Healthcare professional guide for SPRAVATO® (esketamine) nasal spray

Version 2

This document has
been approved by
HSA as of 08-12-2021

Spravato® (esketamine) nasal spray

Contents

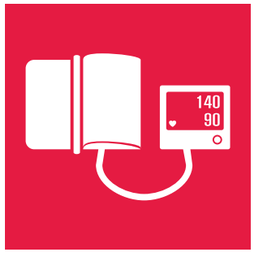
1. Introduction

Please read the Health Sciences Authority (HSA) approved package insert carefully before prescribing SPRAVATO® (esketamine nasal spray).

This guide informs healthcare professionals about the four identified risks that may occur following SPRAVATO® treatment: transient dissociative states and perception disorders (dissociation), disturbances in consciousness (sedation), blood pressure increased and drug abuse. This guide describes the risks and explains how to minimise and manage them.

Transient dissociative states and perception disorders

Disturbances in consciousness



Blood pressure increased

Drug abuse

Please advise patients, their caregivers and close family to read the accompanying patient guide to support their understanding of the risks that may occur with SPRAVATO® treatment.

What is SPRAVATO®?

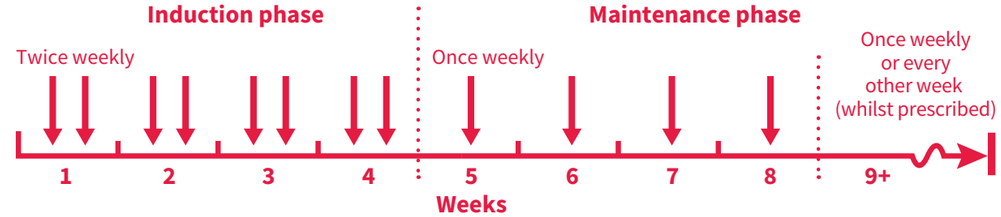
SPRAVATO® for patients with treatment-resistant depression (TRD)

Indication: SPRAVATO®, in combination with an SSRI or SNRI, is indicated for adults with treatment-resistant major depressive disorder who have not responded to at least two different treatments with antidepressants in the current moderate-to-severe depressive episode.[1]

SPRAVATO® was shown to rapidly improve symptoms of depression, which was maintained over the course of 1 year.[1]

SPRAVATO® dosing regimen: Treatment-resistant depression[1]

Co-administered with an SSRI/SNRI



Starting dose:[1]

Adults (<65 years old)

Starting dose of **56 mg**, increasing to **84 mg**, based on efficacy and tolerability

Elderly (65 years of age and older)

Starting dose of **28 mg**, increasing to **56 mg** or **84 mg**, based on efficacy and tolerability

SNRI=serotonin and norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor

SPRAVATO® for acute short-term treatment of psychiatric emergency due to major depressive disorder (MDD-PE)

Indication: SPRAVATO®, co-administered with oral antidepressant therapy, is indicated in adults with a moderate-to-severe episode of major depressive disorder, as acute short-term treatment for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency.[1]

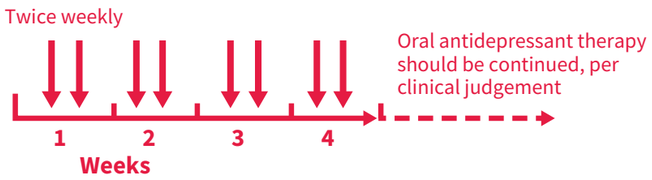
The effectiveness of SPRAVATO® in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated.

The use of SPRAVATO® does not preclude the need for hospitalisation if clinically warranted, even if patients experience improvement after an initial dose of SPRAVATO®. The treatment with SPRAVATO® should always be part of the comprehensive clinical care plan.

SPRAVATO® dosing regimen: A psychiatric emergency due to major depressive disorder[1]

Co-administered with oral antidepressant therapy

Acute short-term treatment



Starting dose of **84 mg** for adults <65 years old, reducing to **56 mg**, based on tolerability

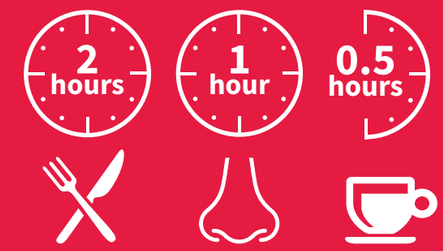
SPRAVATO® has not been studied in elderly (65 years of age and older) patients with a moderate-to-severe episode of major depressive disorder as acute short-term treatment in a psychiatric emergency.[1]

How is SPRAVATO® administered?

SPRAVATO® is intended to be self-administered by the patient under the direct supervision of a healthcare professional.[1] Patients should be seated during SPRAVATO® administration with their head tilted back at a 45-degree angle.[1] Please refer to the dosing and administration guide under the HSA approved package insert for full details.

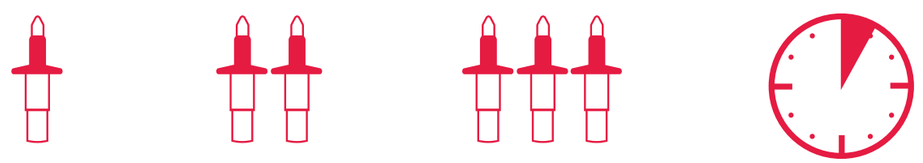
The decision to prescribe SPRAVATO® should be determined by a psychiatrist. Post-dose monitoring should be performed by a healthcare professional experienced in blood pressure monitoring.[1]

Patients may experience nausea and vomiting after SPRAVATO® administration. Therefore, patients should be advised not to eat for 2 hours prior and not to drink liquids for 30 minutes prior to administration. Patients should also be advised not to use any nasally administered corticosteroids or decongestants for 1 hour prior to SPRAVATO® administration.[1]



A single device contains 28 mg of esketamine

Each device delivers two sprays (one spray in each nostril) [1]



Healthcare facility requirements for SPRAVATO® administration

- Blood pressure monitoring equipment at the dosing facility.
- When treating patients with clinically significant or unstable cardiovascular or respiratory conditions, appropriate resuscitation equipment and healthcare professionals with training in cardiopulmonary resuscitation should be available.

Conditions that require specific consideration

- Only initiate treatment with SPRAVATO® in patients with clinically significant or unstable cardiovascular or respiratory conditions if the benefit outweighs the risk. Examples of conditions which should be considered include, but are not limited to[1]:
  - » Significant pulmonary insufficiency, including chronic obstructive pulmonary disease
  - » Patients with uncontrolled brady- or tachyarrhythmias that lead to haemodynamic instability
  - » Patients with a history of a myocardial infarction. These patients should be clinically stable and cardiac symptom free prior to administration
  - » Haemodynamically significant valvular heart disease or heart failure (New York Heart Association, Class III-IV).
- Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts and should receive careful monitoring during treatment.[1]

Monitoring patients before and after SPRAVATO® administration

Pre-administration

- Discuss the possible side effects with the patient, but reassure them that symptoms should alleviate relatively quickly.
- Measure the patient's blood pressure and ensure it is in a safe range for SPRAVATO® administration[1]:
  - » <140/90 mmHg for patients <65 years of age
  - » <150/90 mmHg for patients ≥65 years of age.
    If their blood pressure is elevated, rest and repeat the measurement.
- Confirm that the patient has avoided[1]:
  - » Eating for 2 hours
  - » Using nasally administered corticosteroids or decongestants for 1 hour
  - » Drinking liquids for 30 minutes.
- Consider the individual patient's benefit and risk before deciding whether to start SPRAVATO® treatment.

Post-administration

Patients should be monitored after SPRAVATO® administration at each treatment session by a healthcare professional experienced in blood pressure monitoring:

- Measure the patient's blood pressure at around 40 minutes after administering the full dose of SPRAVATO® (after administering the last nasal spray) and subsequently as clinically warranted.[1]
  - » If their blood pressure is elevated, continue to regularly measure it until it returns to acceptable levels.
- Closely monitor the patient for signs of dissociation, sedation and respiratory depression, and any other adverse events.[1] Most adverse events in clinical trials were transient and resolved by 1.5 hours post-dose.[2]
- Patients with clinically significant or unstable cardiovascular or respiratory conditions should be closely monitored.[1]
- The most commonly observed adverse reactions in patients with treatment-resistant depression treated with SPRAVATO® were dissociation (40.4%), dizziness (36.7%), nausea (26.8%), somnolence (25.4%), headache (24.0%), vertigo (17.7%), dysgeusia (17.1%), hypoaesthesia (16.7%), anxiety (12.9%), and vomiting (10.4%).[1]
- Older adults (≥65 years of age) should be carefully monitored, as they may be at increased risk of falling when they start moving around after treatment.

Readiness-to-leave

- In a Phase 3 clinical trial, 93.2% of patients were ready to leave by 1.5 hours after taking SPRAVATO®, while all patients were ready to leave by 3 hours after taking SPRAVATO®.[2]
- Because of the possibility of sedation, dissociation and elevated blood pressure, patients must be monitored by a healthcare professional until they are considered clinically stable.[1]
- The decision on the patient's readiness-to-leave should be made by the treating physician with the help of the 'Readiness-to-leave Checklist for Healthcare Professionals' provided with this guide.

Driving a motor vehicle or operating machinery needs complete mental alertness and motor co-ordination. Instruct patients not to drive or operate machinery until the day after SPRAVATO® administration, following a restful sleep.

2. Transient dissociative states and perception disorders

Who is at risk of dissociation?

It is important to review your patient's medical history to assess their prior risk of dissociation

Dissociation occurs more frequently in people with a history of [3,4]:

- Post-traumatic stress disorder (PTSD)
- Childhood maltreatment or traumatic events
- Eating disorders
- Substance abuse (including alcohol)
- Alexithymia
- Anxiety and mood disorders
- Suicidality.

How to assess and manage dissociation

There is no specific guidance for the management of dissociation; however, healthcare professionals involved in the SPRAVATO® clinical trials have found the following steps helpful:

- Pre-administration
  - » Make the patient aware that they may experience dissociation but reassure them that symptoms should alleviate relatively quickly and may be a positive or negative experience.
  - » Provide a safe, comfortable and calm environment for SPRAVATO® administration; avoiding bright lights or too many concurrent stimuli may be helpful.
  - » It may be helpful to suggest the patient focuses on pleasant thoughts or listens to music during the session.

- Post-administration
  - » Identify dissociation if the patient reports symptoms or behaves in a way indicative of dissociation.
  - » Offer the patient support and assistance if they express concern while experiencing dissociation.
  - » Although most cases of dissociation in SPRAVATO® clinical trials did not require pharmacological intervention,[5] prescribing benzodiazepines, based on clinical judgement, may be helpful for patients experiencing a high degree of anxiety.
  - » In the event of visual dissociative experiences, it may help to advise the patient not to close their eyes.
  - » If the patient does experience dissociation, reassure them that their symptoms should alleviate relatively quickly.
  - » Observe the patient until they are ready to leave based on clinical judgement.

Driving a motor vehicle or operating machinery needs complete mental alertness and motor co-ordination. Instruct patients not to drive or operate machinery until the day after SPRAVATO® administration, following a restful sleep.

3. Disturbances in consciousness (sedation)

Who is at risk of sedation?

What increases the risk of sedation?

- Certain CNS depressant medications, such as benzodiazepines or opioids, can increase sedation. If your patient is receiving these medications, closely monitor for sedation following SPRAVATO® administration.[1]
- Alcohol can also increase sedation[1]; therefore, advise your patients to avoid alcohol for a day before and after their SPRAVATO® treatment.
- Patients with certain medical conditions may be at increased risk of sedation and need careful consideration before initiating SPRAVATO® treatment. See the section entitled ‘Conditions that require specific consideration’ on page 4 for further details.

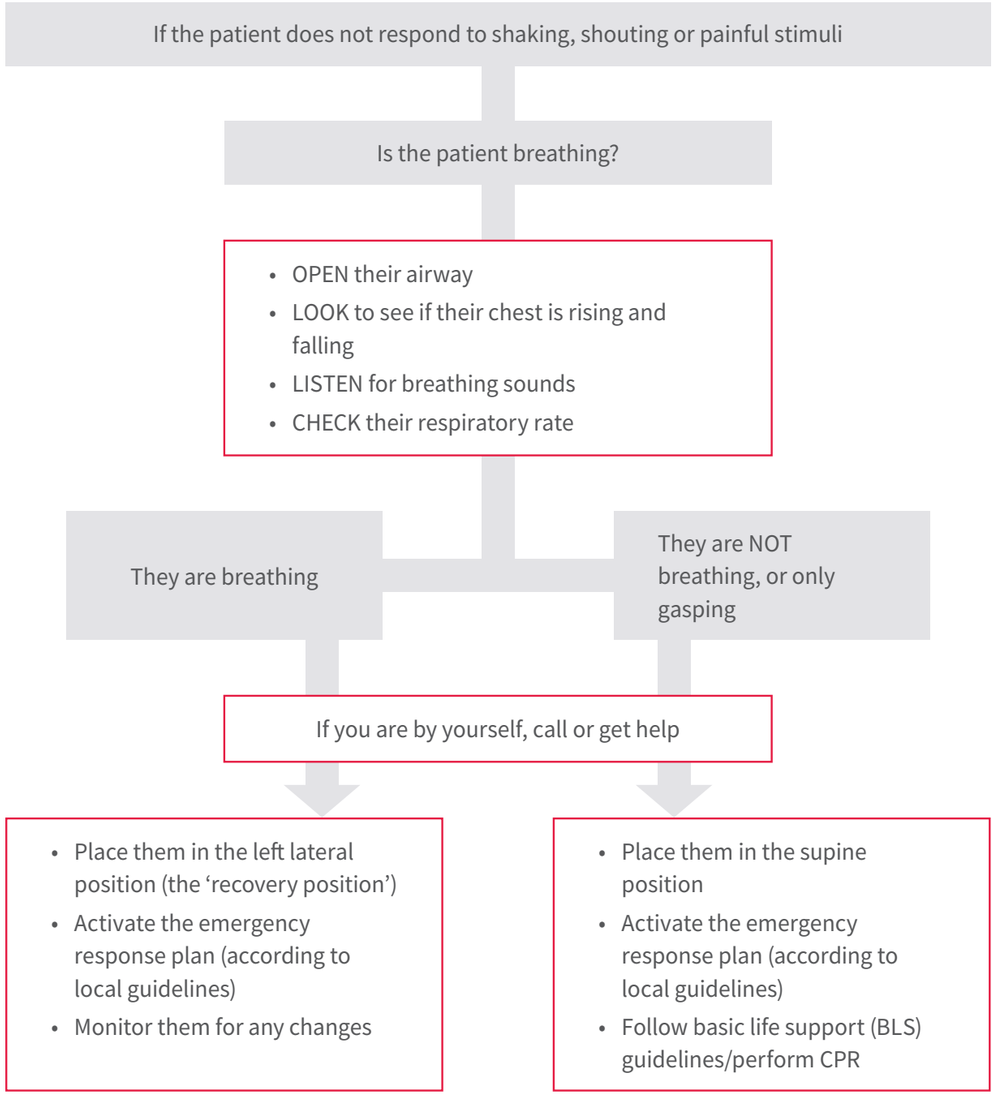
Consider the individual patient’s benefit and risk before deciding whether to start SPRAVATO® treatment.

How to assess and manage sedation

- Pre-administration
  - » Consider the patient’s comedications and assess the individual patient’s benefit and risk prior to initiation of SPRAVATO® treatment.
  - » Ensure close monitoring if any of their current medications may increase their risk of sedation.
  - » Make the patient aware that they may experience sedation but reassure them that symptoms should alleviate relatively quickly.
  - » Provide a safe and secure environment for SPRAVATO® administration.

- Post-administration
  - » The patient should be monitored by a healthcare professional after SPRAVATO® administration.
  - » Rare cases of deep, delayed or prolonged sedation have been reported. Sedation typically showed an onset at around 15 minutes after dosing, with symptoms peaking at 30 to 45 minutes post-dose and resolving by 1.5 hours post-dose.
  - » Potential sedation should be evaluated regularly by assessing the patient’s response to stimuli.
  - » In the event of loss of consciousness, closely monitor the patient for respiratory depression and change in haemodynamic parameters (see Figure 4 for guidance).
  - » Observe the patient until they are ready to leave based on clinical judgement.

Figure 1: What to do in an emergency[6]



4. Blood pressure increased

Who is at risk of increased blood pressure

Contraindications

- SPRAVATO® is contraindicated in patients for whom an increase in blood pressure or intracranial pressure poses a serious risk,[1] including:
  - » Patients with aneurysmal vascular disease (including intracranial, thoracic or abdominal aorta, or peripheral arterial vessels)
  - » Patients with history of intracerebral haemorrhage

It is important to obtain a full medical history for any patient who may receive Spravato® to evaluate the individual patient's benefit and risk for Spravato® and level of risk for increased blood pressure

- Patients with certain conditions may be at increased risk of blood pressure increase and need careful consideration before initiating Spravato® treatment.[1] See the section entitled 'Conditions that require specific consideration' on page 4 for further details.
- Blood pressure should be closely monitored when esketamine is used concomitantly with psychostimulants (e.g. amphetamines, methylphenidate, modafinil, armodafinil) or monoamine oxidase inhibitors, such as tranylcypromine, selegiline, phenelzine.[1]

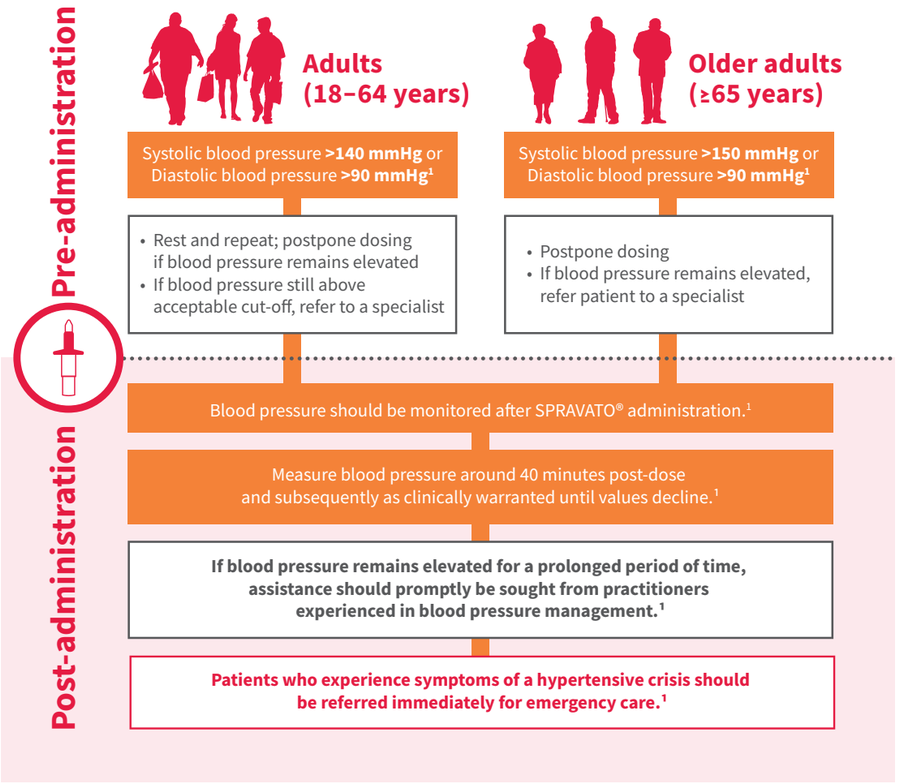
How to assess and monitor for increased blood pressure

- Pre-administration
  - » Blood pressure should be measured before SPRAVATO® administration.
  - » If a patient's blood pressure is elevated (see Figure 2 for guidance values), please reconfirm their blood pressure.
  - » If a patient's blood pressure is still elevated, consider lifestyle or pharmacological intervention to reduce blood pressure prior to starting SPRAVATO® treatment.
  - » Consider the patient's comedications and assess the individual patient's benefit and risk before deciding whether to delay SPRAVATO® treatment.
- Post-administration
  - » Blood pressure should be measured at around 40 minutes post-administration.
  - » In case of elevation:
    - – Blood pressure should be rechecked (at least prior to discharge) to ensure it returns to a stable and acceptable level
    - – If needed (for example if blood pressure remains elevated for over 90 minutes), discuss the case with a specialist to consider the need for a short-acting antihypertensive medication with ongoing monitoring until blood pressure returns to stable and acceptable levels.
    - – If a patient's blood pressure remains elevated, seek assistance from practitioners experienced in blood pressure management.

How to recognise a hypertensive episode

- Monitor for signs of a hypertensive episode, which can include[7]:
  - » Headache
  - » Chest pain
  - » Shortness of breath
  - » Vertigo
  - » Nausea.
- Refer patients with symptoms of a hypertensive crisis for immediate emergency care.

Figure 2: Monitoring and managing increased blood pressure



5. Drug abuse

Who is at risk of drug abuse?

- Carefully assess each patient's risk for abuse or misuse prior to prescribing SPRAVATO®. Individuals with a history of drug abuse or dependence may be at greater risk for abuse and misuse of SPRAVATO®.[1]

How to assess and monitor for signs of drug abuse

- Continually monitor patients receiving SPRAVATO® for the development of behaviours or conditions of abuse or misuse, including drug-seeking behaviour.
- Signs of abuse may include: attempted diversion (attempt to obtain more nasal sprays), drug-seeking behaviour (requesting more frequent or higher doses of SPRAVATO® without medical need), and other symptoms of drug craving or withdrawal. If patients present with interstitial cystitis, that may be a sign that they are abusing street ketamine (no cases of SPRAVATO®-related interstitial cystitis were observed in any of the clinical trials[1]).
- If abuse is suspected, monitor symptoms and consult with local abuse support systems and specialists.

How to minimise the risk of drug abuse?

- The potential for abuse, misuse and diversion of SPRAVATO® is minimised due to the administration taking place under the direct supervision of a healthcare professional.[1]
- SPRAVATO® is only used in the clinic/facility under direct healthcare professional supervision; patients cannot use SPRAVATO® alone at home.
- In Singapore, SPRAVATO® is a controlled drug with strict supply and procurement requirements.
- The single-use nasal spray device contains minimal residual product once used and should be carefully disposed of according to local regulations.

6. Risk minimisation timeline

1. Preparation

- Carefully evaluate eligible patients considering their comorbidities, comedications and individual risk for the identified risks
- Discuss the identified risks with the patient and explain the symptoms they may experience
- Advise the patient to avoid:
  - » Eating for 2 hours
  - » Using a nasally administered corticosteroid or decongestant for 1 hour
  - » Drinking liquids for 30 mins
- Instruct the patient to plan to travel home by public transport or arrange for someone else to drive them home after taking SPRAVATO®

2. Pre-administration

- Provide a safe and calm environment for SPRAVATO® administration
- Measure blood pressure and ensure it is within acceptable range
- Ensure the patient knows how to self-administer SPRAVATO®
- Confirm that, prior to SPRAVATO® administration, the patient has avoided:
  - » Eating for 2 hours
  - » Using a nasally administered corticosteroid or decongestant for 1 hour
  - » Drinking liquids for 30 mins

3. Post-administration

- Regularly monitor the patient for adverse events
- Measure the patient's blood pressure at around 40 minutes post-dose and subsequently as clinically warranted

4. Readiness to leave

- Use the accompanying readiness-to-leave checklist to determine whether the patient is ready to leave
- Confirm blood pressure is at acceptable levels
- Ensure the patient is clinically stable before they go home
- Check how the patient is feeling before they leave
- Ensure the patient has planned to travel home by public transport or has arranged for someone else to drive them home

For additional information, please refer to the local approved package insert, which is available on the Singapore Health Sciences Authority (HSA) website.

Alternatively, please contact
Johnson & Johnson International (Singapore) Pte Ltd
2 Science Park Drive, #07-13, Ascent,
Singapore Science Park 1,
Singapore 118222.

References

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