

## Spravato<sup>®</sup> (esketamine nasal spray): Guide for healthcare professionals

This guide informs healthcare professionals (HCPs) about the four identified risks that may occur following Spravato<sup>®</sup> treatment: transient dissociative states and perception disorders (dissociation), disturbances in consciousness (sedation), increased blood pressure and drug abuse. This guide describes the risks and explains how to minimise and manage them. As well as these risks, there are other side effects associated with Spravato<sup>®</sup>, which are listed in the guide. The HCP should consult the HCP checklist to aid the decision process in evaluating when, following Spravato<sup>®</sup> administration, a patient is deemed stable and safely allowed to leave the healthcare setting. This HCP guide is not intended to replace the Summary of Product Characteristics (SmPC) and should be read in conjunction with it.



**Adverse events should be reported. Healthcare professionals are asked to report suspected adverse events via: HPRA Pharmacovigilance Website: [www.hpra.ie](http://www.hpra.ie). Adverse events should also be reported to Janssen Sciences Ireland UC on 0044 1494 567447 or email [dsafety@its.jnj.com](mailto:dsafety@its.jnj.com).**

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These are risk mitigation materials required as part of the market authorisation

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## Contraindications

- Spravato<sup>®</sup> is contraindicated in patients with hypersensitivity to the active substance, ketamine, or to any of the excipients<sup>1</sup>
- Spravato<sup>®</sup> is contraindicated in patients for whom an increase in blood pressure or intracranial pressure poses a serious risk,<sup>1</sup> including:
  - Patients with aneurysmal vascular disease (including intracranial, thoracic or abdominal aorta, or peripheral arterial vessels)
  - Patients with history of intracerebral haemorrhage
  - Patients who have experienced a recent (within 6 weeks) cardiovascular event, including myocardial infarction.

Please read the summary of product characteristics (SmPC) before prescribing Spravato<sup>®</sup> which includes a full list of warnings and precautions.

## What is Spravato®?

Spravato® (esketamine) contains the active substance esketamine, which belongs to a group of medicines called antidepressants.

### 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.<sup>1</sup>

### 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 (see section 5.1 of the SmPC for a description of the populations studied).<sup>1</sup>

The effectiveness of Spravato® in preventing suicide or in reducing suicidal ideation or behaviour 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®.<sup>1</sup> The treatment with Spravato® should always be part of the comprehensive clinical care plan.<sup>1</sup>

## Introduction

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), increased blood pressure and drug abuse. This guide describes the risks and explains how to minimise and manage them.

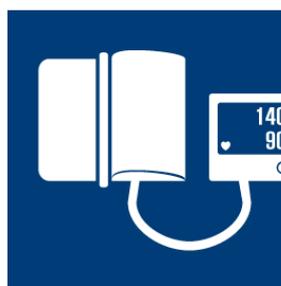
As well as these risks, there are other side effects associated with Spravato®. The most commonly observed adverse reactions in treatment-resistant depression patients treated with Spravato® were dizziness (31%), dissociation (27%), nausea (27%), headache (23%), somnolence (18%), dysgeusia (18%), vertigo (16%), hypoaesthesia (11%), vomiting (11%), and blood pressure increased (10%).<sup>1</sup> Please see page 6 for a full list of adverse events.



Transient dissociative states and perception disorders



Disturbances in consciousness



Increased blood pressure



Drug abuse

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

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

## How is Spravato<sup>®</sup> administered?

Spravato<sup>®</sup> is intended to be self-administered by the patient under the direct supervision of a healthcare professional.<sup>1</sup> Patients should be seated during Spravato<sup>®</sup> administration with their head tilted back at a 45-degree angle. Please refer to the instructions for use or to the SmPC for full details.

Spravato<sup>®</sup> shall be used in line with the approved indication according to the SmPC and the decision to prescribe Spravato<sup>®</sup> should be determined by a psychiatrist. Post-dose monitoring should be performed by an appropriately qualified healthcare professional experienced in blood pressure monitoring.<sup>1</sup>

Patients may experience nausea and vomiting after Spravato<sup>®</sup> 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<sup>®</sup> administration.<sup>1</sup>

### A single device contains 28 mg of esketamine

Each device delivers two sprays (one spray in each nostril)<sup>1</sup>

28 mg



One device

56 mg



Two devices

84 mg



Three devices

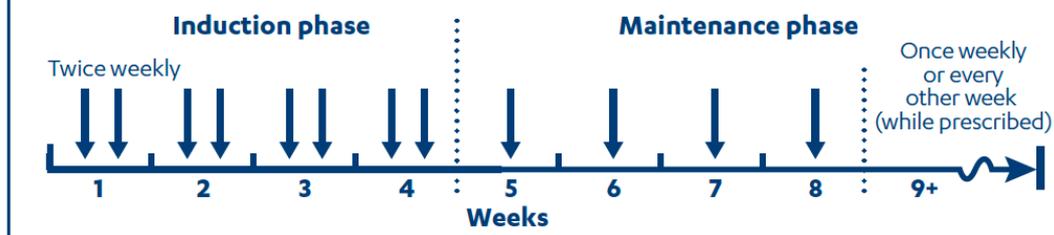
5 mins' rest



between each device<sup>1</sup>

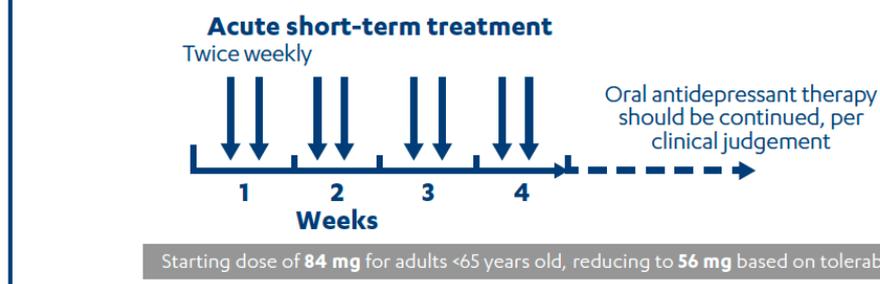
### Spravato<sup>®</sup> dosing regimen: treatment-resistant major depressive disorder<sup>1</sup>

In combination with an SSRI or SNRI



### Spravato<sup>®</sup> dosing regimen: A psychiatric emergency due to major depressive disorder<sup>1</sup>

Co-administered with oral antidepressant therapy



Spravato<sup>®</sup> has not been studied in elderly (65 years of age and older) patients with a moderate to severe episode of major depressive disorder in a psychiatric emergency.<sup>1</sup>

# Management of patients before and after Spravato<sup>®</sup> administration

## Pre-administration

- Discuss the possible side effects with the patient.
- Measure the patient's blood pressure and ensure it is in an acceptable range for Spravato<sup>®</sup> administration<sup>1</sup>:
  - <140/90 mmHg for patients <65 years of age
  - <150/90 mmHg for patients ≥65 years of age.
- Consider the individual patient's benefit and risk before deciding whether to start Spravato<sup>®</sup> treatment.

## Post-administration

Patients should be observed after Spravato<sup>®</sup> administration at each treatment session by an appropriately qualified healthcare professional experienced in blood pressure monitoring:

- Measure the patient's blood pressure at its peak at around 40 minutes after administering the full dose of Spravato<sup>®</sup> (after administering the last nasal spray) and subsequently as clinically warranted.<sup>1</sup>
  - If their blood pressure is elevated, continue to regularly measure it until it returns to acceptable levels.
- Closely observe the patient for signs of dissociation, sedation and respiratory depression, and any other adverse events. Most adverse events in clinical trials were transient and resolved by 1.5 hours post-dose.<sup>1</sup>
- Patients with clinically significant or unstable cardiovascular or respiratory conditions require additional precautions. In these patients, Spravato<sup>®</sup> should be administered in a setting where appropriate resuscitation equipment and healthcare professionals with training in cardiopulmonary resuscitation are available.
- Please refer to page 6 for the full list of adverse events.
- Older adults (≥65 years of age) should be carefully observed, as they may be at increased risk of falling when they start moving around after treatment.<sup>1</sup>

## Readiness-to-Leave

- Because of the possibility of sedation, dissociation and elevated blood pressure, patients must be observed by a healthcare professional until the patient is considered clinically stable and ready to leave.<sup>1</sup>
- The decision on when the patient is clinically stable should be made by the treating healthcare professional with the help of the 'Readiness-to-leave checklist for healthcare professionals' provided with this guide.
- The checklist should be signed and dated to document the time that the patient was ready to leave. The checklist will be retained at the healthcare institution following standard procedures.



**WARNING:** As Spravato can have a major influence on the ability to drive and use machines, instruct patients **not to engage in potentially hazardous activities** requiring complete mental alertness and motor coordination, such as driving a vehicle or operating machinery, until the next day after Spravato<sup>®</sup> administration following a restful sleep.

## Adverse events observed in patients treated with Spravato®

System organ class	Adverse drug reaction			
	Frequency			
	Very common	Common	Uncommon	Rare
<b>Psychiatric disorders</b>	Dissociation	Anxiety, euphoric mood, confusional state, derealisation, irritability, hallucination including visual hallucination, agitation, illusion, panic attack, time perception altered	Psychomotor retardation, emotional distress, dysphoria	
<b>Nervous system disorders</b>	Dizziness, headache, somnolence, dysgeusia, hypoaesthesia	Paraesthesia, sedation, tremor, mental impairment, lethargy, dysarthria, disturbance in attention	Nystagmus, psychomotor hyperactivity	Seizure
<b>Eye disorders</b>		Vision blurred		
<b>Ear and labyrinth disorders</b>	Vertigo	Tinnitus, hyperacusis		
<b>Cardiac disorders</b>		Tachycardia	Bradycardia	
<b>Vascular disorders</b>		Hypertension	Hypotension	
<b>Respiratory, thoracic and mediastinal disorders</b>		Nasal discomfort, throat irritation, oropharyngeal pain, nasal dryness including nasal crusting, nasal pruritus		Respiratory depression
<b>Gastrointestinal disorders</b>	Nausea, vomiting	Hypoaesthesia oral, dry mouth	Salivary hypersecretion	
<b>Skin and subcutaneous tissue disorders</b>		Hyperhidrosis	Cold sweat	
<b>Renal and urinary disorders</b>		Pollakiuria, dysuria, micturition urgency		
<b>General disorders and administration site conditions</b>		Feeling abnormal, feeling drunk, asthenia, crying, feeling of body temperature change	Gait disturbance	
<b>Investigations</b>	Blood pressure increased			

## ► Transient dissociative states and perception disorders

### What is the evidence of dissociation with Spravato®?

- In Phase 3 clinical trials, 27% of patients experienced dissociation following Spravato® administration, as determined by adverse event reporting.<sup>1</sup>
- Most adverse events linked to dissociation were reported as mild or moderate in intensity, with <4% of events reported as severe across the Phase 3 studies.<sup>1</sup>
- Dissociation symptoms typically resolved by 1.5 hours post-dose, and the severity tended to reduce over time with repeated treatments.

### 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
  - 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 clinically stable based on clinical judgement.

## ► Disturbances in consciousness (sedation)

### What is the evidence of disturbances in consciousness with Spravato®?

- Adverse reactions of sedation (9.3%) and somnolence (18.2%) were primarily mild or moderate in severity, occurred on the day of dosing and resolved spontaneously the same day.<sup>1</sup>
- Sedation generally resolved within 1.5 hours post-dose.<sup>1</sup>
- In clinical trials, all cases of sedation resolved spontaneously and haemodynamic parameters remained within the normal range. During post-marketing use, rare cases of respiratory depression have been observed.<sup>1</sup>

### 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.<sup>1</sup>
- Alcohol can also increase sedation<sup>1</sup>; 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 ‘Contraindications’ section on page 2 for further details.
- Risk factors for sedation also includes old age (elderly patients).

### 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.
- 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 (follow your healthcare institution guidelines).
- Observe the patient until they are ready to leave based on clinical judgement.

## ► Blood pressure increased

### What is the evidence of increased blood pressure with Spravato®?

- Spravato® administration can transiently raise blood pressure, lasting approximately 1–2 hours.<sup>1</sup> In clinical trials, increases in blood pressure peaked at approximately 40 minutes post-administration.<sup>1</sup>
- In TRD trials, the frequency of markedly abnormal blood pressure elevations (systolic  $\geq 40$  mmHg increase; diastolic  $\geq 25$  mmHg increase) was higher in older adult patients ( $\geq 65$  years of age) than in younger patients.
- In TRD clinical trials, the incidence of increased systolic blood pressure ( $\geq 180$  mmHg) was 3% and diastolic blood pressure ( $\geq 110$  mmHg) was 4% in patients receiving Spravato® plus oral antidepressants.<sup>1</sup>

### Who is at risk of increased blood pressure?

- Spravato® is contraindicated in patients for whom an increase in blood pressure or intracranial pressure poses a serious risk, including:<sup>1</sup>
  - Patients with aneurysmal vascular disease (including intracranial, thoracic, or abdominal aorta, or peripheral arterial vessels)
  - Patients with history of intracerebral haemorrhage
  - Recent (within 6 weeks) cardiovascular event, including myocardial infarction.
- In patients receiving Spravato® plus oral antidepressants in TRD trials, increases in blood pressure over time were:<sup>1</sup>
  - About 7 to 9 mmHg in systolic and 4 to 6 mmHg in diastolic blood pressure at 40 minutes post-dose
  - About 2 to 5 mmHg in systolic and 1 to 3 mmHg in diastolic blood pressure at 1.5 hours post-dose.

**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.**

- Blood pressure should be closely monitored when Spravato® is used concomitantly with psychostimulants (e.g. amphetamines, methylphenidate, modafinil, armodafinil) or other medicinal products that may increase blood pressure (e.g. xanthine derivatives, ergometrine, thyroid hormones, vasopressin, or monoamine oxidase inhibitors, such as, tranylecypromine, selegiline, phenelzine).<sup>1</sup>

# How to assess and monitor for increased blood pressure

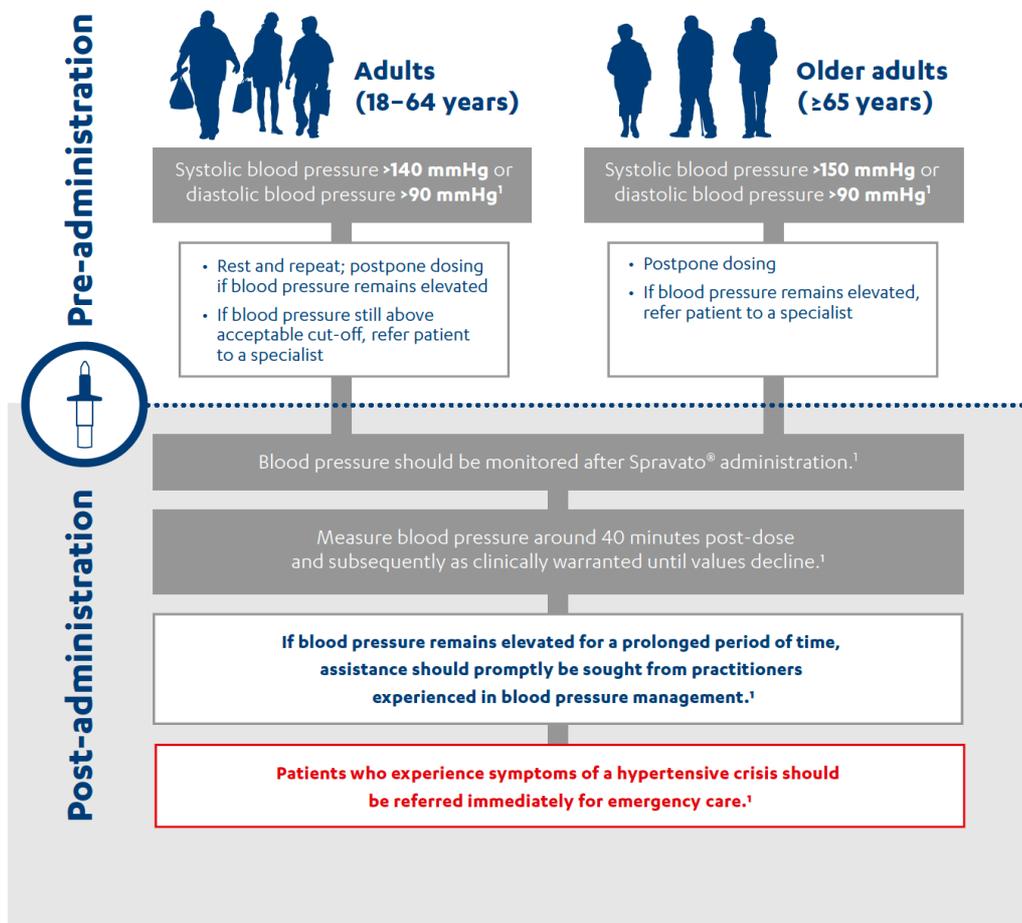
## Pre-administration<sup>1</sup>

- Blood pressure should be measured before Spravato<sup>®</sup> administration.
- If a patient's blood pressure is elevated (see Figure 1 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<sup>®</sup> treatment.
- Consider the patient's comedications and assess the individual patient's benefit and risk before deciding whether to delay Spravato<sup>®</sup> treatment.

## Post-administration<sup>1</sup>

- Blood pressure should be measured at around 40 minutes post-administration and subsequently as clinically warranted.
- 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 blood pressure remains elevated for a prolonged period of time, assistance should promptly be sought from practitioners experienced in blood pressure management.

Figure 1. Monitoring and managing increased blood pressure



## ► Drug abuse

- Ketamine, the racemic mixture of arketamine and esketamine, is a medicinal product that has been reported to be abused.<sup>1</sup> Spravato<sup>®</sup> contains esketamine and may be subject to abuse and diversion.<sup>1</sup>
- In real-world clinical practice, the risk of abuse with Spravato<sup>®</sup> is minimised by supervised administration.<sup>1</sup>

### What is the evidence of drug abuse with Spravato<sup>®</sup>?

In a study of abuse potential conducted in recreational polydrug users (n=41), single doses of esketamine nasal spray (84 mg and 112 mg) and the positive control drug intravenous ketamine (0.5 mg/kg infused over 40 minutes), produced significantly greater scores than placebo on subjective ratings of "drug liking" and on other measures of subjective drug effects.<sup>1</sup>

### Reducing the risk of drug abuse with Spravato<sup>®</sup> in clinical practice

- The potential for abuse, misuse and diversion of Spravato<sup>®</sup> is minimised due to the administration taking place in a clinical setting, under the direct supervision of a healthcare professional.<sup>1</sup>
  - In Ireland, Spravato<sup>®</sup> is determined a schedule 3 controlled drug (CD) under the Misuse of Drugs Act 1977. The Act has been amended on several occasions by subsequent legislation.<sup>2</sup>
  - All Schedule 3 CDs must be stored in a safe.<sup>3</sup>
  - The pharmacist will only further distribute Spravato<sup>®</sup> upon receipt of a valid controlled drug prescription from a consultant psychiatrist.
  - At the time of administration, the healthcare professional will record the date, name and address of the patient (proof of the patient's identity is required), name of the prescriber and quantity dispensed.
  - A healthcare professional will hand Spravato<sup>®</sup> to the patient in the appropriate clinical setting. The patient will self-administer Spravato<sup>®</sup> under direct supervision, returning the used device to the healthcare professional.
  - Patient-returned CDs should be promptly destroyed. While awaiting destruction, patient-returned Schedule 3 CDs should be stored in the CD safe, segregated from 'live' stock and clearly labelled 'Patient-returned CDs for destruction'.<sup>3</sup>
- Spravato<sup>®</sup> is administered at low doses and infrequently (28–84 mg twice a week at its most frequent dosing phase, gradually decreasing to once every 2 weeks).<sup>1</sup>

## Who is at risk of drug abuse?

Carefully assess each patient's risk for abuse or misuse prior to prescribing Spravato<sup>®</sup>. Individuals with a history of drug abuse or dependence may be at greater risk for abuse and misuse of Spravato<sup>®</sup>.<sup>1</sup>

### How to assess and monitor for signs of drug abuse

- Continually monitor patients receiving Spravato<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>-related interstitial cystitis were observed in any of the clinical trials<sup>1</sup>).
- If abuse is suspected, monitor symptoms and consult with local abuse support systems and specialists.

## Risk minimisation timeline

Preparation	Pre-administration	Post-administration	End of Monitoring Period
<ul style="list-style-type: none"> <li>• Carefully evaluate eligible patients considering their comorbidities, comedications and individual risk for the four identified risks</li> <li>• Discuss all side effects, including the four identified risks with the patient and explain the symptoms they may experience</li> <li>• Advise the patient to avoid:               <ul style="list-style-type: none"> <li>- Eating for 2 hours</li> <li>- Using a nasally administered corticosteroid or decongestant for 1 hour</li> <li>- Drinking liquids for 30 mins</li> </ul> </li> <li>• If the patient is not hospitalised, instruct them to plan to travel home by public transport or arrange for someone else to drive them home after taking Spravato<sup>®</sup></li> <li>• Evaluate the patient's risk of drug abuse</li> </ul>	<ul style="list-style-type: none"> <li>• Provide a safe and calm environment for Spravato<sup>®</sup> administration</li> <li>• Measure blood pressure and ensure it is within the acceptable range</li> <li>• Ensure the patient knows how to self-administer Spravato<sup>®</sup></li> <li>• Confirm that, prior to Spravato<sup>®</sup> administration, the patient has avoided:               <ul style="list-style-type: none"> <li>- Eating for 2 hours</li> <li>- Using a nasally administered corticosteroid or decongestant for 1 hour</li> <li>- Drinking liquids for 30 mins</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Regularly monitor the patient for adverse events</li> <li>• Measure the patient's blood pressure at around 40 minutes post-dose and subsequently as clinically warranted</li> </ul>	<ul style="list-style-type: none"> <li>• Use the accompanying 'Readiness-to-leave checklist for healthcare-professionals' to determine when the patient is clinically stable</li> <li>• Confirm blood pressure is at acceptable levels</li> <li>• If the patient is not hospitalised:               <ul style="list-style-type: none"> <li>- Ensure the patient is clinically stable before they go home</li> <li>- Check how the patient is feeling before they leave</li> <li>- Ensure the patient has planned to travel home by public transport or has arranged for someone else to drive them home</li> </ul> </li> </ul>

**Notes**

**Notes**

## Notes

## Notes

## References

1. Spravato® (esketamine) Summary of Product Characteristics. Janssen Cilag International NV. Available from: <https://www.medicines.ie/medicines/spravato-28-mg-nasal-spray-solution-35070/spc>.
2. Irish Statute Book. Misuse of Drugs Regulations 2017. Available from <http://www.irishstatutebook.ie/eli/2017/si/173/made/en/print>
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