Spravato® (esketamine) CIII nasal spray

# Pathway to Acquire SPRAVATO® from an Authorized Specialty Distributor

## Indication

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

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

## Important Safety Information

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

***See full prescribing information for complete boxed warning***

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

Please see Important Safety Information, including Boxed WARNINGS, on pages 6-9.
Please see full Prescribing Information, including Boxed WARNINGS, for SPRAVATO®.

Once your site has decided to become a certified SPRAVATO® treatment center, it is important to understand which pathway to acquire SPRAVATO®. SPRAVATO® has a controlled distribution network that ensures SPRAVATO® is distributed only to REMS-certified pharmacies and REMS-certified healthcare settings. SPRAVATO® will not be delivered or dispensed directly to patients.

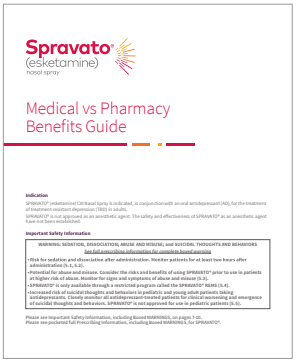
Certified physician practices/clinics that want to proceed with the buy-and-bill pathway will need to purchase SPRAVATO® from a SPRAVATO® Authorized Specialty Distributor (SD). In the buy-and-bill pathway, a healthcare provider purchases a drug from a specialty distributor. After administering the drug, the provider submits a claim for reimbursement for the drug and any other medical services associated with the treatment.

### Distributors vs Wholesalers

**Full-line wholesalers** buy the product line, inventory it, and distribute a manufacturer's entire pharmaceutical product line unless otherwise arranged.[1]

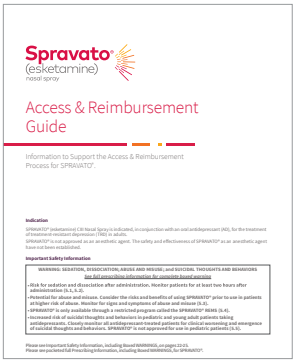
**Specialty distributors** sell specialty products primarily to independent physician-owned or operated clinics, hospitals, and outpatient clinics owned by hospitals.[1]

## Additional Information on Benefits, Billing, and Reimbursement for SPRAVATO® Can Be Found in the Following Resources:




### Medical vs Pharmacy Benefits Guide

Please refer to this guide for information to support obtaining SPRAVATO® under your patient's relevant benefit design, which can be downloaded from: **spravatotreatmentcenter.com/resources_and_tools**




### Access & Reimbursement Guide

Please refer to this guide for information to support the access and reimbursement process for SPRAVATO®, which can be downloaded from: **spravatotreatmentcenter.com/resources_and_tools**

**Please see Important Safety Information, including Boxed WARNINGS, on pages 6-9.**
**Please see full Prescribing Information, including Boxed WARNINGS, for SPRAVATO®.**

Spravato® (esketamine) C-III nasal spray

# Buy-and-Bill Pathway


If your 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/resources_and_tools**

# What to Expect With the Application Process

**When your site engages with a SPRAVATO® Authorized SD, here's what to expect in order to get an account established:**

- Have REMS certification confirmation from SPRAVATO® REMS Administrator available
- Complete a new customer application with the SPRAVATO® Authorized SD

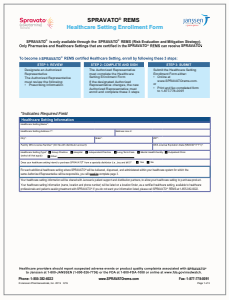
**New customer applications typically require sites to:**

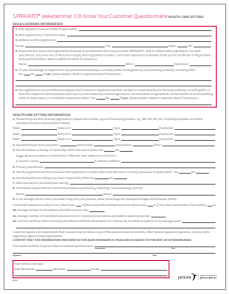
- Submit required information for the SPRAVATO® Authorized SD to perform credit and background checks
- Submit copies of all applicable DEA certifications and applicable licenses
- Provide business background information (ie, type of business, estimated volume, list of company offices, information on key individuals)
- Provide credit references

# Steps to Acquire SPRAVATO® Through a SPRAVATO® Authorized SD

REMS

## STEP 1
### Become a REMS-certified Site and Complete the Know Your Customer Form





**1** Complete the SPRAVATO® REMS certification process and maintain confirmation receipt from SPRAVATO® REMS Administrator

**What is the SPRAVATO® REMS (Risk Evaluation and Mitigation Strategy)?**

REMS is a program required by the Food and Drug Administration to manage known or potential serious risks associated with a drug product.

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

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

Learn more about the SPRAVATO® REMS from **spravatorems.com**

**2** Complete the Know Your Customer Form and send to SPRAVATO® REMS Administrator

**NOTE:** Completion of the Know Your Customer Form is required to become eligible to receive SPRAVATO® from an Authorized SD.

**Please see Important Safety Information, including Boxed WARNINGS, on pages 6-9.**
**Please see full Prescribing Information, including Boxed WARNINGS, for SPRAVATO®.**

Spravato® (esketamine) CIII nasal spray

# Steps to Acquire SPRAVATO® Through a SPRAVATO® Authorized SD (continued)

## STEP 2
### Connect With a SPRAVATO® Authorized SD


Spravato® (esketamine) nasal spray

Authorized SPRAVATO® Distributor List

1. Refer to the Authorized SPRAVATO® Distributor List on **spravatotreatmentcenter.com/resources_and_tools** that provides information on Authorized SDs approved to distribute SPRAVATO®

2. Contact a SPRAVATO® Authorized SD to set up an account. Your certified SPRAVATO® treatment center will need to set up an account with a SPRAVATO® Authorized SD in order to buy-and-bill
   - If your certified SPRAVATO® treatment center already has an account with an Authorized SD that is listed on the Authorized SPRAVATO® Distributor List, you can use your current Authorized SD account

**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.

## STEP 3
### SPRAVATO® Authorized SD Review and Status of Application

1. 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

2. Application decision: Approximately 7-10 days after a completed application is received

   **Once approved, account is now eligible to procure product from the SPRAVATO® Authorized SD**

**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 you have chosen to contract with.

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

## Indication

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

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

## Important Safety Information

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

***See full prescribing information for complete boxed warning***

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

### CONTRAINDICATIONS

SPRAVATO® is contraindicated in patients with:

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

### WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

Important requirements of the SPRAVATO® REMS include the following:

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

(continued on next page)

**Please see full Prescribing Information, including Boxed WARNINGS, for SPRAVATO®.**

Spravato® (esketamine) CIII nasal spray

# Important Safety Information for SPRAVATO® (esketamine) CIII Nasal Spray (continued)

- 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 dosages. Increases in BP peak approximately 40 minutes after SPRAVATO® administration and last approximately 4 hours.

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

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

BP should be monitored for at least 2 hours after SPRAVATO® administration. Measure blood pressure around 40 minutes post-dose and subsequently as clinically warranted until values decline. If BP remains high, promptly seek assistance from practitioners experienced in BP management. Refer patients experiencing symptoms of a hypertensive crisis (e.g., chest pain, shortness of breath) or hypertensive encephalopathy (e.g., sudden severe headache, visual disturbances, seizures, diminished consciousness or focal neurological deficits) immediately for emergency care.

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

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

**Cognitive Impairment**

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

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

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

(continued on next page)

**Please see full Prescribing Information, including Boxed WARNINGS, for SPRAVATO®.**

Spravato® (esketamine) CIII nasal spray

# Important Safety Information for SPRAVATO® (esketamine) CIII Nasal Spray (continued)

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

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

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

## DRUG INTERACTIONS

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

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

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

## USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

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

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

## DRUG ABUSE AND DEPENDENCE

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

**Abuse:** Individuals with a history of drug abuse or dependence may be at greater risk for abuse and misuse of SPRAVATO®. Abuse is the intentional, non-therapeutic use of a drug, even once, for its psychological or physiological effects. Misuse is the

(continued on next page)

**Please see full Prescribing Information, including Boxed WARNINGS, for SPRAVATO®.**

Spravato® (esketamine) CIII nasal spray

## Important Safety Information for SPRAVATO® (esketamine) CIII Nasal Spray (continued)

intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed. Careful consideration is advised prior to use of individuals with a history of substance use disorder, including alcohol.

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

**ADVERSE REACTIONS**

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

**Please see full Prescribing Information, including Boxed WARNINGS, for SPRAVATO®.**

cp-79821v2

# References


1. Fein AJ. 2018 MDM Market Leaders: Top Pharmaceutical Distributors. 2017. https://www.mdm.com/2017-top-pharmaceuticals-distributors. Accessed June 20, 2019.
2. SPRAVATO® [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. February 2020.


Spravato® (esketamine) CIII nasal spray

Please see Important Safety Information, including Boxed WARNINGS, on pages 6-9.
Please see full Prescribing Information, including Boxed WARNINGS, for SPRAVATO®.

janssen Neuroscience
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Spravato® (esketamine) CIII
nasal spray