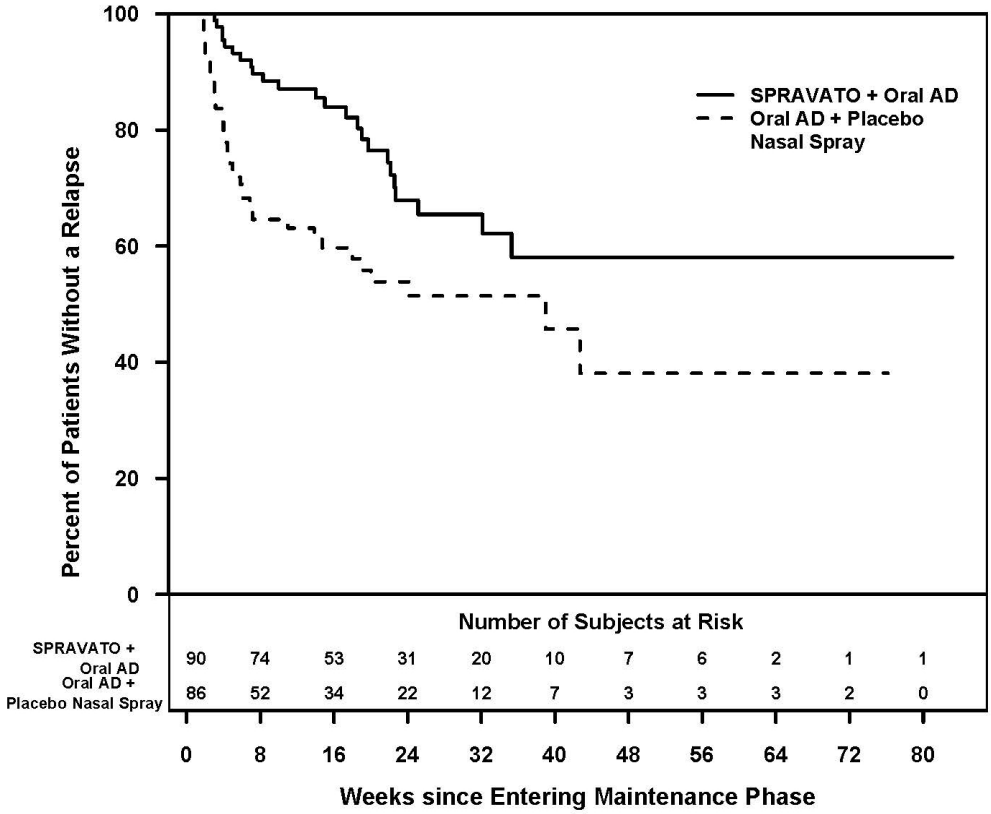
The maintenance of antidepressant efficacy was demonstrated in a relapse prevention trial. Study SUSTAIN-1 (TRD3003) was a long-term randomised, double-blind, parallel-group, active-controlled, multicentre, relapse prevention study. The primary outcome measure to assess the prevention of depressive relapse was measured as time to relapse. Overall a total of 705 patients were enrolled; 437 directly enrolled; 150 transferred from TRD3001, and 118 transferred from TRD3002. Patients directly enrolled were administered Spravato (56 mg or 84 mg twice weekly) plus oral AD in a 4-week open label induction phase. At the end of the open label induction phase, 52% of patients were in remission (MADRS total score ≤ 12) and 66% of patients were responders (≥ 50% improvement in MADRS total score). Patients who were responders (455), continued receiving treatment with Spravato plus oral AD in a 12-week optimisation phase. After the induction phase, patients received Spravato weekly for 4 weeks and starting from week 8, an algorithm (based on the MADRS) was used to determine the dosing frequency; patients in remission (i.e., MADRS total score was ≤ 12) were dosed every other week, however, if the MADRS total score increased to > 12, then the frequency was

increased to weekly dosing for the next 4 weeks; with the objective of maintaining the patient on the lowest dosing frequency to maintain response/remission. At the end of 16 weeks of treatment period, patients in stable remission (n=176) or stable response (n=121) were randomised to continue with Spravato or stop Spravato and switch to placebo nasal spray. Stable remission was defined as MADRS total score ≤ 12 in at least 3 of the last 4 weeks of the optimisation phase and stable response was defined as ≥ 50% reduction in the MADRS total score from baseline for the last 2 weeks of the optimisation phase, but not in stable remission.

Stable remission

Patients in stable remission who continued treatment with Spravato plus oral AD experienced a statistically significantly longer time to relapse of depressive symptoms than did patients on a newly initiated oral AD (SNRI: duloxetine, venlafaxine extended release; SSRI: escitalopram, sertraline) plus placebo nasal spray (Figure 1). Relapse was defined as a MADRS total score ≥ 22 for 2 consecutive weeks or hospitalisation for worsening depression or any other clinically relevant event indicative of relapse. The median time to relapse for a newly initiated oral AD (SNRI: duloxetine, venlafaxine extended release; SSRI: escitalopram, sertraline) plus placebo nasal spray group was 273 days, whereas the median was not estimable for Spravato plus oral AD, as this group never reached 50% relapse rate.

Figure 1: Time to relapse in patients in stable remission in study TRD3003 (full analysis set)



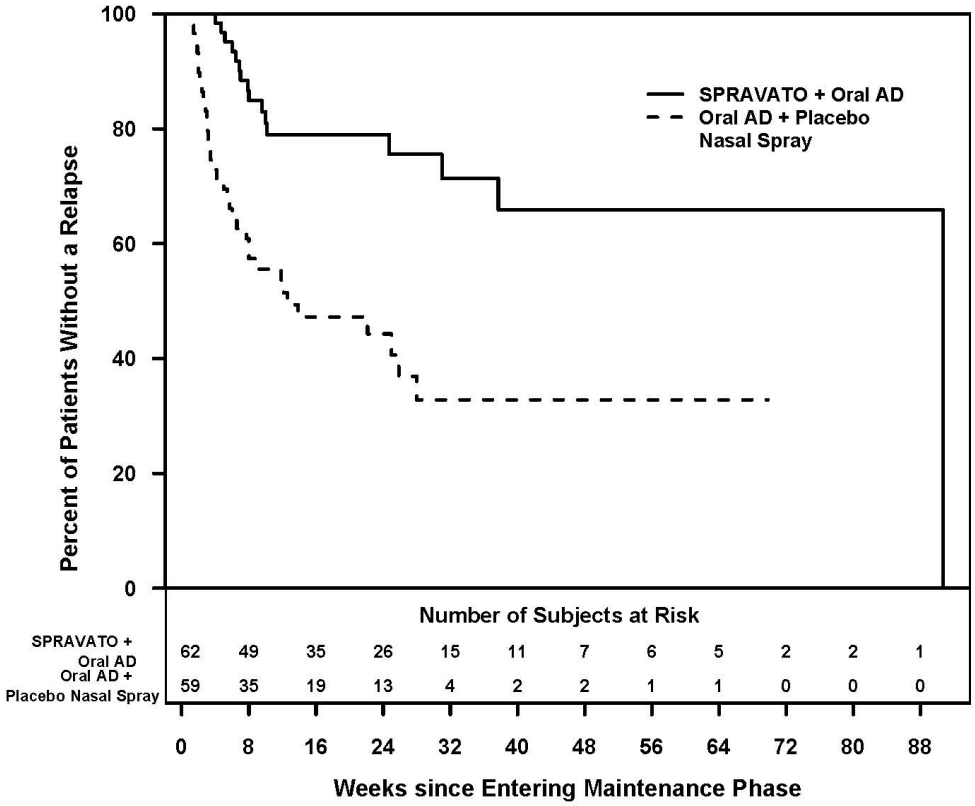
For patients in stable remission, the relapse rate based on Kaplan-Meier estimates during the 12- and 24-weeks double-blind follow up period was 13% and 32% for Spravato and 37% and 46% for placebo nasal spray, respectively.

Stable response

The efficacy results were also consistent for patients in stable response who continued treatment with Spravato plus oral AD; patients experienced a statistically significantly longer time to relapse of depressive symptoms than did patients on a newly initiated oral AD (SNRI: duloxetine, venlafaxine

extended release; SSRI: escitalopram, sertraline) plus placebo nasal spray (Figure 2). The median time to relapse for a newly initiated oral AD (SNRI: duloxetine, venlafaxine extended release; SSRI: escitalopram, sertraline) plus placebo nasal spray group (88 days) was shorter compared to Spravato plus oral AD group (635 days).

Figure 2: Time to relapse in patients in stable response in study TRD3003 (full analysis set)



For patients in stable response, the relapse rate based on Kaplan-Meier estimates during the 12- and 24-weeks double-blind follow up period was 21% and 21% for Spravato and 47% and 56% for placebo nasal spray, respectively.

Enrollment in TRD3003 was staggered over approximately 2 years. The maintenance phase was of variable duration and continued until the individual patient had a relapse of depressive symptoms or discontinued for any other reason, or the study ended because the required number of relapse events occurred. Exposure numbers were influenced by the study stopping at a pre-determined number of relapses based on the interim analysis. After an initial 16 weeks of treatment with Spravato plus oral AD, the median duration of exposure to Spravato in the maintenance phase was 4.2 months (range: 1 day to 21.2 months) in Spravato-treated patients (stable remission and stable response). In this study, 31.6% of patients received Spravato for greater than 6 months and 7.9% of patients received Spravato for greater than 1 year in the maintenance phase.

Dosing frequency

The dosing frequency used the majority of the time during the maintenance phase is shown in Table 7. Of the patients randomised to Spravato, 60% received 84 mg and 40% received 56 mg dose.

Table 7: Dosing frequency used the majority of the time; maintenance phase (Study TRD3003)				
	Stable Remission		Stable Responders	
	Spravato + Oral AD (N=90)	Oral AD + Placebo Nasal Spray (N=86)	Spravato + Oral AD (N=62)	Oral AD + Placebo Nasal Spray (N=59)
Majority dosing frequency				
Weekly	21 (23.3%)	27 (31.4%)	34 (54.8%)	36 (61.0%)
Every other week	62 (68.9%)	48 (55.8%)	21 (33.9%)	19 (32.2%)
Weekly or every other week	7 (7.8%)	11 (12.8%)	7 (11.3%)	4 (6.8%)

Treatment-resistant depression – Short-term study in Japanese patients

The efficacy of Spravato was also evaluated in a short-term (4-week) randomised, double-blind, active-controlled study (TRD2005) in 202 adult Japanese patients with TRD. Patients received 4 weeks of induction treatment with Spravato fixed-dose of 28 mg, 56 mg, 84 mg or placebo nasal spray in addition to continued current oral AD. The primary efficacy endpoint was change in MADRS total score from baseline to day 28. The baseline demographic and disease characteristics of patients were similar between the Spravato plus AD and placebo nasal spray plus AD groups.

In study TRD2005, no statistically significant difference in change in MADRS total scores from baseline at the end of the 4-week induction phase was observed for any of the Spravato plus oral AD dosages compared with oral AD plus placebo nasal spray (Table 8).

Table 8: Primary efficacy results for change in MADRS total score for 4-week TRD2005 Study in Japanese patients (MMRM)				
Treatment group	**Number of patients**	**Mean baseline score (SD)**	**LS mean change from baseline to end of week 4 (SE)**	**LS mean difference (90% CI)[†,#]**
Spravato 28 mg + oral AD	41	38.4 (6.1)	-15.6 (1.8)	-1.0 -5.77; 3.70
Spravato 56 mg + oral AD	40	37.9 (5.4)	-14.0 (1.9)	0.6 -4.32; 5.47
Spravato 84 mg + oral AD	41	35.9 (5.3)	-15.5 (1.8)	-0.9 -5.66; 3.83
Oral AD + placebo nasal spray	80	37.7 (5.7)	-14.6 (1.3)	

SD = standard deviation; SE = standard error; LS Mean = least-squares mean; CI = confidence interval; AD = antidepressant.

† Difference (Spravato + oral AD minus Oral AD + placebo nasal spray) in least-squares mean change from baseline.

Confidence interval is based on the Dunnett adjustment.

Treatment-resistant depression – Short-term study in Chinese patients

The efficacy of Spravato was also evaluated in a short-term (4-week) randomised, double-blind, active-controlled study (TRD3006) in 252 adult patients (224 Chinese patients, 28 non-Chinese patients) with TRD.

Patients received 4 weeks of induction treatment with flexibly dosed Spravato (56 mg or 84 mg) or placebo nasal spray, in addition to a newly initiated oral AD. The primary efficacy endpoint was change in MADRS total score from baseline to day 28. The baseline demographic and disease characteristics of patients were similar between the Spravato plus AD and placebo nasal spray plus AD groups.

In study TRD3006, no statistically significant difference in change in MADRS total scores from baseline at the end of the 4-week induction phase was observed for Spravato plus oral AD compared with oral AD plus placebo nasal spray (Table 9).

Table 9: Primary efficacy results for change in MADRS total score for 4-week TRD3006 Study (MMRM)

Treatment group	Number of patients[#]	Mean baseline score (SD)	LS mean change from baseline to end of week 4 (SE)	LS mean difference (95% CI)[†]
All patients				
Spravato (56 mg or 84 mg) + oral AD	124	36.5 (5.21)	-11.7 (1.09)	-2.0 -4.64; 0.55
Oral AD + placebo nasal spray	126	35.9 (4.50)	-9.7 (1.09)	
Chinese population				
Spravato (56 mg or 84 mg) + oral AD	110	36.2 (5.02)	-8.8 (0.95)	-0.7 -3.35; 1.94
Oral AD + placebo nasal spray	112	35.9 (4.49)	-8.1 (0.95)	

SD = standard deviation; SE = standard error; LS Mean = least-squares mean; CI = confidence interval; AD = antidepressant.

[#] Two patients did not receive oral AD and were not included in the efficacy analysis.

[†] Difference (Spravato + oral AD minus Oral AD + placebo nasal spray) in least-squares mean change from baseline.

Acute short-term treatment of psychiatric emergency due to Major Depressive Disorder

Spravato was investigated in two identical Phase 3 short-term (4-week) randomised, double-blind, multicentre, placebo-controlled studies, Aspire I (SUI3001) and Aspire II (SUI3002) in adult patients with moderate to severe MDD (MADRS total score >28) who had affirmative responses to MINI questions B3 ("Think [even momentarily] about harming or of hurting or of injuring yourself: with at least some intent or awareness that you might die as a result; or think about suicide [i.e., about killing yourself]?") and B10 ("Intend to act on thoughts of killing yourself in the past 24 hours?"). In these studies, patients received treatment with Spravato 84 mg or placebo nasal spray twice-weekly for 4 weeks. All patients received comprehensive standard of care (SOC) treatment, including an initial inpatient hospitalisation and a newly initiated or optimised oral antidepressant (AD) therapy (AD monotherapy or AD plus augmentation) as determined by the investigator. In the physician's opinion, acute psychiatric hospitalisation was clinically warranted due to the subject's immediate risk of suicide. After the first dose, a one-time dose reduction to Spravato 56 mg was allowed for patients unable to tolerate the 84 mg dose.

The baseline demographic and disease characteristics of patients in SUI3001 and SUI3002 were similar between the Spravato plus SOC or placebo nasal spray plus SOC groups. The median patient age was 40 years (range 18 to 64 years), 61% were female; 73% Caucasian and 6% Black; and 63% of patients had at least one prior suicide attempt. Prior to entering the study, 92% of the patients were receiving antidepressant therapy. During the study, as part of standard of care treatment, 40% of patients received AD monotherapy, 54% of patients received AD plus augmentation regimen, and 6% received both AD monotherapy/AD plus augmentation regimen.

The primary efficacy measure was the reduction of symptoms of MDD as measured by the change from baseline MADRS total score at 24 hours after first dose (Day 2).

In SUI3001 and SUI3002, Spravato plus SOC demonstrated statistical superiority on the primary efficacy measure compared to placebo nasal spray plus SOC (see Table 10).

Table 10: Primary Efficacy Results for Change from Baseline in MADRS Total Score at 24 Hours After First Dose (Studies SUI3001 and SUI3002) (ANCOVA BOCF[*])					
Study No.	**Treatment Group[‡]**	**Number of Patients**	**Mean Baseline Score (SD)**	**LS Mean Change from Baseline to 24 hr Post First Dose (SE)**	**LS Mean Difference (95% CI)[§]**
Study 1 (SUI3001)	Spravato 84 mg + SOC	112	41.2 (5.87)	-15.7 (1.05)	-3.7 (-6.41; -0.92)[¶] P=0.006
	Placebo nasal spray + SOC	112	41.0 (6.29)	-12.1 (1.03)	–
Study 2 (SUI3002)	Spravato 84 mg + SOC	114	39.5 (5.19)	-15.9 (1.02)	-3.9 (-6.65; -1.12)[¶] P=0.006
	Placebo nasal spray + SOC	113	39.9 (5.76)	-12.0 (1.06)	–
Pooled Studies 1 and 2	Spravato 84 mg + SOC	226	40.3 (5.60)	-15.8 (0.73)	-3.8 (-5.69; -1.82)
	Placebo nasal spray + SOC	225	40.4 (6.04)	-12.1 (0.73)	–

SD=standard deviation; SE=standard error; LS Mean=least-squares mean; CI=confidence interval; SOC=standard of care

[*] ANCOVA analysis using Baseline Observation Carried Forward: In SUI3001, 2 subjects (1 subject in each group) did not have the Day 2 (24 hours post first dose) MADRS total score and in SUI3002, 6 subjects (4 subjects in Esketamine and 2 subjects in Placebo) did not have the Day 2 (24 hours post first dose) MADRS total score. For these subjects, it is assumed that the depression level returns to the baseline level (i.e. the depression level is the same as the start of treatment) and the MADRS total scores from baseline were carried forward for the analysis

[‡] Nasally administered esketamine or placebo

[§] Difference (Spravato + SOC minus placebo nasal spray + SOC) in least-squares mean change from baseline

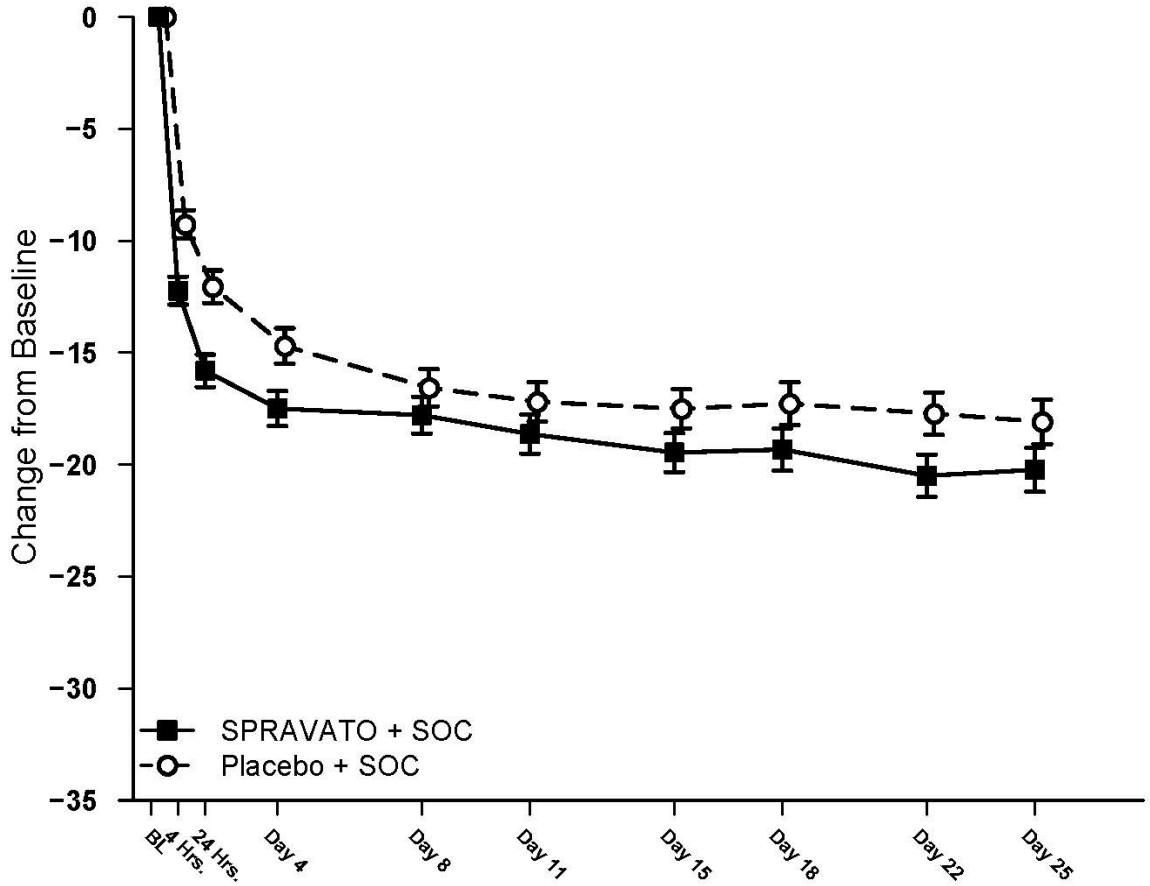
[¶] Treatment groups that were statistically significantly superior to placebo nasal spray + SOC.

The treatment differences (95% CI) in change from baseline in MADRS total score at Day 2 (24 hours post first dose) between Spravato + SOC and placebo + SOC were -4.70 (-7.16; -2.24) for the subpopulation that reported a prior suicide attempt (N=284) and -2.34 (-5.59; 0.91) for the subpopulation that did not report a prior suicide attempt (N=166).

Time course of treatment response

In both SUI3001 and SUI3002, Spravato's treatment difference compared to placebo was observed starting at 4 hours. Between 4 hours and Day 25, the end of the treatment phase, both the Spravato and placebo groups continued to improve; the difference between the groups generally remained but did not appear to increase over time through Day 25. Figure 3 depicts time course of the primary efficacy measure of change in MADRS total score using pooled studies SUI3001 and SUI3002.

Figure 3: Least Squares Mean Change from Baseline in MADRS Total Score Over Time in SUI3001 and SUI3002* (Pooled Data, Safety Analysis Set) – ANCOVA BOCF



* Note: In these studies, after the first dose, a one-time dose reduction to Spravato 56 mg was allowed for patients unable to tolerate the 84 mg dose. Approximately 16% of patients had reduction in Spravato dosage from 84 mg to 56 mg twice weekly.

Remission rates

In the Phase 3 studies, the percentage of patients who achieved remission (MADRS total score ≤12 at any given time during the study) was greater in the Spravato + SOC group than in the placebo + SOC group at all timepoints during the 4-week double-blind treatment phase (Table 11).

Table 11: Patients Who Achieved Remission of MDD; Double-blind Treatment Phase; Full Efficacy Analysis Set						
	SUI3001		SUI3002		Pooled Studies (SUI3001 and SUI3002)	
	Placebo + SOC 112	Spravato + SOC 112	Placebo + SOC 113	Spravato + SOC 114	Placebo + SOC 225	Spravato + SOC 226
Day 1, 4 hours post first dose Patients with Remission of MDD	9 (8.0%)	12 (10.7%)	4 (3.5%)	12 (10.5%)	13 (5.8%)	24 (10.6%)
Day 2, 24 hours post first dose Patients with Remission of MDD	10 (8.9%)	21 (18.8%)	12 (10.6%)	25 (21.9%)	22 (9.8%)	46 (20.4%)
Day 25 (predose) Patients with Remission of MDD	38 (33.9%)	46 (41.1%)	31 (27.4%)	49 (43.0%)	69 (30.7%)	95 (42.0%)
Day 25 (4 hours postdose) Patients with Remission of MDD	42 (37.5%)	60 (53.6%)	42 (37.2%)	54 (47.4%)	84 (37.3%)	114 (50.4%)

SOC = standard of care
Note: Remission is based on a MADRS total score of ≤12. Subjects who did not meet such criterion or discontinued prior to the time point for any reason are not considered to be in remission.

Effects on suicidality
Overall patients in both treatment groups experienced improvement in the severity of their suicidality as measured by the Clinical Global Impression – Severity of Suicidality - revised (CGI-SS-r) scale at the 24-hour endpoint, though there was no statistically significant difference between treatment groups.

The long-term efficacy of Spravato to prevent suicide has not been established.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Spravato in the treatment of major depressive disorder in one or more subsets of the paediatric population (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

The mean absolute bioavailability of 84 mg esketamine administered as a nasal spray is approximately 48%.

Esketamine is rapidly absorbed by the nasal mucosa following nasal administration and can be measured in plasma within 7 minutes following a 28 mg dose. The time to reach maximum plasma concentration (t_{max}) is typically 20 to 40 minutes after the last nasal spray of a treatment session (see section 4.2).

Dose-dependent increases in the maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC_{∞}) of esketamine nasal spray were produced by doses of 28 mg, 56 mg and 84 mg.

The pharmacokinetic profile of esketamine is similar after a single dose and repeat dose administration with no accumulation in plasma when esketamine is administered twice a week.

Distribution

The mean steady-state volume of distribution of esketamine administered by the intravenous route is 709 L.

The proportion of the total concentration of esketamine that is bound to proteins in human plasma is on average 43 to 45%. The degree to which esketamine is bound to plasma proteins is not dependent on hepatic or renal function.

Esketamine is not a substrate of transporters P-glycoprotein (P-gp; multidrug resistance protein 1), breast cancer resistance protein (BCRP), or organic anion transporter (OATP) 1B1, or OATP1B3. Esketamine does not inhibit these transporters or multi-drug and toxin extrusion 1 (MATE1) and MATE2-K, or organic cation transporter 2 (OCT2), OAT1, or OAT3.

Biotransformation

Esketamine is extensively metabolised in the liver. The primary metabolic pathway of esketamine in human liver microsomes is N-demethylation to form noresketamine. The main cytochrome P450 (CYP) enzymes responsible for esketamine N-demethylation are CYP2B6 and CYP3A4. Other CYP enzymes, including CYP2C19 and CYP2C9, contribute to a much smaller extent. Noresketamine is subsequently metabolised via CYP-dependent pathways to other metabolites, some of which undergo glucuronidation.

Elimination

The mean clearance of esketamine administered by the intravenous route was approximately 89 L/hour. After C_{max} was reached following nasal administration, the decline in esketamine concentrations in plasma was rapid for the first few hours and then more gradual. The mean terminal half-life following administration as a nasal spray generally ranged from 7 to 12 hours.

Following intravenous administration of radiolabelled esketamine, approximately 78% and 2% of administered radioactivity was recovered in urine and faeces, respectively. Following oral administration of radiolabelled esketamine, approximately 86% and 2% of administered radioactivity was recovered in urine and faeces, respectively. The recovered radioactivity consisted primarily of esketamine metabolites. For the intravenous and oral routes of administration, < 1% of the dose was excreted in the urine as unchanged drug.

Linearity/non-linearity

Esketamine exposure increases with dose from 28 mg to 84 mg. The increase in C_{max} and AUC values was less than dose-proportional between 28 mg and 56 mg or 84 mg, but it was nearly dose proportional between 56 mg and 84 mg.

Interactions

Effect of other medicinal products on esketamine

Hepatic enzyme inhibitors
Pre-treatment of healthy subjects with oral ticlopidine, an inhibitor of hepatic CYP2B6 activity, (250 mg twice daily for 9 days prior to and on the day of esketamine administration) had no effect on the C_{max} of esketamine administered as a nasal spray. The AUC_{∞} of esketamine was increased by approximately 29%. The terminal half-life of esketamine was not affected by ticlopidine pre-treatment.

Pre-treatment with oral clarithromycin, an inhibitor of hepatic CYP3A4 activity, (500 mg twice daily for 3 days prior to and on the day of esketamine administration) increase the mean C_{max} and AUC_{∞} of

nasally administered esketamine by approximately 11% and 4%, respectively. The terminal half-life of esketamine was not affected by clarithromycin pre-treatment.

Hepatic enzyme inducers
Pre-treatment with oral rifampicin, a potent inducer of the activity of multiple hepatic CYP enzymes such as CYP3A4 and CYP2B6, (600 mg daily for 5 days prior to esketamine administration) decreased the mean C_{max} and AUC_{∞} values of esketamine administered as a nasal spray by approximately 17% and 28%, respectively.

Other nasal spray products
Pre-treatment of subjects with a history of allergic rhinitis and pre-exposed to grass pollen with oxymetazoline administered as a nasal spray (2 sprays of 0.05% solution administered at 1 hour prior to nasal administration of esketamine) had minor effects on the pharmacokinetics of esketamine.

Pre-treatment of healthy subjects with nasal administration of mometasone furoate (200 mcg per day for 2 weeks with the last mometasone furoate dose administered at 1 hour prior to nasal administration of esketamine) had minor effects on the pharmacokinetics of esketamine.

Effect of esketamine on other medicinal products

Nasal administration of 84 mg esketamine twice a week for 2 weeks reduced the mean plasma AUC_{∞} of oral midazolam (single 6 mg dose), a substrate of hepatic CYP3A4, by approximately 16%.

Nasal administration of 84 mg esketamine twice a week for 2 weeks did not affect the mean plasma AUC of oral bupropion (single 150 mg dose), a substrate of hepatic CYP2B6.

Special populations

Elderly (65 years of age and older)
The pharmacokinetics of esketamine administered as a nasal spray was compared between elderly but otherwise healthy subjects and younger healthy adults. The mean esketamine C_{max} and AUC_{∞} values produced by a 28 mg dose were 21% and 18% higher, respectively, in elderly subjects (age range 65 to 81 years) compared with younger adult subjects (age range 22 to 50 years). The mean esketamine C_{max} and AUC_{∞} values produced by an 84 mg dose were 67% and 38% higher in elderly subjects (age range 75 to 85 years) compared with younger adult subjects (age range 24 to 54 years). The terminal half-life of esketamine was similar in the elderly and younger adult subjects (see section 4.2).

Renal impairment
Relative to the subjects with normal renal function (creatinine clearance [CL_{CR}], 88 to 140 mL/min), the C_{max} of esketamine was on average 20 to 26% higher in subjects with mild (CL_{CR}, 58 to 77 mL/min), moderate (CL_{CR}, 30 to 47 mL/min), or severe (CL_{CR}, 5 to 28 mL/min, not on dialysis) renal impairment following administration of a 28 mg dose of esketamine nasal spray. The AUC_{∞} was 13 to 36% higher in the subjects with mild to severe renal impairment.

There is no clinical experience with esketamine administered as a nasal spray in patients on dialysis.

Hepatic impairment
The C_{max} and AUC_{∞} of esketamine produced by a 28 mg doses were similar between subjects with Child-Pugh class A (mild) hepatic impairment and healthy subjects. The C_{max} and AUC_{∞} of esketamine were 8% higher and 103% higher, respectively, in subjects with Child-Pugh class B (moderate) hepatic impairment, relative to healthy subjects.

There is no clinical experience with esketamine administered as a nasal spray in patients with Child-Pugh class C (severe) hepatic impairment (see section 4.2 and 4.4).

Race
The pharmacokinetics of esketamine nasal spray was compared between healthy Asian subjects and Caucasian subjects. Mean plasma esketamine C_{max} and AUC_{∞} values produced by a single, 56 mg dose of esketamine were approximately 14% and 33% higher, respectively, in Chinese subjects compared to Caucasians. On average, esketamine C_{max} was 10% lower and AUC_{∞} was 17% higher in Korean subjects, relative to Caucasian subjects. A population pharmacokinetic analysis was conducted that included Japanese patients with treatment-resistant depression, in addition to healthy Japanese subjects. Based on this analysis, for a given dose, the plasma esketamine C_{max} and AUC_{24h} in Japanese subjects were approximately 20% higher relative to non-Asian subjects. The mean terminal half-life of esketamine in the plasma of Asian subjects ranged from 7.1 to 8.9 hours and was 6.8 hours in Caucasian subjects.

Gender and body weight
No significant differences in the pharmacokinetics of esketamine nasal spray were observed for gender and total body weight (> 39 to 170 kg) based on population PK analysis.

Allergic rhinitis
The pharmacokinetics of a single, 56 mg dose of esketamine administered as a nasal spray was similar in subjects with allergic rhinitis who were exposed to grass pollen compared to healthy subjects.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, neurotoxicity, reproductive toxicity, and carcinogenic potential. Animal studies with ketamine showed evidence of developmental neurotoxicity. The potential for esketamine to have neurotoxic effects on developing foetuses cannot be excluded (see section 4.6).

Genotoxicity

Esketamine was not mutagenic with or without metabolic activation in the Ames test. Genotoxic effects with esketamine were seen in a screening *in vitro* micronucleus test in the presence of metabolic activation. However, intravenously-administered esketamine was devoid of genotoxic properties in an *in vivo* bone marrow micronucleus test in rats and an *in vivo* Comet assay in rat liver cells.

Reproductive toxicity

In an embryo foetal developmental toxicity study with nasally administered ketamine in rats, the offspring was not adversely affected in the presence of maternal toxicity at doses resulting in exposure up to 6-fold higher than human exposure, based on AUC values. In an embryo foetal developmental toxicity study with nasally administered ketamine in rabbits, skeletal malformations were observed and foetal body weight was reduced at maternally toxic doses. Exposure in rabbits was in the region of human exposure based on AUC values.

Published studies in animals (including primates) at doses resulting in light to moderate anaesthesia demonstrate that the use of anaesthetic agents during the period of rapid brain growth or synaptogenesis results in cell loss in the developing brain, that can be associated with prolonged cognitive deficiencies. The clinical significance of these non-clinical findings in not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate
Disodium edetate
Sodium hydroxide (for pH adjustment)

Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Type-I glass vial with a chlorobutyl rubber stopper. The filled and stoppered vial is assembled into a manually-activated nasal spray device. The device dispenses two sprays.

Within each pack, each device is individually packaged in a sealed blister.

Pack sizes of 1, 2, 3, or 6 nasal spray devices and in multipacks containing 12 (4 packs of 3) or 24 (8 packs of 3) nasal spray devices.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1410/001 (1 spray container)
EU/1/19/1410/002 (2 spray containers)
EU/1/19/1410/003 (3 spray containers)
EU/1/19/1410/004 (6 spray containers)
EU/1/19/1410/005 (24 spray containers)
EU/1/19/1410/006 (12 spray containers)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 December 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Janssen Pharmaceutica NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to special and restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Spravato in each Member State (MS), the Marketing Authorisation Holder (MAH) must agree about the content and format of the **educational materials (EM) and the controlled access programme (CAP)**, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA).

The MAH shall ensure that in each MS where Spravato is marketed a CAP is implemented to prevent/minimise the important identified risk of Drug abuse.

Spravato is intended to be self-administered by the patient under direct Healthcare Professional (HCP) supervision, and should be dispensed to the healthcare settings where administration takes place, as agreed at the MS level, based on local legal requirements and/or local healthcare systems. When the administration is intended for outpatients, it should only be reserved to an environment where the patient is appropriately followed-up.

Spravato may induce transient sedation, dissociative and perception disorders and/or increase blood pressure. Patients must, therefore, be monitored by a HCP during and after each treatment session including an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting. In patients with clinically significant or unstable cardiovascular or respiratory conditions, Spravato should be administered in a setting where appropriate resuscitation equipment and healthcare professionals with training in cardiopulmonary resuscitation are available.

The following EM should be provided to HCPs (and acknowledgement of receipt recorded):

- **The HCP guide**, aiming at addressing the risks of transient dissociative states and perception disorders, drug abuse, disturbances in consciousness, and blood pressure increased, should incorporate adequate reference to patient's safety, and highlight that:
  - All patients must be monitored accordingly after Spravato administration until considered clinically stable to leave the healthcare setting;
  - In patients with clinically significant or unstable cardiovascular or respiratory conditions, Spravato should be administered in a clinical setting where equipment for cardiopulmonary resuscitation and staff trained in cardiopulmonary resuscitation are available;
  - Due to the potential risk of cardiac adverse events, the patient's blood pressure should be carefully monitored before and after Spravato intake.
- The "Healthcare professional checklist" (attached to the HCP guide): the objective of this EM is to aid HCPs in evaluating when, following Spravato administration, a patient is deemed stable and safely allowed to leave the clinic/facility where Spravato has been administered.

The following EM should be provided to patients:

- The **guide for patients**, aiming at addressing the risks of transient dissociative states and perception disorders, drug abuse, disturbances in consciousness and blood pressure increased. The objective of this EM is to detail:
  - Which adverse effects to expect following Spravato administration, and how to minimise those effects;
  - Risk factors/groups/ signs of abuse and dependence, which should be regularly assessed and monitored;
  - The procedure for Spravato intranasal administration, including preparation (fasting for 2 hours, no drinking for 30 minutes) and patient's monitoring;

The guide for patients also aims at increasing awareness about:

- The steps for Spravato self-administration under direct HCP supervision;
- Monitoring of blood pressure before and after Spravato dosing;
- Requirements for HCP supervision and post-dose observation, until the HCP confirms the patient is clinically stable and is allowed to leave the clinic/facility where Spravato has been administered;
- The influence of Spravato on the patient's ability to drive or operate machinery

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (for 1 and 6 nasal spray devices)

1. NAME OF THE MEDICINAL PRODUCT

Spravato 28 mg nasal spray, solution
esketamine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each nasal spray device contains esketamine hydrochloride corresponding to 28 mg esketamine.

3. LIST OF EXCIPIENTS

Excipients: Citric acid monohydrate, disodium edetate, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Nasal spray, solution

1 nasal spray device
6 nasal spray devices

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Nasal use
Do not prime or test before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1410/001 (1 spray container)
EU/1/19/1410/004 (6 spray containers)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

spravato

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (for 2 and 3 nasal spray devices)

1. NAME OF THE MEDICINAL PRODUCT

Spravato 28 mg nasal spray, solution
esketamine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each nasal spray device contains esketamine hydrochloride corresponding to 28 mg esketamine.

3. LIST OF EXCIPIENTS

Excipients: Citric acid monohydrate, disodium edetate, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Nasal spray, solution

2 nasal spray devices
3 nasal spray devices

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
nasal use
Do not prime or test before use.

56 mg pack = 2 nasal spray devices
84 mg pack = 3 nasal spray devices

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1410/002 (2 spray containers)
EU/1/19/1410/003 (3 spray containers)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

spravato

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Spravato 28 mg nasal spray, solution
esketamine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

NASAL SPRAY/DEVICE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Spravato 28 mg nasal spray, solution
esketamine
nasal use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

28 mg

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (for 3 nasal spray devices) AS INTERMEDIATE PACK / COMPONENT OF A MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Spravato 28 mg nasal spray, solution
esketamine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each nasal spray device contains esketamine hydrochloride corresponding to 28 mg esketamine.

3. LIST OF EXCIPIENTS

Excipients: Citric acid monohydrate, disodium edetate, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Nasal spray, solution

3 nasal spray devices
Component of a multipack, cannot be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
nasal use
Do not prime or test before use.

84 mg pack = 3 nasal spray devices

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1410/005
EU/1/19/1410/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

spravato

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR MULTIPACKS COMPRISING 12 NASAL SPRAY DEVICES (4 packs of 3 nasal spray devices) or 24 NASAL SPRAY DEVICES (8 packs of 3 nasal spray devices) INCLUDING BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Spravato 28 mg nasal spray, solution
esketamine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each nasal spray device contains esketamine hydrochloride corresponding to 28 mg esketamine.

3. LIST OF EXCIPIENTS

Excipients: Citric acid monohydrate, disodium edetate, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Nasal spray, solution

Multipack: 24 (8 packs of 3) nasal spray devices
Multipack: 12 (4 packs of 3) nasal spray devices

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
nasal use
Do not prime or test before use.

84 mg pack = 3 nasal spray devices

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1410/005 (8 packs, each containing 3 spray containers)
EU/1/19/1410/006 (4 packs, each containing 3 spray containers)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Spravato 28 mg nasal spray, solution
esketamine

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Spravato is and what it is used for

What Spravato is
Spravato contains the active substance esketamine. This belongs to a group of medicines called anti-depressants and you have been given this medicine to treat your depression.

What Spravato is used for
Spravato is used in adults to reduce the symptoms of depression, such as, feeling sad, anxious, or worthless, sleeping difficulties, change in appetite, loss of interest in favourite activities, feeling of being slowed down. It is given, together with another antidepressant, if you have tried at least 2 other antidepressant medicines but they have not helped.

Spravato is also used in adults to rapidly reduce symptoms of depression in a situation requiring immediate treatment (also known as a psychiatric emergency).

2. What you need to know before you use Spravato

Do not use Spravato
- if you are allergic to esketamine, a similar medicine called ketamine used for anaesthesia, or any of the other ingredients of this medicine (listed in section 6).
- if you have ever had certain conditions such as:
  - an aneurysm (a weak spot in a blood vessel wall where it widens or bulges out)
  - bleeding in the brain
- if you recently had a heart attack (within 6 weeks)
  This is because Spravato can cause a temporary increase in blood pressure that may lead to serious complications in these conditions.

Do not use Spravato if any of the above apply to you. If you are not sure, talk to your doctor before using Spravato - your doctor will decide whether or not you can use this medicine.

Warnings and precautions
Talk to your doctor before using Spravato if you have:
- a heart problem which is not well controlled such as: poor blood flow in the blood vessels of the heart frequently with chest pain (such as angina), high blood pressure, heart valve disease or heart failure
- ever had problems with the blood supply to your brain (such as a stroke)
- ever had problems with drug abuse – prescribed medicines or illegal drugs
- ever had a condition called psychosis - where you believe in things that are not true (delusions) or see, feel, or hear things that are not there (hallucinations)
- ever had a condition called bipolar disorder, or symptoms of mania (where you become very over-active or over excited)
- ever had an overactive thyroid that is not properly treated (hyperthyroidism)
- ever had lung problems causing breathing difficulty (pulmonary insufficiency), including Chronic Obstructive Pulmonary Disease (COPD)
- sleep apnoea and are extremely overweight
- ever had slow or fast heartbeats causing shortness of breath, palpitations or chest discomfort, feeling light-headed or fainting
- had a serious head injury or serious problems affecting the brain, particularly where there is increased pressure in the brain
- severe liver problems.

If any of the above apply to you (or you are not sure), talk to your doctor before using Spravato. Your doctor will decide whether you should use this medicine.

Depression getting worse
Tell your doctor or go to the nearest hospital straight away if you have thoughts of harming or killing yourself at any time.

You may find it helpful to talk to a relative or a close friend if you are depressed and ask them if they think your depression is getting worse or if they are worried about your behaviour. You might ask them to read this leaflet.

Blood pressure
Spravato can increase your blood pressure for about 1 to 2 hours after you use it so your blood pressure will be measured before you start using Spravato and after using it.

If your blood pressure is high before using this medicine, your doctor will decide whether to start the medicine or wait until your blood pressure is lower. If your blood pressure goes up after using this medicine and stays high for more than a few hours, you may need to have some more tests.

This medicine may cause a temporary increase in your blood pressure after taking a dose. Your blood pressure will be checked before and after using this medicine. Tell the medical staff right away if you get chest pain, shortness of breath, sudden severe headache, change in vision, or seizures (fits) after using this medicine.

Tell your doctor if you get any of the below while you are using Spravato
- difficulty with your attention, judgment and thinking (see also “Driving and using machines” and “Possible side effects”). During and after each use of this medicine, your doctor will check your condition and decide how long to monitor you.
- sleepiness (sedation), fainting, dizziness, spinning sensation, anxiety, or feeling disconnected from yourself, your thoughts, feelings, space and time (dissociation), difficulties in breathing (respiratory depression). Tell the medical staff right away if your feel like you cannot stay awake or if you feel like you are going to pass out.
- pain when urinating or seeing blood in your urine – these could be signs of bladder problems. These can occur with high doses of a similar medicine (called ketamine) used over a long period.

Tell your doctor if you get any of the above while you are taking Spravato.

Elderly (>65 years)
If you are elderly (>65 years), you will be carefully monitored as you may be at increased risk of falling when you start moving around after treatment.

Children and adolescents
Do not give this medicine to children and adolescents younger than 18 years of age. This is because Spravato has not been studied for treatment-resistant depression in this age group.

Other medicines and Spravato
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Using Spravato with certain medicines may cause side effects. Especially tell your doctor if you take:
- Medicines used to treat nervous disorders or severe pain (for example, benzodiazepines, opioids), or medicines or beverages containing alcohol
- Stimulants such as those used for conditions such as narcolepsy or medicines for ADHD (for example, amphetamines, methylphenidate, modafinil, armodafinil)
- Medicines that can increase your blood pressure, such as, thyroid hormones, asthma medications such as xanthine derivatives, medications for child birth bleeding (ergometrine) and heart medication such as vasopressin.
- Medicines for depression or Parkinson's disease known as monoamine oxidase inhibitors (MAOIs) (for example, tranylcypromine, selegiline, phenelzine).

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

Contraception
If you are able to become pregnant you must use contraception during treatment. Talk with your doctor about suitable methods of contraception.

Pregnancy
Do not use Spravato if you are pregnant.

If you become pregnant while being treated with Spravato, talk to your doctor straight away – to decide whether to stop treatment and to learn about other options for treatment.

Breast-feeding
Do not use Spravato if you are breast-feeding. Talk to your doctor before using Spravato if you are breast-feeding. Your doctor will discuss with you whether to stop breast-feeding or stop using this medicine. Your doctor will take into account the benefit of breast-feeding for you and your child, and the benefit of treatment for you.

Driving and using machines
Spravato can make you feel sleepy, dizzy, and have other side effects that can temporarily affect your ability to drive vehicles or use machines and do activities that need you to be completely alert. After being treated with this medicine, do not take part in these activities until the next day following a restful sleep.

3. How to use Spravato

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

You will use the Spravato nasal spray yourself - under the supervision of your doctor or other healthcare professional in a healthcare setting, such as, the doctor's office or clinic.

Your doctor or other healthcare professional will show you how to use the nasal spray device (see also Instructions for use).

How much to use
Your doctor will decide if you need 1, 2 or 3 nasal spray devices and how often you should go to the doctor's office or clinic for the medicine.
- One nasal spray device delivers two sprays (one spray per nostril)
- Spravato is used twice a week for the first 4 weeks

If your treatment is continued:
- Spravato is usually used once a week for the following 4 weeks
- After this, Spravato is usually used either once a week or once every 2 weeks

During and after each use of this medicine, your doctor will check you and decide how long to monitor you.

Food and drink
Some patients using Spravato may experience nausea or vomiting. You should avoid eating for 2 hours before treatment and not drinking liquids for 30 minutes before using this medicine.

Nasal sprays
If you need steroid or decongestant medicines as a nasal spray, avoid using them during the hour before your Spravato treatment.

If you use more Spravato than you should
You will use this medicine under the supervision of your doctor in the doctor's office or clinic. Therefore, it is unlikely that you will use too much.

If you use too much Spravato, you are more likely to get side effects (see "Possible side effects").

If you stop using Spravato
It is important to make sure you come in for your scheduled appointments, so that this medicine is effective for you.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor if you notice any of the following side effects.

Very common (may affect more than 1 in 10 people)
- feeling disconnected from yourself, your thoughts, feelings and things around you
- feeling dizzy
- headache
- feeling sleepy
- change in sense of taste
- decreased feeling or sensitivity, including around the mouth area
- spinning sensation ("vertigo")
- vomiting
- nausea
- increased blood pressure

Common (may affect up to 1 in 10 people)
- feeling anxious
- feeling extremely happy ("euphoria")
- feeling confused

- feeling detached from reality
- feeling irritable
- seeing, feeling, hearing or smelling things that are not there (hallucinations)
- feeling agitated
- eyes, ears, or sense of touch are deceived or tricked in some way (something is not what it seems to be)
- panic attacks
- change in perception of time
- unusual feeling in the mouth (such as tingling or a crawling feeling)
- muscle tremors
- problems with thinking
- feeling very sleepy with low energy
- difficulty speaking
- difficulty concentrating
- blurred vision
- persistent ringing in the ears (tinnitus)
- increased sensitivity to noise or sounds
- fast heartbeat
- high blood pressure
- nasal discomfort
- irritated throat
- sore throat
- nasal dryness including dry crusts in the nose
- itchy nose
- decreased feeling or sensitivity in the mouth
- dry mouth
- excessive sweating
- frequent need to pass urine
- pain when passing urine
- urgent need to pass urine
- feeling abnormal
- feeling drunk
- feeling weak
- crying
- feeling of body temperature change

Uncommon (may affect up to 1 in 100 people)
- thoughts, speech and physical movements slow down
- emotional distress
- feeling uneasy or tense
- fast eye movements that you cannot control
- being hyperactive
- increased saliva
- cold sweats
- problems walking

Rare (may affect up to 1 in 1,000 people)
- difficulties in breathing (respiratory depression)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Spravato

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the label. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Spravato contains
The active substance is esketamine.
Each nasal spray device contains esketamine hydrochloride corresponding to 28 mg esketamine.

The other ingredients are:

Citric acid monohydrate
Disodium edetate
Sodium hydroxide (for pH adjustment)
Water for injections

What Spravato looks like and contents of the pack
Spravato is a nasal spray solution. This medicine is a clear, colourless solution, provided in a single-use nasal spray device.

Spravato is available in pack sizes containing 1, 2, 3, or 6 nasal spray devices and as multipacks containing 12 (4 packs of 3) or 24 (8 packs of 3) nasal spray devices.

Each nasal spray device is individually packaged in a sealed blister.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Janssen-Cilag International NV
Turnhoutseweg 30
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Manufacturer
Janssen Pharmaceutica NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in {**MM/YYYY**} OR {**month YYYY**}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

The following information is intended for healthcare professionals only:

Instructions for Use
SPRAVATO
(esketamine)
Nasal Spray Device

28 mg per device

Each nasal spray device delivers
28 mg esketamine as two sprays.

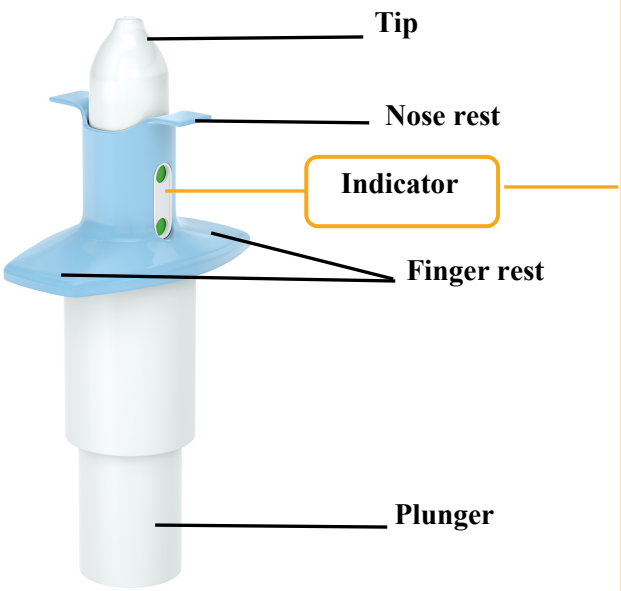
Important

This device is intended for administration by the patient, **under supervision of a healthcare professional**. Read these Instructions for Use in full before training and supervising patient.

Need help?

For additional assistance or to share your feedback refer to the Package Leaflet for the contact information of the local representative of the Marketing Authorisation Holder.

Nasal Spray Device



Each nasal spray device delivers 28 mg esketamine as two sprays.

Indicator

One device contains 2 sprays
(1 spray for each nostril)

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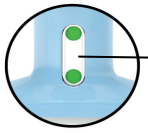
2 green dots (0 mg delivered)



Device full

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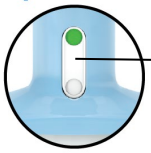
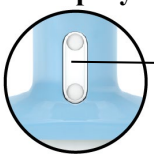
1 green dot



One spray delivered

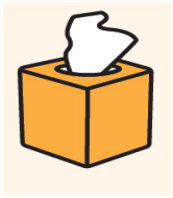
No green dots
Two sprays (28 mg) delivered



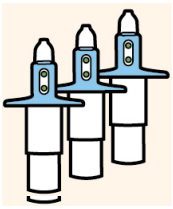
Device empty

Step 1 Get ready

Before first device only:



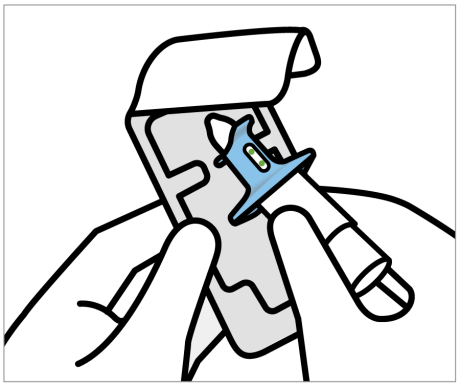
Instruct patient to blow nose **before first device only**.



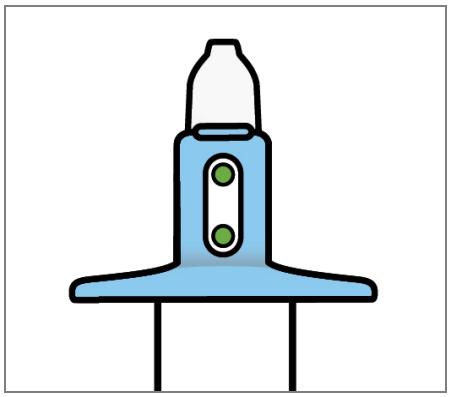
Confirm required number of devices.

28 mg = 1 device
56 mg = 2 devices
84 mg = 3 devices

Step 2 Prepare device

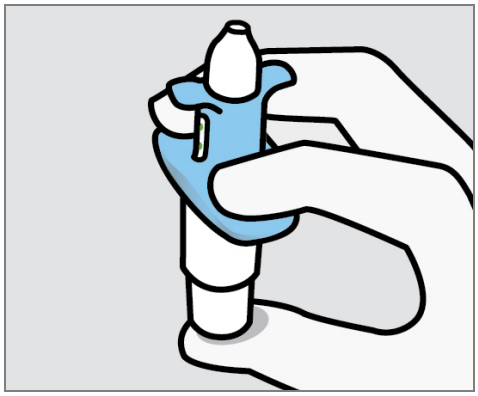


- Check expiration date ('EXP'). If expired, get a new device.
- Peel blister and remove device.



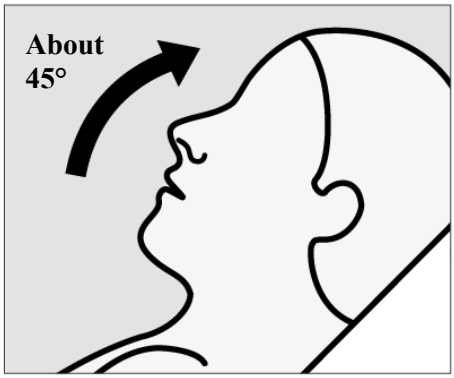
- **Do not prime device.** This will result in a loss of medicine.
- Check that indicator shows **2 green dots**. If not, dispose of device and get a new one.
- Hand device to patient.

Step 3 Prepare patient



Instruct the patient to:

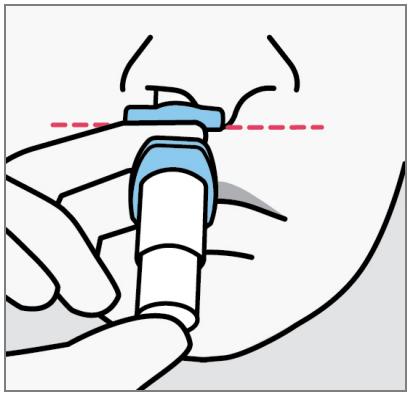
- Hold device as shown with the thumb gently supporting the plunger.
- **Do not** press the plunger.



Instruct the patient to:

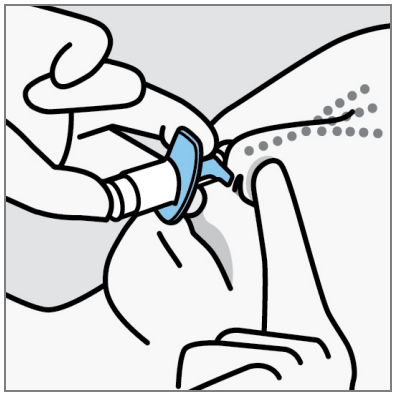
- Recline head at about **45 degrees** during administration to keep medicine inside the nose.

Step 4 Patient sprays once into each nostril



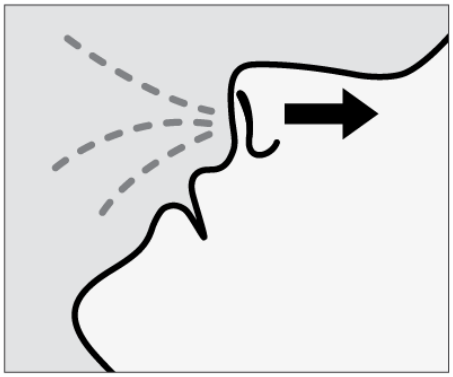
Instruct the patient to:

- Insert tip straight into the **first nostril**.
- Nose rest should touch the **skin between the nostrils**.



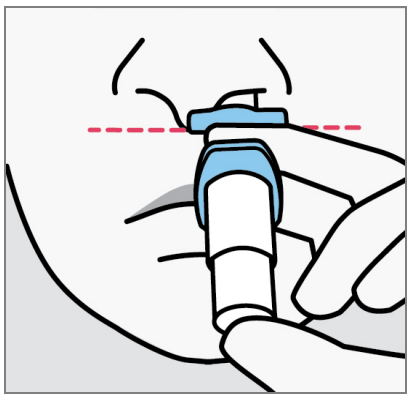
Instruct the patient to:

- Close opposite nostril.
- **Breathe in through nose** while pushing plunger all the way up until it stops.



Instruct the patient to:

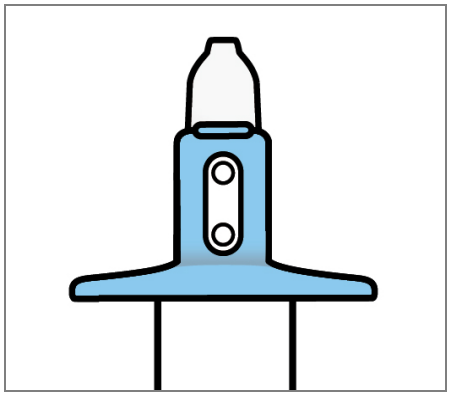
- **Sniff gently** after spraying to keep medicine inside nose.



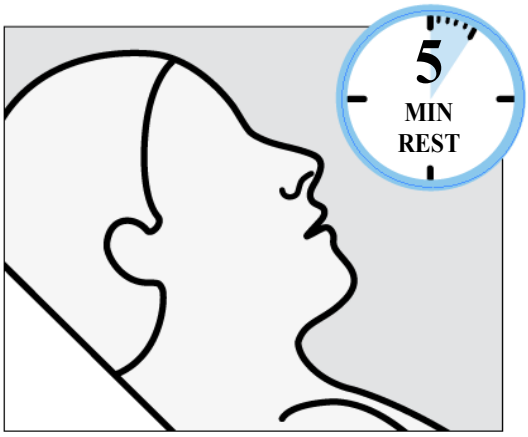
Instruct the patient to:

- Switch hands to insert **tip** into the **second nostril**.
- Repeat Step 4 to deliver second spray.

Step 5 Confirm delivery and rest



- Take device from patient.
- Check that indicator shows **no green dots**. If you see a green dot, have patient spray again into the second nostril.
- Check indicator again to confirm device is empty.

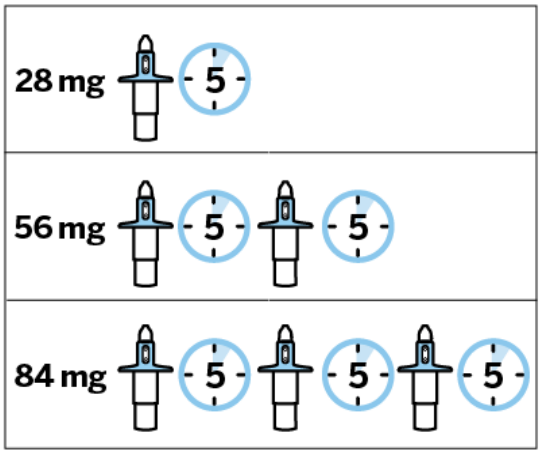


Instruct the patient to:

- Rest in a comfortable position (preferably, semi-reclined) for **5 minutes after each device**.
- If liquid drips out, dab nose with a tissue.

Do not blow nose.

Next device (if required)



- **Repeat Steps 2-5** if more than one device is required.

IMPORTANT: Ensure that patient **waits 5 minutes after each device** to allow medicine to absorb.

Disposal

Dispose of used device(s) in accordance with local requirements.

Revised: {month YYYY}

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for esketamine (for centrally authorised product only), the scientific conclusions of CHMP are as follows:

In view of available data on respiratory depression from spontaneous reports including in some cases a close temporal relationship, a positive re-challenge and in view of a plausible mechanism of action, the PRAC Rapporteur considers a causal relationship between esketamine (for centrally authorised product only) and respiratory depression is at least a reasonable possibility. The PRAC Rapporteur concluded that the product information of products containing esketamine (for centrally authorised product only) should be amended accordingly.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for esketamine (for centrally authorised product only) the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing esketamine (for centrally authorised product only) is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.