



A Guide to the SPRAVATO[®] REMS

The SPRAVATO[®] REMS Helps Facilitate Safe and Appropriate Use of SPRAVATO[®]

A Risk Evaluation and Mitigation Strategy (REMS) manages known or potential risks associated with a drug and is required by the US Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks.

Due to the risks of serious adverse outcomes resulting from sedation, dissociation, and respiratory depression caused by SPRAVATO[®] administration, as well as the risks of abuse and misuse, SPRAVATO[®] is available only through a restricted distribution program called the SPRAVATO[®] REMS. The SPRAVATO[®] REMS supports safe and appropriate use for treatment of patients.



SPRAVATO[®] is intended for patient administration under the direct observation of a healthcare provider. **SPRAVATO[®] is intended for use only in a certified healthcare setting and must never be dispensed directly to a patient for home use.**

For complete details on the SPRAVATO[®] REMS, visit [SPRAVATOREMS.COM](https://www.spravatorems.com).



Please see Indications and Important Safety Information, including Boxed WARNINGS, on pages 5-8. Please see full [Prescribing Information](#), including Boxed WARNINGS, and [Medication Guide](#) for SPRAVATO[®].

Steps for Enrolling in the SPRAVATO® REMS

All healthcare settings must be certified in the SPRAVATO® REMS to receive, dispense, and treat patients with SPRAVATO®.

1 Identify your healthcare setting type and designate an Authorized Representative (AR) to oversee REMS compliance



Outpatient

Covers outpatient medical offices and clinics



Inpatient

Covers inpatient units, inpatient pharmacies, and emergency departments

The AR can be any individual working in the healthcare setting who will be responsible for ensuring implementation and compliance with the SPRAVATO® REMS.

2 Determine your acquisition pathway

Consider acquiring SPRAVATO® through a pathway that is compatible with your patient's benefit design. You may choose to acquire SPRAVATO® through buy and bill, a specialty pharmacy, or both. **Indicate your chosen method(s) on the SPRAVATO® REMS enrollment form by selecting the appropriate boxes.** If you decide to make changes to your acquisition pathway in the future, your Authorized Representative must reach out to the SPRAVATO® REMS to update this information.



Buy and bill is the process of acquiring SPRAVATO® through an authorized specialty distributor and is typically covered under the medical benefit.*



The specialty pharmacy pathway is the process of acquiring SPRAVATO® through a REMS-certified specialty pharmacy.

3 Complete REMS enrollment online or by fax

To enroll in REMS online, you must create an online account by filling out and submitting the registration form at SPRAVATOREMS.com.†



Options for enrolling in REMS

- Use the online registration to ensure all required fields on the enrollment are accurately captured before submission
- If using a paper form, ensure all answers are legible



Most common reasons for delays in REMS enrollment include an incomplete healthcare setting enrollment form

- Missing, incorrect, or expired DEA number
- Missing signature and/or date
- The addresses for the healthcare setting and DEA number do not match

For REMS enrollment support, contact the SPRAVATO® REMS: 1-855-382-6022 (Monday – Friday, 8 AM to 8 PM ET).

*Selecting buy and bill during this step is not a commitment to a contract or purchasing agreement.

†The enrollment form may also be submitted by fax.

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Spravato®
(esketamine) 
28 mg nasal spray

An Additional Step Must Be Completed for Buy and Bill

4 Treatment centers interested in the buy-and-bill pathway must complete the Janssen Know Your Customer (KYC) Questionnaire to purchase, receive, and dispense SPRAVATO®.



Complete the KYC Questionnaire Electronically*

Once the buy-and-bill option is selected on the REMS Outpatient Enrollment Form, you will automatically be sent a KYC Questionnaire by the SPRAVATO® REMS Administrator.

Once the KYC Questionnaire is reviewed, your treatment center will receive an email from the SPRAVATO® REMS conveying the outcome of the review. Incomplete forms may delay the processing of the KYC questionnaire.

If you're currently a REMS-certified SPRAVATO® treatment center and would like to start using the buy-and-bill process, contact the REMS Coordinating Center at 1-855-382-6022.

For KYC questionnaire support, contact Janssen: ra-kycquestionnaire@its.jnj.com.

*Fax is available upon request.

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Maintaining Compliance With the SPRAVATO® REMS Requirements

Ongoing SPRAVATO® REMS requirements for patient treatment (outpatient setting)

Prior to starting treatment



Enroll each patient in the SPRAVATO® REMS by completing the **Patient Enrollment Form**

After each treatment session



Dose 1



Dose 2



Dose 3

Record each patient's treatment in a **Patient Monitoring Form** and submit it to REMS within 7 days*

Enroll patients and submit forms using the online **Prescriber Portal** or via fax. Using the **Prescriber Portal** will enable you to also set up delegate access to support **Patient Monitoring Form** submissions.†

Ongoing SPRAVATO® REMS requirements for treatment center staff



Maintain proper documentation of standard operating procedures, training protocols, and training logs

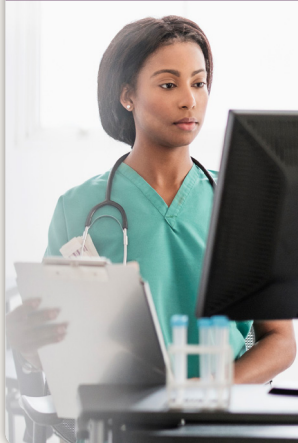


Keep current inventory logs of all shipments of SPRAVATO® received and patient dispensing information



Maintain up-to-date contact information for the Authorized Representative and communicate this information to the SPRAVATO® REMS coordinator

Potential required audits your treatment center may encounter



- As a REMS-certified SPRAVATO® treatment center, you may be selected for a **REMS audit**. Communication will come from the REMS mailbox email address spravato_surveys@ubc.com with the subject line "SPRAVATO Audit Questionnaire"
- Buy-and-bill-approved REMS-certified SPRAVATO® treatment centers may also be selected for a separate **KYC audit** to ensure controlled substance compliance. Communication will come from the KYC mailbox email address ra-kycquestionnaire@its.jnj.com with the subject line "Janssen SPRAVATO Know Your Customer Audit Questionnaire"
- If you are selected for either audit, it is important to comply with all information requests in the requested time frame. Any inability to comply can impact patient continuity of care‡

For ongoing compliance support, including portal and/or REMS audit-related questions, contact SPRAVATO® REMS: 1-855-382-6022 (Monday – Friday, 8 AM to 8 PM ET).
For KYC audit-related questions, contact Janssen: ra-kycquestionnaire@its.jnj.com.

*Inpatient healthcare settings are not required to enroll patients or submit the Patient Monitoring Form after each treatment.

†Delegates cannot enroll new patients in the SPRAVATO® REMS or designate additional delegates. They can only submit Patient Monitoring Forms.

‡The Knowledge, Attitude, and Behavior (KAB) Survey will also come from the SPRAVATO® REMS. It is sometimes confused with the REMS Audit Questionnaire. However, the KAB Survey is optional.

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Indications and Important Safety Information

Indications:

SPRAVATO® (esketamine) CIII Nasal Spray is indicated, in conjunction with an oral antidepressant, for the treatment of:

- Treatment-resistant depression (TRD) in adults.
- Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior.

Limitations of Use:

- The effectiveness of SPRAVATO® in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use of SPRAVATO® does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of SPRAVATO®.
- 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; RESPIRATORY DEPRESSION; ABUSE AND MISUSE; and SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning

- **Risk for sedation, dissociation, and respiratory depression after administration. Monitor patients for at least two hours after administration (5.1, 5.2, 5.3).**
- **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 (5.4).**
- **SPRAVATO® is only available through a restricted program called the SPRAVATO® REMS (5.5).**
- **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 (5.6).**

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: SPRAVATO® may cause sedation or loss of consciousness. In some cases, patients may display diminished or less apparent breathing. In clinical trials, 48% to 61% of SPRAVATO®-treated patients developed sedation and 0.3% to 0.4% 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 (e.g., benzodiazepines, opioids, alcohol).

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 84% 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.

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Important Safety Information (continued)

WARNINGS AND PRECAUTIONS (continued)

Respiratory Depression: In postmarketing experience, respiratory depression was observed with the use of SPRAVATO®. In addition, there were rare reports of respiratory arrest.

Because of the risks of respiratory depression, patients must be monitored for changes in respiratory status by a healthcare provider for at least 2 hours (including pulse oximetry) at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting.

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® 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, respiratory depression, 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 and administered in healthcare settings.
 - Patients treated in outpatient settings (e.g., medical offices and clinics) must be 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.

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

Approximately 8% to 19% 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 SPRAVATO®, 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 take into account the balance of benefit and risk in individual patients.

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Important Safety Information (continued)

WARNINGS AND PRECAUTIONS (continued)

Increase in Blood Pressure (continued):

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 (e.g., amphetamines, methylphenidate, modafinil, armodafinil) or monoamine oxidase inhibitors (MAOIs).

In patients with a 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. Compared to placebo-treated subjects, 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®.

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.

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Important Safety Information (continued)

PREGNANCY, EMBRYO-FETAL TOXICITY, AND LACTATION

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*. Advise women of reproductive potential to consider pregnancy planning and prevention.

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/>.

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

SELECT USE IN SPECIFIC POPULATIONS

Geriatric Use: 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. At the end of a 4-week, randomized, double-blind study, there was no statistically significant difference between groups on the primary efficacy endpoint.

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.

ADVERSE REACTIONS

The most common adverse reactions with SPRAVATO® plus oral antidepressant (incidence $\geq 5\%$ and at least twice that of placebo nasal spray plus oral antidepressant) were:

TRD: dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk.

Treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior: dissociation, dizziness, sedation, blood pressure increased, hypoesthesia, vomiting, euphoric mood, and vertigo.

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