PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[N]SPRAVATO®

Esketamine Nasal Spray

Solution, 28 mg esketamine (as esketamine hydrochloride), nasal

Antidepressant

ATC Code: N06AX27

Janssen Inc.
19 Green Belt Drive
Toronto, Ontario
M3C 1L9
www.janssen.com/canada

Date of Initial Approval:
May 19, 2020

Submission Control No: 222855

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

SPRAVATO® (esketamine) is indicated in combination with a SSRI or SNRI, for the treatment of major depressive disorder in adults who have not responded adequately to at least two separate courses of treatment with different antidepressants, each of adequate dose and duration, in the current moderate to severe depressive episode.

1.1 Prescribing Information

SPRAVATO® can only be prescribed by a physician who is experienced and proficient in the management of major depressive disorder and enrolled in the JANSSEN JOURNEY™ Program.

Prior to being prescribed SPRAVATO®, patients must be enrolled in the JANSSEN JOURNEY™ Program. The prescriber must ensure that patients are informed of and understand the conditions of use and risks of treatment with SPRAVATO®. By enrolling, patients attest that they understand and accept the elements discussed with their prescriber.

1.2 Distribution Information

SPRAVATO® is only available through a controlled distribution program called the JANSSEN JOURNEY™ Program. Only pharmacists enrolled in the program can dispense SPRAVATO®.

JANSSEN JOURNEY™ Program requirements include:

- Physicians who prescribe SPRAVATO® and pharmacists who dispense SPRAVATO® are trained on the risks of the product and have agreed to adhere to the requirements of the JANSSEN JOURNEY™ Program.
- SPRAVATO® is only dispensed to sites of care where patients self-administer the product under the direct supervision of a healthcare professional and are monitored by a healthcare professional post-administration.

For more information, please contact the JANSSEN JOURNEY™ Program at 1-833-257-7191 or online at www.JanssenJourneyHCP.ca.

1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available in patients under 18 years of age. SPRAVATO® is not authorized for pediatric use (see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**).

1.4 Geriatrics

Geriatrics (≥ 65 years of age): Initiation of SPRAVATO® is not recommended in patients 65 years and older. In a clinical trial in this population, evidence of efficacy was not established. Greater sensitivity to adverse drug reactions in some older individuals cannot be ruled out (see **DOSAGE AND ADMINISTRATION** and **WARNINGS AND PRECAUTIONS, Special**

Populations, Geriatrics).

2 CONTRAINDICATIONS

SPRAVATO® is contraindicated in patients:

- with a hypersensitivity to esketamine, ketamine, or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.
- for whom an increase in blood pressure or intracranial pressure poses a serious risk, including but not limited to patients with:
    - aneurysmal vascular disease (including intracranial, thoracic or abdominal aorta, or peripheral arterial vessels)
    - arteriovenous malformation
    - history of intracerebral hemorrhage
    - recent (within 6 weeks) major cardiovascular event (such as myocardial infarction or cerebrovascular accident)

  (see **WARNINGS AND PRECAUTIONS, Cardiovascular**)

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Administration and Post-Administration Observation

- **SPRAVATO® must be administered under the direct supervision of a healthcare professional.**
- **Blood pressure must be assessed prior to and following SPRAVATO® administration. Elevations in blood pressure caused by SPRAVATO® peak at approximately 40 minutes post-dose. Include an assessment at this time point and continue to monitor until blood pressure returns to acceptable levels, as clinically warranted.**
- **In the period following administration of SPRAVATO® there is a high risk of dissociation and sedation. Monitor patients for at least 2 hours at each treatment session until clinically stable and ensure that medical support is available to appropriately manage reactions, including the potential for respiratory depression.**
- **An assessment must be performed to determine when the patient is ready to leave the healthcare setting (see SPRAVATO® Administration and Monitoring Checklist in DOSAGE AND ADMINISTRATION, Administration). Instruct patients to arrange safe transportation following treatment with SPRAVATO®.**

(see DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, and ADVERSE REACTIONS).

Cardiovascular and Respiratory Conditions

SPRAVATO® is contraindicated in patients for whom an increase in blood pressure or intracranial pressure poses a serious risk (see CONTRAINDICATIONS).

Carefully assess patients with other clinically significant or unstable cardiovascular, cerebrovascular or respiratory conditions before prescribing SPRAVATO® and initiate treatment only if the benefit outweighs the risk. In these patients, administer SPRAVATO® in a setting where appropriate resuscitation equipment and healthcare professionals with training in cardiopulmonary resuscitation are available (see DOSAGE AND ADMINISTRATION, and WARNINGS AND PRECAUTIONS, Cardiovascular, Respiratory).

Abuse and Misuse

- **SPRAVATO® has the potential to be abused and misused. Consider the risks and benefits of prescribing SPRAVATO® prior to use in patients at higher risk of abuse. Monitor patients for signs and symptoms of abuse and misuse (see WARNINGS AND PRECAUTIONS).**
- **SPRAVATO® is only available through a controlled distribution program called the JANSSEN JOURNEY™ Program (see INDICATIONS).**
- **Take appropriate measures to safeguard SPRAVATO® from diversion.**

Suicidal Thoughts and Behaviours

Rigorously monitor for suicidal ideation or other indicators of potential for suicidal behaviour early in treatment and following any intended or unintended changes to treatment, including dosing modifications, interruption and discontinuation (see WARNINGS AND PRECAUTIONS, Psychiatric).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- A treatment session consists of nasal administration of SPRAVATO® by the patient and post-administration observation **under the direct supervision of a healthcare professional**.
- SPRAVATO® should only be administered in conjunction with a SSRI or SNRI.
- 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 **WARNINGS AND PRECAUTIONS, Driving and Operating Machinery, Neurologic**).

Blood Pressure Assessment Before and After Treatment and Cardiovascular Risk Precautions

- DO NOT administer SPRAVATO® in patients for whom an increase in blood pressure or intracranial pressure poses a serious risk (see **CONTRAINDICATIONS**).

- Carefully assess patients with clinically significant or unstable cardiovascular, cerebrovascular or respiratory conditions before prescribing SPRAVATO® and initiate treatment only if the benefit outweighs the risk. In these patients, administer SPRAVATO® in a setting where appropriate resuscitation equipment and healthcare professionals with training in cardiopulmonary resuscitation are available.

- Assess blood pressure in all patients prior to dosing with SPRAVATO®. If baseline blood pressure is elevated (e.g., >140 mmHg systolic, >90 mmHg diastolic), a decision to delay or avoid SPRAVATO® therapy should take into account the balance of benefit and risk to the individual patient.

- Reassess blood pressure following SPRAVATO® administration. Elevations in blood pressure caused by SPRAVATO® peak at approximately 40 minutes post-dose. Include an assessment at this time point and continue to monitor until blood pressure returns to acceptable levels, as clinically warranted.

- Ensure patient is clinically stable at 2 hours post-dose or continue monitoring. If blood pressure remains high, assistance should be promptly sought from practitioners experienced in blood pressure management. Refer patients experiencing symptoms of a hypertensive crisis (e.g., chest pain, shortness of breath) or hypertensive encephalopathy (e.g., sudden severe headache, visual disturbances, seizures, diminished consciousness or focal neurological deficits) immediately for emergency care.

(see **SERIOUS WARNINGS AND PRECAUTIONS BOX** and **WARNINGS AND PRECAUTIONS, Cardiovascular**).

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 **WARNINGS AND PRECAUTIONS, Gastrointestinal**).

- Instruct patients to abstain from alcohol within 24 hours before and after each treatment session. Do not administer SPRAVATO® if the patient appears intoxicated (see **DRUG INTERACTIONS**).

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 medications within 1 hour before administration of SPRAVATO® (see **DRUG INTERACTIONS**).

Post-Administration Observation

- During and after SPRAVATO® administration, at each treatment session, a healthcare professional must monitor the patient for at least 2 hours until the patient is clinically stable. Monitor patients with delayed or prolonged reactions appropriately.
- Ensure that medical support is available to appropriately manage reactions such as dissociation, anxiety, sedation as well as the potential for respiratory depression.
- Following administration of SPRAVATO®, advise patients to limit ambulatory activity and allow recovery in an area with reduced environmental stimuli.
- An assessment must be performed to determine when the patient is ready to leave the healthcare setting. A **SPRAVATO® Administration and Monitoring Checklist** has been developed to support healthcare professionals in preparing patients for administration and in the monitoring of patients during the post-administration observation period (see **DOSAGE AND ADMINISTRATION, Administration**).
- Instruct patients to arrange safe transportation following treatment with SPRAVATO® (see **WARNINGS AND PRECAUTIONS, Driving and Operating Machinery**).

4.2 Recommended Dose and Dosage Adjustment

Adults

The dosage recommendations for SPRAVATO® are shown in Table 1. Dose adjustments should be made based on efficacy and tolerability to the previous dose with the aim of maintaining the patient on the **lowest dose at the lowest dosing frequency required to maintain an adequate response**. In a single fixed dose study, the efficacy of 84 mg SPRAVATO® was not established over that of 56 mg SPRAVATO® (see **CLINICAL TRIALS**).

Table 1: Recommended Dosing for SPRAVATO®

Induction Phase	Maintenance Phase
Weeks 1-4 (two treatment sessions/week): Starting Day 1 dose: 56 mg (or 28 mg*) Subsequent doses: 56 mg or 84 mg (or 28 mg*)	**Weeks 5-8:** 56 mg or 84 mg (or 28 mg*) once weekly **From Week 9:** 56 mg or 84 mg (or 28 mg*) every 2 weeks or once weekly**
Evaluate therapeutic effect at the end of induction phase. If the patient has not demonstrated an adequate response to SPRAVATO® following 4 weeks of treatment, a decision should be made whether to continue to the maintenance phase or discontinue treatment with SPRAVATO®.	Periodically re-examine the need for continued treatment.

* For patients of Japanese ancestry and patients ≥65 years. All dose changes should be in 28 mg increments. Efficacy in patients ≥65 years was not established; therefore, initiation of SPRAVATO® in this population is not recommended.

** Individualize to the lowest dose and the lowest dosing frequency to maintain remission/response.

Do not continue two treatment sessions per week beyond the induction phase since the safety and efficacy of this approach was not investigated in clinical trials.

After depressive symptoms improve, Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines recommend that treatment be maintained for at least 6 months.

Pediatrics (< 18 years of age): The safety and efficacy of SPRAVATO® have not been established in patients aged 17 years and younger. SPRAVATO® is not authorized for pediatric use (see **INDICATIONS, Pediatrics** and **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**).

Geriatrics (≥ 65 years of age): Initiation of SPRAVATO® is not recommended in patients 65 years and older because evidence of efficacy was not established in this population. Greater sensitivity to adverse drug reactions in some older individuals cannot be ruled out (see **INDICATIONS, Geriatrics**, and **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**).

In a clinical trial, subjects 65 years and older were initiated at 28 mg and maintained on 28 mg, 56 mg or 84 mg (see Table 1) with incremental changes to dose based on response and tolerability (see **CLINICAL TRIALS**).

Race: For patients of Japanese ancestry, the initial SPRAVATO® dose is 28 mg (Day 1, Starting dose, see Table 1). Subsequent dose increases should be 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. However, due to greater and prolonged exposure, patients with moderate hepatic impairment may need to be monitored more carefully post-dose and over a longer period following administration of SPRAVATO®.

SPRAVATO® has not been studied in patients with severe hepatic impairment (Child-Pugh class C). Use in this population is not recommended (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**, and **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

4.3 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 (as esketamine hydrochloride) in two sprays (one spray per nostril). DO NOT prime the device before use. It is intended for administration by the patient **under the direct 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.

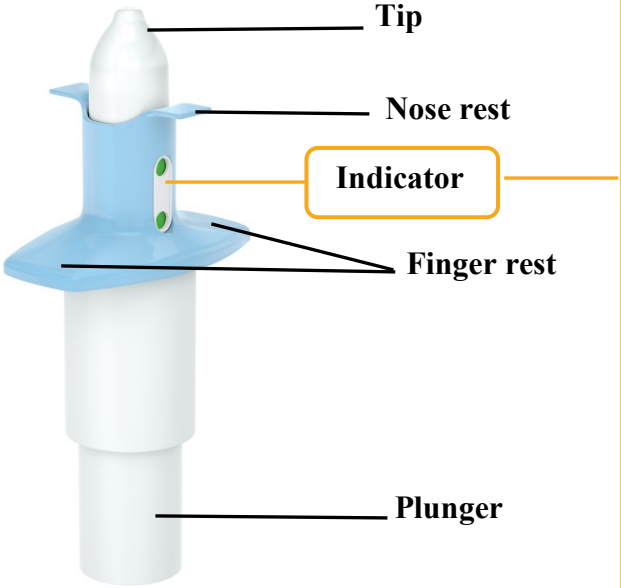
Carefully read the **Instructions for Use** below in full before training and supervising patient.

Instructions for Use

IMPORTANT:

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

Nasal Spray Device

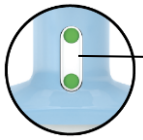


28 mg per device
Each nasal spray device delivers 28 mg esketamine as two sprays.

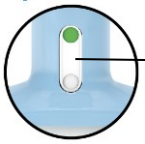
Indicator

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

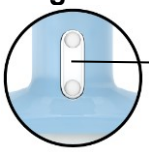
2 green dots (0 mg delivered)



1 green dot



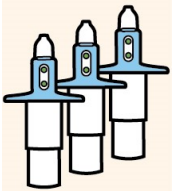
No green dots



Step 1 Get ready

Before first device only:

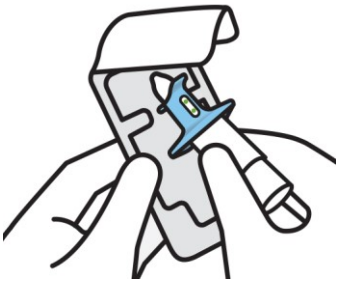
Instruct patient to blow nose **before first device only**.



Confirm required number of devices.

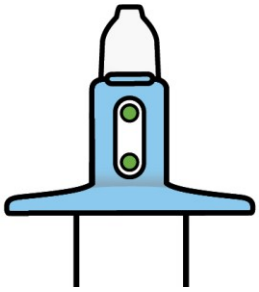
28 mg = 1 device
56 mg = 2 devices
84 mg = 3 devices

Step 2 **Prepare device**



Healthcare professional:

Check the 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:

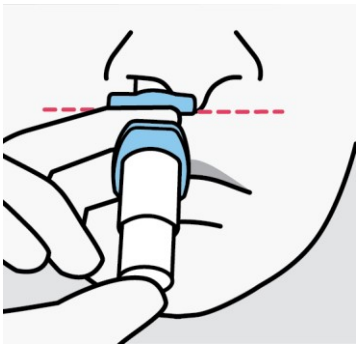
Hold device as shown with the thumb gently supporting the plunger.

Do not press the plunger.

Patient should:

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

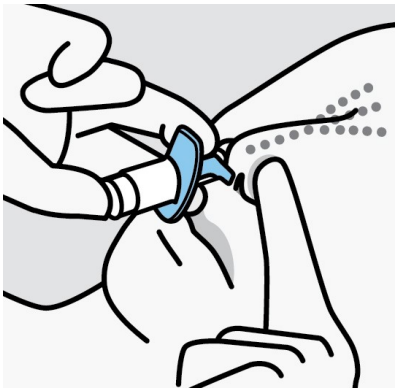
Step 4 **Patient sprays once into each nostril**



Patient should:

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

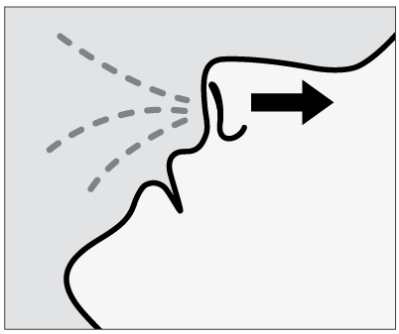
Nose rest should touch the **skin between the nostrils**.



Patient should:

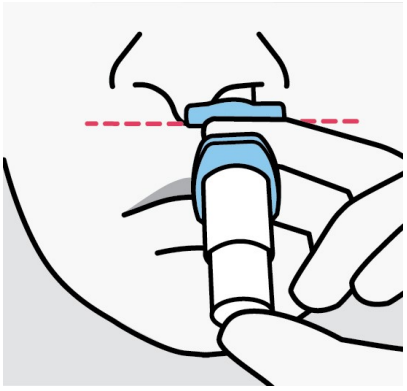
Close opposite nostril.

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



Patient should:

Sniff gently after spraying to keep medication inside nose.

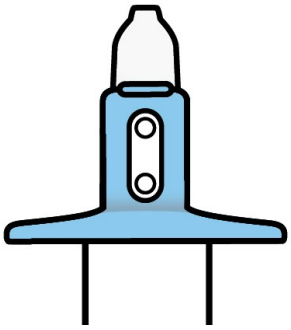


Patient should:

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

Repeat Step 4 to deliver second spray.

Step 5 **Confirm delivery and rest**

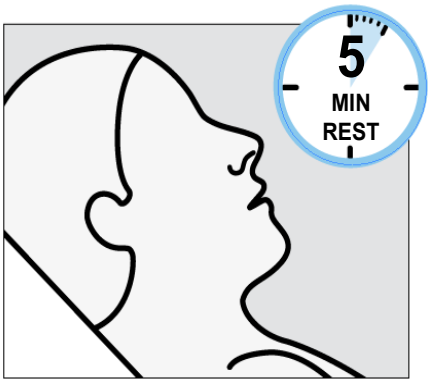


Healthcare professional:

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.



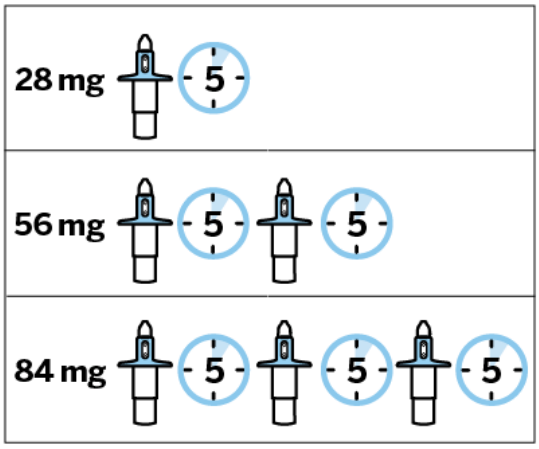
Patient should:

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)

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



Healthcare professional:

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

Step 6 **Post-Administration Observation**

Healthcare professional:

Observe the patient for at least 2 hours until stable and ready to leave.

Reinforce to 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.

A checklist to facilitate administration and monitoring of SPRAVATO® is available below and through the JANSSEN JOURNEY™ Program at 1-833-257-7191 or online at www.JanssenJourneyHCP.ca.

Disposal: Dispose of used device(s) in accordance in with local procedures for controlled substances.

SPRAVATO® Administration and Monitoring Checklist

Patient name:

Date of treatment:

Dose to be administered:

Preparing for the administration

Verify the patient has not:

[ ] **Consumed food** for **at least 2 hours** before administration

[ ] **Consumed fluids** for **at least 30 minutes** before administration

[ ] **Consumed alcohol** within the **last 24 hours** before administration

[ ] **Used a nasal corticosteroid** or **nasal decongestant** for **at least 1 hour** before administration

Additionally confirm:

[ ] The patient has been told that SPRAVATO® is not recommended if she is pregnant or breast-feeding.

[ ] The pre-dose blood pressure has been checked. If the blood pressure is not within the normal range, a decision to delay or avoid SPRAVATO® therapy should be based on the balance of benefit and risk for the individual patient.*

[ ] The use of concomitant medications that may cause sedation or blood pressure changes has been checked.

[ ] Signs or symptoms of urinary tract and bladder problems have been checked for, including pain when urinating or blood in urine.

[ ] Signs of medication abuse or dependence are monitored.

[ ] The patient does not appear intoxicated.

[ ] The patient has been alerted of the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour.

* As a general guide, elevated blood pressure is >140/90 mmHg.

Administration

Before administration:

[ ] Instruct patient to blow their nose (before use of the first device only)

[ ] Ensure patient's head is reclined back at about 45º, which can be achieved using a reclining chair, or a couch and pillows, to support the patient's back and head

[ ] Ensure two green dots are visible on the device before administration

After administration:

[ ] Ensure the full dose has been received (no green dots should be visible on the device)

[ ] Monitor for signs of any treatment-related adverse reactions, such as dissociative effects, sedation, or an increase in blood pressure

Before the patient leaves the office/healthcare setting, ensure:

[ ] The patient has been monitored and is considered clinically stable, regarding:

- [ ] Dissociative symptoms and perception disturbances
- [ ] Sedation and somnolence
- [ ] Changes in blood pressure*

[ ] The patient has been reminded 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 after a restful sleep

[ ] The next treatment session has been scheduled and the patient supplied with a written record as a reminder

For further information, please see **SERIOUS WARNINGS AND PRECAUTIONS BOX**, **DOSAGE AND ADMINISTRATION** and **WARNINGS AND PRECAUTIONS, Cardiovascular**, **Neurologic**, **Psychiatric**; **Special Populations, Pregnant Women**, **Breast-feeding**.

* As a general guide, elevated blood pressure is >140/90 mmHg.

4.4 Missed Dose

If a patient misses treatment sessions and there is a worsening of depressive symptoms, per clinical judgement, adjustment of the dose or frequency of SPRAVATO® may be clinically appropriate.

If sneezing occurs immediately after administration, DO NOT use a replacement device.

If administration in the same nostril occurs, DO NOT use a replacement device.

5 OVERDOSAGE

For management of a suspected drug overdose, contact your regional poison control centre.

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

5.1 Symptoms and Signs

The maximum single esketamine nasal spray dose tested in healthy volunteers was 112 mg, which was associated with higher rates of adverse reactions including dizziness, hyperhidrosis, somnolence, hypoesthesia, feeling abnormal, nausea and vomiting.

Life-threatening symptoms are expected based on experience with ketamine given at 25-fold the usual anesthetic dose. Clinical symptoms are described as convulsions, cardiac arrhythmias, and respiratory arrest. Respiratory depression, apneic episodes and airway complications have been described at doses 5- to 10-fold the usual anesthetic dose, while mild or moderate transient respiratory depression has been reported at anesthetic doses with rapid intravenous administration or high anesthetic doses.

5.2 Treatment

There is no specific antidote for esketamine overdose. In the case of overdose, the possibility of multiple drug involvement should be considered. It is advisable to contact a poison control center 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Intranasal	Solution for intranasal administration Each single-use nasal spray device delivers a total of 28 mg of esketamine (as hydrochloride) in two sprays	Citric acid monohydrate Disodium edetate Sodium hydroxide Water for injection

SPRAVATO® is available as an aqueous solution of esketamine hydrochloride within a single-use nasal spray device. The device delivers two sprays, one spray into each nostril. Total volume of drug 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).

SPRAVATO® Nasal Spray 28 mg is packaged in a sealed blister and placed in cartons. SPRAVATO® is for single use only. Dispose of any unused medicinal product or waste material in accordance with local requirements.

Each SPRAVATO® carton is provided with a separate “Instructions for Use” leaflet and a “Patient Medication Information” leaflet.

7 WARNINGS AND PRECAUTIONS

Cardiovascular

Effect on Blood Pressure and Cardiovascular Risk

SPRAVATO® increases systolic and diastolic blood pressure at all recommended doses. These elevations peak at approximately 40 minutes after drug administration and last approximately 4 hours. A substantial increase in blood pressure could occur even if smaller blood pressure effects were observed with previous administrations (see **ADVERSE REACTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

SPRAVATO® is contraindicated in patients for whom an increase in blood pressure or intracranial pressure poses a serious risk (e.g. patients with aneurysmal vascular disease, arteriovenous malformation, history of intracerebral hemorrhage or recent major cardiovascular event) (see **CONTRAINDICATIONS**).

Carefully assess patients with other clinically significant or unstable cardiovascular and cerebrovascular conditions before prescribing SPRAVATO® and initiate treatment only if the benefit outweighs the risk. In these patients, administer SPRAVATO® in a setting where appropriate resuscitation equipment and healthcare professionals with training in cardiopulmonary resuscitation are available (see **SERIOUS WARNINGS AND PRECAUTIONS BOX** and **DOSAGE AND ADMINISTRATION, Dosing Considerations**). Examples of conditions for which initiation of SPRAVATO® should be carefully considered include, but are not limited to:

- Unstable or poorly controlled hypertension
- History of cardiovascular event, including myocardial infarction (MI), provided these patients are clinically stable and cardiac symptom free prior to dosage administration
- Patients with uncontrolled brady- or tachyarrhythmias that lead to haemodynamic instability
- History of ischemic stroke or transient ischemic attack
- Hemodynamically significant valvular heart disease such as mitral regurgitation, aortic stenosis, or aortic regurgitation
- New York Heart Association (NYHA) Class III-IV heart failure of any etiology.

Carefully assess patients with a history of brain injury, hypertensive encephalopathy, intrathecal therapy with ventricular shunts, or any other condition associated with increased intracranial pressure, and only initiate treatment if the benefit outweighs the risk. In these patients, more intensive post-administration monitoring, including frequent blood pressure and symptom assessment, is warranted. These patients are at increased risk for developing encephalopathy with even small increases in blood pressure.

Approximately 8% to 17% of SPRAVATO®-treated patients and 1% to 3% of placebo-treated patients experienced an increase of more than 40 mmHg in systolic blood pressure and/or

25 mmHg in diastolic blood pressure in the first 1.5 hours after administration at least once during the first 4 weeks of treatment.

Assess blood pressure prior to SPRAVATO® administration. In patients whose blood pressures prior to dose administration are judged to be elevated (as a general guide: >140/90 mm Hg), a decision to delay or avoid SPRAVATO® therapy should take into account the balance of benefit and risk in individual patients. Lifestyle and/or pharmacologic therapies to reduce blood pressure are recommended before starting treatment with SPRAVATO®.

Reassess blood pressure following SPRAVATO® administration. Include an assessment at approximately 40 minutes post-dose and continue to monitor until blood pressure returns to acceptable levels, as clinically warranted (see **DOSING AND ADMINISTRATION, Dosing Considerations**). Ensure patient is clinically stable at 2 hours post-dose or continue monitoring. If blood pressure remains high, assistance should be promptly sought from practitioners experienced in blood pressure management. Refer patients experiencing symptoms of a hypertensive crisis (e.g., chest pain, shortness of breath) or hypertensive encephalopathy (e.g., sudden severe headache, visual disturbances, seizures, diminished consciousness or focal neurological deficits) immediately for emergency care.

Concomitant use of SPRAVATO® with other drugs that increase blood pressure, including, but not limited to, psychostimulants (e.g. amphetamines, methylphenidate), other sympathomimetics, triptans, monoamine oxidase inhibitors (MAOIs), and vascular endothelial growth factor receptor inhibitors should be avoided or undertaken with intensified blood pressure monitoring (see **DRUG INTERACTIONS**).

Inform patients that SPRAVATO® increases blood pressure and heart rate as well as the need to be observed by a healthcare professional until these effects resolve.

Dependence/Tolerance

SPRAVATO® contains esketamine, a Class I Controlled Substance. SPRAVATO® has the potential to be abused, misused, cause physical dependence, and is therefore subject to diversion. Take appropriate measures to safeguard SPRAVATO® from diversion (see **SERIOUS WARNINGS AND PRECAUTIONS BOX**).

SPRAVATO® is only available through a controlled distribution program called the JANSSEN JOURNEY™ Program (see **INDICATIONS**).

Ketamine, the racemic mixture of arketamine and esketamine, is a drug of abuse. Comparable scores on subjective ratings of “drug liking” and on other measures of subjective drug effects were observed between SPRAVATO® (at 84 mg and 112 mg) and intravenous ketamine in recreational polydrug users, suggesting a similar potential for abuse. In clinical trials, very common reactions reported with SPRAVATO® included dissociation, dizziness and somnolence. Common reactions included feeling abnormal, feeling drunk, euphoric mood and hallucinations (see **ADVERSE REACTIONS**).

In published reports, individuals who were dependent on ketamine reported withdrawal symptoms of cravings, anxiety, shaking, sweating, and palpitations.

Individuals with a history of drug abuse or dependence may be at greater risk for abuse and misuse of SPRAVATO®. Careful consideration of the risks and benefits of prescribing SPRAVATO® is advised prior to treatment of individuals with a history of substance use disorder, including alcohol. Assess each patient's risk for abuse or misuse prior to prescribing SPRAVATO® and monitor all patients receiving SPRAVATO® for signs and symptoms of abuse, misuse or dependence including drug seeking behaviour and symptoms of withdrawal. If you suspect substance abuse or misuse, carefully weigh the risks of continuing versus stopping treatment and consult clinical guidelines on depression with comorbid substance use disorder. If needed, refer patient to a psychiatrist with experience in managing this condition.

Driving and Operating Machinery

SPRAVATO® has a major influence on the ability to drive and use machines.

Before SPRAVATO® administration, instruct patients that they cannot 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 and following a restful sleep. Instruct patients to arrange safe transportation following treatment with SPRAVATO®.

Two studies were conducted to assess the effects of SPRAVATO® on the ability to drive. Although the effects of SPRAVATO® 84 mg were comparable to placebo at 8 hours and 18 hours post-dose, two SPRAVATO® -treated subjects in one of the studies discontinued the driving test at 8 hours post-dose due to SPRAVATO® -related adverse reactions (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics**).

Endocrine and Metabolism

Use SPRAVATO® with caution in patients with hyperthyroidism that has not been sufficiently treated due to the increased risk of hypertension and tachycardia. Carefully assess patients before prescribing SPRAVATO® and treatment initiated only if the benefit outweighs the risk.

Gastrointestinal

Nausea and Vomiting

Nausea and vomiting were among the most common adverse drug reactions reported in clinical trials with SPRAVATO®, with approximately 27% and 10% of patients, respectively, reporting reactions. In general, these events occurred and resolved on the day of dosing. Severe events were reported in <2% of patients across trials.

Discuss with patients the potential for nausea and vomiting following administration of SPRAVATO®. Advise patients not to eat for at least 2 hours before administration and not to drink liquids at least 30 minutes prior to administration (see **DOSING AND ADMINISTRATION, Dosing Considerations**).

Genitourinary

Ulcerative or Interstitial Cystitis

Cases of ulcerative or 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 short-term studies, patients treated with SPRAVATO® had a higher incidence of lower urinary tract symptoms, such as pollakiuria, dysuria, micturition urgency, nocturia and cystitis (see **ADVERSE REACTIONS**).

Monitor for urinary tract and bladder symptoms during the course of treatment with SPRAVATO®, and refer to appropriate healthcare provider as clinically warranted.

Hepatic/Biliary/Pancreatic

SPRAVATO® has not been studied in patients with severe hepatic impairment (Child-Pugh class C). Use in this population is not recommended.

Patients with moderate (Child-Pugh class B) hepatic impairment may have stronger or prolonged adverse reactions. Therefore, these patients may need to be monitored more carefully and for a longer period after dosing than those without hepatic impairment.

(see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment** and **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Hepatocellular and cholestatic patterns of elevations in liver enzymes as well as biliary ductal dilatations and hepatic fibrosis have been reported following exposure to ketamine, especially with repeated doses, chronic use or misuse. Since a potential for hepatotoxicity with the use of SPRAVATO® cannot be excluded, consider periodic monitoring of liver function and treatment discontinuation if clinically significant elevations are observed (see **ADVERSE REACTIONS, Post-Market Adverse Reactions**).

Monitoring and Laboratory Tests

SPRAVATO® must be administered under the direct supervision of a healthcare professional. Monitor:

- blood pressure prior to and following SPRAVATO® administration. Include an assessment at approximately 40 minutes post-dose and continue to monitor until blood pressure returns to acceptable levels. Intensify monitoring in patients with medical conditions or taking concomitant medications that may exacerbate blood pressure elevations or potentiate the risk of blood pressure elevations for the patient.

- patients for at least 2 hours at each treatment session until clinically stable and ensure that medical support is available to appropriately manage reactions. An assessment must be performed to determine when the patient is ready to leave the healthcare setting (see **SPRAVATO® Administration and Monitoring Checklist** in **DOSAGE AND ADMINISTRATION, Administration**).

- for signs and symptoms of abuse, misuse or dependence.

- for suicidal ideation or other indicators of potential for suicidal behaviour, particularly early in treatment and following any intended or unintended changes to treatment, including dosing modifications, interruption and discontinuation.
- for urinary tract and bladder symptoms.
- liver function periodically.

Neurologic

Cognitive Impairment

SPRAVATO® causes acute adverse reactions (such as somnolence, sedation, dissociative symptoms, perception disturbances, dizziness, vertigo, and anxiety) that impair attention, judgment, thinking, reaction speed and motor skills (see **ADVERSE REACTIONS**). In clinical studies, SPRAVATO® caused a decline in cognitive performance at 40 minutes post-dose. Average 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 and memory impairment have been reported with chronic ketamine use. No adverse effects of SPRAVATO® nasal spray on cognitive functioning were observed in younger patients in a one-year open-label safety study; however, a slowing of reaction time to complete cognitive tasks was observed in elderly patients. The long-term cognitive effects of SPRAVATO® have not been systematically evaluated beyond one year, therefore the risks for cognitive and memory impairment remain unknown.

In animal studies with esketamine and ketamine, findings suggestive of long-term cognitive deficits have been reported (see **NON-CLINICAL TOXICOLOGY**). Long-term neuronal cell loss has been reported with ketamine.

Dizziness and Vertigo

Dizziness and vertigo were among the most common adverse drug reactions reported with SPRAVATO® (reported in 28% to 51% of patients across clinical studies) (see **ADVERSE REACTIONS**). Most events resolved on the day of dosing; however, some were prolonged or had a delayed onset. Severe events were reported in <3% of patients across trials.

Sedation

Sedation and somnolence-related adverse drug reactions were among the most commonly reported with SPRAVATO® (see **ADVERSE REACTIONS**). Most events resolved on the day of dosing; however, some were prolonged or had a delayed onset. Cases of deep sedation were rare.

To Manage Post-Administration Neurologic Reactions

Discuss with patients the potential for acute cognitive impairment, dizziness and sedation following treatment with SPRAVATO®. Advise patients to report any latent or prolonged effects.

Concomitant use with CNS depressants (e.g., benzodiazepines, opioids, alcohol) may increase sedation (see **DRUG INTERACTIONS**). Exercise extra caution and closely monitor for sedation with concomitant use of SPRAVATO® with CNS depressants.

Following SPRAVATO® administration, at each treatment session, patients must be monitored for at least 2 hours until clinically stable. Carefully follow all procedures outlined in **DOSAGE AND ADMINISTRATION, Dosing Considerations**.

(see **SERIOUS WARNINGS AND PRECAUTIONS BOX**)

Psychiatric

Dissociation

Dissociation and derealization-related adverse drug reactions were among the most commonly reported with SPRAVATO® (see **ADVERSE REACTIONS**). In a fixed dose trial, measures of dissociative symptoms were dose-related. In <4% of cases dissociative effects were severe. For some patients, dissociative symptoms can be associated with anxiety or panic, particularly when initiating treatment. Dissociative effects generally occurred and resolved on the day of dosing.

Use SPRAVATO® with caution in patients with presence or history of psychosis. Carefully assess the patient before prescribing SPRAVATO® and initiate treatment only if the benefit outweighs the risk.

Discuss with patients the dissociative properties of SPRAVATO® and what subjective experiences they may encounter, including derealization, feeling drunk or abnormal, perceptual disturbances and hallucinations.

Following SPRAVATO® administration, at each treatment session, patients must be monitored for at least 2 hours until clinically stable. Carefully follow all procedures outlined in **DOSAGE AND ADMINISTRATION, Dosing Considerations**.

(see **SERIOUS WARNINGS AND PRECAUTIONS BOX**)

Mania and Bipolar Disorder

Mania was observed with SPRAVATO® in clinical trials.

Use SPRAVATO® with caution in patients with the presence or history of mania or bipolar disorder. Carefully assess the patient before prescribing SPRAVATO® and initiate treatment only if the benefit outweighs the risk.

Suicide

Cases of completed suicide were observed in patients with exposure to SPRAVATO® in clinical trials including in patients with no known history of suicidal behavior or who achieved remission of depression. These events occurred during open-label, uncontrolled phases of clinical studies. Therefore, it is not possible to reliably assess the causal relationship of these events to treatment with SPRAVATO®.

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide related events). 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. Ensure these patients receive careful monitoring during treatment.

Rigorously monitor for suicidal ideation or other indicators of potential for suicidal behaviour early in treatment and following any intended or unintended changes to treatment, including dosing modifications, interruption and discontinuation. Alert patients (and patient caregivers) to the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to immediately seek medical advice if these symptoms present (see **SERIOUS WARNINGS AND PRECAUTIONS BOX**).

Respiratory

Respiratory depression may occur at high doses or following rapid intravenous injection of anesthetic doses of esketamine or ketamine.

Ensure that medical support is available to appropriately manage the potential for respiratory depression.

Carefully assess patients with clinically significant or unstable respiratory conditions before prescribing SPRAVATO® and initiate treatment only if the benefit outweighs the risk. In these patients, administer SPRAVATO® in a setting where appropriate resuscitation equipment and healthcare professionals with training in cardiopulmonary resuscitation are available. Examples of conditions for which initiation of SPRAVATO® should be carefully considered include, but are not limited to:

- Significant pulmonary insufficiency, including COPD.
- Sleep apnea with morbid obesity (BMI ≥35).

(see **SERIOUS WARNINGS AND PRECAUTIONS BOX** and **DOSAGE AND ADMINISTRATION**)

7.1 Special Populations

7.1.1 Pregnant Women

The use of SPRAVATO® should be avoided in women of childbearing potential intending to become pregnant and during pregnancy, with careful consideration given to the potential hazard to the child and potential benefits to the mother. To avoid exposing the fetus 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®. If a woman becomes pregnant during treatment, SPRAVATO® should be discontinued and the patient should be counseled about the potential risk to the fetus and clinical/therapeutic options as soon as possible.

The risks of SPRAVATO® during pregnancy have not been studied. Human data in pregnant women during clinical trials with SPRAVATO® were very limited. 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 fetuses cannot be excluded (see **NON-CLINICAL TOXICOLOGY, Reproductive Toxicity**).

Pregnancy Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including SPRAVATO®, during pregnancy. Encourage pregnant women exposed to SPRAVATO® to enroll in the National Pregnancy Registry for Antidepressants. Information on the registry can also be found by calling: 1-866-961-2388 or at the following website: https://womensmentalhealth.org/research/pregnancyregistry/antidepressants/

7.1.2 Breast-feeding

The use of SPRAVATO® should be avoided in women who are breast-feeding. Advise patients either not to undergo therapy with SPRAVATO® while breast-feeding or discontinue breast-feeding if treatment with SPRAVATO® is initiated.

The risks of SPRAVATO® during breast-feeding have not been studied in humans. There are no data available to assess the effects of esketamine on human milk production, its presence in human milk, or effects on the breastfed infant. Esketamine is expected to be excreted to human milk based on its detection in the plasma of lactating rat pups (see **NON-CLINICAL TOXICOLOGY, Reproductive Toxicity**), and published data showing presence of ketamine in the milk of cows exposed to intravenously-administered ketamine.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available in patients under 18 years of age. SPRAVATO® is not authorized for pediatric use (see **INDICATIONS, Pediatrics**).

7.1.4 Geriatrics

Initiation of SPRAVATO® is not recommended in patients 65 years and older because evidence of efficacy was not established in this population (see **INDICATIONS** and **CLINICAL TRIALS**).

Pharmacokinetic analysis showed that mean esketamine C_{max} and AUC values were higher in elderly patients compared with younger adult patients (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**). Therefore, in clinical studies, SPRAVATO® was initiated at 28 mg and could be titrated to 56 mg or 84 mg (see **DOSAGE AND ADMINISTRATION**).

There was no evidence of a meaningful difference in safety profile in patients 65 years of age and older in a study compared to studies conducted in adults <65 years of age. However, a greater sensitivity of elderly patients (e.g., risk of fall) cannot be ruled out (see **ADVERSE REACTIONS**).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

SPRAVATO® was evaluated for safety in 1601 patients with major depressive disorder (who were non-responders to at least two oral antidepressant treatments, of adequate dosage and duration, in the current major depressive episode) from five Phase 3 studies (3 short-term and 2 long-term studies). Of all SPRAVATO® treated patients in the completed Phase 3 studies, 479 (29.9%) received at least 6 months of treatment exposure, and 178 (11.1%) received at least 12 months of exposure.

In the Phase 3 program, the most commonly observed adverse reactions in patients treated with SPRAVATO® plus oral antidepressant were dissociation, dizziness, nausea, sedation, headache, vertigo, dysgeusia, hypoesthesia, blood pressure increased, anxiety and vomiting. The majority of these events were transient, occurring and resolving on the day of administration.

Including an ongoing long-term trial, serious adverse events considered by the investigator to be related to SPRAVATO® and reported by at least 2 patients were suicidality (2 of suicidal ideation and 1 of suicide attempt), hypertension (1 of increased blood pressure and 1 hypertensive emergency) and anxiety (1 of anxiety disorder and 1 of anxiety). The most common adverse events leading to SPRAVATO® discontinuation (in order of decreasing frequency) were: anxiety, depression, blood pressure increased, dizziness, suicidal ideation, dissociation, nausea, vomiting, headache, muscular weakness, vertigo, hypertension, panic attack and sedation. In a given study, each were reported with an incidence of ≤ 2%.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 3 shows the incidence of adverse reactions that occurred in adult patients (aged 18 to <65) with major depressive disorder who have not responded to ≥2 previous courses of treatment. The data is from a safety pool of two short-term (4 week) randomized, double-blind, placebo-controlled studies.

Table 3: Treatment emergent adverse events occurring in ≥1% patients treated with SPRAVATO® + oral antidepressant and greater than placebo + oral antidepressant in data pool of 2 short-term (4 week) clinical trials in adults (18 to <65 years of age) with major depressive disorder who have not responded to ≥2 previous courses of treatment

	SPRAVATO®* + oral antidepressant‡ (N=346)	Placebo + oral antidepressant‡ (N=222)
Cardiac disorders		
Tachycardia†	6 (2%)	1 (0%)
Ear and labyrinth disorders		
Vertigo†	78 (23%)	6 (3%)
Gastrointestinal disorders		

	SPRAVATO®* + oral antidepressant‡ (N=346)	Placebo + oral antidepressant‡ (N=222)
Nausea	98 (28%)	19 (9%)
Vomiting	32 (9%)	4 (2%)
Diarrhoea	23 (7%)	13 (6%)
Dry mouth	19 (5%)	7 (3%)
Constipation	11 (3%)	3 (1%)
Dyspepsia	7 (2%)	4 (2%)
Abdominal discomfort	6 (2%)	0
General disorders and administration site conditions		
Feeling drunk	19 (5%)	1 (0%)
Feeling abnormal	12 (3%)	0
Crying	7 (2%)	2 (1%)
Infections and infestations		
Urinary tract infection	6 (2%)	3 (1%)
Investigations		
Blood pressure increased†	36 (10%)	6 (3%)
Weight increased	4 (1%)	0
Metabolism and nutrition disorders		
Increased appetite	5 (1%)	0
Musculoskeletal and connective tissue disorders		
Muscle spasms	8 (2%)	0
Back pain	4 (1%)	2 (1%)
Nervous system disorders		
Dizziness†	101 (29%)	17 (8%)
Sedation†	79 (23%)	21 (9%)
Headache†	70 (20%)	38 (17%)
Dysgeusia†	66 (19%)	30 (14%)
Hypoesthesia†	63 (18%)	5 (2%)
Lethargy†	37 (11%)	12 (5%)
Dysarthria†	15 (4%)	0
Tremor†	12 (3%)	2 (1%)
Mental impairment	11 (3%)	2 (1%)
Tunnel vision	5 (1%)	2 (1%)
Migraine	4 (1%)	1 (0%)
Psychiatric disorders		
Dissociation†	142 (41%)	21 (9%)
Anxiety†	45 (13%)	14 (6%)
Insomnia	29 (8%)	16 (7%)
Euphoric mood	15 (4%)	2 (1%)
Libido decreased	5 (1%)	0
Psychomotor retardation	5 (1%)	0
Depression	4 (1%)	0
Renal and urinary disorders		
Pollakiuria†	11 (3%)	1 (0%)
Dysuria	6 (2%)	0
Respiratory, thoracic and mediastinal disorders		
Nasal discomfort†	23 (7%)	11 (5%)

	SPRAVATO®* + oral antidepressant‡ (N=346)	Placebo + oral antidepressant‡ (N=222)
Throat irritation	23 (7%)	9 (4%)
Oropharyngeal pain	9 (3%)	5 (2%)
Rhinorrhea	7 (2%)	2 (1%)
Upper-airway cough syndrome	6 (2%)	3 (1%)
Cough	4 (1%)	0
Epistaxis	4 (1%)	2 (1%)
Skin and subcutaneous tissue disorders		
Hyperhidrosis	14 (4%)	5 (2%)
Pruritus	7 (2%)	1 (0%)

* SPRAVATO® administered at recommended 56 mg or 84 mg doses on fixed or flexible regimens.

‡ Investigators selected from one of duloxetine, venlafaxine extended release; escitalopram or sertraline.

† The following terms were combined:
Anxiety includes: anxiety; anticipatory anxiety; anxiety disorder; generalized anxiety disorder; agitation; fear; nervousness; tension; panic attack; panic disorder; panic reaction; feeling jittery; irritability; psychogenic tremor.
Blood pressure increased includes: blood pressure increased; blood pressure systolic increased; blood pressure diastolic increased; hypertension; hypertensive heart disease; hypertensive crisis.
Dissociation includes: dissociation; depersonalization/derealization disorder; derealization; dissociative disorder; flashback; hallucination; auditory hallucination; somatic hallucination; visual hallucination; illusion; hyperacusis; tinnitus; diplopia; vision blurred; ocular discomfort; photophobia; visual impairment; dysesthesia; oral dysesthesia; paresthesia; paresthesia oral; pharyngeal paresthesia; time perception altered; daydreaming; delusional perception; feeling hot; feeling cold; feeling of body temperature change.
Dizziness includes: dizziness; dizziness postural; procedural dizziness; dizziness exertional.
Dysarthria includes: dysarthria; speech disorder; slow speech.
Dysgeusia includes: dysgeusia; hypogeusia.
Headache includes: headache; sinus headache.
Hypoesthesia includes: hypoesthesia; hypoesthesia oral; hypoesthesia teeth; pharyngeal hypoesthesia; intranasal hypoesthesia.
Lethargy includes: lethargy; fatigue; listless.
Nasal discomfort includes: nasal discomfort; nasal crusting; nasal dryness, nasal pruritus.
Sedation includes: sedation; somnolence; altered state of consciousness; depressed level of consciousness; hypersomnia; stupor.
Tachycardia includes: sinus tachycardia; tachycardia; heart rate increased; extrasystole.
Tremor includes: tremor; intention tremor.
Vertigo includes: vertigo; vertigo positional.

Scale-based incidences of dissociation and sedation

In the short-term (4-week) fixed-dose trial in adults (18 to <65 years of age), scale-based incidences of dissociation and sedation were dose-related.

- Based on a scale of dissociative symptoms, the Clinician-Administered Dissociative States Scale (CADSS), the incidence of dissociation (CADSS total score >4 post-dose) was 61% in patients treated with SPRAVATO® 56 mg + oral antidepressant and 69% in patients treated with SPRAVATO® 84 mg + oral antidepressant, compared to 5% in patients treated with placebo + oral antidepressant.

- Based on an objective scale of sedation, the Modified Observer's Alertness/Sedation scale (MOAA/s), the incidence of sedation (MOAA/s score <5) was 50% in patients treated with SPRAVATO® 56 mg + oral antidepressant and 61% in patients treated with SPRAVATO® 84 mg + oral antidepressant, compared to 11% in patients treated with placebo + oral antidepressant.

Geriatric patients (≥65 years of age)

The safety of SPRAVATO® in geriatric patients (≥65 years of age) was evaluated in a 4-week placebo-controlled Phase 3 study. In this study, SPRAVATO® was initiated at 28 mg and could be titrated to 56 mg or 84 mg, twice-weekly, due to tolerability concerns. On Day 25, the proportions of patients receiving 28 mg, 56 mg and 84 mg were 10%, 26% and 65%, respectively. There was no evidence of a meaningful difference in safety profile in patients 65 years of age and older in this study compared to studies conducted in adults under 65 years of age. However, a greater sensitivity of elderly patients (e.g., risk of fall) cannot be ruled out. In a long-term (52-week) study, a slowing of reaction time to complete cognitive tasks was observed in elderly patients from Week 20.

Long-term studies

In a relapse-prevention study and a long-term (up to 52 weeks) open-label study with SPRAVATO®, there was no evidence of a meaningful difference in safety profile compared to short-term studies.

8.3 Less common Clinical Trial Adverse Reactions

Treatment-related adverse events occurring in ≥ 2 patients treated with SPRAVATO® + oral antidepressant and greater than placebo + oral antidepressant are listed below:

Cardiac disorders: palpitations

Ear and labyrinth disorders: ear discomfort, hypoacusis

Gastrointestinal disorders: salivary hypersecretion

General disorders: asthenia, malaise, thirst

Musculoskeletal disorders: musculoskeletal stiffness, myalgia

Nervous system disorders: amnesia, balance disorder, disturbance in attention

Psychiatric disorders: abnormal dreams, affect liability, bradyphrenia, confusional state, disorientation, restlessness

Renal and urinary disorders: micturition urgency

Respiratory disorders: dyspnea, nasal congestion, sneezing

Vascular disorders: hot flush

8.4 Post-Market Adverse Reactions

Hepatobiliary toxicity has been reported with acute and chronic use of ketamine. Clinically important elevations in liver enzymes, suggestive of both hepatocellular and cholestatic changes are a potential risk of acute use of ketamine. Liver enzyme elevations and biliary ductal dilatations are potential risks of repeated, chronic use or misuse of ketamine. Both the biochemical and

structural hepatobiliary changes may be reversible.

9 DRUG INTERACTIONS

9.1 Overview

Drug interactions of greatest clinical significance were pharmacodynamic in nature.

Concomitant use of SPRAVATO® with CNS depressants (e.g., benzodiazepines, opioids, alcohol) may increase sedation. Therefore, dose adjustments should be considered and patients closely monitored following administration of SPRAVATO®.

Concomitant use of SPRAVATO® with other drugs having pressor effects [e.g. psychomotor stimulants, monoamine oxidase inhibitors (MAOIs), sympathomimetics, triptans and vascular endothelial growth factor receptor inhibitors] should be avoided or undertaken with intensified blood pressure monitoring.

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

9.2 Drug-Drug Interactions

Pharmacodynamic Interactions

Central Nervous System Depressants

Concomitant use with CNS depressants (e.g., benzodiazepines, opioids, alcohol) may increase sedation. Alcohol should not be consumed within 24 hours prior to and following SPRAVATO® administration (see **DOSING AND ADMINISTRATION, Dosing Considerations**).

Closely monitor for sedation with concomitant use of SPRAVATO® with CNS depressants. Diazepam is known to increase the half-life of racemic ketamine and prolongs its pharmacodynamic effects. Dose adjustments may therefore be considered with concomitant use with SPRAVATO® (see **WARNINGS AND PRECAUTIONS, Psychiatric**).

Central Nervous System Stimulants

Due to an increased risk of clinically significant blood pressure elevations and potential for hypertensive crisis, avoid concomitant use of SPRAVATO® with psychostimulants (e.g., amphetamines, methylphenidate, modafinil, armodafinil) or undertake with intensified blood pressure monitoring.

Monoamine Oxidase Inhibitors (MAOIs)

SPRAVATO® is only indicated in combination with a SSRI or SNRI, which are contraindicated with a MAOI. Due to an increased risk of clinically significant blood pressure elevations and potential for hypertensive crisis, avoid concomitant use of SPRAVATO® with MAOIs.

Other Drugs that Increase Blood Pressure

Concomitant use with other drugs that increase blood pressure, including, but not limited to, other sympathomimetics, triptans and vascular endothelial growth factor receptor inhibitors (e.g., pazopanib, sunitinib, sorafenib) should be avoided. Closely monitor blood pressure if concomitant use of SPRAVATO® with other drugs that increase blood pressure cannot be avoided (see **WARNINGS AND PRECAUTIONS, Cardiovascular**).

Pharmacokinetic Interactions

The drugs listed in Table 4 are based on completed drug interactions studies.

Table 4: Established Drug-Drug Interactions

Drug Common Name Study Design	Source of Evidence	Effect*	Clinical comment
Effect of other nasal spray products on esketamine			
Oxymetazoline hydrochloride 2 nasal sprays of 0.05% solution in each nostril administered at 1 hour prior to nasal administration of esketamine	CT	↔ esketamine	Patients who require a nasal decongestant on a dosing day should be advised not to administer these medications within 1 hour before administration of SPRAVATO®. (see **DOSAGE AND ADMINISTRATION**)
Mometasone furoate 2 nasal sprays of 50 μg/spray in each nostril (total dose, 200 μg) administered once daily for 2 weeks with the last dose administered at 1 hour prior to nasal administration of esketamine	CT	↔ esketamine	Patients who require a nasal corticosteroid on a dosing day should be advised not to administer these medications within 1 hour before administration of SPRAVATO®. (see **DOSAGE AND ADMINISTRATION**)
Effect of CYP2B6 inhibitors on esketamine			
Ticlopidine 250 mg twice daily for 9 days prior to and on the day of esketamine administration	CT	↑ esketamine C_{max}: ↔ AUC_{∞}: ↑ 29% $T_{1/2}$: ↔	No dose adjustment is necessary.
Effect of CYP3A4 inhibitors on esketamine			
Clarithromycin 500 mg twice daily for 3 days prior to and on the day of esketamine administration	CT	↑ esketamine C_{max}: ↑ 11% AUC_{∞}: ↑ 4% $T_{1/2}$: ↔	No dose adjustment is necessary.

Drug Common Name Study Design	Source of Evidence	Effect*	Clinical comment
Effect of CYP3A4 and CYP2B6 inducers on esketamine			
Rifampicin 600 mg daily for 6 days prior to esketamine administration	CT	↓ esketamine C_{max}: ↓ 17% AUC_{∞}: ↓ 28%	No dose adjustment is necessary.
Effect of esketamine on another drug metabolized by CYP3A4			
Midazolam Single 6 mg oral dose following nasal administration of 84 mg esketamine twice a week for 2 weeks.	CT	↓ Midazolam AUC_{∞}: ↓ 16%	No dose adjustment is necessary.
Effect of esketamine on another drug metabolized by CYP2B6			
Bupropion Single 150 mg oral dose following nasal administration of 84 mg esketamine twice a week for 2 weeks.	CT	↔ Bupropion	No dose adjustment is necessary.

Legends: CT = Clinical Trial; C_{max}= maximum concentration; AUC_{∞} = AUC from time 0 to infinity; $T_{1/2}$ = half-life
* ↑= increase; ↓= decrease; ↔ = no change

In Vitro Studies

Enzyme Systems:

Esketamine has modest induction effects on CYP2B6 and CYP3A4 in human hepatocytes. Esketamine and its major metabolites did not induce CYP1A2. Esketamine and its major circulating metabolites did not demonstrate any significant inhibition of CYPs or UGTs, aside from a weak reversible inhibition of CYP3A4 by noresketamine.

Transporter Systems:

Esketamine and its active metabolite noresketamine were 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. In addition, noresketamine was not a substrate of the transporters OAT1, OAT3, OCT1 and OCT2. However, the concentration of esketamine used in these experiments fell below the concentration obtained in humans after a therapeutic dose (84 mg) of esketamine. Esketamine and its major circulating metabolites did not inhibit these transporters or multi-drug and toxin extrusion 1 (MATE1) and MATE2-K, or organic cation transporter 2 (OCT2), OAT1, or OAT3.

9.3 Drug-Food Interactions

Interactions with food have not been established.

9.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Esketamine is the S-enantiomer of racemic ketamine and it is an activity-dependent glutamate receptor modulator. It is a non-selective, non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor. The mechanism by which esketamine exerts its antidepressant effect is unknown. The major circulating metabolite of esketamine (noresketamine) demonstrated activity at the same receptor with less affinity.

10.2 Pharmacodynamics

Effect on driving

Two studies were conducted to assess the effects of SPRAVATO® on driving abilities, one study in adult subjects with major depressive disorder and one study in healthy subjects. On-road driving performance was assessed by the mean standard deviation of the lateral position (SDLP), a measure of driving impairment.

Subjects with major depressive disorder: A single-blind, placebo-controlled study in 25 adult subjects with major depressive disorder evaluated the effects of a single 84 mg dose of SPRAVATO® on next day driving. An ethanol beverage was the positive control. The SDLP after administration of SPRAVATO® was similar to placebo. There was no impact on any driving parameter on next day driving.

Healthy subjects: A randomized, double-blind, crossover, placebo-controlled study in 23 healthy subjects evaluated the effects of a single 84 mg dose of SPRAVATO® on driving. Mirtazapine 30 mg was the positive control. Although the SDLP, assessed at 8 hours after SPRAVATO® administration, was similar to placebo, two SPRAVATO® treated subjects discontinued the test due to adverse reactions that interfered with driving ability (i.e. pressure behind the eyes, paresthesia of the hands and feet, headache, anxiety and light sensitivity). Subjects also reported requiring “more effort” to complete the test 8 hours after SPRAVATO® administration.

Cardiac Electrophysiology and Hemodynamics

The effects of single doses of esketamine (84 mg nasal spray and 0.8 mg/kg solution intravenously infused over 40 minutes) on ECG interval parameters and blood pressure were evaluated in a randomized, double-blind, placebo-, and positive-controlled, 4-period, crossover study in 60 healthy subjects. Maximum plasma concentrations produced by the intravenous infusion were approximately 3-times higher than the maximum concentrations produced by the nasal dose of 84 mg. Esketamine caused an increase in heart rate and shortening of the QTcP and PR intervals. During treatment with the 84 mg intranasal dose, the difference from placebo in mean change from baseline heart rate was 14.5 bpm (90% CI 12.6, 16.4) at 25 minutes post-dose, 11.3 bpm (90% CI 9.4, 13.3) at 50 minutes post-dose, 7.1 bpm (90% CI 5.2, 9.0) at 1.5 hours post-dose, and 3.3 bpm (90% CI 1.3, 5.2) at 3 hours post-dose. In subjects receiving esketamine 84 mg intranasal, the maximum differences from placebo in mean change from baseline QTcP and PR intervals were -5.8 ms (90% CI -8.0, -3.5) and -5.9 ms (90% CI -7.8, -3.9), respectively, both at 25 minutes post-dosing.

Esketamine significantly increased systolic and diastolic blood pressure. In the esketamine 84 mg intranasal treatment arm, the differences from placebo in mean change from baseline systolic blood pressure were 18.2 mmHg (95% CI 15.3, 21.1) at 50 minutes post-dosing and 11.8 mmHg (95% CI 8.8, 14.7) at 90 minutes post-dosing. The differences from placebo in mean change from baseline diastolic blood pressure were 11.3 mmHg (95% CI 9.5, 13.2) at 50 minutes post-dosing and 6.6 mmHg (95% CI 4.8, 8.5) at 90 minutes post-dosing.

10.3 Pharmacokinetics

Table 5: Summary of Nasally Administered Esketamine Pharmacokinetic Parameters in Healthy Subjects

Esketamine	C_{max} (ng/mL)	T_{max} (h)	$t_{½}$ (h)	$AUC_{0-\infty}$ (ng*h/mL)
28 mg	49.7 – 70.5	0.33 – 0.67	7 – 12	128 – 183
56 mg	71.8 – 117	0.50 – 0.77		216 – 317
84 mg	95.0 – 174	0.53 – 0.83		310 – 489

Note: After intravenous administration of a 28-mg dose of esketamine, the calculated CL is 89 L/h and Vd is 709 L.

Absorption

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

The time to reach maximum plasma concentration (t_{max}) is typically 20 minutes to 40 minutes after the last nasal spray of a treatment session (see **DOSAGE AND ADMINISTRATION**).

Dose-dependent, linear increases in the plasma C_{max} and AUC_{∞} of esketamine nasal spray were produced by doses of 28 mg, 56 mg and 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.

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.

The inter-subject variability of esketamine ranges from 27% to 66% for C_{max} and 18% to 45% for AUC_{∞}. The intra-subject variability of esketamine is approximately 15% for C_{max} and 10% for AUC_{∞}.

Distribution

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

The proportion of protein-bound esketamine in human plasma was approximately 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.

The brain-to-plasma ratio of noresketamine is 4- to 6-times lower than that of esketamine.

There is evidence from humans and animal models that esketamine and ketamine can cross the placental barrier. Ketamine has been shown to be rapidly distributed to fetal tissues, including monkey brain.

Metabolism

Esketamine is extensively metabolized in the liver. The primary metabolic pathway of esketamine in human liver microsomes is N-demethylation to noresketamine. The main CYP enzymes responsible for esketamine N-demethylation are CYP2B6 and CYP3A4, while other CYP enzymes, including CYP2C19 and CYP2C9, contribute to a lesser extent. Noresketamine is subsequently metabolized via CYP-dependent pathways to other metabolites, some of which undergo glucuronidation.

In simulated gastric fluid, there is no evidence that N-nitroso-esketamine is formed out of the fraction of the nasally-administered dose of esketamine that is orally absorbed.

Excretion

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 ranged from approximately 7 to 12 hours.

Following intravenous or oral administration, esketamine-derived metabolites were primarily recovered in urine (≥ 78% of a radiolabeled dose) and to a lesser extent in feces (≤ 2% of a radiolabeled dose). Less than 1% of the dose was excreted in the urine as unchanged drug.

Special Populations

Elderly (65 years of age and older)

The pharmacokinetics of esketamine administered as a nasal spray were compared between elderly 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.

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 dose 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. The $t_{1/2}$ values for subjects with moderate hepatic impairment was also slightly longer than was seen in healthy subjects (mean [±SD] 18.7[2.2] vs 16.5[12.1] respectively).

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

Ethnic Origin

The pharmacokinetics of esketamine nasal spray were 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% greater in Korean subjects, relative to Caucasian subjects. In Japanese subjects, both parameters were approximately 40% higher relative to Caucasian subjects in one study, but 46% and 48% higher for C_{max} and AUC_{∞} in another study. In this second study, a higher incidence of treatment-emergent adverse events was noted in comparison 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 to 7.3 hours in Caucasian subjects.

Sex

A population pharmacokinetic analysis including healthy subjects (138 males and 118 females) and patients with major depressive disorder (203 males and 361 females) indicated that the pharmacokinetics of esketamine, administered as a nasal spray, are 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.

11 STORAGE, STABILITY AND DISPOSAL

Store SPRAVATO® at 15°C to 30°C in the original package.

Keep out of the sight and reach of children.

Used devices should be disposed of in accordance with local procedures for controlled substances.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: esketamine hydrochloride

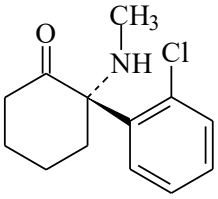
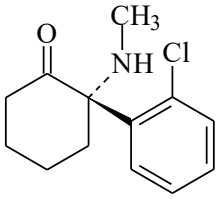
Chemical name: (S)-2-(o-chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride

Molecular formula and molecular mass:

Esketamine free base: $C_{13}H_{16}ClNO$, 237.7 g/mol;

Esketamine hydrochloride: $C_{13}H_{16}ClNO \cdot HCl$, 274.2g/mol

Structural formula:

Esketamine free base	Esketamine hydrochloride
	 , HCl

Physicochemical properties: The drug substance is a white to almost white, crystalline powder. The drug substance is freely soluble in demineralized water (pH 3.8), citrate buffer (pH 3 and 5), and slightly soluble in phosphate buffer (pH 7). The drug substance has a dissociation constant pK_a of 7.5 (basic amine moiety).

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The efficacy and safety of SPRAVATO® (esketamine) nasal spray was evaluated for the treatment of major depressive disorder in adults (aged 18 to <65) who did not respond adequately to at least two different antidepressants in three Phase 3 studies (see Table 6). Two of the three studies, a short-term (4-week) double-blind, placebo-controlled, flexible dose study (TRD3002), and a long-term randomized withdrawal study (TRD3003) supported the efficacy of SPRAVATO® in adults aged 18 to <65. A short-term (4-week) double-blind placebo-controlled, fixed-dose study (TRD3001) did not.

A fourth study evaluated the efficacy and safety of SPRAVATO® for the treatment of major depressive disorder in geriatric patients (≥65 years of age) who did not respond adequately to at least two different antidepressants. In this short-term (4-week) double-blind placebo-controlled,

flexible dose study, SPRAVATO® was initiated at 28 mg twice-weekly to facilitate tolerability and could be titrated to 56 mg or 84 mg administered twice-weekly. However, this study was not supportive of efficacy in this population.

All studies evaluated subjects who met DSM-5 criteria for major depressive disorder and were non-responders to at least two courses of different oral antidepressant treatment, of adequate dosage and duration, in the current major depressive episode. Subjects were excluded if they had conditions that included poorly controlled hypertension, bipolar disorder, suicidal ideation with intent to act within the past 6 months, or a history suicidal behaviour within the past year.

Short-Term Studies

Patients in TRD3001 and TRD3002 initiated treatment on Day 1 with either SPRAVATO® plus a newly initiated daily oral antidepressant or placebo plus a newly initiated daily oral antidepressant. The oral antidepressant could be one of either duloxetine, venlafaxine extended release, escitalopram, or sertraline, as determined by the investigator based on the patient's prior treatment history. SPRAVATO® doses of 56 mg or 84 mg were fixed in Study TRD3001 and flexible in Study TRD3002. All patients received SPRAVATO® 56 mg on Day 1. In Study TRD3001, dose was either maintained on 56 mg or titrated to 84 mg on the second administration day according to the randomized fixed dosing regimen. In Study TRD3002, SPRAVATO® could be titrated between 56 mg and 84 mg from the second administration day onward, based on investigator discretion. All subjects received study drug twice weekly during a 4-week double-blind induction phase.

Table 6: Summary of patient demographics for clinical trials (double blind phases)

Study No.	Trial design	Dosage and route of administration	Study subjects (n = number)*	Mean age years (SD) range	Gender (%M / %F)
TRD3001	Fixed dose, randomized, multicenter, double-blind, placebo-controlled parallel group	Placebo (i.n.) + oral antidepressant	n = 113	46.8 (11.4) 18, 64	28 / 72
		SPRAVATO® 56 mg (i.n.) + oral antidepressant	n = 115	46.4 (11.2) 22, 64	30 / 70
		SPRAVATO® 84 mg + oral antidepressant	n = 114	45.7 (11.1) 18, 64	31 / 69
TRD3002	Flexible dose, randomized, multicenter, double-blind, placebo-controlled parallel group	Placebo (i.n.) + oral antidepressant	n = 109	46.4 (11.1) 20, 64	42 / 58
		SPRAVATO® 56/84 mg (i.n.) + oral antidepressant	n = 114	45 (12.6) 19, 64	34 / 66

Study No.	Trial design	Dosage and route of administration	Study subjects (n = number)*	Mean age years (SD) range	Gender (%M / %F)
TRD3003	Randomized withdrawal, multicenter, double-blind, placebo-controlled	**Stable Remitters**			
		Placebo (i.n.) + oral antidepressant	n = 86	46.2 (11.2) 19, 64	31 / 69
		SPRAVATO® 56/84 mg (i.n.) + oral antidepressant	n = 90	45.4 (12.1) 19, 64	36 / 64
		Stable Responders			
		Placebo (i.n.) + oral antidepressant	n = 59	46.7 (9.8) 24, 64	29 / 71
		SPRAVATO® 56/84 mg (i.n.) + oral antidepressant	n = 62	47.2 (11.0) 23, 63	39 / 61

i.n. = intranasal
* Based on full analysis set (all randomized subjects who received at least 1 dose each of i.n. medication and oral antidepressant)
‡ Investigators selected from one of duloxetine, venlafaxine extended release; escitalopram or sertraline.

The baseline demographic and disease characteristics of patients in TRD3001 and TRD3002 were similar between the SPRAVATO® plus oral antidepressant and the placebo plus oral antidepressant groups.

In Study TRD3001, 77% of subjects were Caucasian and 6% were African American (16% were undefined). Subjects were enrolled in North America (United States and Canada: 45%), Europe (25%) and Other Region (30%). At the time of screening the mean duration of the current episode of depression was 203 weeks. Approximately 57% initiated oral antidepressant treatment with a SNRI and 43% with a SSRI.

In Study TRD3002, 93% of subjects were Caucasian and 5% were African American. Subjects were enrolled in Europe (60%) and the North America (United States: 40%). At the time of screening the mean duration of the current episode of depression was 115 weeks. Approximately 68% initiated oral antidepressant treatment with a SNRI and 32% with a SSRI.

The primary efficacy measure in both studies was change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score at the end of the 4-week double-blind induction phase. The MADRS is a ten-item, clinician-rated scale used to assess severity of depressive symptoms. Scores on the MADRS range from 0 to 60, with higher scores indicating more severe depression.

A fixed sequence approach was applied to adjust for multiplicity and to control type I error across the primary and key secondary efficacy endpoints: onset of clinical response by Day 2 (24 hours), change in Sheehan Disability Scale (SDS) total score and change in Patient Health Questionnaire-9 (PHQ-9) total score.

Randomized Withdrawal Study

Study TRD3003 was a long-term randomized, double-blind, parallel-group, active-controlled, multicenter randomized withdrawal study. Overall, a total of 705 patients were enrolled:

- 437 directly enrolled
- 150 transferred from TRD3001, and
- 118 transferred from TRD3002.

Induction Phase: Patients directly enrolled were administered SPRAVATO® (56 mg or 84 mg twice-weekly) plus a newly initiated open-label oral antidepressant (either duloxetine, venlafaxine extended release, escitalopram, or sertraline, as determined by the investigator based on the patient's prior treatment history) in a 4-week open-label induction phase. Patients who responded continued receiving treatment with SPRAVATO® plus oral antidepressant in a 12-week optimization phase.

Optimization Phase: A total of 455 patients who responded to SPRAVATO® (273 direct entry, 112 from TRD3001 and 70 from TRD3002) continued to receive SPRAVATO® during the 12-week optimization phase. In the initial 4 weeks of the optimization phase, patients were administered SPRAVATO® (56 mg or 84 mg) on a weekly basis. Thereafter, an algorithm (based on the MADRS) was used to determine dosing frequency, with the objective of maintaining the patient on the lowest dosing frequency to maintain response/remission.

- MADRS total score >12: once weekly dosing for the next 4 weeks
- MADRS total score ≤12: once every 2 weeks

Maintenance Phase: At the end of 16 weeks of treatment period (4 weeks in the induction phase plus a total of 12 weeks in the optimization phase), 176 patients in stable remission and 121 patients with a stable response were separately randomized (1:1) to either continue with SPRAVATO® or switch to placebo in the double-blind maintenance phase. In all cases, subjects continued treatment with the same oral antidepressant. 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.

The primary endpoint was time to relapse in the stable remitter group.

Stable remission was defined as MADRS total score ≤12 at least 3 of the last 4 weeks of the optimization phase.

Stable response was defined as ≥50% reduction in the MADRS total score from baseline for the last 2 weeks of the optimization phase, but not in stable remission.

Relapse was defined as a MADRS total score ≥22 for two consecutive weeks or hospitalization for worsening depression or any other clinically relevant event indicative of relapse.

The baseline demographic and disease characteristics of the patients randomized to the double-blind maintenance phase were similar between the SPRAVATO® plus oral antidepressant and the placebo plus oral antidepressant groups (see Table 6). The majority of patients (90%) were Caucasian and 4% were of African descent. Subjects were enrolled in North America (United States and Canada: 26%), Europe (58%) and Other Region (17%). At the time of screening the mean duration of the current episode of depression was 120 weeks. Approximately 64% of patient were taking a SNRI and 36% with a SSRI.

14.2 Study Results

Short-Term Studies

In the fixed dose study TRD3001, for the primary efficacy measure of improvement in depressive symptoms (change in MADRS total scores from baseline at the end of the 4-week induction phase), SPRAVATO® 84 mg plus oral antidepressant did not demonstrate statistical superiority compared to placebo plus oral antidepressant. Therefore, in accordance with the pre-defined testing sequence, the SPRAVATO® 56 mg plus oral antidepressant treatment group and key secondary endpoints could not be formally evaluated.

In this study, withdrawal rate was 16% in the SPRAVATO® 84 mg group and 5% in each the placebo and SPRAVATO® 56 mg groups. Eleven of the 19 subjects in the SPRAVATO® 84 mg group discontinued after receiving the first dose (56 mg).

In the flexible dose study TRD3002, for the primary efficacy measure of improvement in depressive symptoms (change in MADRS total scores from baseline at the end of the 4-week induction phase), SPRAVATO® plus oral antidepressant demonstrated clinically meaningful and statistical superiority compared to placebo plus oral antidepressant. Key secondary endpoints were either not statistically significant (onset of clinical response by Day 2) or could not be formally evaluated (SDS total score and PHQ-9 total score).

In this study, 67% of patients randomized to SPRAVATO® were receiving 84 mg by the last test day (Day 28). Withdrawal rate was 16% in the SPRAVATO® group and 11% in the placebo group.

Table 7: Primary Efficacy Results for Change in MADRS Total Score for 4 Week Clinical Trials (MMRM)

Study No.	Treatment Group§	Number of Patients‡	Mean Baseline Score (SD)	LS Mean Change from Baseline to end of Week 4	LS Mean Difference (95% CI)	2-sided p-value
TRD3001	SPRAVATO® 56 mg + oral antidepressant	115	37.4 (4.8)	-18.8	-4.1 (-7.7, -0.5)	N.E.
	SPRAVATO® 84 mg + oral antidepressant	114	37.8 (5.6)	-18.5	-3.2 (-6.9, 0.5)	0.09
	Placebo + oral antidepressant	113	37.5 (6.2)	-14.8	-	-
TRD3002	SPRAVATO® (56 mg or 84 mg) + oral antidepressant	114	37.0 (5.7)	-19.8	-4.0 (-7.3; -0.6)	0.02
	Placebo + oral antidepressant	109	37.3 (5.7)	-15.8	-	-

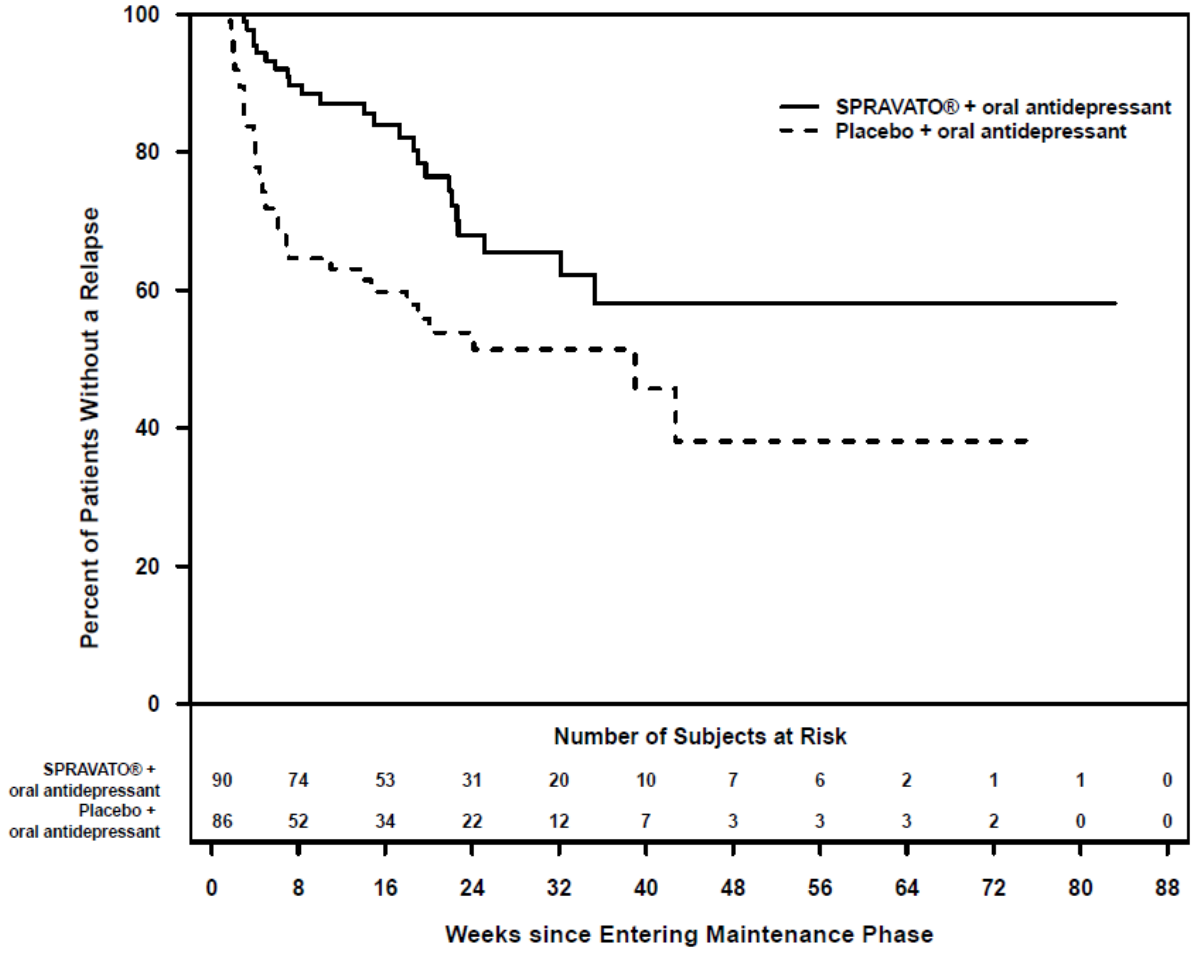
MMRM = mixed-effects model for repeated measures; SD = standard deviation; LS Mean = least-squares mean;
CI = unadjusted confidence interval
§ Nasally administered esketamine or placebo; oral antidepressant = newly initiated oral antidepressant
N.E. Not formally evaluated in accordance with the pre-defined testing sequence
‡ Based on full analysis set (all randomized subjects who received at least 1 dose each of i.n. medication and oral antidepressant)

Randomized Withdrawal Study

Stable Remission

Patients in stable remission who continued treatment with SPRAVATO® plus oral antidepressant experienced a statistically significant longer time to relapse of depressive symptoms than did patients on placebo plus oral antidepressant (Figure 1).

Figure 1: Time to Relapse in Patients in Stable Remission in Study TRD3003 (Full Analysis Set)

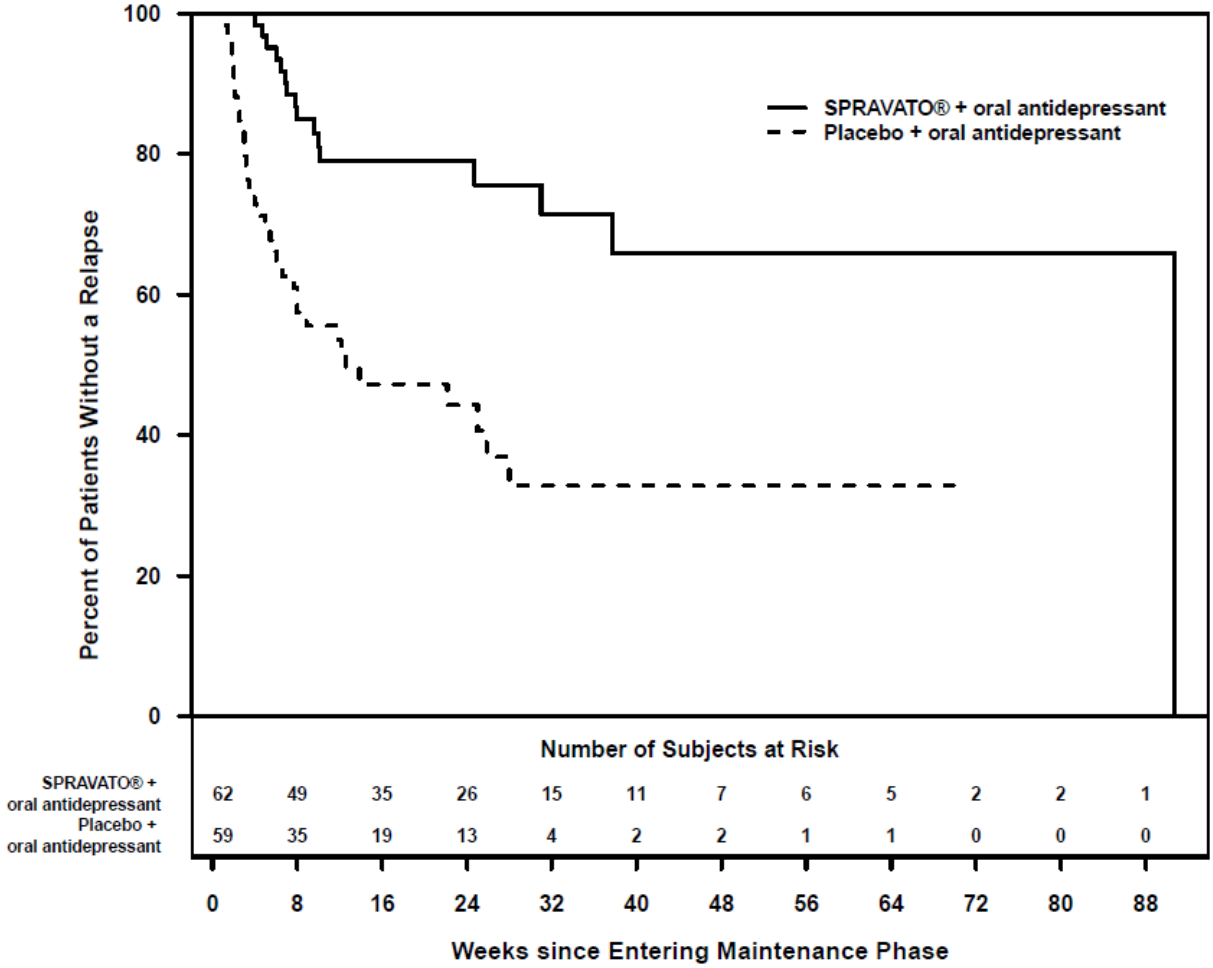


For patients in stable remission, the estimated hazard ratio (95% CI) of SPRAVATO® plus oral antidepressant relative to placebo plus oral antidepressant based on weighted estimates was 0.49 (95% CI: 0.29, 0.84).

Stable Response

Patients with a stable response who continued treatment with SPRAVATO® plus oral antidepressant experienced a statistically significant longer time to relapse of depressive symptoms than did patients on placebo plus oral antidepressant (Figure 2).

Figure 2: Time to Relapse in Patients in Stable Response in Study TRD3003 (Full Analysis Set)



For patients with a stable response, the estimated hazard ratio (95% CI) of SPRAVATO® plus oral antidepressant relative to placebo plus oral antidepressant based on Cox proportional hazards model was 0.30 (95% CI: 0.16, 0.55).

Of the subjects randomized to SPRAVATO®, 60% received 84 mg and 40% received 56 mg dose. The dosing frequency used the majority of the time is shown in Table 8.

Table 8: Dosing Frequency Used the Majority of the Time; Maintenance Phase (Study TRD3003)

	Stable Remission		Stable Responders	
	SPRAVATO® + oral antidepressant (N=90)	**Placebo + oral antidepressant (N=86)**	**SPRAVATO® + oral antidepressant (N=62)**	**Placebo + oral antidepressant (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%)

15 MICROBIOLOGY

Not applicable.

16 NON-CLINICAL TOXICOLOGY

16.1 General Toxicity

Toxicity was evaluated based on maximum feasible doses rather than maximum tolerated doses. Therefore, No Observable Adverse Effect Levels (NOAEL) were determined mainly on pharmacological action, rather than systemic toxicity.

Once-daily or intermittent (3 days a week) nasal administration of esketamine to rats at doses up to 9 mg/day for 3 months or once daily for 6 months resulted in serious central nervous system-related clinical signs (ataxia, changes in level of activity, unsteady gait). These may be related, at least in part, to the anesthetic properties of esketamine. Reduced scores in motor activity and coordination, as well as impaired spatial learning were noted after 5, 13 or 21 weeks of administration. Microscopic changes to the nasal epithelium were limited to the highest dose (9 mg/day) after 3 months of administration, but also included the intermediate dose (3 mg/day) in the 6-month study. Due to a possible contamination issue with the 6-month study plasma samples, the data from the 6-month time-point of the 2-year rat carcinogenicity study was used as a surrogate to establish a safety margin. The NOAEL in the chronic toxicity study is established at 3 mg/day, which provides a safety margin based on AUC of less than 1-fold the maximum recommended human dose (MRHD) (0.4 times).

Once-daily or intermittent (3 days a week) nasal administration of esketamine to dogs at doses up to 72 mg/day for 3 months or once daily for 9 months resulted in serious central nervous system-related clinical signs. These included ataxia, rubbing nose and shaking head, increased activity, uncoordinated gait, as well as vomiting; these observations may be related, at least in part, to the anesthetic properties of esketamine. Reduced weight gain and increased heart rate were noted at the highest dose of 72 mg/day. Increased heart rates were still noted in females after 1 month without administration of esketamine. After 9 months of daily administration, microscopic changes to the olfactory epithelium were noted in the intermediate and high dose groups 48 and 72 mg/day). At the NOAEL of 48 mg/day, for 3 or 9 months, the extent of exposure (AUC) was 1.4 times the AUC at the MRHD of 84 mg.

16.2 Neurotoxicity

Published animal studies have demonstrated that the administration of ketamine (at relevant doses) increases neuronal loss and cellular changes in the brain, resulting in long-term cognitive deficits.

In a single-dose neurotoxicity study where esketamine was nasally-administered to rats (up to 9 mg/rat), there were no histological brain lesions noted, at exposures lower than those achieved with ketamine (when resulting in lesions). The exposure (AUC_{0-t}) of esketamine in this study provided a safety margin 2-times the exposure at the MRHD.

In the 6-month rat repeated-dose toxicology study, there were some decreases in motor function and learning observed at the highest dose of esketamine (9 mg/rat). In the 9-month dog study, there were no comparably detailed neurological assessments.

The clinical significance of these nonclinical findings is not known.

16.3 Carcinogenicity and Mutagenicity

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* Comet assay in rat liver cells.

The weight of evidence indicates that esketamine lacks genotoxic potential *in vivo*.

The carcinogenic potential of esketamine is considered low; however, due to the unsustained exposure throughout the treatment period, it is not possible to fully ascertain the risk to humans.

Once-daily nasal administration of esketamine did not increase the incidence of tumors in a 2-year rat carcinogenicity study at doses up to 9 mg/day. However, exposure to esketamine at this dose was lower than the human exposure at the MRHD of 84 mg after 6 months of administration. Esketamine did not increase the incidence of tumors with once-daily subcutaneous administration in a 6-month study in transgenic (Tg.rasH2) mice at doses up to 70 mg/kg/day (reduced to 40 mg/kg/day at Week 17 of 26 due to lack of tolerability). The lowest dose of 10 mg/kg/day was associated with the least adverse events, with an exposure corresponding to 1.7 times the AUC at the MRHD.

16.4 Reproductive Toxicity

In an embryo-fetal developmental toxicity study with nasally-administered ketamine in rats, the offspring were not adversely affected in the presence of maternal toxicity at doses up to 150 mg/kg/day. In rats, the AUC-based safety margin estimated for esketamine at the 150 mg/kg/day dose of ketamine was 12-fold compared to the maximum recommended human dose (MRHD) of esketamine of 84 mg. In an embryo-fetal developmental toxicity study with nasally-administered ketamine in rabbits, fetal body weight was reduced at maternally toxic doses (30 mg/kg/day). In rabbits, the estimated exposure to esketamine at the administered ketamine dose with the least observed maternal toxicity (10 mg/kg/day) corresponded to 1% of the maximum exposure of 84 mg in humans.

Ketamine, the racemic mixture of arketamine and esketamine, administered intravenously at anesthetic dose levels to female rats in the second trimester of pregnancy showed developmental neurotoxicity, caused neuronal cell abnormalities in the brains of their offspring, which showed behavioural changes and impaired memory up to young adult age. When female monkeys were treated intravenously with ketamine at anesthetic dose levels in the third trimester of pregnancy, neuronal cell death was observed in the brains of their fetuses. Ketamine-induced neuronal cell death was also observed with early postnatal intraperitoneal or subcutaneous treatment of rat and mice pups, a period of rapid brain growth. This period of brain development translates into the third trimester of human pregnancy. It cannot be excluded that esketamine induces neurotoxicity

in developing fetuses (see **WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women**).

In a pre- and postnatal developmental toxicity study with nasally-administered esketamine up to 9 mg/day in rats, slight gestational delays in dams were observed at doses ≥ 3 mg/day, while in pups, pre-weaning sensorimotor delays and post-weaning motor activity decreases were observed (in pups from dams at all dose levels). Esketamine was detected in the plasma of lactating pups (that were not directly administered esketamine), indicating that esketamine passes in the mother's milk (see **WARNINGS AND PRECAUTIONS, Breast-feeding**).

16.5 Fertility

In a fertility and early embryonic developmental toxicity study in rats, esketamine nasally-administered at 0.9, 3, or 9 mg/day caused maternal and paternal toxicity at 3 and 9 mg/day, which corresponds to exposure equivalent to 0.3 and 0.6 times the mean exposures of esketamine at the 84 mg MRHD. Fertility and reproductive capacities were not adversely affected at any dose in males, but some females of the higher dose group had fewer successful implants, leading to smaller litters.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[N]SPRAVATO®
Esketamine nasal spray

Read this carefully before you start using **SPRAVATO®** because it contains important information for you. Keep this leaflet. You may need to read it again.

This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **SPRAVATO®**.

Serious Warnings and Precautions

SPRAVATO® can only be given to you to use under the supervision of a healthcare professional in their office or clinic. You must never take SPRAVATO® home with you. It is only available through a controlled distribution program called the JANSSEN JOURNEY™ Program. SPRAVATO® can only be given to you by healthcare professionals with experience in treating depression who are enrolled in the program. You must also be enrolled in the program by a healthcare professional before taking SPRAVATO®. By enrolling you confirm that you understand the risks and conditions of use explained to you by your healthcare professional.

Increased Blood Pressure:
SPRAVATO® can raise your blood pressure. This usually occurs about 40 minutes after you have taken your dose. Your healthcare professional must check your blood pressure before you take SPRAVATO® and periodically after you have taken your dose. You will be monitored until your blood pressure returns to a stable safe level.

Dissociation and Sedation:
SPRAVATO® can also make you feel disconnected from yourself, your thoughts, space and time, and things around you (dissociation). It can also make you feel:

- sleepy (sedated)
- faint
- dizzy / a spinning sensation (vertigo)
- anxious

Your healthcare provider should be prepared to handle these side effects, including if you experience shallow breathing during your treatment session.

If you feel any of these effects are:

- unusually intense
- delayed (you experience them after you leave the supervision of your healthcare professional), or
- prolonged (lasts several hours or into the next day)

Talk to your healthcare professional.

Because there is a risk of dissociation and sedation, you will be monitored for **at least 2 hours** after you have taken your dose. Your healthcare professional will decide when you

can leave their office or clinic. You cannot drive after the appointment. You will need to make arrangements for getting home safely after your appointment.

Heart, Brain and Breathing Problems:
Do NOT take SPRAVATO® if you have any condition for which high blood pressure or high pressure within your brain (intracranial pressure) poses a serious risk.

Before you take SPRAVATO® your healthcare professional will check for any heart, brain and breathing problems and decide if you can take this medicine. If your condition:

- is unstable, or
- presents an important safety concern

You should take SPRAVATO® only where appropriate medical equipment and healthcare professionals trained in emergency care are available.

Abuse and Misuse:
There is a risk for misuse, abuse and dependence with SPRAVATO® treatment. Tell your healthcare professional about any current or past substance use problems. Your healthcare professional will assess you for any signs of abuse and misuse before and during treatment with SPRAVATO®. If you feel like you are craving SPRAVATO® or experiencing symptoms of withdrawal (such as agitation, the shakes or unusual discomfort) in the days following treatment with SPRAVATO®, tell your healthcare professional right away.

Suicidal Thoughts and Behaviours:
Depression and other serious mental illnesses can cause suicidal thoughts and actions. Your healthcare professional should monitor you carefully for thoughts of suicide or the potential for suicidal behaviour especially when:

- you start treatment with SPRAVATO®
- when there are changes in your treatment schedule or dose, and
- when you stop taking SPRAVATO®

Suicide can occur in patients who are taking or have taken SPRAVATO®.

At any time during or after treatment with SPRAVATO®, tell your doctor or go to the nearest hospital right away if you feel:

- that your depression is getting worse
- you have thoughts of harming or killing yourself
- there are sudden and unusual changes in your mood and behaviour

Ask your friends and family if they think your depression is getting worse or if they are worried about your behaviour.

What is SPRAVATO® used for?
SPRAVATO® is a nasal spray used to treat adults with major depressive disorder that:

- is moderate to severe in intensity and
- has not responded to two or more separate courses of treatment in the current episode of depression

Separate courses refers to previous treatment with different antidepressants, each given at adequate doses for an adequate amount of time.

SPRAVATO® nasal spray is used together with an antidepressant taken by mouth that is either:

- a selective serotonin reuptake inhibitor (SSRI) or
- a serotonin and norepinephrine reuptake inhibitor (SNRI)

SPRAVATO® is not for use in children or adolescents.

If you are 65 years or older, talk to your doctor before starting SPRAVATO®. SPRAVATO® may not be an effective treatment for you and you may be more sensitive to experiencing side effects.

How does SPRAVATO® work?
SPRAVATO® contains a medicine called esketamine. Esketamine belongs to a group of medicines that work on N-methyl-D-aspartate (NMDA) receptors. It works by changing the activity of certain natural substances in the brain.

What are the ingredients in SPRAVATO®?
Medicinal ingredients: esketamine
Non-medicinal ingredients: citric acid monohydrate, disodium edetate, sodium hydroxide, and water for injection

SPRAVATO® comes in the following dosage forms:
Solution (single-use nasal spray): 28 mg
Each nasal spray device delivers only 2 sprays for a total dose of 28 mg esketamine (as esketamine hydrochloride)

Do not use SPRAVATO® if you:
- are allergic to
    - esketamine
    - a similar medicine called ketamine
    - any of the other ingredients in SPRAVATO® (see **What are the ingredients in SPRAVATO®** above)
- have any condition for which high blood pressure or high pressure within your brain (intracranial pressure) poses a serious risk
- have a weak portion of the blood vessel wall (aneurysmal vascular disease), including in your brain, chest or abdominal aorta, arms and legs
- have an abnormal connection between your veins and arteries (arteriovenous malformation)
- have ever had bleeding in the brain
- had a major heart event (such as heart attack) or stroke within the last 6 weeks

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take SPRAVATO®. Talk about any health conditions or problems you may have, including if you:
- have heart problems such as:
    - poor blood flow in the blood vessels of the heart frequently with chest pain (such as angina)
    - high blood pressure that is not under control
    - a history of a heart attack
    - a slow or fast heartbeat causing shortness of breath, palpitations or chest discomfort, feeling light-headed or fainting
    - heart valve disease
    - heart failure

- have ever had a stroke or problems with the blood supply to your brain
- have ever had a problem with substance use, including prescribed or illegal drugs, or alcohol
- have 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) or have an irrational fear that someone is trying to harm you (paranoia)
- have a history of mania or bipolar disorder
- have ever had an overactive thyroid (hyperthyroidism)
- have urinary tract and bladder problems
- have ever had lung or breathing problems such as:
    - a condition where your heart valve does not pump enough blood out to the lungs (called pulmonary insufficiency)
    - a condition where your breathing stops and starts while you sleep (called sleep apnea)
- have ever had a serious head injury or serious problems affecting the brain, particularly where there is increased pressure in the brain
- have liver problems
- take any medication, including all prescription, over the counter or natural health products

Other warnings you should know about:

Driving and Machines: SPRAVATO® can significantly impair your ability to drive and use machines. **You must:**

- wait until the next day, after you have had a restful sleep, before driving or operating machinery or doing tasks that require you to be completely alert
- arrange a safe way to get home after your treatment

Urinary or Bladder Problems: Tell your doctor if you feel pain when urinating or see blood in your urine. These could be signs of urinary or bladder problems. Urinary or bladder problems have been seen in patients using high doses of a similar medicine called ketamine, over a long period of time.

Difficulty Thinking Clearly: Tell your healthcare professional if you have difficulty thinking or remembering. People aged 65 and older may have a slower reaction time after taking SPRAVATO® for a long time.

Patients of Japanese Ancestry: Tell your healthcare professional if you are of Japanese ancestry. Your healthcare professional may change your dose.

Laboratory Tests: Your healthcare professional may ask you to take a blood test while you are taking SPRAVATO® to check your liver function.

Pregnancy: SPRAVATO® use during pregnancy may harm your unborn baby.
You should not take SPRAVATO® if you:

- are pregnant or plan to become pregnant
- are a woman of childbearing potential unless you use highly effective contraception (birth control) during and up to 6 weeks after taking your last dose.

Talk to your healthcare professional about methods to prevent pregnancy during treatment with SPRAVATO® and tell your healthcare professional right away if you become pregnant during treatment.

There is a pregnancy registry for women who are exposed to antidepressants, including SPRAVATO®, during pregnancy. The purpose of the registry is to collect information about the health of pregnant women and their baby. If you become pregnant during treatment with SPRAVATO®, talk to your healthcare professional about registering with the National Pregnancy Registry for Antidepressants. Information on the registry can also be found by:

- calling: 1-844-405-6185 or
- online at https://womensmentalhealth.org/clinical-and-researchprograms/pregnancyregistry/antidepressants/

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 decide if you stop breast-feeding or stop using this medicine. Your doctor will take into account the benefit of breast-feeding for your child, and the benefit of treatment for you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with SPRAVATO®:

- Nasal Sprays (such as oxymetazoline hydrochloride, mometasone furoate): do NOT use a steroid or decongestant nasal spray within 1 hour before your treatment with SPRAVATO®.

- Central Nervous System Depressants (such as benzodiazepines, opioids, alcohol): they may make you feel more sleepy if taken together with SPRAVATO®.

- Psychostimulants (such as amphetamines, methylphenidate, modafinil, armodafinil): when taken together with SPRAVATO®, these types of medicines can cause a severe increase in blood pressure.

- Monoamine Oxidase Inhibitors (MAOIs): when taken together with SPRAVATO®, these types of medicines can cause a severe increase in blood pressure.

- Other Drugs that Increase Blood Pressure [such as sympathomimetics, triptans and vascular endothelial growth factor receptor inhibitors (e.g., pazopanib, sunitinib, sorafenib)]: when taken together with SPRAVATO®, these types of medicines can cause a severe increase in blood pressure.

How to take SPRAVATO®:
You will use the SPRAVATO® nasal spray yourself – **under the supervision of a healthcare professional in their office or clinic**. **SPRAVATO® is never to be taken home or used without a healthcare professional present.**

It can only be given to you by healthcare professionals with experience in treating depression who are enrolled in the JANSSEN JOURNEY™ program. Patients must also be enrolled in the program by a healthcare professional before taking SPRAVATO®.

Your healthcare professional will go through a checklist to verify medical information before and after your treatment.

Before you go for your treatment:

- Some patients may experience nausea or vomiting while taking SPRAVATO®. You should avoid eating 2 hours before and drinking liquids 30 minutes before taking your dose.
- If you are taking a steroid or decongestant nasal spray, do NOT use it within 1 hour before your treatment.
- **Do NOT** drink alcohol within 24 hours of your treatment session and 24 hours after each treatment session.
- SPRAVATO® can make you feel disconnected or sleepy. Since you cannot drive, you must make arrangements to get home safely after your appointment.

Before taking your dose:

- Your healthcare professional will show you how to use the nasal spray device. Follow their instructions exactly. You should also read the Instructions for Use. It can be found in the package carton.

Adult Dose:

Each nasal spray device delivers 2 sprays (one in each nostril) for a total of 28 mg.
Your healthcare professional will decide if you need to use 1 (28 mg), 2 (56 mg) or 3 (84 mg) nasal spray devices and how often you should come to their office or clinic to take the medicine.

- Weeks 1-4: your dose should be taken twice per week
- Weeks 5-8: your dose is taken once per week
- Week 9 and onwards: your healthcare professional will decide if your dose should be taken once per week or once every 2 weeks

Tell your healthcare professional if you are of Japanese ancestry or if you are 65 years or older. Your healthcare professional may need to change your dose.

After you have taken your dose:

- Your healthcare professional will confirm that you have taken your full dose.
    - 2 green dots on the device tells you that the nasal spray is full,
    - 1 green dot tells you that one spray was used, and
    - no green dots indicates that the full dose of 2 sprays was used.
- You will be monitored for **at least 2 hours.**
- Your healthcare professional will also monitor your blood pressure and will decide when you can leave their office or clinic.
- It is best to recover in a neutral environment (i.e., few distractions). Try to limit your movement.

Overdose:

This medicine will be given to you under the supervision of your healthcare professional in their office or clinic. Taking too much SPRAVATO® may make you more likely to experience side effects such as:

- feeling dizzy
- excessive sweating
- feeling sleepy
- feeling abnormal
- numbness
- nausea and vomiting

Missed Dose:
Contact your healthcare professional right away if you miss your treatment session. Your healthcare professional may change your dose or how often you should take SPRAVATO®.

What are possible side effects from using SPRAVATO®?
These are not all the possible side effects you may feel when taking SPRAVATO®. If you experience any side effects not listed here, contact your healthcare professional.

Very common:
- change in sense of taste
- decreased feeling or sensitivity, including around the mouth area
- feeling anxious
- feeling disconnected from yourself, your thoughts, feelings and things around you
- feeling dizzy or a spinning sensation (“vertigo”)
- feeling tired, sluggish or have low energy
- feeling very sleepy
- headache
- increased blood pressure
- nausea or vomiting

Common:
- abdominal pain or discomfort
- crying
- constipation
- cough
- diarrhea
- difficulty passing urine
- trouble sleeping
- difficulty speaking
- dry mouth
- excessive sweating
- fast or irregular heartbeat
- feeling drunk or abnormal
- feeling extremely happy (“euphoria”)
- frequent need to pass urine
- increased appetite
- itchy skin
- low sex drive
- migraine
- muscle tremors or spasms
- nose bleed
- nose or throat discomfort
- problems with thinking
- tunnel vision
- weight gain

Uncommon:
- abnormal dreams
- confusion or disorientation

- ear discomfort
- feeling hot
- hearing loss
- increased saliva
- mood swings
- muscle stiffness or pain
- nasal congestion
- restlessness
- sneezing

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON **Anxiety:** feeling irritable, nervous or panic-stricken	√		
Sedation: strong or prolonged feeling of sleepiness		√	
Dissociation: feeling disconnected from yourself, your thoughts, feelings and things around you		√	
Vertigo: dizziness or a spinning sensation		√	
Increase in Blood Pressure: headache, stronger and possibly faster heartbeat, chest pain, dizziness, excessive tiredness, and blurred vision		√	
COMMON **Hallucinations:** seeing or hearing things that are not there.		√	
Increase in Heart Rate or Changes in Heart Rhythm: dizziness, fainting, feeling a rapid, pounding, or irregular heartbeat. This is more likely if you have heart disease, an overactive thyroid, take certain other drugs, or are more than 65 years old.		√	

Problems with Thinking: confusion, disorientation, difficulty paying attention or remembering		√	
UNKNOWN **Allergic Reaction:** difficulty swallowing or breathing, wheezing; drop in blood pressure; feeling sick to your stomach and throwing up; hives or rash; swelling of the face, lips, tongue or throat.			√
Withdrawal: cravings, anxiety, shaking, sweating, and palpitations		√	
Liver Disorder: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting loss of appetite			√
Respiratory Depression (also known as hypoventilation): slow, shallow or weak breathing; blue lips, fingers, toes; confusion; headaches			√
Suicide: thoughts or actions about hurting or killing yourself		√	
Cystitis (bladder infection): increased need to urinate, pain in the pelvis or lower back, frequent urination during the night, cloudy urine that may contain blood, burning sensation when passing urine		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
SPRAVATO® is only available through a controlled distribution program. It will be stored by your healthcare professional. **SPRAVATO® is never to be given to you to take home**.

Do not use the nasal spray after the expiry date which is on package carton and device.

If you want more information about SPRAVATO®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp)
- For questions, concerns, or the full product monograph go to: www.janssen.com/canada, or by calling 1-800-567-3331 or 1-800-387-8781.

This leaflet was prepared by Janssen Inc.
Toronto, Ontario M3C 1L9

Last Revised May 19, 2020