PROFESSIONAL INFORMATION

SCHEDULING STATUS

Schedule 5

1. NAME OF THE MEDICINE

SPRAVATO® Nasal Spray

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 is indicated, in conjunction with an oral antidepressant (SSRI or SNRI), for the treatment of treatment-resistant depression (TRD) in adult patients who have not responded adequately to treatment with at least two different antidepressants of adequate dose and duration to treat the current depressive episode.

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4.2 Posology and method of administration

SPRAVATO should be administered in conjunction with an oral antidepressant (AD).

A treatment session consists of nasal administration of SPRAVATO and post-administration observation under the supervision of a healthcare professional. 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). Total volume of medicine product per device to be delivered is 0,2 mL containing a total of 32,3 mg of esketamine hydrochloride (equivalent to 28 mg of esketamine).

To prevent loss of medication, 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.

Blood pressure assessment before and after treatment

Assess blood pressure prior to dosing with SPRAVATO *(See section 4.4).*
If baseline blood pressure is elevated (e.g., > 140 mmHg systolic, > 90 mmHg diastolic), consider the risks of short term increases in blood pressure and benefit of SPRAVATO treatment in patients with treatment-resistant SPRAVATO *(See section 4.4).*
Do not administer SPRAVATO if an increase in blood pressure or intracranial pressure poses a serious risk *(See section 4.3).*

After dosing with SPRAVATO, blood pressure must be reassessed approximately 40 minutes after dosing and subsequently as clinically warranted.

If blood pressure has normalised and the patient appears clinically stable, both physically and mentally for at least two hours, the patient may be discharged at the end of the post-dose monitoring period; if not, continue to monitor *(See section 4.4)*

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 – Gastrointestinal disorders*).

Patients who require nasal corticosteroid or nasal decongestant on a dosing day should be advised not to administer these medications within 1 hour before administration of SPRAVATO.

Dosage – Adults

Administer SPRAVATO in conjunction with an oral antidepressant (AD)

The dosage recommendations for SPRAVATO are shown in Table 1. Dose adjustments should be made based on efficacy and tolerability to the previous dose.

Table 1: Recommended Dosing for SPRAVATO

Induction Phase	**Maintenance Phase**
Weeks 1-4 (two treatment sessions/week): Starting Day 1 dose*: 56 mg Subsequent doses: 56 mg or 84 mg	**Weeks 5-8:** 56 mg or 84 mg once weekly **From Week 9:** 56 mg or 84 mg every 2 weeks or once weekly **

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Evidence of therapeutic benefit should be evaluated at the end of induction phase to determine need for continued treatment.	Periodically re-examine the need for continued treatment

* For patients ≥ 65 years Day 1 starting dose is 28 mg

** Dosing frequency should be individualised to the lowest frequency to maintain remission/response

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

Post-administration observation

During and after SPRAVATO administration at each treatment session, a healthcare professional should observe the patient until the patient is stable based on clinical judgment. Before SPRAVATO administration, instruct patients not to engage in potentially hazardous activities, such as driving a motor vehicle or operating machinery until the next day after a restful sleep (*See* section *4.4 - Effect on Blood pressure, Potential for Cognitive and Motor Impairment and Effect on ability to Drive and use Machines).*

Missed treatment session(s)

In case one or two treatment sessions are missed, schedule the next session when the next dosage session was scheduled to occur based on current treatment frequency. If more than 2 treatment sessions have been missed, per clinical judgment, adjustment of the dose or frequency of SPRAVATO may be clinically appropriate.

Special populations

Paediatrics (17 years of age and younger)

The safety and efficacy of SPRAVATO have not been established in patients aged 17

years and younger.

Elderly (65 years of age and older)

In elderly patients the initial SPRAVATO dose is 28 mg (Day 1, Starting Dose, *See Table 1*).

Subsequent doses should be increased in increments of 28 mg up to 56 mg or 84 mg, based on efficacy and tolerability.

Hepatic impairment

No dosage adjustment is necessary in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) 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 section 5.2 – Special populations, Hepatic impairment*).

4.3 Contraindications

SPRAVATO is contraindicated:

- In patients with known hypersensitivity to esketamine, ketamine, or to any of the excipients
- In patients for whom an increase in blood pressure or intracranial pressure poses a serious risk (*See section 4.4 - Effect on blood pressure*)
- Patients with known aneurysmal vascular disease (including intracranial, thoracic, or abdominal aorta, or peripheral arterial blood vessels)
- History of intracerebral haemorrhage
- Arteriovenous malformation

4.4 Special warnings and precautions for use

Effect on blood pressure

SPRAVATO can cause transient increases in systolic and/or diastolic blood pressure which peak at approximately 40 minutes after medicine administration and last approximately 1-2 hours (*See section 4.8*). Patients with cardiovascular and cerebrovascular conditions should be carefully assessed before prescribing SPRAVATO and treatment initiated only if the benefit outweighs the risk (*See section 4.3*). Examples of conditions which should be carefully considered include:

- Unstable or poorly controlled hypertension
- History (within 6 weeks) of cardiovascular event including myocardial infarction (MI). Patients with a history of an MI should be clinically stable and cardiac symptom free prior to dosage administration.
- History (within 6 months) of ischaemic stroke or transient ischaemic attack.
- Haemodynamically significant valvular heart disease such as mitral valve regurgitation, mitral valve stenosis, aortic valve stenosis, or aortic valve regurgitation.
- New York Heart Association (NYHA) Class III-IV heart failure of any aetiology.

Blood pressure should be assessed prior to dosing with SPRAVATO. In patients whose blood pressures prior to dose administration and are 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 consider lifestyle and/or pharmacologic therapies to reduce blood pressure before starting treatment with SPRAVATO. The

decision whether or not 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 until blood pressure returns to acceptable levels. If blood pressure remains too high, 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.

Closely monitor blood pressure with concomitant use of SPRAVATO with psychostimulants or monoamine oxidase inhibitors (MAOIs) (*See section 4.5).*

Dissociation

The most common psychological effects of SPRAVATO were dissociative or perceptual changes (including distortion of time, space and illusions), derealization and depersonalization (61 % to 75 % of SPRAVATO-treated patients developed dissociative or perceptual changes based on the Clinician Administered Dissociative Symptoms Scale) *(See section 4.8)*.

Given its potential to induce dissociative effects, carefully assess patients with psychosis before administering SPRAVATO; treatment should be initiated only if the benefit outweighs the risk.

Because of the risks of dissociation, patients must be monitored by a healthcare provider for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting.

Sedation

In clinical trials, 49 % to 61 % of SPRAVATO-treated patients developed sedation based on the Modified Observer's Alertness/Sedation scale (MOAA/s) (*See section 4.8),* and 0,3 % of SPRAVATO-treated patients experienced loss of consciousness (MOAA/s score of 0).

Because of the possibility of delayed or prolonged sedation, patients must be monitored by a healthcare provider for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting (*See section 4.2*).

Closely monitor for sedation with concomitant use of SPRAVATO with CNS depressants *(See section 4.5).*

Potential for Cognitive and Motor Impairment

SPRAVATO has been reported to cause somnolence, sedation, dissociative symptoms, perception, disturbances, dizziness, vertigo and anxiety during clinical trials (*See section 4.8*). The effects may impair attention, judgment, thinking, reaction speed and motor skills. Tolerance to above effects may develop after a few treatment sessions. At each treatment session, patients should be monitored by a healthcare professional to assess when the patient is considered clinically stable (*See section 4.2).*

Cognitive Impairment

Short-Term Cognitive Impairment

In a study in healthy volunteers, a single dose of SPRAVATO caused cognitive performance decline 40 minutes post-dose. Compared to placebo-treated subjects, SPRAVATO-treated subjects required a greater effort to complete cognitive tests at 40 minutes post-dose. Cognitive performance and mental effort were comparable between

SPRAVATO and placebo at 2 hours post-dose. Sleepiness was comparable after 4 hours post-dose.

Long-Term Cognitive Impairment

Long-term 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 clinical trials, the effect of esketamine nasal spray on cognitive functioning was evaluated over time and performance remained stable. However, the long-term cognitive effects of SPRAVATO have not been evaluated beyond one year.

Urinary tract symptoms

Cases of interstitial cystitis have been reported in subjects using ketamine for recreational use or for treatment of chronic pain at high doses with long term use. In clinical studies with esketamine nasal spray, subjects were assessed for symptoms of cystitis, bladder pain and interstitial cystitis. No cases of esketamine – related interstitial cystitis was observed in any of the studies, which involved treatment for up to a year.

Drug abuse and dependence

Abuse

Individuals with a history of drug abuse or dependence may be at greater risk for abuse and misuse of SPRAVATO. Careful consideration is advised prior to treatment of individuals with a history of substance use disorder, including alcohol. Monitoring for signs of abuse or dependence is recommended.

The potential for abuse, misuse and diversion of SPRAVATO is minimised due to the product's design and the administration taking place under the supervision of a healthcare professional.

Ketamine, the racemic mixture of arketamine and esketamine, has been reported as a drug of abuse. 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 other measures of subjective drug effects.

Dependence

Dependence and tolerance have been reported with prolonged use of ketamine. Individuals who were dependent on ketamine reported withdrawal symptoms of cravings, anxiety, shaking, sweating and palpitations. Monitoring for signs of dependence is recommended.

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 of history of mania or bipolar disorder
- Hyperthyroidism that has not been sufficiently treated
- Significant pulmonary insufficiency
- Patients with known uncontrolled brady or tachydysrhythmias that lead to haemodynamic instability

- History of brain injury, hypertensive encephalopathy, intrathecal therapy with ventricular shunts, or any other condition associated with increased intracranial pressure.

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide related events). The 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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Concomitant use with CNS depressants (e.g., benzodiazepines, opioids, alcohol) may increase sedation. Closely monitor for sedation with concomitant use of SPRVAVATO with CNS depressants.

Concomitant use with psychostimulants (e.g., amphetamines, methylphenidate, modafinil, armodafinil) may increase blood pressure. Closely monitor blood pressure with concomitant use of SPRAVATO with psychostimulants.

Concomitant use with monoamine oxidase inhibitors (MAOIs) (e.g., tranylcypromine, selegiline, phenelzine) may increase blood pressure. Closely monitor blood pressure with concomitant use of SPRAVATO with MAOIs.

Pharmacokinetic interactions

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 *(See section 5.2).*

Effect of other medicines on esketamine

Hepatic enzyme inhibitors

Pretreatment 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 maximum plasma concentration (C_{max}) of esketamine administered as a nasal spray. The area under the plasma concentration-time curve $AUC_{(0\text{-}inf)}$ of esketamine was increased by approximately 29 %. The terminal half-life of esketamine was not affected by ticlopidine pretreatment.

Pretreatment 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 $AUC_{(0\text{-}inf)}$ of nasally administered esketamine by approximately 11 % and 4 %, respectively. The terminal half-life of esketamine was not affected by clarithromycin pretreatment.

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 $AUC_{(0\text{-}inf)}$ values of esketamine administered as a nasal spray by approximately 17 % and 28 %, respectively.

Other Nasal Spray Products

Concomitant use of SPRAVATO with other nasally administered medicinal products has been evaluated in the following pharmacokinetic interaction studies. Pretreatment of

subjects with 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.

Pretreatment 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 medicines

Nasal administration of 84 mg esketamine twice a week for 2 weeks reduced the mean plasma $AUC_{(0\text{-}inf)}$ 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 $AUC_{(0\text{-}inf)}$ of oral bupropion (single 150 mg dose), a substrate of hepatic CYP2B6.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

To avoid exposing the foetus to esketamine, women of reproductive potential should be advised to use highly effective contraception during and up to 6 weeks after the last treatment with SPRAVATO.

Pregnancy

SPRAVATO is not recommended during pregnancy. The risks of SPRAVATO during pregnancy have not been studied. Human data in pregnant women during clinical trials with esketamine exposure are too limited to be conclusive. Animal studies with ketamine, the racemic mixture of arketamine and esketamine, show evidence of developmental neurotoxicity. The potential for esketamine to have neurotoxic effects on foetuses cannot be excluded. If a woman becomes pregnant while being treated with SPRAVATO, treatment with esketamine should be discontinued and the patient should be counselled about the potential risk to the foetus and clinical/therapeutic options as soon as possible.

Breastfeeding

Esketamine is present in human milk. There are no data on the effects of SPRAVATO on the breastfed infant or on milk production. Published studies with ketamine in juvenile animals report neurotoxicity. Because of the potential for neurotoxicity, advise patients that breastfeeding is not recommended during treatment with SPRAVATO.

Fertility

In a fertility and early embryonic development (Segment I) study in rats, oestrous cycle irregularities were observed at an intranasal esketamine dose of 45 mg/kg/day and a delay in mating was observed ≥ 15 mg/kg/day. Due to the lack of overall changes to mating and fertility indices, the NOAEL in this study was considered 45 mg/kg/day which produce AUC exposure that was 0,6 times the AUC exposure at the maximum recommended human dose (MRHD).

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, instruct patients not to engage in potentially hazardous activities requiring complete mental alertness and motor coordination, such as driving a motor vehicle or operating machinery, until the next day following a restful sleep (*See section 4.4.- Potential for Cognitive and Motor Impairment).*

4.8 Undesirable effects

Summary of the safety profile

The most commonly observed adverse reactions in treatment-resistant depression patients treated with SPRAVATO were dizziness (30 %), nausea (27 %), dissociation (26 %), headache (24 %), somnolence (18 %), vertigo (18%), dysgeusia (17 %), hypoaesthesia (11 %), and vomiting (10 %).

Tabulated list of adverse reactions

Adverse reactions reported with esketamine are listed in the table below. 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 2: Tabulated list of adverse reactions

System Organ Class	Adverse Drug Reaction		
	Frequency		
	Very common	**Common**	**Uncommon**
Psychiatric disorders	dissociation	euphoric mood, agitation, anxiety, illusion, irritability, panic attack, time perception altered, hallucination including visual hallucination, derealisation	
Nervous system disorders	dizziness, headache, dysgeusia, somnolence, hypoaesthesia	mental impairment, tremor, lethargy, dysarthria, paraesthesia, sedation	
Eye disorders		blurred vision	
Ear and labyrinth disorders	vertigo	hyperacusis, tinnitus	
Cardiac disorders		tachycardia	
Vascular disorders		hypertension	
Respiratory, thoracic and mediastinal disorders		nasal discomfort, nasal dryness including nasal crusting, nasal pruritus	
Gastrointestinal disorders	nausea, vomiting	dry mouth, oral hypoaesthesia	salivary hypersecretion

Skin and subcutaneous tissue disorders		hyperhidrosis	
Renal and urinary disorders		pollakiuria, dysuria, micturition urgency	
General disorders and administration site conditions		feeling abnormal, feeling drunk, feeling of body temperature change	
Investigations		increased blood pressure	

Dissociation/perceptual changes

Dissociation (26 %) was one of the most common psychological effects of esketamine. Other related terms included derealisation (1,9 %), depersonalisation (1,7 %), illusions (1,5 %), 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

Adverse reactions of sedation (9,1 %) and somnolence (18,0 %) 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.

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.

Changes in Blood Pressure

In clinical trials, 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 %.

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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the :**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: **https://www.sahpra.org.za/Publications/Index/8**.

4.9 Overdose

No cases of overdose were reported in clinical studies with SPRAVATO. 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

There is limited clinical trial experience with esketamine nasal spray doses higher than the maximum recommended dose of 84 mg. 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, hypothesis, feeling abnormal, nausea and vomiting.

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Management

There is no specific antidote for esketamine overdose. In the case of overdose, the possibility of multiple medicine involvement should be considered. It is advisable to contact a poison control centre to obtain the latest recommendations for the management of an overdose. 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

A.1.2 Psychoanaleptics (antidepressants)

Mechanism of action

Esketamine, the S-enantiomer of racemic ketamine, is an antidepressant with a novel mechanism of action. It is a non-selective, non-competitive, antagonist of the *N*-methyl-*D*-aspartate (NMDA) receptor, ionotropic glutamate receptor.

Putative aetiological contributors of depression, including stress and other conditions, are known to cause structural and functional impairment of synapses in brain regions involved with the regulation of mood and emotional behaviour. Evidence within the literature suggests that 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 signaling that restore synaptic function in these brain regions. Unlike other antidepressant therapies, esketamine's primary antidepressant action does not directly involve monoamine, GABA, or opioid receptors.

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, linear increases in the plasma C_{max} and $AUC_{(0\text{-}inf)}$ 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 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 medicine.

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 $AUC_{(0\text{-}inf)}$ 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 $AUC_{(0\text{-}inf)}$ values produced by an 84 mg dose were 67 % and 38 % higher, respectively, 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.

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 $AUC_{(0\text{-}inf)}$ 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 $AUC_{(0\text{-}inf)}$ 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 $AUC_{(0\text{-}inf)}$ 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.

Race

The pharmacokinetics of esketamine nasal spray was compared between healthy Asian subjects and Caucasian subjects. Mean plasma esketamine C_{max} and $AUC_{(0\text{-}inf)}$ values produced by a single, 56 mg dose of esketamine were approximately 14 % and 33 % higher, respectively, in Chinese subjects compared to Caucasians. Both parameters were approximately 40 % higher in Japanese subjects, relative to Caucasian subjects. On average, esketamine C_{max} was 10 % lower and $AUC_{(0\text{-}inf)}$ was 17 % greater in Korean subjects, relative to Caucasian 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.

Sex

A population pharmacokinetic analysis was conducted that included healthy subjects (138 males and 118 females) and patients with major depressive disorder (203 males and 361 females). The results indicated that the pharmacokinetics of esketamine administered as a nasal spray is not influenced by sex.

Body Weight

A population pharmacokinetic analysis was conducted that included 256 healthy subjects and 564 patients with major depressive disorder. The total body weight of the subjects ranged from 39 to 170 kg. The results indicated that the pharmacokinetics of esketamine administered as a nasal spray is not influenced by body weight.

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.

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

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The medicinal product is packaged in a primary container consisting of a Type-I glass vial with a rubber stopper. The filled and stoppered vial is assembled into a manually-activated single-use nasal spray device. The device dispenses two sprays delivering a total volume of 0,2 mL of medicinal product.

SPRAVATO is available in pack sizes containing 1, 2, 3, or 6 single-use nasal spray devices.

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

1 nasal spray device (28 mg)

2 nasal spray device (56 mg)

3 nasal spray device (84 mg)

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. HOLDER OF CERTIFICATE OF REGISTRATION

JANSSEN PHARMACEUTICA (PTY) LTD

(Reg. No. 1980/011122/07)

2 Medical Road, Halfway House,

Midrand 1685, South Africa

MedInfoZA@its.jnj.com

8. REGISTRATION NUMBER

53/1.2/0732

9. DATE OF FIRST AUTHORISATION

06 April 2022

Instructions for Use

SPRAVATO nasal spray

(esketamine)

Nasal Spray Device

28 mg per device

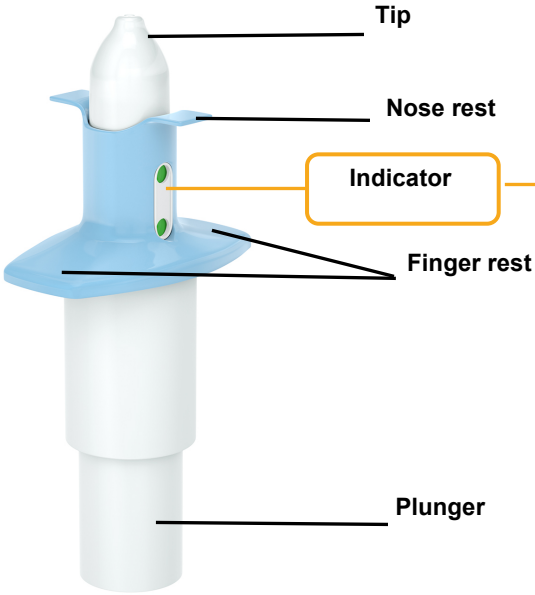
Important

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

Need help?

Ask your doctor about any questions you may have.

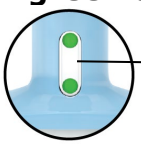
Nasal Spray Device



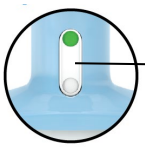
Indicator

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

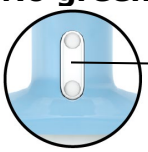
2 green dots (0 mg delivered)



1 green dot



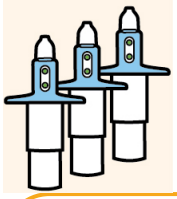
No green dots (28 mg delivered)



Step 1 Get ready

Before first device only:

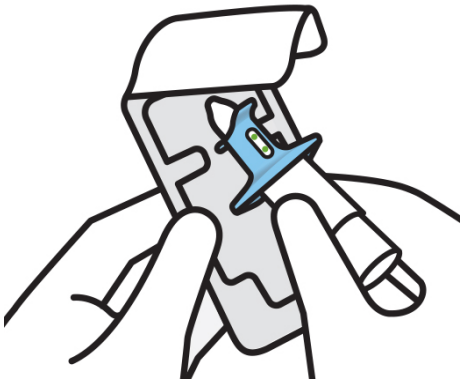
Instruct patient to blow nose **before first device only**.



Confirm required number of devices.

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

Step 2 Prepare device

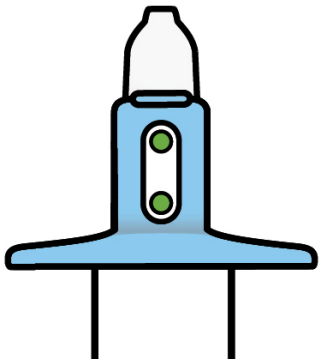


Healthcare professional:

Check expiration date ('EXP').

If expired, get a new device.

Peel blister and remove device.



Healthcare professional:

Do not prime device.

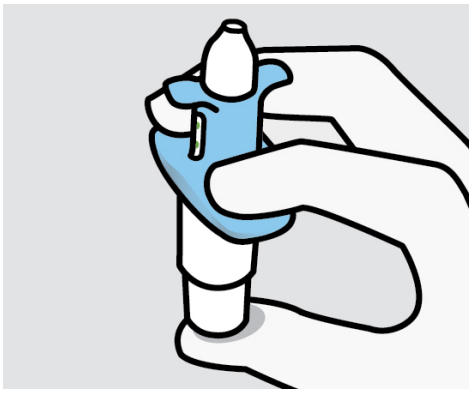
This will result in a loss of medication.

Check that indicator shows **2 green dots**. If not, dispose of device and get

a new one.

Hand device to patient.

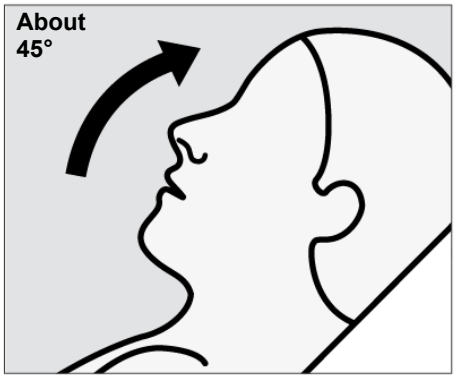
Step 3 Prepare patient



Patient should:

Hold device as shown with the thumb gently supporting the plunger.

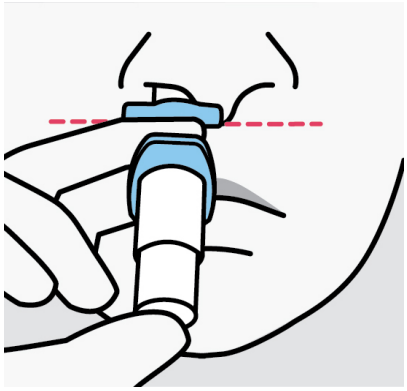
Do not press the plunger.



Patient should:

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

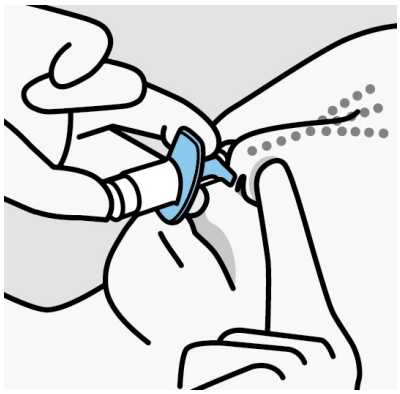
Step 4 Patient sprays once into each nostril



Patient should:

Insert tip straight into the **first nostril**.

Nose rest should touch the **skin between the nostrils**.

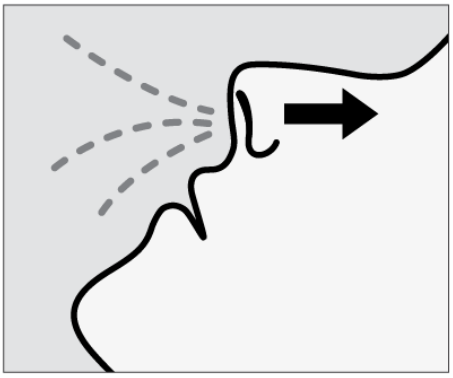


Patient should:

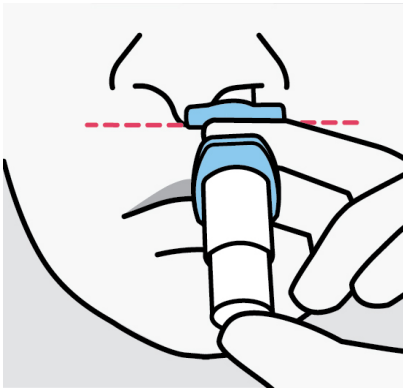
Close opposite nostril.

Breathe in through nose while pushing plunger all the way up until it

stops.



Patient should: Sniff gently after spraying to keep medication inside nose.

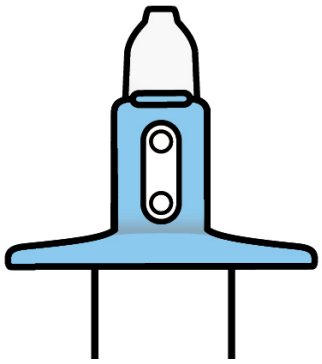


Patient should:

Switch hands to insert tip into the **second nostril**.

Repeat Step 4 to deliver second spray.

Step 5 Confirm delivery and rest

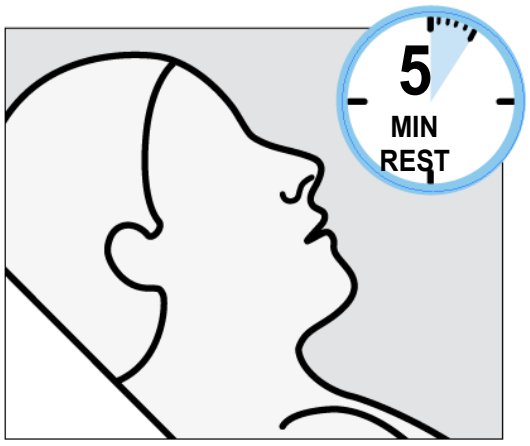


Healthcare professional:

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.



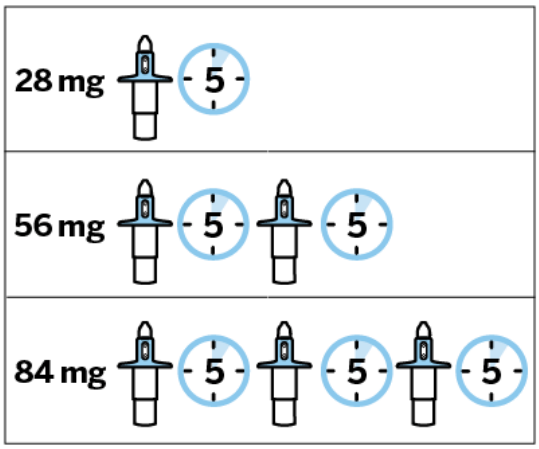
Patient should:

Rest in a comfortable position (preferably, semi-reclined) for **5 minutes after each device**.

Do not blow nose.

If liquid drips out, dab nose with a tissue.

Next device (if required)



Healthcare professional:

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

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

Disposal

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