Spravato®
(esketamine) CIII
nasal spray

Dosing and Administration

Indication

SPRAVATO® (esketamine) CIII Nasal Spray is indicated, in conjunction with an oral antidepressant (AD), for the treatment of treatment-resistant depression (TRD) in adults.

SPRAVATO® is not approved as an anesthetic agent. The safety and effectiveness of SPRAVATO® as an anesthetic agent have not been established.

Important Safety Information

WARNING: SEDATION, DISSOCIATION; ABUSE AND MISUSE; and SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning

- **Risk for sedation and dissociation after administration. Monitor patients for at least two hours after administration (5.1, 5.2).**
- **Potential for abuse and misuse. Consider the risks and benefits of using SPRAVATO® prior to use in patients at higher risk of abuse. Monitor for signs and symptoms of abuse and misuse (5.3).**
- **SPRAVATO® is only available through a restricted program called the SPRAVATO® REMS (5.4).**
- **Increased risk of suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. SPRAVATO® is not approved for use in pediatric patients (5.5).**

Please see Important Safety Information, including Boxed WARNINGS, on pages 25 through 29.
Please see full Prescribing Information, including Boxed WARNINGS.

What is SPRAVATO®?

SPRAVATO® is the first and only NMDA* receptor antagonist approved in conjunction with an oral antidepressant for adult patients with treatment-resistant depression (TRD).[1]

*NMDA=N-methyl-D-aspartate.

Spravato®
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SPRAVATO® REMS
(RISK EVALUATION AND MITIGATION STRATEGY)

SPRAVATO® can only be administered at a REMS-certified treatment center

Please see Important Safety Information, including Boxed WARNINGS, on pages 25 through 29.
Please see full Prescribing Information, including Boxed WARNINGS.

Spravato® (esketamine) CIII nasal spray

SPRAVATO® REMS

REMS

The goal of the REMS (Risk Evaluation and Mitigation Strategy) is to mitigate the risks of serious adverse outcomes resulting from sedation and dissociation caused by SPRAVATO® administration, and abuse and misuse of SPRAVATO®, by:

- Ensuring that SPRAVATO® is only dispensed and administered to patients in a medically supervised healthcare setting that monitors these patients
- Ensuring pharmacies and healthcare settings that dispense SPRAVATO® are certified
- Ensuring that each patient is informed about the serious adverse outcomes resulting from sedation and dissociation and need for monitoring
- Enrollment of all patients in the REMS (registry) to further characterize the risks

- Because of the possibility of delayed or prolonged sedation or dissociation in some cases, all patients must be monitored by a healthcare professional for at least 2 hours following each treatment session, until the clinician determines the patient is safe to leave

SPRAVATO® is intended for patient administration under the direct observation of a healthcare provider, and patients are required to be monitored by a healthcare provider for at least 2 hours after SPRAVATO® administration. SPRAVATO® must never be dispensed directly to a patient for home use.

For more information on SPRAVATO® REMS, please call **855-382-6022** or visit **SPRAVATOrems.com**.

Please see Important Safety Information, including Boxed WARNINGS, on pages 25 through 29.
Please see full Prescribing Information, including Boxed WARNINGS.

Spravato® (esketamine) CIII nasal spray

SPRAVATO® REMS (continued)

Sedation

Sedation was reported in 2 ways in the clinical studies: through adverse event reports, and by using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) Scale.

- Adverse events of sedation were reported in approximately 23% of patients treated with SPRAVATO® at any dose (N=346)
- Based on the MOAA/S Scale, 49% to 61% of patients treated with SPRAVATO® developed sedation
- 0.3% of patients treated with SPRAVATO® experienced loss of consciousness*

Dissociation

Dissociation was reported in 2 ways in the clinical studies: through adverse event reports, and by using the Clinician-Administered Dissociative States Scale (CADSS).

- Adverse events of dissociation were reported in approximately 41% of patients treated with SPRAVATO® at any dose (N=346)
- Based on the CADSS, 61% to 75% of patients treated with SPRAVATO® developed dissociative or perceptual changes
- In clinical trials, dissociation was reported as transient and occurred on the day of dosing†

*Based on the MOAA/S Scale.
†Based on the CADSS Scale.

Spravato® (esketamine) CIII nasal spray

DOSING

Spravato® (esketamine) C-III
nasal spray

SPRAVATO® Doses[1]

Each device contains: an aqueous solution of esketamine.
Each device delivers: 2 sprays, 1 spray into each nostril.

- Total volume to be delivered (per device): 0.2 mL, equivalent to 28 mg of esketamine

56 mg =

84 mg =

Day 1 starting dose

Please see Important Safety Information, including Boxed WARNINGS, on pages 25 through 29.
Please see full Prescribing Information, including Boxed WARNINGS.

Spravato® (esketamine) C-III nasal spray

DOSING SCHEDULE

Spravato® (esketamine) C-III
nasal spray

SPRAVATO® Dosing Schedule[1]

INDUCTION (twice weekly)	MAINTENANCE (once weekly)	(weekly or every 2 weeks)
WEEKS 1-4	WEEKS 5-8	WEEKS 9 AND AFTER*
Day 1 starting dose: **56 mg** Subsequent doses: **56 mg** or **84 mg**	**56 mg** or **84 mg** once weekly	**56 mg** or **84 mg** every 2 weeks or once weekly

- In Study 2 (long-term), 39% of patients received the 56-mg dose, and 61% received the 84-mg dose of SPRAVATO®
- SPRAVATO® does not require daily dosing and should be administered in conjunction with an oral antidepressant (AD)

*Dosing frequency should be individualized to the lowest frequency required to maintain remission/response.

Spravato® (esketamine) C III nasal spray

Missed Treatment Sessions[1]

If a patient misses treatment sessions and there is worsening of depression symptoms, per clinical judgment, consider returning to the patient's previous dosing schedule (ie, every 2 weeks to once weekly, once or twice per week).

Please see Important Safety Information, including Boxed WARNINGS, on pages 25 through 29.
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Spravato® (esketamine) C-III nasal spray

APPROPRIATE USE

Spravato® (esketamine) CIII
nasal spray

Appropriate Use of SPRAVATO®[1]

ABUSE, MISUSE, DEPENDENCE

- SPRAVATO® is a Schedule III controlled substance and may be subject to abuse and diversion. Assess each patient's risk for abuse or misuse prior to prescribing SPRAVATO®, and monitor all patients receiving SPRAVATO® for the development of these behaviors or conditions, including drug-seeking behavior, while on therapy

- Individuals with a history of drug abuse or dependence are at greater risk; therefore, use careful consideration prior to treatment of individuals with a history of substance use disorder. Monitoring for signs of abuse is recommended

- Physical dependence has been reported with prolonged off-label use of ketamine. In Study 1, there were no withdrawal symptoms captured up to 4 weeks after cessation of SPRAVATO® treatment. Monitor SPRAVATO®-treated patients for symptoms and signs of physical dependence upon discontinuation of the drug

CONTRAINDICATIONS

- SPRAVATO® is contraindicated in patients with:
  - Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels) or arteriovenous malformation
  - History of intracerebral hemorrhage
  - Hypersensitivity to esketamine, ketamine, or any of the excipients

COGNITION

- In a study in healthy volunteers, a single dose of SPRAVATO® caused cognitive performance decline 40 minutes post dose. Cognitive performance and mental effort were comparable between SPRAVATO® and placebo at 2 hours post dose
- Long-term cognitive and memory impairment have been reported with repeated off-label ketamine misuse or abuse
- No adverse effects of SPRAVATO® nasal spray on cognitive functioning were observed in a one-year open-label safety study; however, the long-term cognitive effects of SPRAVATO® have not been evaluated beyond one year

Please see Important Safety Information, including Boxed WARNINGS, on pages 25 through 29.
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Spravato® (esketamine) C III nasal spray

Appropriate Use of SPRAVATO®[1] (continued)

ADDITIONAL PATIENT CONSIDERATIONS

Pregnancy & lactation

- SPRAVATO® is not recommended for women who are pregnant or may become pregnant, or in women who are breastfeeding. Women who become pregnant should stop taking SPRAVATO® and the patient should be counseled about the potential risk to the fetus
- SPRAVATO® was not assessed in pregnant women. SPRAVATO® may cause fetal harm when administered to pregnant women

Pediatric use (17 years of age and younger)

- The safety and effectiveness of SPRAVATO® in pediatric patients have not been evaluated

Geriatric use (≥65 years of age)[1]

- No overall differences in safety were observed between patients 65 years of age and older and those younger than 65 years of age
- The efficacy of SPRAVATO® for the treatment of TRD in geriatric patients was evaluated in a 4-week, randomized, double-blind study comparing intranasal SPRAVATO® plus an oral antidepressant to intranasal placebo plus an oral antidepressant in patients ≥65 years of age
- At the end of 4 weeks, there was no statistically significant difference between groups on the primary efficacy endpoint

Hepatic impairment

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

Psychosis

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

DRUG INTERACTIONS

- **CNS depressants:** closely monitor for sedation with concomitant use of SPRAVATO® with CNS depressants, including benzodiazepines, opioids, and alcohol
- **Psychostimulants and monoamine oxidase inhibitors (MAOIs):** closely monitor blood pressure with concomitant use of SPRAVATO® with psychostimulants (including amphetamines, methylphenidate, modafinil, and armodafinil) and MAOIs

Please see Important Safety Information, including Boxed WARNINGS, on pages 25 through 29.
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Spravato® (esketamine) CIII nasal spray

BEFORE ADMINISTRATION

Spravato® (esketamine) CIII nasal spray

Before Administering SPRAVATO®[1]

- It is recommended that healthcare professionals wear protective gloves while assisting patients with the administration of an unused SPRAVATO® nasal spray device and for handling and disposing of used devices

- Assess blood pressure prior to administration
  - Do not administer SPRAVATO® if an increase in blood pressure or intracranial pressure poses a serious risk
  - Before prescribing SPRAVATO®, patients with other cardiovascular and cerebrovascular conditions should be carefully assessed to determine whether the potential benefits of SPRAVATO® outweigh its risks

- Since nausea and vomiting can occur, patients should be advised to refrain from:
  - Eating at least 2 hours in advance of administration
  - Drinking 30 minutes prior to administration

- Patients who require a nasal corticosteroid or nasal decongestant on a dosing day should administer these medications at least 1 hour before SPRAVATO®

- 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 following a restful sleep
- Patients will need to arrange transportation home following treatment with SPRAVATO®

Spravato® (esketamine) CIII nasal spray

INSTRUCTIONS FOR USE

Spravato® (esketamine) CIII
nasal spray

Device At-A-Glance[1]

Tip

Nose rest

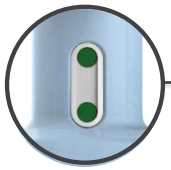
Indicator (see right)

Finger rest

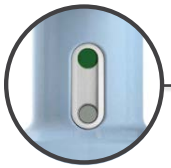
Plunger

Indicator

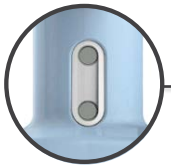
One device contains 2 sprays (1 spray for each nostril)



2 green dots
Device full



1 green dot
One spray delivered



No green dots
Device empty

IMPORTANT:

SPRAVATO® is for nasal use only. Do not prime device.
This will result in loss of medication.

Spravato® (esketamine) C III nasal spray

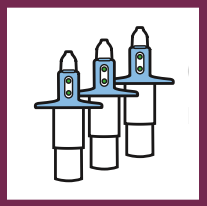
How to Use SPRAVATO®[1]

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

STEP 1 - Get ready

Before first device only:

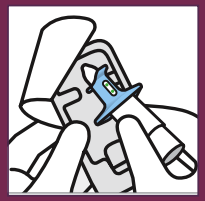
- Instruct patient to blow nose **before first device only**



56 mg = 2 devices
84 mg = 3 devices

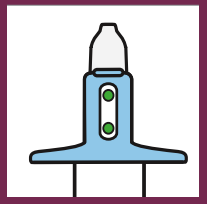
Confirm required number of devices.

STEP 2 - Prepare device



Healthcare professional:

- Check expiration date (“EXP”). If expired, get a new device
- Peel blister and remove device



Healthcare professional:

- **Do not prime device.** This will result in a loss of medication
- Check that indicator shows **2 green dots.** If not, dispose of device and get a new one
- Hand device to patient

STEP 3 - Prepare patient

Instruct the patient to:

- Hold device as shown with the thumb gently supporting the plunger
- **Do not** press the plunger

Instruct the patient to:

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

Please see Important Safety Information, including Boxed WARNINGS, on pages 25 through 29.
Please see full Prescribing Information, including Boxed WARNINGS.

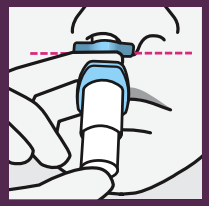
Spravato® (esketamine) CIII nasal spray

How to Use SPRAVATO®[1] (continued)

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

STEP 4 - Patient sprays once into each nostril

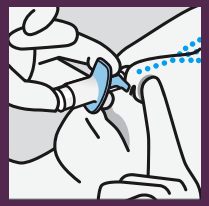
A



Instruct the patient to:

- Insert tip straight into the **first nostril**
- Nose rest should touch the **skin between the nostrils**

B



Instruct the patient to:

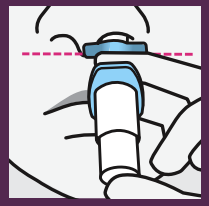
- Close opposite nostril
- **Breathe in through nose** while pushing plunger all the way up until it stops

C

Instruct the patient to:

- **Sniff gently** after spraying to keep medication inside nose

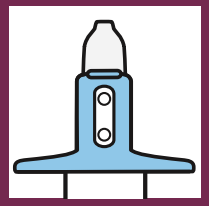
D



Instruct the patient to:

- 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

Instruct the patient to:

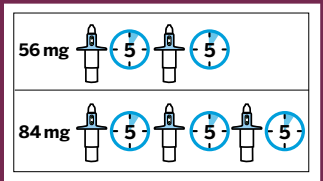
- Rest in a comfortable position (preferably semi-reclined) for **5 minutes after each device**
- If liquid drips out, dab nose with a tissue

⚠ **Do not** blow nose.

How to Use SPRAVATO®[1] (continued)

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

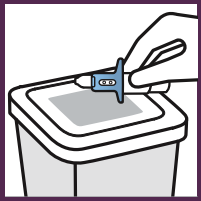
NEXT DEVICE



Healthcare professional:

- **Repeat Steps 2-5** for the next device

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



- Dispose of used device(s) per facility procedure for a Schedule III drug product and per applicable federal, state, and local regulations
- Janssen offers a SPRAVATO® Disposal Program. If your healthcare setting wishes to use this program, **contact 1-800-JANSSEN for more information**

Please see Important Safety Information, including Boxed WARNINGS, on pages 25 through 29.
Please see full Prescribing Information, including Boxed WARNINGS.

Spravato® (esketamine) C III nasal spray

MONITORING & DISCHARGE

Spravato® (esketamine) CIII nasal spray

Monitoring & Discharge[1]

Sedation

- Because of a possibility of delayed or prolonged sedation, patients must be monitored by a healthcare professional for at least 2 hours following each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave

Dissociation

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

Blood Pressure

- SPRAVATO® caused increases in systolic blood pressure (SBP) and/or diastolic blood pressure (DBP), which peak at approximately 40 minutes after administration and last approximately 4 hours:
  - 40 minutes post dose, mean placebo-adjusted increases in SBP=7 to 9 mmHg and DBP=4 to 6 mmHg
  - If blood pressure is decreasing and the patient appears clinically stable for at least 2 hours, the patient may be discharged at the end of the post-dose monitoring period
- Assess blood pressure prior to, and approximately 40 minutes after dosing with SPRAVATO® and subsequently as clinically warranted until values decline

Other Adverse Reactions

- The most commonly observed reactions (incidence ≥5% and at least twice that of placebo plus oral antidepressant) were dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk

Patients will require transportation from the treatment center

- Instruct patients not to engage in potentially hazardous activities requiring complete mental alertness and motor coordination, such as driving a motor vehicle or operating machinery, until the next day following a restful sleep

Please see Important Safety Information, including Boxed WARNINGS, on pages 25 through 29.
Please see full Prescribing Information, including Boxed WARNINGS.

Spravato® (esketamine) CIII nasal spray

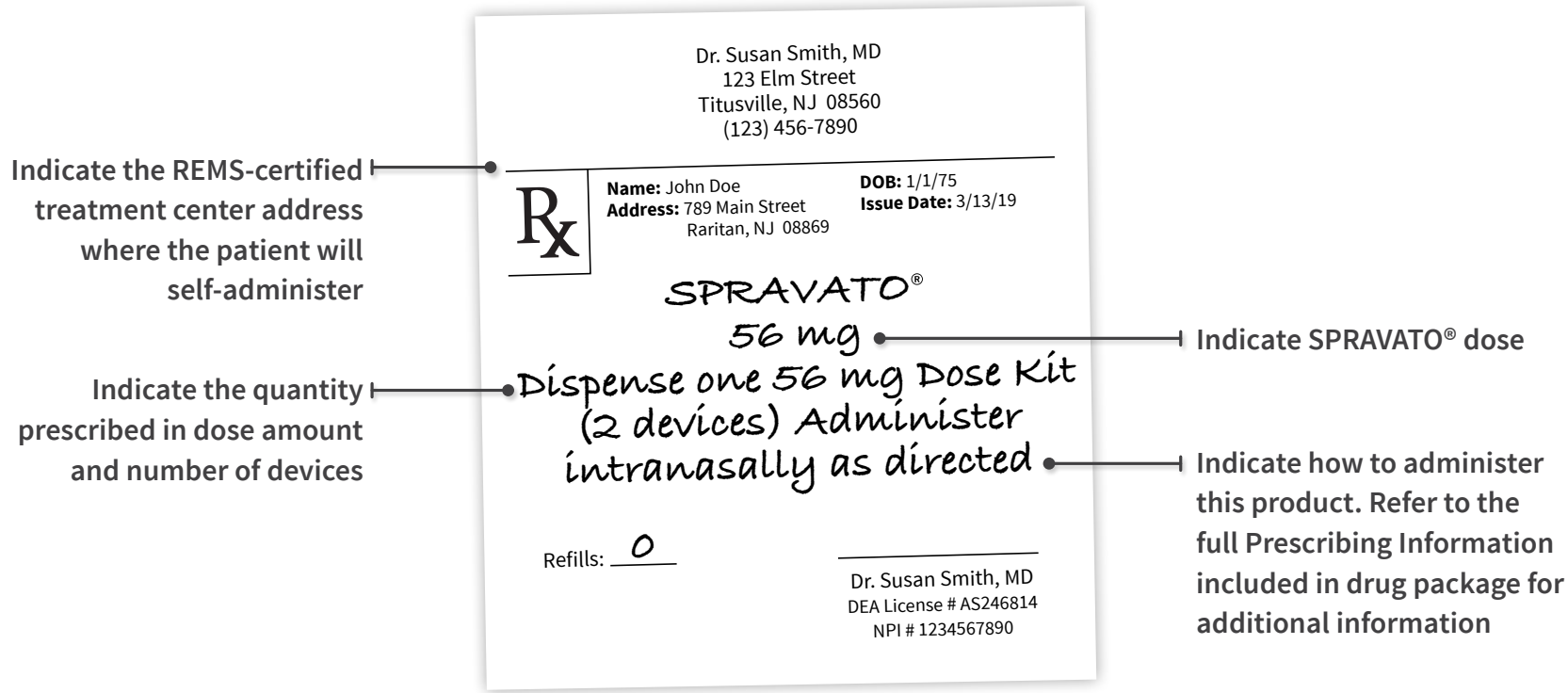
HOW TO PRESCRIBE

Please see Important Safety Information, including Boxed WARNINGS, on pages 25 through 29.
Please see full Prescribing Information, including Boxed WARNINGS.

Spravato® (esketamine) C-III
nasal spray

Prescribing SPRAVATO®

An example prescription for a single 56-mg dose is shown below. Subsequent dosage adjustments should be made based on efficacy and tolerability of the previous dose, to optimize therapeutic benefit.



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Please see full Prescribing Information, including Boxed WARNINGS.

Spravato® (esketamine) C-III nasal spray

Reference

1. SPRAVATO® [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. February 2020.

Indication

SPRAVATO® (esketamine) CIII Nasal Spray is indicated, in conjunction with an oral antidepressant (AD), for the treatment of treatment-resistant depression (TRD) in adults.

SPRAVATO® is not approved as an anesthetic agent. The safety and effectiveness of SPRAVATO® as an anesthetic agent have not been established.

Important Safety Information

WARNING: SEDATION, DISSOCIATION; ABUSE AND MISUSE; and SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning

- **Risk for sedation and dissociation after administration. Monitor patients for at least two hours after administration (5.1, 5.2).**
- **Potential for abuse and misuse. Consider the risks and benefits of using SPRAVATO® prior to use in patients at higher risk of abuse. Monitor for signs and symptoms of abuse and misuse (5.3).**
- **SPRAVATO® is only available through a restricted program called the SPRAVATO® REMS (5.4).**
- **Increased risk of suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. SPRAVATO® is not approved for use in pediatric patients (5.5).**

CONTRAINDICATIONS

SPRAVATO® is contraindicated in patients with:

- Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation
- History of intracerebral hemorrhage
- Hypersensitivity to esketamine, ketamine, or any of the excipients

WARNINGS AND PRECAUTIONS

Sedation: In clinical trials, 49% to 61% of SPRAVATO®-treated patients developed sedation and 0.3% of SPRAVATO®-treated patients experienced loss of consciousness.

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

Closely monitor for sedation with concomitant use of SPRAVATO® with CNS depressants *[see Drug Interaction (7.1)]*.

SPRAVATO® is available only through a restricted program under a REMS.

Spravato® (esketamine) CIII nasal spray

Important Safety Information (continued)

Dissociation: The most common psychological effects of SPRAVATO® were dissociative or perceptual changes (including distortion of time, space and illusions), derealization and depersonalization (61% to 75% of SPRAVATO®-treated patients developed dissociative or perceptual changes). Given its potential to induce dissociative effects, carefully assess patients with psychosis before administering SPRAVATO®; treatment should be initiated only if the benefit outweighs the risk.

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

SPRAVATO® is available only through a restricted program under a REMS.

Abuse and Misuse: SPRAVATO® contains esketamine, a Schedule III controlled substance (CIII), and may be subject to abuse and diversion. Assess each patient's risk for abuse or misuse prior to prescribing and monitor all patients for the development of these behaviors or conditions, including drug-seeking behavior, while on therapy. Individuals with a history of drug abuse or dependence are at greater risk; therefore, use careful consideration prior to treatment of individuals with a history of substance use disorder and monitor for signs of abuse or dependence.

SPRAVATO® is available only through a restricted program under a REMS.

SPRAVATO® Risk Evaluation and Mitigation Strategy (REMS): SPRAVATO® is available only through a restricted program called the SPRAVATO® REMS because of the risks of serious adverse outcomes from sedation, dissociation, and abuse and misuse.

Important requirements of the SPRAVATO® REMS include the following:

- Healthcare settings must be certified in the program and ensure that SPRAVATO® is:
  - Only dispensed in healthcare settings and administered to patients who are enrolled in the program.
  - Administered by patients under the direct observation of a healthcare provider and that patients are monitored by a healthcare provider for at least 2 hours after administration of SPRAVATO®.
- Pharmacies must be certified in the REMS and must only dispense SPRAVATO® to healthcare settings that are certified in the program.

Further information, including a list of certified pharmacies, is available at www.SPRAVATOrems.com or 1-855-382-6022.

Suicidal Thoughts and Behaviors in Adolescents and Young Adults: In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included adult and pediatric patients, the incidence of suicidal thoughts and behaviors in patients age 24 years and younger was greater than in placebo-treated patients. SPRAVATO® is not approved in pediatric (<18 years of age) patients.

There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied.

Monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing SPRAVATO® and/or the concomitant oral antidepressant, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

Spravato® (esketamine) CIII nasal spray

Important Safety Information (continued)

Increase in Blood Pressure: SPRAVATO® causes increases in systolic and/or diastolic blood pressure (BP) at all recommended dosages. Increases in BP peak approximately 40 minutes after SPRAVATO® administration and last approximately 4 hours.

Approximately 8% to 17% of SPRAVATO®-treated patients experienced an increase of more than 40 mmHg in systolic BP and/or 25 mmHg in diastolic BP in the first 1.5 hours after administration at least once during the first 4 weeks of treatment. A substantial increase in blood pressure could occur after any dose administered even if smaller blood pressure effects were observed with previous administrations. SPRAVATO® is contraindicated in patients for whom an increase in BP or intracranial pressure poses a serious risk (e.g., aneurysmal vascular disease, arteriovenous malformation, history of intracerebral hemorrhage). Before prescribing, patients with other cardiovascular and cerebrovascular conditions should be carefully assessed to determine whether the potential benefits of SPRAVATO® outweigh its risk.

Assess BP prior to administration of SPRAVATO®. In patients whose BP is elevated prior to SPRAVATO® administration (as a general guide: >140/90 mmHg), a decision to delay SPRAVATO® therapy should be taken into account to balance the benefit and risk in individual patients.

BP should be monitored for at least 2 hours after SPRAVATO® administration. Measure blood pressure around 40 minutes post-dose and subsequently as clinically warranted until values decline. If BP remains high, promptly seek assistance from practitioners experienced in BP 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.

Closely monitor blood pressure with concomitant use of SPRAVATO® with psychostimulants or monoamine oxidase inhibitors (MAOIs) *[see Drug Interactions (7.2, 7.3)]*.

In patients with history of hypertensive encephalopathy, more intensive monitoring, including more frequent blood pressure and symptom assessment, is warranted because these patients are at increased risk for developing encephalopathy with even small increases in blood pressure.

Cognitive Impairment

Short-Term Cognitive Impairment: In a study in healthy volunteers, a single dose of SPRAVATO® caused cognitive performance decline 40 minutes post-dose. SPRAVATO®-treated subjects required a greater effort to complete the cognitive tests at 40 minutes post-dose. Cognitive performance and mental effort were comparable between SPRAVATO® and placebo at 2 hours post-dose. Sleepiness was comparable after 4 hours post-dose.

Long-Term Cognitive Impairment: Long-term cognitive and memory impairment have been reported with repeated ketamine misuse or abuse. No adverse effects of SPRAVATO® nasal spray on cognitive functioning were observed in a one-year open-label safety study; however, the long-term cognitive effects of SPRAVATO® have not been evaluated beyond one year.

Impaired Ability to Drive and Operate Machinery: Before SPRAVATO® administration, instruct patients not to engage in potentially hazardous activities requiring complete mental alertness and motor coordination, such as driving a motor vehicle or operating machinery, until the next day following a restful sleep. Patients will need to arrange transportation home following treatment with SPRAVATO®.

Important Safety Information (continued)

Ulcerative or Interstitial Cystitis: Cases of ulcerative or interstitial cystitis have been reported in individuals with long-term off-label use or misuse/abuse of ketamine. In clinical studies with SPRAVATO® nasal spray, there was a higher rate of lower urinary tract symptoms (pollakiuria, dysuria, micturition urgency, nocturia, and cystitis) in SPRAVATO®-treated patients than in placebo-treated patients. No cases of esketamine-related interstitial cystitis were observed in any of the studies, which involved treatment for up to a year.

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

Embryo-fetal Toxicity: SPRAVATO® may cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to an infant exposed to SPRAVATO® *in utero*. Advise women of reproductive potential to consider pregnancy planning and prevention.

DRUG INTERACTIONS

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

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

Monoamine oxidase inhibitors (MAOIs): Concomitant use may increase blood pressure. Closely monitor blood pressure with concomitant use of MAOIs.

USE IN SPECIFIC POPULATIONS

Pregnancy: SPRAVATO® is not recommended during pregnancy. SPRAVATO® may cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to an infant exposed to SPRAVATO® *in utero*. There are risks to the mother associated with untreated depression in pregnancy. If a woman becomes pregnant while being treated with SPRAVATO®, treatment with SPRAVATO® should be discontinued and the patient should be counseled about the potential risk to the fetus.

Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including SPRAVATO®, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or online at *https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/*.

Lactation: SPRAVATO® is present in human milk. Because of the potential for neurotoxicity, advise patients that breastfeeding is not recommended during treatment with SPRAVATO®.

Females and Males of Reproductive Potential: SPRAVATO® may cause embryo-fetal harm when administered to a pregnant woman. Consider pregnancy planning and prevention for females of reproductive potential during treatment with SPRAVATO®.

Pediatric Use: The safety and effectiveness of SPRAVATO® in pediatric patients have not been established.

Geriatric Use: Of the total number of patients in Phase 3 clinical studies exposed to SPRAVATO®, 12% were 65 years of age and older, and 2% were 75 years of age and older. No overall differences in the safety profile were observed between patients 65 years of age and older and patients younger than 65 years of age.

Spravato® (esketamine) CIII nasal spray

Important Safety Information (continued)

The mean esketamine C_{max} and AUC values were higher in elderly patients compared with younger adult patients.

The treatment of TRD in geriatric patients was evaluated in a 4-week, randomized, double-blind study comparing flexibly-dosed intranasal SPRAVATO® plus a newly initiated oral antidepressant compared to intranasal placebo plus a newly initiated oral antidepressant in patients ≥65 years of age. At the end of four weeks, there was no statistically significant difference between groups on the primary efficacy endpoint of change from baseline to Week 4 on the Montgomery-Åsberg Depression Rating Scale (MADRS).

Hepatic Impairment: SPRAVATO®-treated patients with moderate hepatic impairment may need to be monitored for adverse reactions for a longer period of time.

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

DRUG ABUSE AND DEPENDENCE

Controlled Substance: SPRAVATO® contains esketamine hydrochloride, the (S)-enantiomer of ketamine and a Schedule III controlled substance under the Controlled Substances Act.

Abuse: Individuals with a history of drug abuse or dependence may be at greater risk for abuse and misuse of SPRAVATO®. Abuse is the intentional, non-therapeutic use of a drug, even once, for its psychological or physiological effects. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed. Careful consideration is advised prior to use of individuals with a history of substance use disorder, including alcohol.

SPRAVATO® may produce a variety of symptoms including anxiety, dysphoria, disorientation, insomnia, flashback, hallucinations, and feelings of floating, detachment and to be "spaced out." Monitoring for signs of abuse and misuse is recommended.

ADVERSE REACTIONS

The most common adverse reactions with SPRAVATO® plus oral AD (incidence ≥5% and at least twice that of placebo nasal spray plus oral AD) were dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk.

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Please see full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO®.