Spravato® (esketamine) CIII
28 mg 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; 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).**

Please see additional Important Safety Information on pages 11-13.
Please see full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO®.
Provide the Medication Guide to your patients and encourage discussion.

Acquire SPRAVATO® Through Buy and Bill

SPRAVATO® has a controlled distribution network that ensures its distribution only to Risk Evaluation and Mitigation Strategy (REMS)–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

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

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 **www.spravatotreatmentcenter.com/education**

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

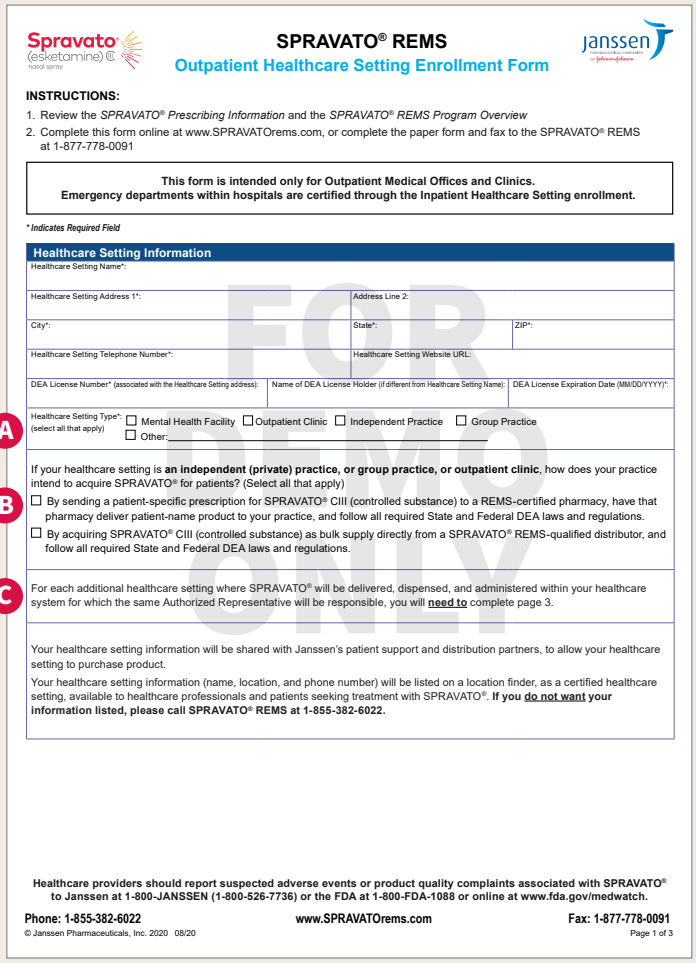
Treatment centers that want to utilize the buy-and-bill pathway must be a SPRAVATO® REMS-certified treatment center and must have or establish an account with a SPRAVATO® authorized specialty distributor (SD).

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 SPRAVATO® directly from a SPRAVATO® REMS-qualified distributor.

Location C

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

NOTE: Each additional healthcare setting within your healthcare system 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)

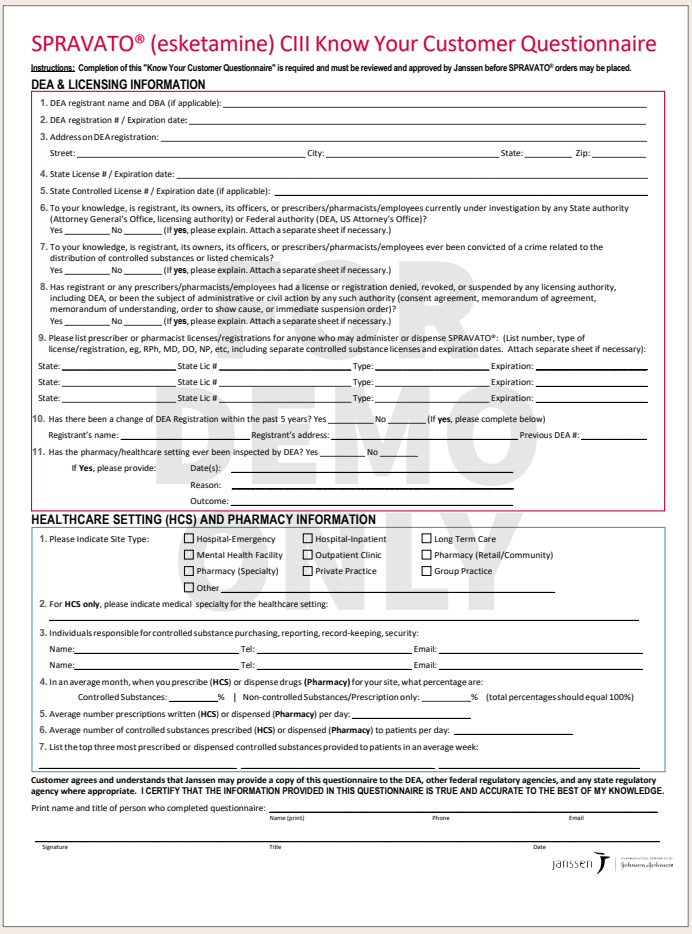
For more information about SPRAVATO® REMS, please visit www.spravatorems.com. SPRAVATO® REMS forms and instructions can be found at www.spravatorems.com/healthcare-settings.html

Spravato® (esketamine) C III 28 mg nasal spray

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

STEP 2
Complete the SPRAVATO® *Know Your Customer Questionnaire (KYC)*

- The completion of Step 1 will trigger the SPRAVATO® REMS Administrator to send a *Know Your Customer Questionnaire* to the email on file
- Complete the *Know Your Customer Questionnaire* in its **entirety** and submit electronically, using the eKYC form link in the confirmation email provided during the REMS enrollment process, or via 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

janssen

- Upon successful completion of this process and Johnson & Johnson's approval, 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, 8:00 AM – 8:00 PM ET).

eKYC= electronic Know Your Customer.

Please see Important Safety Information on pages 11-13.
Please see full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO®.
Provide the Medication Guide to your patients and encourage discussion.

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28 mg nasal spray

Connect With a SPRAVATO® Authorized Specialty Distributor (SD)

STEP 3
Contact a SPRAVATO® Authorized SD

The distributors listed below are authorized to dispense SPRAVATO® to REMS-certified treatment centers that buy and bill. **These SDs 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® SDs

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]	[1-614-553-6301]	www.cardinalhealth.com
CuraScript Specialty Distribution	[1-877-599-7748]	N/A	www.curascriptsd.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.

*Providers with psychiatry specialty only.

Establish an Account With a SPRAVATO® Authorized SD

STEP 4
Familiarize yourself with the SPRAVATO® SD account set-up process

While each SD has its own unique processes and requirements, this flow is common to all:

1 Initiate account setup

- Treatment center contacts authorized SPRAVATO® SD
- SD provides treatment center with requirements and forms for completion

2 Treatment center gathers licenses/documentation and completes forms

- Controlled substance questionnaire
- New account form
- Ordering set-up form
- Credit application & agreement

(See page 7)

3 Treatment center submits forms

- Completed signed forms and requested copies of licensures are submitted via SD portal or email

(See page 8)

4 SD reviews submitted forms and documentation

- SD approves application

OR

- Incomplete forms are returned to the treatment center (restart # 2)

5 Account approval notification

- Treatment center receives new account information and ordering instructions

6 Treatment center begins placing orders for SPRAVATO®

- Order placement is now available for your practice/ treatment center

Establish an Account With a SPRAVATO® Authorized SD (cont'd)

2 Treatment center gathers licenses/documentation and completes forms

STEP 4 (cont'd)

Organize forms and professional documentation in advance for greater efficiency

Key information that may be needed to establish your SPRAVATO® SD account:

Business information

- ☐ Business legal name and address
- ☐ Shipping address
- ☐ Proof of business registration
- ☐ Health industry number (HIN)
- ☐ National provider identifier (NPI)
- ☐ Global locator number (GLN)

Licenses/certifications

- ☐ Practitioner state medical license number
- ☐ Practitioner DEA license
- ☐ State board of pharmacy license number
- ☐ Controlled substance state license (if applicable)
- ☐ SPRAVATO® REMS certification for buy and bill

Financial information

- ☐ Tax identification number
- ☐ Credit/bank references
- ☐ Tax exemption certificates

SD requirements may vary. Adhere to specific requirements communicated from the SD during the application process.

If you're unsure about the information being requested, have any questions, or need assistance, contact your SD representative—they are there to help you

Establish an Account With a SPRAVATO® Authorized SD (cont'd)

3 Treatment center submits forms

STEP 4 (cont'd)
Prevent delays by avoiding common errors

Common errors

- **Mismatched information with official documents**
  - Inconsistencies between the information on the form and what is on official documents (eg, DEA license, business license)
- **Errors or omissions on forms**
  - Typos, inaccurate business details, or leaving required fields blank
- **Eligibility Error**
  - All healthcare settings must be certified in the SPRAVATO® REMS and have completed a *Know Your Customer Questionnaire (KYC)* before beginning SD contracting
- **Forgetting to attach documentation**
  - Not attaching required documents such as licenses, permits, tax information, or photographs of center (when required)

Tips to avoid errors

- **Read carefully**
  - Follow all instructions provided by the SD
- **Gather information**
  - Have your licenses, business, and financial documentation available before you begin
- **Ensure consistency**
  - Confirm the information you provide matches exactly with your licenses and other official documents
- **Double-check**
  - Proofread all entries for errors and accuracy; be sure you attach/upload all required documents

Following approval of your KYC Questionnaire, contact Johnson & Johnson Health Care Systems (JJHCS) to start your physician pricing agreement. This can be done alongside the SD account setup

Contact JJHCS at:
Email: RA-HCSUS-ContractP@ITS.JNJ.com

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 to the payer for reimbursement of the drug and any other medical services associated with the treatment.

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

- Acquire drug supply from an authorized SD
- Store and handle product in accordance with state and federal regulations
- Before treatment, 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 SD for product acquired at discounted rate within the timeline agreed upon with the SD†,‡

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

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 payers. It is important to check with individual payers, 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 payer 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 (KYC)* helps Janssen better understand each healthcare setting's current handling of controlled substances (if any) and gather Drug Enforcement Administration (DEA) and licensing information.

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

How do SPRAVATO® full-line wholesalers differ from SPRAVATO® SDs?

- **SPRAVATO® authorized full-line wholesalers** primarily distribute to pharmacies as well as inpatient and outpatient hospitals[2]
- **SPRAVATO® authorized SDs** primarily sell to independent physician-owned or operated clinics[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 at **spravatotreatmentcenter.com/education**

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

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.

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.

(continued on next page)

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
28 mg nasal spray

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

Suicidal Thoughts and Behaviors in Adolescents and Young Adults (cont'd)

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 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®.

(continued on next page)

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

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.

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 ≥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-170362v5

References:

1. SPRAVATO® [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.
2. Fein AJ. The 2018-19 economic report on pharmaceutical wholesalers and specialty distributors. Drug Channels Institute. October 2019. Accessed July 29, 2024. https://www.drugchannels.net/2018/10/ new-201819-economic-report-on.html

Please see full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO®. Provide the Medication Guide to your patients and encourage discussion.

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Spravato® (esketamine) CIII 28 mg nasal spray