Yvonne Ford, *Untitled*

Artwork from Reflections Art in Health, a user-led charity that promotes positive mental health through the creative arts

Risk minimisation measures in patients treated with Spravato®▼ (esketamine) nasal spray

The risk minimization activities have been approved by Saudi FDA

Version 1

Janssen
PHARMACEUTICAL COMPANIES OF Johnson&Johnson

Contents

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See the end of this booklet (page 37) for how to report adverse reactions.

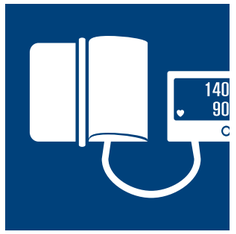
Introduction

Please read the summary of product characteristics (SmPC) 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® is an N-methyl-D-aspartate (NMDA) receptor antagonist that, 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 that was maintained over the course of 1 year.[1]

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

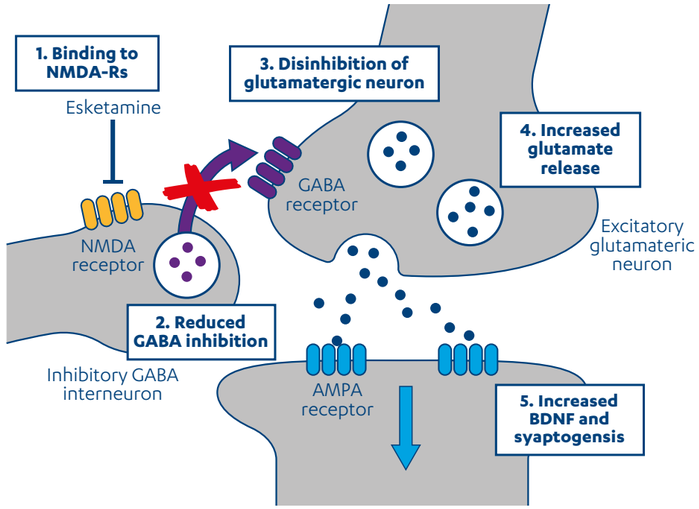
How does Spravato® work?

Esketamine is the S-enantiomer of racemic ketamine. It is a non-selective, non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor (Figure 1).[1,2] Esketamine has approximately four-fold greater affinity for the NMDA receptor than arketamine (*R*-ketamine, the *R*-enantiomer of ketamine).[3]

Through NMDA receptor antagonism, esketamine produces a transient increase in glutamate release leading to increases in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) stimulation and subsequently to increases in neurotrophic signalling, which may contribute to the restoration of synaptic function in brain regions involved with the regulation of mood and emotional behaviour. Restoration of dopaminergic neurotransmission in brain regions involved in the reward and motivation, and decreased stimulation of brain regions involved in anhedonia, may contribute to the rapid response.[1]

Due to the way Spravato® works, it is associated with certain side effects, including the four identified risks discussed here: transient dissociative states and perception disorders (dissociation), disturbances in consciousness (sedation), blood pressure increased and drug abuse.[1]

Figure 1



AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF=brain-derived neurotrophic factor; GABA=γ-aminobutyric acid; NMDA-R=N-methyl-D-aspartate receptor

How is Spravato® administered?

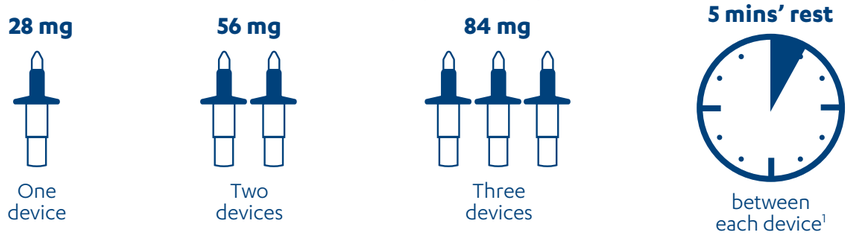
Spravato® is intended to be self-administered by the patient under the direct supervision of a healthcare professional.[1] Patients should be seated during Spravato® administration with their head tilted back at a 45-degree angle.[1] Please refer to the dosing and administration guide or to the SmPC 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]

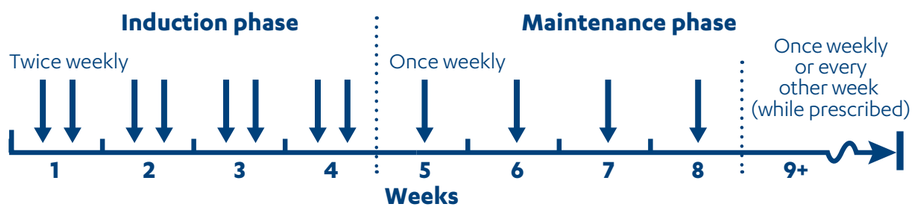
Patients may experience nausea and vomiting after Spravato® administration. Therefore, patients should be advised not to eat for 2 hours prior and not to drink liquids for 30 minutes prior to administration. Patients should also be advised not to use any nasally administered corticosteroids or decongestants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



Spravato® dosage[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.[1]

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
  - Sleep apnoea with morbid obesity (BMI ≥35)
  - 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).

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.[4]
- 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 dizziness (30%), nausea (27%), dissociation (26%), headache (24%), somnolence (18%), vertigo (18%), dysgeusia (17%), hypoaesthesia (11%), and vomiting (10%).[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.[1]

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®.[4]
- 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.

Transient dissociative states and perception disorders	Disturbances in consciousness (sedation)	Blood pressure increased	Drug abuse	Local prescribing guidance

Transient dissociative states and perception disorders

What are transient dissociative states and perception disorders (dissociation)?

Dissociation describes a range of experiences.* It may include: transient distortions of time and space; change in perception of what people feel, see or hear (for example sounds appearing louder, colours appearing brighter); or the subjective feeling of being separated from the surrounding environment or one's own body.

Some have described the experience as observing things from outside of yourself. Dissociation is a non-psychotic state. Some people have described it as a positive or negative experience, but in clinical trials it was transient and usually reduced in intensity after repeated Spravato® dosing.[1]

*Including amnesia, depersonalisation, derealisation and identity disturbance[8]

What is the evidence of dissociation with Spravato®?

- In Phase 3 clinical trials, 26% of patients experienced dissociation following Spravato® administration, as determined by adverse event reporting (Figure 2A).[1]
- 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.[1]
- In a long-term trial, <1% of patients experienced dissociation severe enough that they discontinued Spravato®.[6]
- Dissociation symptoms typically resolved by 1.5 hours post-dose (Figure 2B) and the severity tended to reduce over time with repeated treatments.[1]

Across all Phase 3 trials of Spravato®, 10 patients received medication for dissociation. No medications were used specifically for the management of dissociation, but rather for agitation or anxiety.[7]

In Phase 3 clinical trials, dissociation was also assessed using the Clinician-Administered Dissociative States Scale (CADSS) score[8] to evaluate the severity and time course of any dissociative experiences.

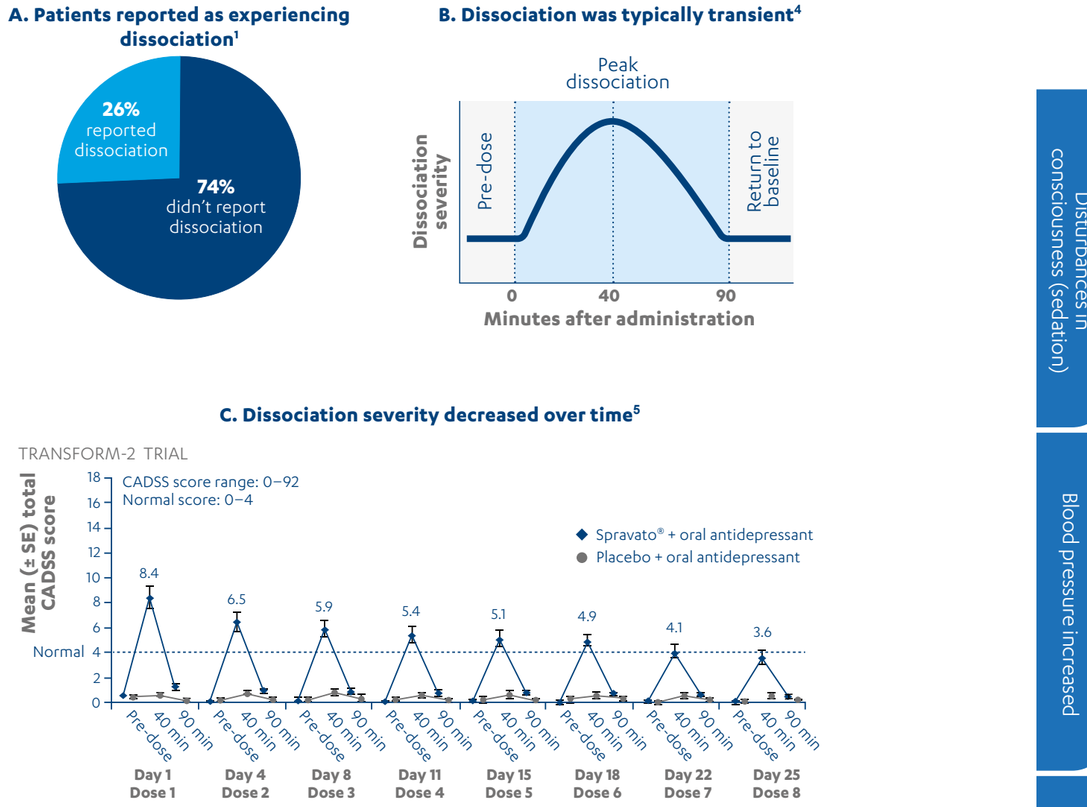
- Dissociation severity, as assessed by CADSS score, tended to reduce over time with repeated Spravato® treatment (Figure 2C).[5]
- In a fixed-dose clinical trial, a slightly higher proportion of subjects in the 84-mg arm than in the 56-mg arm had increased dissociative symptoms.[9]

A post hoc analysis* showed that if a patient experienced dissociation in Week 1, they often experienced dissociation in Weeks 2–4. On the other hand, if a patient did not experience dissociation in Week 1, they often did not experience dissociation in Weeks 2–4.[10]

Another post hoc analysis showed that changes in bodily sensations, general perceptual changes, and a general sense of being disconnected from one's own experience (depersonalisation) were the most common CADSS items in patients with clinician-reported adverse events of dissociation.[11]

*From TRANSFORM-1 & -2 trials

Figure 2



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 [8,12]:

- 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,[7] 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.

Disturbances in consciousness (sedation)

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

The phrase 'disturbances in consciousness' includes a range of reported symptoms from sedation, altered state of consciousness, consciousness fluctuating, depressed level of consciousness and loss of consciousness, to lethargy, somnolence, sopor and stupor.[13]

- In clinical trials, 21.7% of patients experienced 'disturbances in consciousness' (a term that includes a range of symptoms*) following Spravato® administration as determined by adverse event reporting; 94.8% of these events were reported as mild or moderate.[13]
- Five patients discontinued the Phase 3 clinical trials† due to 'disturbances in consciousness' events.‡,[13]
- Sedation typically started shortly after administration and peaked at 30 to 45 minutes after Spravato® administration.[14]
- Sedation generally resolved within 1.5 hours post-dose.[1]
- All cases of sedation resolved spontaneously; no respiratory depression was observed, and haemodynamic parameters remained within the normal range.[1]

*As defined by the MedDRA terms sedation, altered state of consciousness, consciousness fluctuating, depressed level of consciousness, loss of consciousness, lethargy, somnolence, sopor or stupor[13]
†All in the SUSTAIN-2 trial; no discontinuations due to 'disturbances in consciousness' events were observed in TRANSFORM-1, -2 or -3, or SUSTAIN-1
‡As defined by the MedDRA terms sedation, somnolence or depressed level of consciousness

What is the evidence of sedation with Spravato®?

Sedation is a spectrum of symptoms ranging from mild drowsiness to loss of consciousness or anaesthesia.[15]

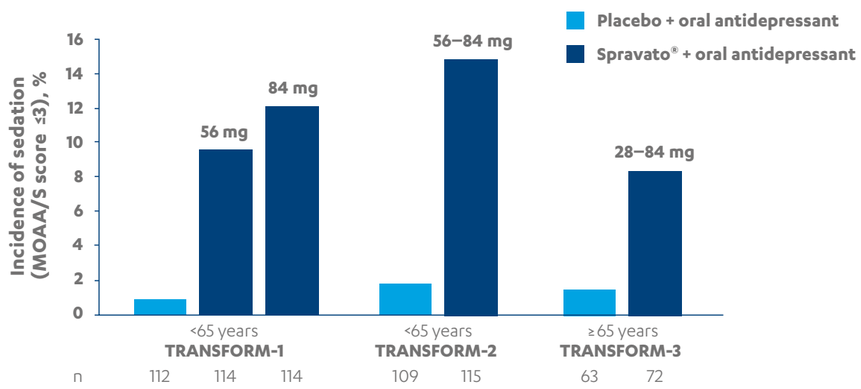
- Sedation was evaluated in detail during the Spravato® clinical trials using the Modified Observer's Assessment of Alertness and Sedation (MOAA/S) scale.[14]
  - The incidence of moderate or greater sedation, defined as MOAA/S score ≤3, was 8 to 15% in Spravato®-treated patients compared with 0.9 to 1.8% in placebo-treated patients (Figure 3).[13]
  - Sedation was mostly mild (MOAA/S score of 4) with only 11 patients treated with Spravato® experiencing severe sedation (MOAA/S score of 0 or 1).[14]
  - An important mechanism for some of the outlying sedation values may have been concomitant benzodiazepine use.[14]
  - A post hoc analysis* revealed that if a patient experienced somnolence (a symptom of sedation) in the first week, they often had somnolence in subsequent weeks. On the other hand, if a patient did not experience somnolence in Week 1, they often did not experience somnolence in Weeks 2–4.[10]

MOAA/S scale[14]

5	readily responds to name spoken in normal tone (awake)
4	lethargic response to name spoken in normal tone
3	responds only after name is called loudly and/or repeatedly
2	responds only after mild prodding or shaking
1	responds only after painful stimuli
0	no response to painful stimuli

Figure 3

Incidence of sedation in Spravato® clinical trials[13]



*From the TRANSFORM-1 & -2 trials

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 6 for further details.

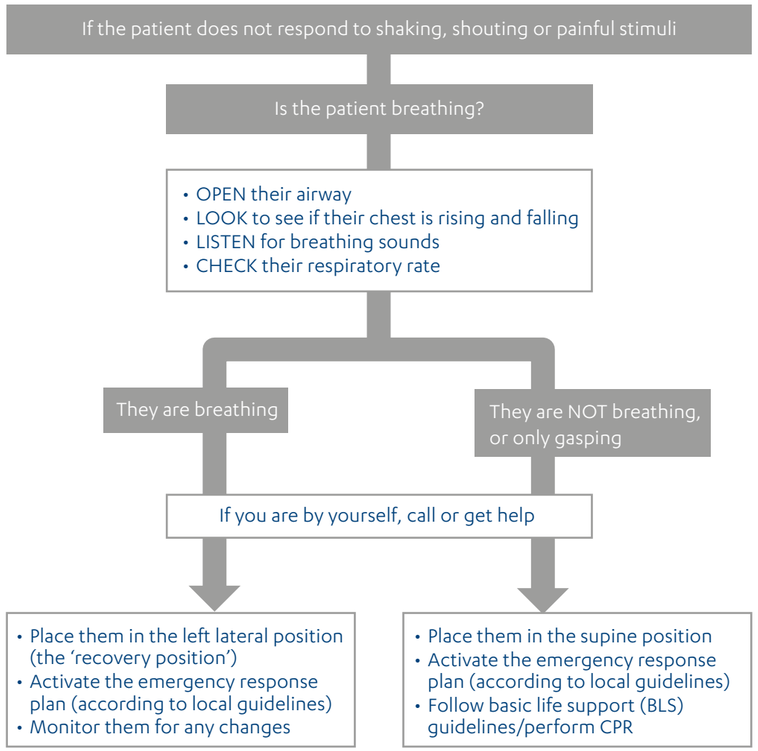
Consider the individual patient's benefit and risk before deciding whether to start Spravato® treatment.

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.
  - 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 4: What to do in an emergency[16]



Blood pressure increased

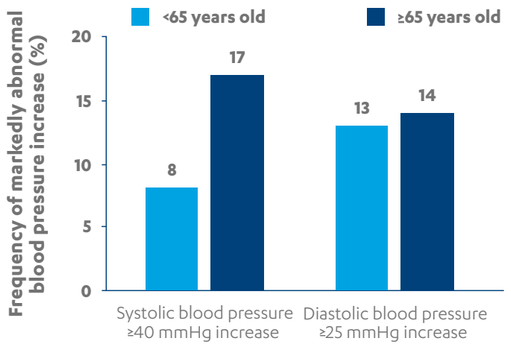
What is the evidence of increased blood pressure with Spravato®?

- Spravato® administration can transiently raise blood pressure, lasting approximately 1–2 hours.[1]
- In clinical trials, the frequency of markedly abnormal blood pressure elevations (systolic ≥40 mmHg increase; diastolic ≥25 mmHg increase) was higher in older adult patients (≥65 years of age) than in younger patients (Figure 5A).[1]
- The incidence of increased systolic blood pressure (≥180 mmHg) was 3% and diastolic blood pressure (≥110 mmHg) was 4% in patients receiving Spravato® plus oral antidepressant.[1]
- Less than 1% of patients in a long-term study discontinued Spravato® because of increased blood pressure.[6]

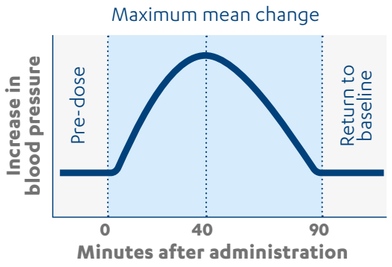
- Similar to dissociation, increase in blood pressure peaked at approximately 40 minutes post-administration (Figure 5B).[4]
- Treatment-emergent adverse events of increased blood pressure were transient, and mostly mild to moderate in severity.[17]

Figure 5

A. Frequency of markedly abnormal blood pressure elevations in patients receiving Spravato® plus oral antidepressant[1]



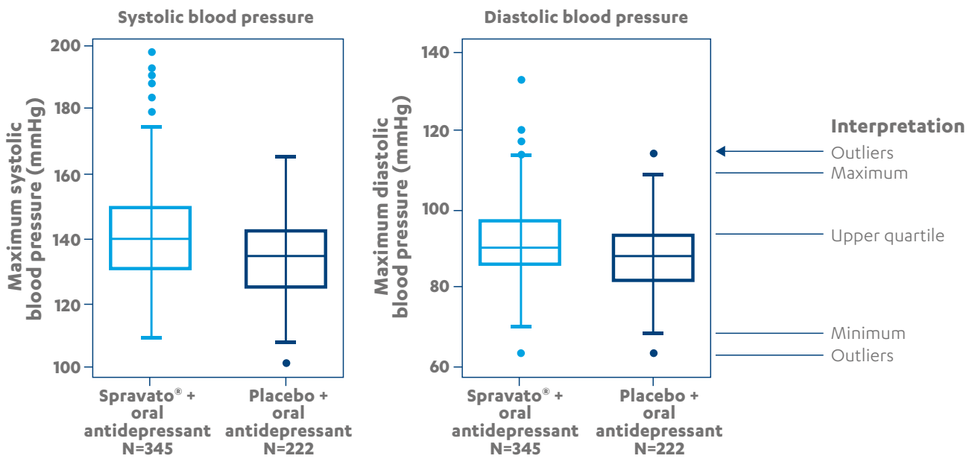
B. Change in blood pressure with Spravato®[4]



- In patients receiving Spravato® plus oral antidepressant in clinical trials, increases in blood pressure over time were[1]:
  - 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.
- The range of maximum blood pressure readings for patients aged 18–64 treated with Spravato® is illustrated in Figure 6.[17]

Figure 6

Mean maximum post-dose blood pressure*,[17]



*Pooled results from induction phase of 4-week double-blind studies of patients aged 18–64 years

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
  - Patients who have experienced a recent (within 6 weeks) cardiovascular event, including myocardial infarction.

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 6 for further details.
- Blood pressure should be closely monitored when esketamine 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 tranylcypromine, selegiline, phenelzine).[1]

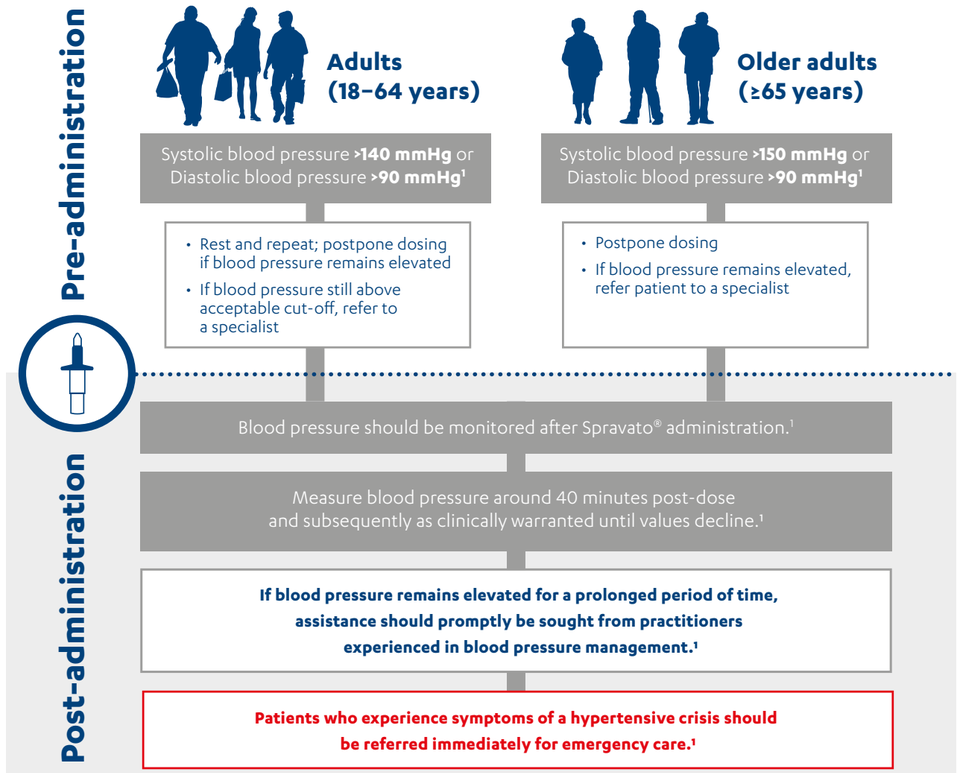
How to assess and monitor for increased blood pressure

- Pre-administration
  - Blood pressure should be measured before Spravato® administration.
  - If a patient's blood pressure is elevated (see Figure 7 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. Further information on managing hypertension can be found in the European Society of Cardiology (ESC) guidelines (www.escardio.org)
    - » 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[18]:
  - Headache
  - Chest pain
  - Shortness of breath
  - Vertigo
  - Nausea.
- Refer patients with symptoms of a hypertensive crisis for immediate emergency care.

Figure 7. Monitoring and managing increased blood pressure



Were other cardiovascular events observed with Spravato®?

- Other cardiovascular adverse events were not considered clinically important identified risks.[17]
- In Phase 3 studies, the proportion of subjects with adverse events related to abnormal heart rate following Spravato® administration was low (0.2%).[17]
- No clinically relevant effects on ECG parameters were observed in the Spravato® clinical development programme.[17]

Drug abuse

What is the evidence of drug abuse with Spravato®?

- Ketamine, the racemic mixture of arketamine and esketamine,[1] has a well-known potential for recreational abuse.[19] Spravato® contains esketamine and may be subject to abuse and diversion.[1]
- However, there were no reports of drug-seeking behaviour (e.g. requests for dosing changes and/or diversion of kits) during the Phase 3 clinical trials.[20]
- In real-world clinical practice, the risk of abuse with Spravato® is minimised by supervised administration.[1]

- 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.[1]
- Based on the PWC-20* results, there was no evidence from clinical trials to suggest a distinct withdrawal syndrome after cessation of treatment with Spravato®.[20]
- Data from all clinical trials with Spravato® were examined for the occurrence of adverse events related to the CNS and suggestive of drug abuse. The most common post-dose adverse events that could be associated with drug abuse were dizziness, somnolence and dissociation.[20]
  - Symptoms were predominantly reported shortly after dosing with Spravato®, were transient and self-limiting, and mild or moderate in intensity.[20]

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 under direct healthcare professional supervision; patients cannot use Spravato® alone at home.
  - In most European countries, 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.
- Spravato® 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).[1] In contrast, non-prescription use of ketamine may range from 10–250 mg among recreational users, to 4000 mg among frequent abusers.[21]
- In a long-term clinical trial, 38% of patients taking Spravato® decreased dosing from weekly to once every 2 weeks; based on depression scores, some patients (24%) remained on weekly dosing, while others (38%) had variable dosing frequency.[6]
- There were no reports of patients requesting an increase in dose or dosing frequency (a potential early indicator of drug-seeking behaviour) in the Spravato® clinical trials.[20]

*Physician Withdrawal Checklist 20-Item

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.

Local prescribing guidance

SPRAVATO▼ 28 mg nasal spray, solution
PRESCRIBING INFORMATION

ACTIVE INGREDIENT(S): Esketamine hydrochloride.

Please refer to Summary of Product Characteristics (SmPC) before prescribing.

INDICATION(S): In combination with a SSRI or SNRI, 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.

DOSAGE & ADMINISTRATION: Decision to prescribe should be determined by a psychiatrist. Self administered under the direct supervision of a healthcare professional (HCP). Treatment session consists of nasal administration and a post administration observation period, in an appropriate clinical setting. Before treatment: assess blood pressure (BP). If baseline BP is elevated, risks of short term increases in BP and benefit of treatment should be considered. Should not be administered if an increase in BP or intracranial pressure poses a serious risk. Additional precautions: patients with clinically significant / unstable cardiovascular / respiratory conditions: only administer in a setting where resuscitation equipment and HCPs with training in cardiopulmonary resuscitation are available. Post administration: assess BP 40 minutes after treatment, subsequently as clinically warranted. Monitor patients BP, for sedation and dissociation, until considered clinically stable and ready to leave. Adults <65 years: Induction phase: weeks 1-4: day 1 dose of 56 mg, then 56 mg or 84 mg twice weekly. Maintenance phase: weeks 5-8: 56 mg or 84 mg once weekly. From week 9: 56 mg or 84 mg every 2 weeks or once weekly. Adults ≥65 years: Induction phase: weeks 1-4: day 1 dose of 28 mg, then 28 mg, 56 mg or 84 mg twice weekly. Maintenance phase: weeks 5-8: 28 mg, 56 mg or 84 mg once weekly. From week 9: 28 mg, 56 mg or 84 mg every 2 weeks or once weekly. All dose changes in 28 mg increments. Evaluate evidence of therapeutic benefit at the end of induction phase and in maintenance phase, to determine need for continued treatment. After depressive symptoms improve, treatment is recommended for at least 6 months. Children: no data. Hepatic impairment: no dose adjustment for mild (Child Pugh class A) or moderate (Child Pugh class B) hepatic impairment. Caution when using maximum dose of 84 mg with moderate hepatic impairment. Not recommended in severe hepatic impairment (Child Pugh class C). Renal impairment: no dose adjustment in mild to severe renal impairment. Patients on dialysis not studied.

CONTRAINDICATIONS: Hypersensitivity to active substance, ketamine, or excipients. Patients for whom an increase in BP or intracranial pressure poses a serious risk: aneurysmal vascular disease (including intracranial, thoracic, or abdominal aorta, or peripheral arterial vessels), history of intracerebral haemorrhage, recent (within 6 weeks) cardiovascular event, including myocardial infarction.

SPECIAL WARNINGS & PRECAUTIONS: Neuropsychiatric and motor impairments: somnolence, sedation, dissociative symptoms, perception disturbances, dizziness, vertigo, anxiety occurred during clinical trials. At each treatment session monitor patients until considered stable as attention, judgment, thinking, reaction speed and motor skills may be impaired. Respiratory depression: concomitant use with CNS depressants may increase risk for sedation. Closely monitor for sedation and respiratory depression. Effect on BP: transient increases in systolic and/or diastolic BP with peak at approx. 40 minutes post administration, lasts approx. 1 2 hours. Monitor BP.

Local prescribing guidance

If BP remains elevated seek assistance from practitioners experienced in BP management; symptoms of a hypertensive crisis, refer immediately for emergency care. Cardiovascular or respiratory conditions: clinically significant or unstable cardiovascular / respiratory conditions: only initiate treatment if benefit outweighs the risk. Suicide/suicidal thoughts or clinical worsening: monitor patients closely as risk persists until significant remission occurs, risk of suicide may increase in the early stages of recovery. Carefully monitor patients with history of suicide related events or who exhibit significant degree of suicidal ideation prior to treatment, they are known to be at greater risk of suicidal thoughts/suicide attempts. Provide closely supervision in early treatment and following dose changes. Alert patients and caregivers of the need to monitor for any clinical worsening, suicidal behaviour/thoughts and unusual changes in behaviour. Seek medical advice immediately if symptoms present. Drug abuse, dependence, withdrawal: Spravato contains esketamine and may be subject to abuse and diversion. Patients with history of drug abuse or dependence may be at greater risk. Prior to prescribing, assess patient's risk for abuse or misuse. While on therapy, monitor for the development of abuse or misuse, including drug seeking behaviour. Other populations at risk: use with caution in patients with presence/history of psychosis, mania or bipolar disorder; hyperthyroidism that has not been sufficiently treated; history of brain injury, hypertensive encephalopathy, intrathecal therapy with ventricular shunts, or any other condition associated with increased intracranial pressure. Hepatotoxicity reported with chronic ketamine use, cannot exclude the potential for such an effect due to long-term. Urinary tract symptoms: monitor for urinary tract and bladder symptoms during treatment. Refer to appropriate healthcare provider when symptoms persist.

SIDE EFFECTS: Very common: dizziness, nausea, dissociation, headache, somnolence, vertigo, dysgeusia, hypoaesthesia, vomiting. Common: euphoric mood, agitation, anxiety, illusion, irritability, panic attack, time perception altered, hallucination including visual hallucination, derealisation, mental impairment, tremor, lethargy, dysarthria, paraesthesia, sedation, vision blurred, hyperacusis, tinnitus, tachycardia, hypertension, nasal discomfort, nasal dryness including nasal crusting, nasal pruritus, dry mouth, hypoaesthesia oral, hyperhidrosis, pollakiuria, dysuria, micturition urgency, feeling abnormal, feeling drunk, feeling of body temperature change, BP increased. Refer to SmPC for other side effects.

PREGNANCY: Not recommended. Discontinue treatment if a woman becomes pregnant and counsel about the potential risk to the foetus and clinical/therapeutic options as soon as possible.

LACTATION: Discontinue breast-feeding or discontinue / abstain from treatment.

INTERACTIONS: Closely monitor for increase in sedation in concomitant use with CNS depressants (benzodiazepines, opioids, alcohol). Closely monitor BP when concomitantly used with psychostimulants (amphetamines, methylphenidate, modafanil, armodafinil), xanthine derivatives, ergometrine, thyroid hormones, vasopressin, or MAOIs, such as, tranylcypromine, selegiline, phenelzine.
Refer to SmPC for full details of interactions.

LEGAL CATEGORY: Prescription Only Medicine (POM).

MARKETING AUTHORISATION HOLDER:
Janssen-Cilag International NV, Turnhoutseweg 30, B-2340 Beerse, Belgium.

How to report adverse events

SFDA (National Pharmacovigilance and Drug Safety Department)
Email: npc.drug@sfda.gov.sa
Telephone: 19999
Fax: +966 11 2057662
Online: http://ade.sfda.gov.sa

For full prescribing information, please refer to the data sheet or contact Johnson & Johnson Middle East FZ LLC, Saudi Branch at Mawheba Building,3rd Floor, Al-Olaya Road, AlWaroud District P.OBox:55031 Riyadh:11533 Kingdom of Saudi Arabia
Tel.: +966114339133
Fax: +966112153190
To report Adverse Events/Product Complaint or any Medical Information Inquiries, please contact us at Email: GCC-PV2@its.jnj.com
Hotline: 00966540015811

Risk minimisation timeline

Preparation

- Carefully evaluate eligible patients considering their comorbidities, comedications and individual risk for the four identified risks
- Discuss the four 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®

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

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

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

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.

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Artwork from Reflections Art in Health, a user-led charity that promotes positive mental health through the creative arts