Spravato® (esketamine) CIII
28 mg nasal spray

Referring Your Appropriate Patients with Treatment-Resistant Depression (TRD) to a REMS-Certified SPRAVATO® Treatment Center

A complete step-by-step guide to the referral process.

Indication:

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

- Treatment-resistant depression (TRD) in adults.

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.

REMS=Risk Evaluation and Mitigation Strategy.

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).**

(continued on page 3)

Please see additional Important Safety Information throughout this guide and full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO®.

The Referral Journey

Spravato® (esketamine) C-III
28 mg nasal spray

Click on icon to learn more

1. Identify appropriate patient for SPRAVATO®

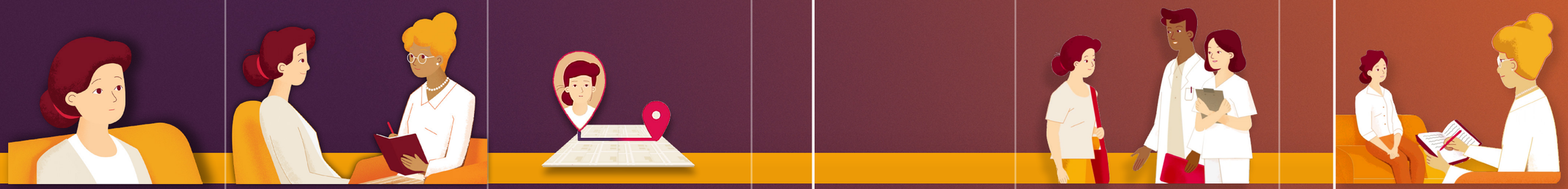
2. Educate patient and set expectations

3. Locate a treatment center with patient

4. Establish relationship with treatment center

8. Continue care of your patient during SPRAVATO® treatment

Referring Physician



Patient

5. Obtain all patient information

6. Consult on first visit

7. Begin treatment on second visit

Treatment Center

Treatment center=REMS-certified SPRAVATO® treatment center.

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The Referral Journey

Return to Referral Journey visual

Spravato® (esketamine) C III
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Step 1: Identify appropriate adult patients for SPRAVATO®

Adult patients with TRD are those with challenging-to-treat major depressive disorder (MDD) who have not adequately responded to at least 2 different oral antidepressants of adequate dose and duration in their current depressive state.[1]

Step 2: Educate patients about SPRAVATO®

Consider these points when setting expectations about the treatment experience and SPRAVATO®:

- SPRAVATO® nasal spray can only be administered at a REMS-certified treatment center
- Review the benefits and risks associated with SPRAVATO®, including Boxed WARNINGS for sedation, dissociation, abuse and misuse, and suicidal thoughts and behaviors[1]
- SPRAVATO® is administered by patients under the direct observation of a healthcare provider who will continue to monitor them for at least 2 hours after administration for side effects[1]
- All patients treated at an outpatient setting must enroll in the REMS program (done at the treatment center)[1]
- Provide your patients with a copy of the **Medication Guide**[1]
- For additional information, patients can go to **spravato.com/trd/preparing-for-treatment**

Important Safety Information (continued)

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

(continued on page 4)

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The Referral Journey

Return to Referral Journey visual

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Step 3: Locate a treatment center

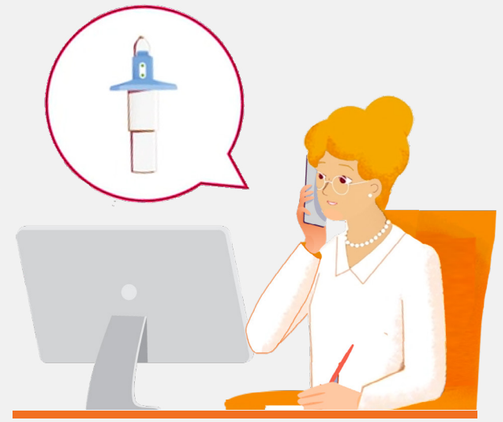
- Go to **spravatohcp.com/find-a-center**
- Enter patient's ZIP Code to help identify the treatment center that is most convenient for them
- Call the treatment center to determine if they accept your patient's insurance

Step 4: Proactively start a relationship with the treatment center

If you don't already have one, now is the time to establish rapport with the treatment center.

- Gaining a better understanding of their processes and procedures and speaking to care coordinators may allow for easier referrals in the future
- It might be helpful to find out if they have an intake form on their website that provides instructions for referrers
- Once the referral has been made, the treatment center may ask for additional information about your patient

You might want to specify your preference for SPRAVATO® since some centers may offer additional treatment options.



Important Safety Information (continued)

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

(continued on page 5)

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The Referral Journey

Return to Referral Journey visual

Spravato® (esketamine) C-III
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Step 5: Treatment center requests and obtains all patient information

Providing patient information to the treatment center may help ensure timely coordination of care and a more seamless experience for your patient. Below is some information you may need to provide:

Patient information

- Name
- Date of birth
- Gender
- Phone number
- Address
- Caregiver's name and phone number

Patient insurance information

- Primary insurance
- Policy #
- Group #
- Policyholder's name
- Card/BIN #

Clinical information

- Diagnosis
- Laboratory procedures/ tests and dates
- Medical history
- Medication history

It's helpful to include your contact information in case the treatment center has questions.

If your adult patients with TRD choose to call for an appointment themselves, be sure to advise them to request an initial consultation for SPRAVATO®. Your patient should not expect to get SPRAVATO® treatment on their first visit to the treatment center.

Step 6: First visit: patient has consultation only

Once your patient is referred to a REMS-certified SPRAVATO® treatment center, the treatment center generally handles all paperwork:

- Takes your patient's history and confirms TRD diagnosis
- Registers your patient in the REMS program
- Performs an insurance review
- Verifies billing and payment process to ensure the treatment center can get reimbursed

The healthcare provider at the treatment center helps your patient build a treatment plan and discusses risks of abuse, misuse, sedation, and dissociation.

- Your patient is unlikely to receive SPRAVATO® until the second visit

Important Safety Information (continued)

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.

(continued on page 6)

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The Referral Journey

Return to Referral Journey visual

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Step 7: Second visit: patient begins treatment with SPRAVATO®

- On treatment days, your patients will learn how to administer SPRAVATO® under the supervision of a healthcare provider
- Patients will be monitored for possible side effects for at least 2 hours and may want to listen to music, read, or just relax during this time
- Patients will need to plan for rides after treatment because they cannot drive, operate machinery, or do anything where they need to be completely alert until the next day after a restful sleep[1]

Step 8: Continuing care during treatment

As the referring physician, you may want to consider the following:

- Check in with your patient following treatment
- Schedule a follow-up visit
- Align with the treatment center on your role in your patient's treatment plan
- Reassure your patients that you are still involved and available to answer questions or address concerns
- Remember that your patients will still come to you for other treatments

Important Safety Information (continued)

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.

(continued on page 7)

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Important Safety Information (continued)

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.

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.

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cp-79821v6

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

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