Spravato® (esketamine) CIII nasal spray

Pathway to Acquire SPRAVATO® from an Authorized Specialty Distributor

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; 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 additional Important Safety Information, including Boxed WARNINGS, on pages 10-13.
Please see full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO®.
Provide the Medication Guide to your patients and encourage discussion.

Acquiring SPRAVATO® Through Buy-and-Bill

SPRAVATO® has a controlled distribution network that ensures SPRAVATO® is distributed only to REMS (Risk Evaluation and Mitigation Strategy)-certified pharmacies and REMS-certified healthcare settings. SPRAVATO® will not be delivered or dispensed directly to patients.

Once your site has decided to become a REMS-certified SPRAVATO® treatment center, it is important to understand the various procurement models available to acquire SPRAVATO®.

The buy-and-bill model is the preferred way to ensure access for patients whose coverage is under the medical benefit. The model can be used exclusively or in conjunction with other procurement models to provide the widest range of coverage options for your appropriate SPRAVATO® adult patient population.

Buy-and-bill considerations at treatment centers

- Treatment center purchases multiple devices to have on hand, as needed
- Drug supply is not pre-assigned to specific patients, allowing for dosing and scheduling flexibility[1]
- Treatment center is responsible for all elements of the treatment process (such as prior authorization, treatment administration, and reimbursement claim submission) and storage and handling of inventory in accordance with state and federal regulations
- Treatment center may be eligible for manufacturer discount and rebate programs

Intended audience

This resource provides guidance on how to acquire SPRAVATO® from an Authorized Specialty Distributor. The intended audience for this resource is independent physician-owned and -operated offices or any hospital-owned outpatient clinics primarily operated by a physician and classified as a physician class of trade. Pharmacies, hospitals, and other classes of trade should refer to the Authorized SPRAVATO® Distributor List for a list of full-line wholesalers on **spravatotreatmentcenter.com/education**

Become a REMS-Certified SPRAVATO® Buy-and-Bill Treatment Center

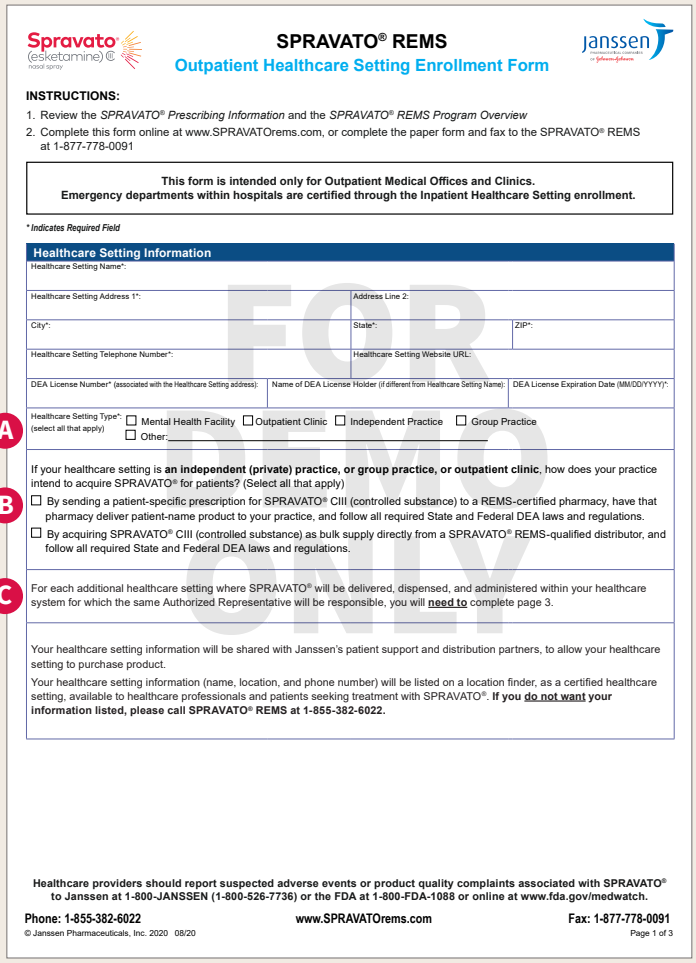
Treatment centers that want to utilize the buy-and-bill pathway must be a SPRAVATO® REMS-certified treatment center and must establish or have an account with a SPRAVATO® Authorized Specialty Distributor (SD).

Complete the following steps to acquire SPRAVATO® through the buy-and-bill pathway.

REMS

STEP 1

Complete the SPRAVATO® *REMS Outpatient Healthcare Setting Enrollment Form* online or by fax to initiate REMS certification



Spravato® (esketamine) C-III nasal spray

SPRAVATO® REMS
Outpatient Healthcare Setting Enrollment Form

janssen

INSTRUCTIONS:

1. Review the *SPRAVATO® Prescribing Information* and the *SPRAVATO® REMS Program Overview*
2. Complete this form online at www.SPRAVATOrems.com, or complete the paper form and fax to the SPRAVATO® REMS at 1-877-778-0091

This form is intended only for Outpatient Medical Offices and Clinics.
Emergency departments within hospitals are certified through the Inpatient Healthcare Setting enrollment.

** Indicates Required Field*

Healthcare Setting Information

Healthcare Setting Name*:

Healthcare Setting Address 1*: | Address Line 2:

City*: | State*: | ZIP*:

Healthcare Setting Telephone Number*: | Healthcare Setting Website URL:

DEA License Number* (associated with the Healthcare Setting address): | Name of DEA License Holder (if different from Healthcare Setting Name): | DEA License Expiration Date (MM/DD/YYYY)*:

A Healthcare Setting Type* (select all that apply) ☐ Mental Health Facility ☐ Outpatient Clinic ☐ Independent Practice ☐ Group Practice ☐ Other:_____

If your healthcare setting is **an independent (private) practice, or group practice, or outpatient clinic**, how does your practice intend to acquire SPRAVATO® for patients? (Select all that apply)

B ☐ By sending a patient-specific prescription for SPRAVATO® CIII (controlled substance) to a REMS-certified pharmacy, have that pharmacy deliver patient-name product to your practice, and follow all required State and Federal DEA laws and regulations.

☐ By acquiring SPRAVATO® CIII (controlled substance) as bulk supply directly from a SPRAVATO® REMS-qualified distributor, and follow all required State and Federal DEA laws and regulations.

C For each additional healthcare setting where SPRAVATO® will be delivered, dispensed, and administered within your healthcare system for which the same Authorized Representative will be responsible, you will **need to** complete page 3.

Your healthcare setting information will be shared with Janssen's patient support and distribution partners, to allow your healthcare setting to purchase product.

Your healthcare setting information (name, location, and phone number) will be listed on a location finder, as a certified healthcare setting, available to healthcare professionals and patients seeking treatment with SPRAVATO®. **If you do not want your information listed, please call SPRAVATO® REMS at 1-855-382-6022.**

FOR DEMO ONLY

Healthcare providers should report suspected adverse events or product quality complaints associated with SPRAVATO® to Janssen at 1-800-JANSSEN (1-800-526-7736) or the FDA at 1-800-FDA-1088 or online at www.fda.gov/medwatch.

Phone: 1-855-382-6022 **www.SPRAVATOrems.com** **Fax: 1-877-778-0091**

Location A

Select the appropriate box for your healthcare setting type

Location B

Indicate that your healthcare setting intends to acquire bulk supply of SPRAVATO® directly from a SPRAVATO® REMS-qualified distributor

Location C

Complete page 3 of the form for any additional healthcare settings for which the same Authorized Representative will be responsible.

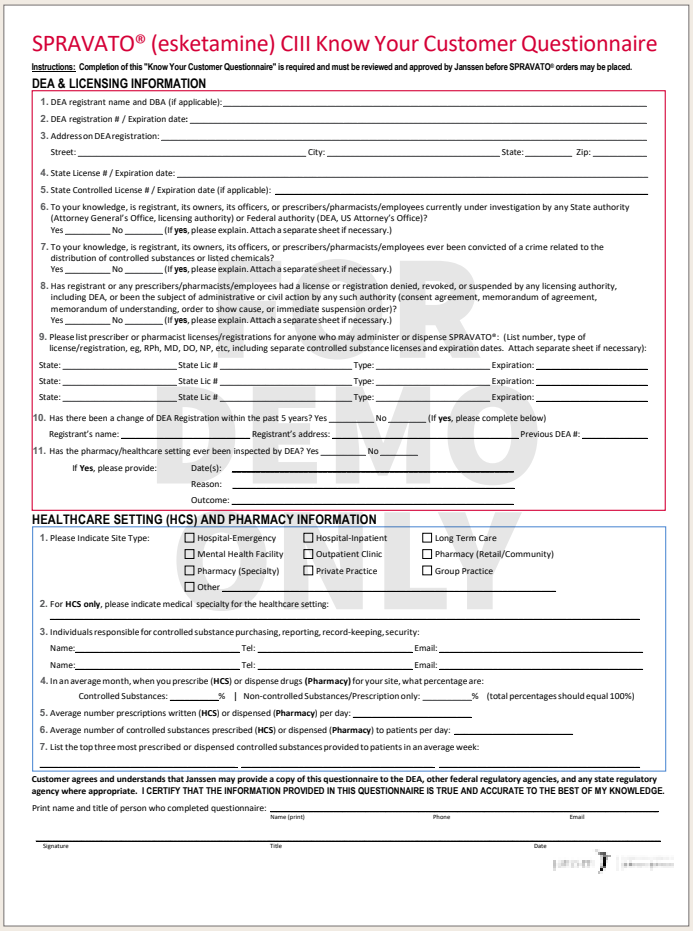
NOTE: Each additional healthcare setting that intends to also purchase product directly from a distributor will be required to complete the *Know Your Customer Questionnaire* (see STEP 2 on the next page for more information)

For more information about SPRAVATO® REMS, please see page 9 of this resource. SPRAVATO® REMS forms and instructions can be found at **https://www.spravatorems.com/healthcare-settings.html**

Become a REMS-Certified SPRAVATO® Buy-and-Bill Treatment Center (cont'd)

STEP 2
Complete the SPRAVATO® Know Your Customer Questionnaire

- The completion of the above steps will trigger a Janssen Controlled Substance *Know Your Customer Questionnaire* to be sent to the email on file by the SPRAVATO® REMS Administrator
- Complete the *Know Your Customer Questionnaire* in its **entirety** and send by fax (1-877-778-0091) to the SPRAVATO® REMS Administrator



SPRAVATO® (esketamine) CIII Know Your Customer Questionnaire

Instructions: Completion of this "Know Your Customer Questionnaire" is required and must be reviewed and approved by Janssen before SPRAVATO® orders may be placed.

DEA & LICENSING INFORMATION

1. DEA registrant name and DBA (if applicable): _____
2. DEA registration # / Expiration date: _____
3. Address on DEA registration: _____
   Street: _____ City: _____ State: _____ Zip: _____
4. State License # / Expiration date: _____
5. State Controlled License # / Expiration date (if applicable): _____
6. To your knowledge, is registrant, its owners, its officers, or prescribers/pharmacists/employees currently under investigation by any State authority (Attorney General's Office, licensing authority) or Federal authority (DEA, US Attorney's Office)?
   Yes _____ No _____ (If **yes**, please explain. Attach a separate sheet if necessary.)
7. To your knowledge, is registrant, its owners, its officers, or prescribers/pharmacists/employees ever been convicted of a crime related to the distribution of controlled substances or listed chemicals?
   Yes _____ No _____ (If **yes**, please explain. Attach a separate sheet if necessary.)
8. Has registrant or any prescribers/pharmacists/employees had a license or registration denied, revoked, or suspended by any licensing authority, including DEA, or been the subject of administrative or civil action by any such authority (consent agreement, memorandum of agreement, memorandum of understanding, order to show cause, or immediate suspension order)?
   Yes _____ No _____ (If **yes**, please explain. Attach a separate sheet if necessary.)
9. Please list prescriber or pharmacist licenses/registrations for anyone who may administer or dispense SPRAVATO®: (List number, type of license/registration, eg, RPh, MD, DO, NP, etc, including separate controlled substance licenses and expiration dates. Attach separate sheet if necessary):
   State: _____ State Lic # _____ Type: _____ Expiration: _____
   State: _____ State Lic # _____ Type: _____ Expiration: _____
   State: _____ State Lic # _____ Type: _____ Expiration: _____
10. Has there been a change of DEA Registration within the past 5 years? Yes _____ No _____ (If **yes**, please complete below)
    Registrant's name: _____ Registrant's address: _____ Previous DEA #: _____
11. Has the pharmacy/healthcare setting ever been inspected by DEA? Yes _____ No _____
    If **Yes**, please provide: Date(s): _____
    Reason: _____
    Outcome: _____

HEALTHCARE SETTING (HCS) AND PHARMACY INFORMATION

1. Please Indicate Site Type:
   ☐ Hospital-Emergency ☐ Hospital-Inpatient ☐ Long Term Care
   ☐ Mental Health Facility ☐ Outpatient Clinic ☐ Pharmacy (Retail/Community)
   ☐ Pharmacy (Specialty) ☐ Private Practice ☐ Group Practice
   ☐ Other _____
2. For **HCS only**, please indicate medical specialty for the healthcare setting: _____
3. Individuals responsible for controlled substance purchasing, reporting, record-keeping, security:
   Name: _____ Tel: _____ Email: _____
   Name: _____ Tel: _____ Email: _____
4. In an average month, when you prescribe (**HCS**) or dispense drugs (**Pharmacy**) for your site, what percentage are:
   Controlled Substances: _____% | Non-controlled Substances/Prescription only: _____% (total percentages should equal 100%)
5. Average number prescriptions written (**HCS**) or dispensed (**Pharmacy**) per day: _____
6. Average number of controlled substances prescribed (**HCS**) or dispensed (**Pharmacy**) to patients per day: _____
7. List the top three most prescribed or dispensed controlled substances provided to patients in an average week: _____

Customer agrees and understands that Janssen may provide a copy of this questionnaire to the DEA, other federal regulatory agencies, and any state regulatory agency where appropriate. I CERTIFY THAT THE INFORMATION PROVIDED IN THIS QUESTIONNAIRE IS TRUE AND ACCURATE TO THE BEST OF MY KNOWLEDGE.

Print name and title of person who completed questionnaire: _____
Name (print) Phone Email

_____
Signature Title Date

- Upon successful completion of this process and Janssen review, you will receive a confirmation email from SPRAVATO® REMS with a subject line reading "SPRAVATO® REMS Notice – Approved to be on controlled-distribution list"

NOTE: Save copies of REMS certification and *Know Your Customer Questionnaire* approval letters for your documentation.

If you have any questions about the SPRAVATO® REMS or need help with certification or enrollment, call 1-855-382-6022 (Monday – Friday, 8AM – 8PM ET).

Please see Important Safety Information, including Boxed WARNINGS, on pages 10-13.
Please see full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO®.
Provide the Medication Guide to your patients and encourage discussion.

Spravato® (esketamine) CIII nasal spray

Connect With a SPRAVATO® Authorized SD

STEP 3
Contact a SPRAVATO® Authorized Specialty Distributor (SD)

The distributors listed below are authorized to dispense SPRAVATO® to REMS-certified treatment centers who buy-and-bill. **These Specialty Distributors cannot distribute product to customers until they have successfully completed all of STEPS 1 and 2 above and received an "Approved to be on controlled-distribution list" email notification from the SPRAVATO® REMS Administrator.**

Authorized SPRAVATO® Specialty Distributors

Specialty Distributors	Phone Number	Fax	Website
Besse Medical	1-800-543-2111	1-800-543-8695	www.besse.com
Cardinal Health Specialty Distribution	1-877-453-3972	1-877-274-9897	https://www.cardinalhealth.com/en/services/acute/logistics-solutions-acute/distribution/specialty-distribution
CuraScript Specialty Distribution	1-877-599-7748	1-800-862-6208	www.curascriptsd.com
McKesson Specialty Health	1-855-477-9800	—	www.mckessonspecialtyhealth.com

This list is provided for informational purposes only. Janssen Pharmaceuticals, Inc., does not endorse the use of any particular distributor. This information was current at the time of publication.

NOTE: Regardless of any existing Full-Line Wholesaler or Medical and Surgical Supplies Distributor accounts, certified treatment centers need to set up a new account with the SPRAVATO® Authorized SD in order to buy-and-bill.

Connect With a SPRAVATO® Authorized SD (cont'd)

STEP 4
Submit an application and allow time for the SPRAVATO® Authorized SD to review

- New customer applications may require treatment centers to
  - Submit required information for the SPRAVATO® Authorized SD to perform
  - Submit copies of all applicable Drug Enforcement Administration (DEA) certifications and applicable licenses
  - Provide business background information (ie, type of business, estimated volume, list of company offices, information on key individuals)
  - Provide credit reference
- Authorized SD will review information provided by site and may take the following actions
  - Conduct credit and background checks on key site personnel (bankruptcy, criminal)
  - Conduct site visits to confirm legitimacy of business
  - Evaluate if site will meet Authorized SD minimum volume requirements

Application Decision: Approximately 7-10 days after a completed application is received

NOTE: Each SPRAVATO® Authorized SD will have its own processes and requirements that may increase approval time. Please follow the requirements provided by the Authorized SD with which you have chosen to contract.

Once approved, the account is eligible to order from the Authorized SD. However, the treatment center must have also completed **STEPS 1 and 2** in this guide to be approved to receive a controlled substance.

Once **STEPS 1 through 4** of this guide have been successfully completed, the account is eligible to procure SPRAVATO® from its Authorized SD.

Follow the Buy-and-Bill Process for SPRAVATO®

Once your treatment center is fully certified and has an active account with an Authorized SD, you can utilize the buy-and-bill pathway to acquire SPRAVATO® to treat appropriate adult patients who have SPRAVATO® covered under the medical benefit.

In the buy-and-bill model, a healthcare provider purchases a drug from an SD and, after administering the drug, the provider submits a claim for reimbursement for the drug and any other medical services associated with the treatment to the payer.

STEP 5
Follow the buy-and-bill process for SPRAVATO®

Treatment centers intending to buy-and-bill for product...

- Acquire bulk drug supply from an Authorized Specialty Distributor
- Store and handle product in accordance with state and federal regulations
- Identify and verify patient benefits, including prior authorization requirements
- **TREATMENT DAY**
  - Treat patient with drug from inventory
  - Bill payer for product and associated services
- Receive reimbursement for product and associated psychiatric services from payer*
- Pay Specialty Distributor for product acquired at discounted rate†‡
- Subject to eligibility requirements, receive rebate from manufacturer for product acquired

*Payment terms will be subject to payer/provider contract.
†Payment terms are subject to provider/SD contract.
‡Manufacturer discount and rebate depend on program eligibility requirements.

Please see Important Safety Information, including Boxed WARNINGS, on pages 10-13.
Please see full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO®.
Provide the Medication Guide to your patients and encourage discussion.

Spravato® (esketamine) CIII nasal spray

Important Considerations and FAQs

Important Considerations

The information presented is for educational purposes only and is not intended to represent a promise, guarantee or legal advice by Janssen Pharmaceuticals, Inc. about coverage, levels of reimbursement, payments, billings or practice efficiencies. Please consult with your legal counsel or reimbursement specialist for advice specific to your institution.

The SPRAVATO® treatment center is responsible for confirming the applicable billing, coverage, and payment policies with third-party payors. It is important to check with individual payors, local carriers or intermediaries, or your legal counsel, for specific coverage and billing guidance.

SPRAVATO® treatment centers remain responsible for submitting accurate claims for SPRAVATO® or related services in accordance with applicable payor policies.

Frequently Asked Questions

Why is the *Know Your Customer Questionnaire* required to complete the application process?

Since SPRAVATO® is a Class III controlled substance, the *Know Your Customer Questionnaire* helps Janssen better understand each healthcare setting's current handling of controlled substances (if any) and gather DEA and licensing information.

Janssen may provide a copy of this questionnaire to the DEA, other federal regulatory agencies, and any state regulatory agency, where appropriate.

How do Full-Line Wholesalers differ from Specialty Distributors?

- **Full-Line Wholesalers** buy the product line, inventory it, and distribute a manufacturer's entire pharmaceutical product line unless otherwise arranged[2]
- **Specialty distributors** sell specialty products primarily to independent physician-owned or -operated clinics, hospitals, and outpatient clinics owned by hospitals[2]

Do I still need to set up an account with a SPRAVATO® Authorized SD if I am purchasing from a Full-Line Wholesaler?

Regardless of any existing Full-Line Wholesaler or Medical and Surgical Supplies Distributor accounts, certified treatment centers need to set up a new account with the SPRAVATO® Authorized SD in order to buy-and-bill.

Who should I contact if my site is a hospital, institution, or pharmacy?

Contact a SPRAVATO® Authorized Full-Line Wholesaler listed on the SPRAVATO® Authorized Distributor List, which is available on **spravatotreatmentcenter.com/education**

SPRAVATO® REMS

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

SPRAVATO® is available only through a restricted distribution program called the SPRAVATO® REMS because of the risks of serious adverse outcomes resulting from sedation and dissociation caused by SPRAVATO® administration and abuse and misuse of SPRAVATO®. SPRAVATO® is intended for use only in a certified healthcare setting.

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. SPRAVATO® must never be dispensed directly to a patient for home use.

What are the REMS requirements?

1. **Healthcare setting certification**
   All healthcare settings must be certified in the REMS in order to receive, dispense, and/or treat patients with SPRAVATO®.
2. **Pharmacy certification**
   All pharmacies must be certified in the REMS in order to receive and dispense SPRAVATO®.
3. **Patient enrollment**
   Patients in an **outpatient** setting must be enrolled in the REMS with their prescriber in order to receive SPRAVATO® treatment.

Healthcare Settings Type*

All REMS-certified Inpatient and Outpatient Healthcare Settings must have a healthcare provider counsel patients on the safety risk of SPRAVATO® and monitor patients post-dose.

Inpatient healthcare settings

- Covers inpatient units, inpatient pharmacy, emergency departments
- Before prescribing SPRAVATO® treatment, complete and submit the ***inpatient healthcare setting enrollment form***
- Before starting SPRAVATO® treatment, inpatient settings are not required to enroll the patient in the SPRAVATO® REMS
- During SPRAVATO® treatment, inpatient settings do not require the ***patient monitoring form***. Report all suspected adverse events to SPRAVATO® REMS

Outpatient healthcare settings

- Covers outpatient medical offices and clinics
- Before prescribing SPRAVATO® treatment, complete and submit the ***outpatient healthcare setting enrollment form***
- Before starting SPRAVATO® treatment, enroll the patient by completing and submitting the ***patient enrollment form*** to the SPRAVATO® REMS
- During SPRAVATO® treatment, submit the ***patient monitoring form*** and report all suspected adverse events to the SPRAVATO® REMS

*To get started, find more information on how to certify as a healthcare setting and/or pharmacy, and to view all REMS requirements and attestations by type of REMS stakeholder, visit **www.SPRAVATOrems.com or call 1-855-382-6022 (8AM to 9PM ET)**.

Please see Important Safety Information, including Boxed WARNINGS, on pages 10-13.
Please see full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO®.
Provide the Medication Guide to your patients and encourage discussion.

Spravato® (esketamine) CIII nasal spray

Indications and Important Safety Information for SPRAVATO® (esketamine) CIII Nasal Spray

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; 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, 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 *[see Drug Interaction (7.1)]*.

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

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.

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

(continued on next page)

Important Safety Information for SPRAVATO® (esketamine) CIII Nasal Spray (cont'd)

Abuse and Misuse (cont'd)

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 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.

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

(continued on next page)

Important Safety Information for SPRAVATO® (esketamine) CIII Nasal Spray (cont'd)

Increase in Blood Pressure (cont'd)

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®.

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/*.

(continued on next page)

Important Safety Information for SPRAVATO® (esketamine) CIII Nasal Spray (cont'd)

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.

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

The efficacy of SPRAVATO® for 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 antidepressant (incidence ≥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.

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

cp-170362v1

References:

1. SPRAVATO® [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. July 2020.
2. Fein AJ. The 2018-19 economic report on pharmaceutical wholesalers and specialty distributors. Drug Channels Institute. October 2019. Accessed August 20, 2020. https://www.drugchannels.net/2018/10/ new-201819-economic-report-on.html

Spravato® (esketamine) C-III nasal spray

Please see Important Safety Information, including Boxed WARNINGS, on pages 10-13.
Please see full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO®.
Provide the Medication Guide to your patients and encourage discussion.

Janssen Neuroscience

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