Spravato® (esketamine) CIII nasal spray

About SPRAVATO®

SPRAVATO® is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist, and a first-of-its-kind medicine approved by the FDA in two major depressive disorder (MDD) subpopulations with high unmet need.[1,2]

- Taken with an oral antidepressant (AD)
- Nasal spray self-administered under the supervision of a healthcare provider at a Risk Evaluation & Mitigation Strategy (REMS)–certified treatment center
- Healthcare providers should monitor patients for side effects for at least two hours after administration
- Healthcare providers and patients should discuss any history of drug or alcohol abuse

This nasal spray is indicated, in conjunction with an oral antidepressant, in two different subtypes of challenging to treat depression:

Adults with Treatment-Resistant Depression (TRD)

TRD is a debilitating disease that has a profound impact on people's lives.[3] TRD may be defined as a failure of treatment to produce response or remission for patients after two or more treatment attempts of adequate dose and duration during the same depressive episode.[4]

SPRAVATO® may offer significant and sustained improvement of depression symptoms for adults with TRD, many of whom have cycled through multiple treatments without relief.[1,2]

Adults with MDD with Acute Suicidal Ideation or Behavior

Depression symptoms and severity vary by person and may include persistent feelings of sadness, hopelessness or tension; changes in sleep or appetite; difficulty concentrating or performing activities of daily living; lack of interest; and/or thoughts of harming themselves. In adults with MDD, depressive symptoms can sometimes progress to a point where they start actively considering suicide.[5]

SPRAVATO® may address underlying depressive symptoms within 24 hours in patients with MDD and acute suicidal ideation or behavior.[1]

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.

SPRAVATO® Clinical Trial Results

Efficacy

Treatment-Resistant Depression (TRD)[6,7]

Those who took SPRAVATO® and an oral AD experienced greater reduction of depression symptoms at 4 weeks compared to those who received a placebo and an oral AD†

- At 28 days, SPRAVATO® led to a 19.8-point decrease on the MADRS scale from baseline
- Most of the treatment difference between SPRAVATO® and placebo was observed at 24 hours
- Between 24 hours and Day 28, both SPRAVATO® and placebo groups continued to improve
- The difference between the groups generally remained but did not appear to increase over time through Day 28

In a long-term study, in conjunction with an oral AD, patients in stable remission taking SPRAVATO® who continued treatment with the medicine were 51 percent less likely to relapse versus those who switched to placebo*

- Stable remission was defined as a MADRS total score of ≤12 in at least 3 of the last 4 weeks of the optimization phase

**Relapse was defined as a MADRS (Montgomery-Åsberg Depression Rating Scale) total score of ≥22 for 2 consecutive assessments separated by 5 to 15 days and/or hospitalization for worsening depression, or any other clinically relevant event determined per clinical judgment to be suggestive of a relapse of depressive illness.*

MDD with Acute Suicidal Ideation or Behavior[8-10]

Those who took SPRAVATO® and an oral AD experienced a greater reduction of depressive symptoms at 24 hours compared to those who took a placebo plus an oral AD†

- At 24 hours after the first dose of study medication, SPRAVATO® plus comprehensive standard of care led to a decrease of 15.9 and 16.0 points on the MADRS scale in the ASPIRE I and ASPIRE II trials, respectively.
- The mean difference in the reduction of depressive symptoms between the SPRAVATO® and placebo groups was 3.8 points and 3.9 points, respectively

Between 4 hours and Day 25, both the SPRAVATO® and placebo groups continued to improve; the difference between the groups generally remained but did not appear to increase over time through the four-week treatment period

†Based on overall MADRS (Montgomery-Åsberg Depression Rating Scale) score, a standardized rating scale.

Safety

Treatment-Resistant Depression (TRD)

The most common side effects with SPRAVATO® plus oral antidepressant include dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk.

MDD with Acute Suicidal Ideation or Behavior

The most common side effects with SPRAVATO® plus oral antidepressant include dissociation, dizziness, sedation, blood pressure increased, hypoesthesia, vomiting, euphoric mood, and vertigo.

The safety profile observed in the trials for MDD with acute suicidal ideation or behavior was consistent with previous studies of SPRAVATO® in adults with TRD.

These are not all the possible side effects of SPRAVATO®. Learn more about the side effects here.

The Treatment Process

In accordance with the SPRAVATO® REMS Program, patients must be treated at a certified treatment center that has trained healthcare providers to provide patient counseling, medically supervise the administration of SPRAVATO® and monitor patients post-dose. A certified treatment center may be the same or different location from patients' regular healthcare provider office. The first visit may be a consultation to discuss the details with a healthcare provider at the certified SPRAVATO® treatment center to determine if SPRAVATO® is considered an appropriate treatment option. If SPRAVATO® is recommended, the healthcare provider will discuss relevant safety risks and enroll patients in the SPRAVATO® REMS Program prior to treatment initiation.

Administration

- SPRAVATO® is self-administered by the patient under the supervision of a healthcare provider in a certified treatment center
- SPRAVATO® is delivered through a single-use, 28-mg disposable device. Each device contains two sprays, one for each nostril. Patients will require two to three devices per treatment session*

Monitoring and Discharge

- Healthcare provider observation will be required for at least two hours until the provider determines the patient is safe to leave
- Patients should not drive or operate heavy machinery until the next day, following a restful sleep[1]

Careful consideration is advised prior to treatment of individuals with a history of substance use disorder, including alcohol. Monitoring for signs of abuse and dependence is recommended. Patients should work with their doctor to find a treatment plan that's right for them.

Treatment-Resistant Depression (TRD)

- SPRAVATO® is taken twice a week for the first four weeks. After the first four weeks, SPRAVATO® is taken once a week for a month
- After this, SPRAVATO® is usually taken either once a week or once every two weeks*

MDD with Acute Suicidal Ideation or Behavior

- SPRAVATO® is taken twice a week for four weeks
- Evidence of therapeutic benefit should be evaluated to determine need for continued treatment*†

**As determined by the prescribing physician.[1]*
†Treatment beyond four weeks has not been systematically evaluated in adults with MDD with acute suicidal ideation or behavior.

SPRAVATO® REMS

A REMS program is in place to ensure the safety of all patients who are treated with SPRAVATO®. SPRAVATO® is available only through a restricted distribution program called the SPRAVATO® REMS. The goal of the 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 SPRAVATO® is only dispensed and administered to patients in medically supervised healthcare settings that monitor these patients
- Ensuring pharmacies and healthcare settings that dispense SPRAVATO® are REMS-certified
- Ensuring each patient is informed about serious adverse outcomes from dissociation and sedation and the need for monitoring
- Enrolling all patients who receive treatment in an outpatient healthcare setting in a (REMS) registry to further characterize the risks and support safe use

For more information on the SPRAVATO® REMS, please call **855-382-6022** or visit **SPRAVATOREMS.com.**

Access & Support

Janssen CarePath

Once the patient and healthcare provider have decided that SPRAVATO® is right for the patient, Janssen CarePath can help patients find the resources they may need to get started and stay on track. Janssen CarePath will give patients information on their insurance coverage, potential out-of-pocket costs and treatment support, and identify options that may help make their treatment more affordable. Janssen CarePath Care Coordinators can be reached at 844-777-2828, Monday–Friday, 8:00 AM to 8:00 PM ET or patients or caregivers may visit **JanssenCarePath.com/Spravato**.

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 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 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.

(continued on next page)

IMPORTANT SAFETY INFORMATION (continued)

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/*.

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

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