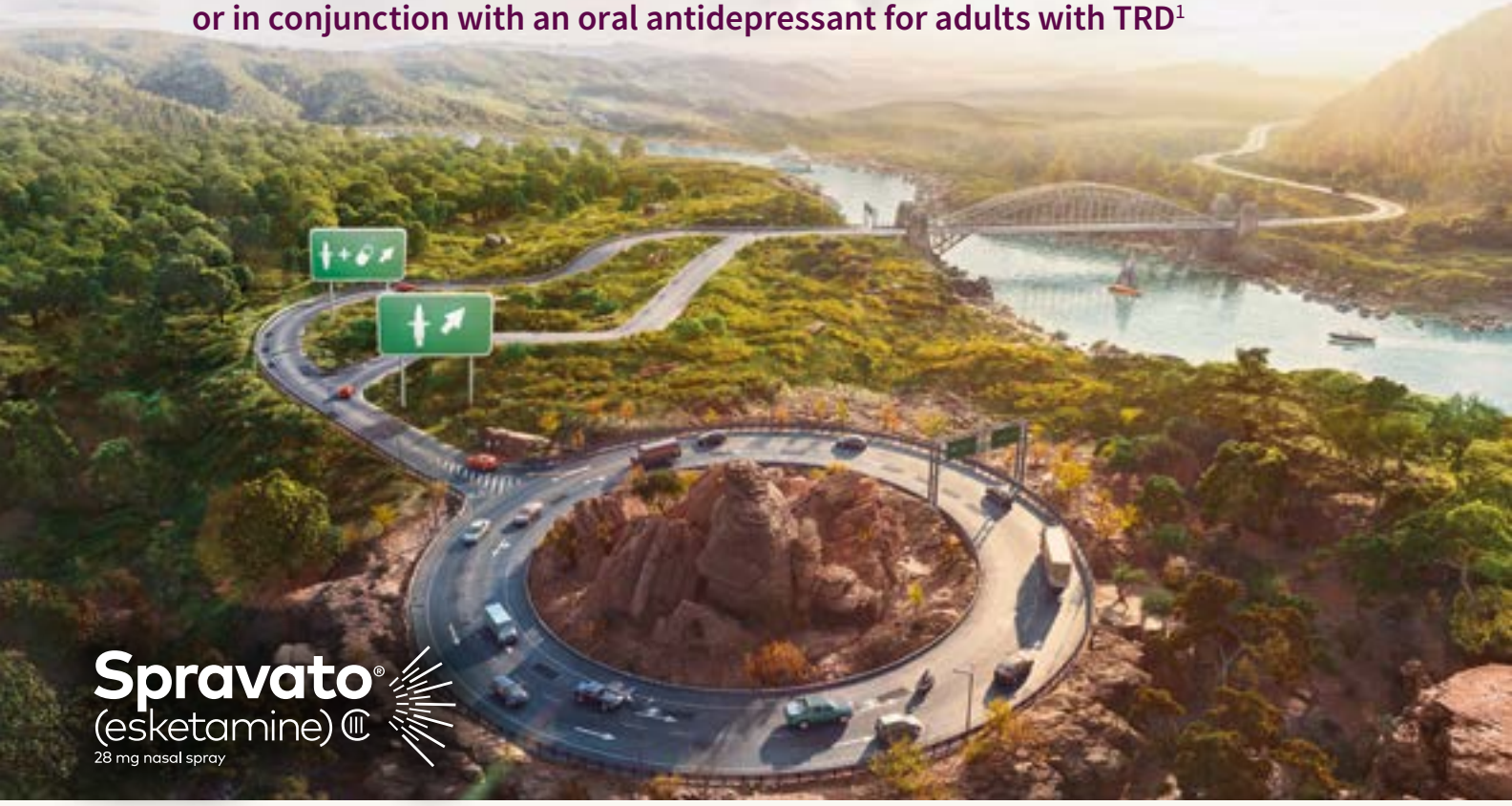
For adults with treatment-resistant depression (TRD) who have had inadequate response to at least 2 oral antidepressants

See where SPRAVATO® can take your patients

SPRAVATO® is the only FDA-approved treatment used as monotherapy or in conjunction with an oral antidepressant for adults with TRD[1]



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).**

Indications:

SPRAVATO® (esketamine) CIII Nasal Spray is indicated for the treatment of:

- Treatment-resistant depression (TRD) in adults as monotherapy or in conjunction with an oral antidepressant.
- Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior in conjunction with an oral antidepressant.

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.

(continued on next page)

Please see additional Important Safety Information on the following pages. Please see full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO®.

Oral ADs don't work for everyone[2]

Patients cycling through current oral medications may wait 4-6 weeks for potential relief.[3]

In the STAR*D trial, 86% of patients on their third line of treatment did not achieve remission.[2]*

AD=antidepressant.

*Remission was defined as a score of ≤5 on the Quick Inventory of Depressive Symptomatology—Self Report (QIDS-SR16).[3]

Whether alone or in combination with an oral antidepressant, SPRAVATO® (esketamine) offers providers and patients a *different approach*

SPRAVATO® provided rapid and superior improvement in depressive symptoms compared to placebo. Most of the treatment difference compared to placebo was observed as early as 24 hours[1]

- In a 4-week clinical study, patients were given either SPRAVATO® + OAD or a placebo nasal spray + OAD[1]*:
  - At 28 days, LS mean decrease from baseline MADRS total score was 19.8 for SPRAVATO® + OAD versus 15.8 for placebo + OAD
- In another clinical study, patients were given either SPRAVATO® alone or a placebo nasal spray alone[1†]:
  - At 28 days, LS mean decrease from baseline MADRS total score was 11.4 for SPRAVATO® 56 mg, 13.0 for SPRAVATO® 84 mg, and 6.3 for placebo

Most adverse events occurred on the day of dosing and the majority (~90%) resolved on the same day[4,5]

- The most common AEs[‡] in patients treated with SPRAVATO® plus OAD were dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk[1]
- The most common AEs[‡] with SPRAVATO® TRD monotherapy were dissociation, nausea, dizziness, headache, anxiety, vomiting, feeling drunk, sedation, and blood pressure increased[1]

SPRAVATO® is the only FDA-approved medication for adults with TRD with 5-year safety and efficacy data[6,7]

LS mean=least-squares mean; MADRS=Montgomery-Åsberg Depression Rating Scale; OAD=oral antidepressant; TRD=treatment-resistant depression.

*Double-blind, placebo-controlled, multicenter, phase 3 study (NCT02418585) in adult patients with TRD randomized to receive SPRAVATO® + OAD (n=114) or placebo + OAD (n=109). Primary efficacy endpoint was LS mean change from baseline MADRS total score at 28 days.[1]

†Double-blind, placebo-controlled, multicenter, phase 4 study (NCT04599855) in adult patients with TRD randomized to receive SPRAVATO® 56 mg (n=86), SPRAVATO® 84 mg (n=95) or placebo (n=197). Primary efficacy endpoint was LS mean change from baseline MADRS total score at 28 days. Key secondary endpoint was change from baseline to Day 2 (approximately 24 hours) in the MADRS total score.[1]

‡Incidence ≥5% and at least twice that of placebo.

Important Safety Information *(continued from first page)*

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.

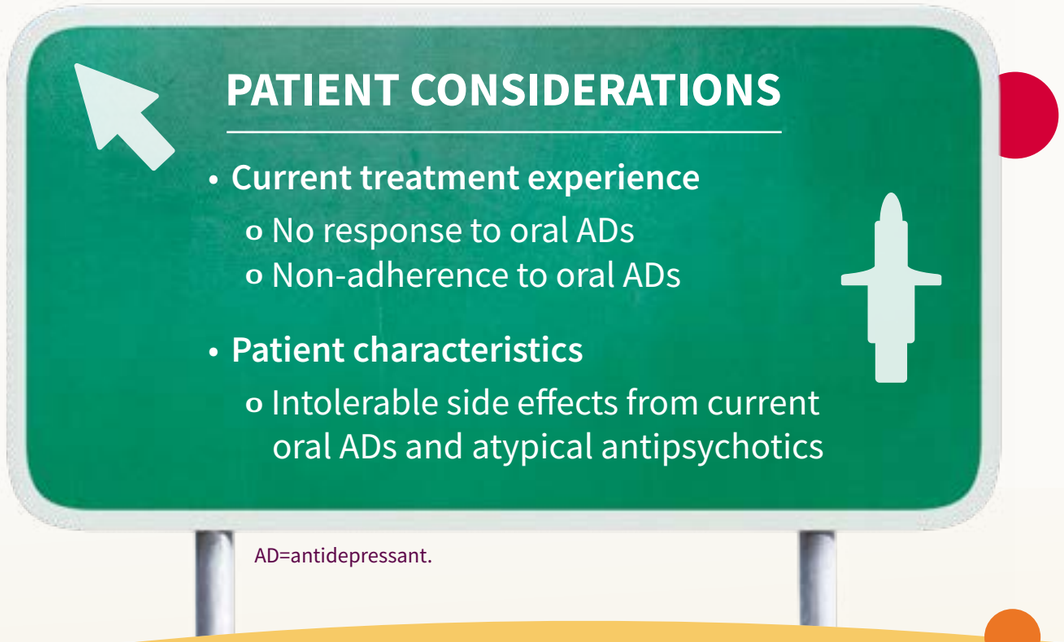
Abuse and Misuse: SPRAVATO® contains esketamine, a Schedule III controlled substance (CIII), and may be subject to abuse and diversion. Assess each patient's risk for abuse or misuse prior to prescribing and monitor all patients for the development of these behaviors or conditions, including drug-seeking 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.

(continued on next page)

Please see additional Important Safety Information on the following pages. Please see full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO®.

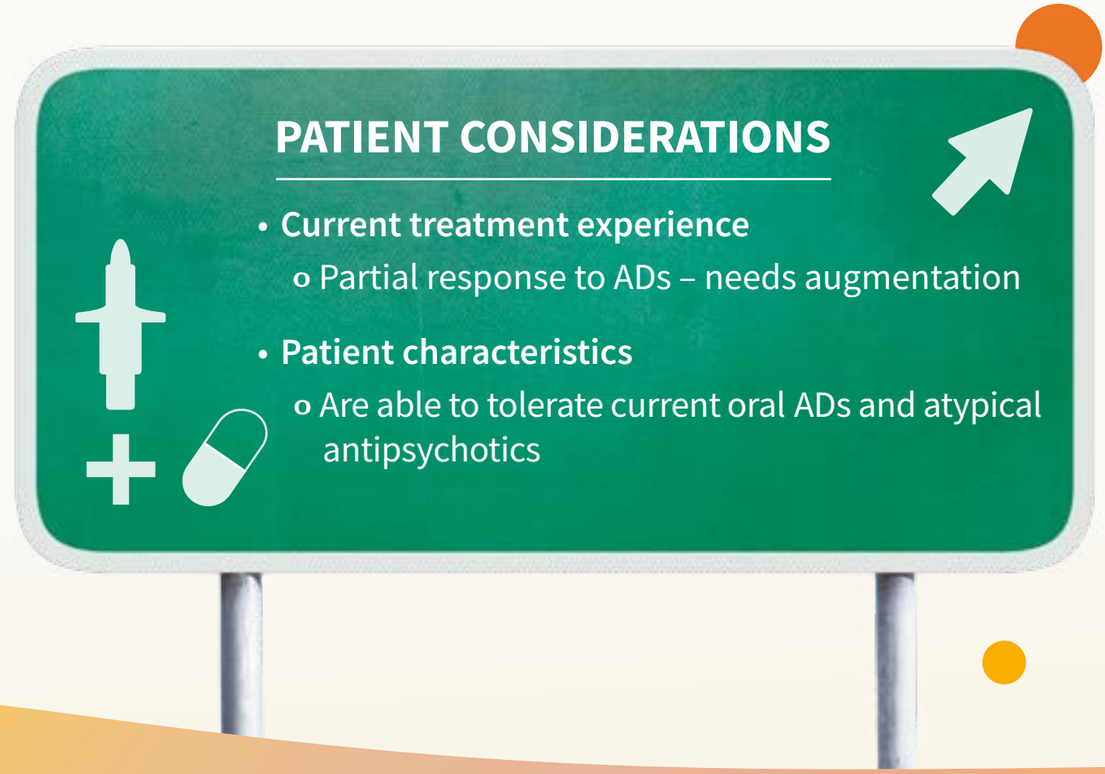
Flexible prescribing options help you choose the right path for patients

SPRAVATO® (esketamine) alone[1]



AD=antidepressant.

SPRAVATO® in combination with an oral AD[1]



Important Safety Information *(continued)*

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 3% 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

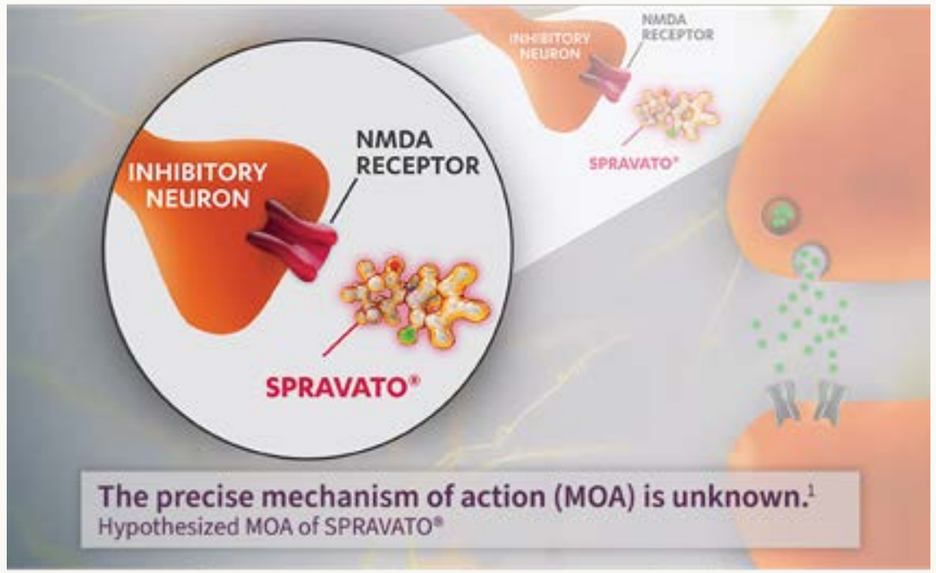
(continued on next page)

Please see additional Important Safety Information on the following pages. Please see full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO®.

SPRAVATO® (esketamine) works differently

Unlike traditional oral antidepressants, SPRAVATO® works on the glutamate pathway[1,8]

- SPRAVATO® targets glutamate, the brain's most abundant excitatory neurotransmitter[1,9]
- SPRAVATO® is the only agent with glutamatergic activity indicated to treat adult patients with MDD who have not responded to at least 2 oral antidepressants[1,8,10]



Important Safety Information *(continued)*

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.

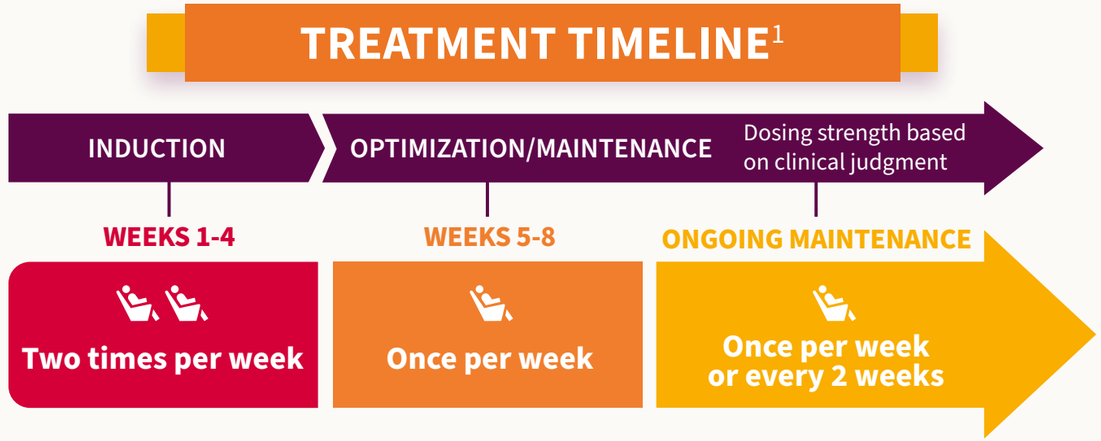
BP should be monitored for at least 2 hours after SPRAVATO® administration. Measure blood pressure around 40 minutes post-dose and subsequently as clinically warranted until values decline. If BP remains high, promptly seek assistance from practitioners experienced in BP management. Refer patients experiencing 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).

Please see additional Important Safety Information on the following pages. Please see full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO®.

Freedom to choose your treatment approach

Based on individual patient response, the treatment plan, dosing, and treatment frequency can be adjusted subject to provider discretion.



Start with 56 mg or 84 mg

- If clinically warranted, you may start a patient on SPRAVATO® alone — without the need to combine it with an oral AD
- SPRAVATO® now offers more flexibility in treatment approach, dosing, and post-induction frequency
- Evidence of therapeutic benefit should be evaluated at the end of the induction phase to determine need for continued treatment

= 56 mg **OR** **= 84 mg** Each single-use device contains 28 mg, which is 2 sprays (1 spray for each nostril)

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. In 1-year and 3-year, long-term, open-label clinical trials in adults, the effect of SPRAVATO® on cognitive functioning remained stable over time as evaluated by the Cogstate computerized battery and Hopkins Verbal Learning Test-Revised.

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

(continued on next page)

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

Learn more about SPRAVATO®

Important Safety Information *(continued)*

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/research/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

TRD: The most commonly observed adverse reactions in patients treated with SPRAVATO® plus oral antidepressant (incidence ≥5% and at least twice that of placebo nasal spray plus oral antidepressant) were 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: The most commonly observed adverse reactions in patients treated with SPRAVATO® plus oral antidepressant (incidence ≥5% and at least twice that of placebo nasal spray plus oral antidepressant) were dissociation, dizziness, sedation, blood pressure increased, hypoesthesia, vomiting, euphoric mood, and vertigo.

The most common adverse reactions with SPRAVATO® TRD monotherapy (≥5% and at least twice that of placebo nasal spray) were dissociation, nausea, dizziness, headache, anxiety, vomiting, feeling drunk, blood pressure increased, and sedation.

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

cp-170362v7

References: 1. SPRAVATO® [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. **2.** Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry.* 2006;163(11):1905-1917. doi:10.1176/ajp.2006.163.11.1905 **3.** Gelenberg AJ, Freeman MP, Markowitz JC, et al. *Practice Guideline for the Treatment of Patients with Major Depressive Disorder.* 3rd ed. American Psychiatric Association; 2010. Accessed May 17, 2024. https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd-1410197717630.pdf **4.** Data on File. SD-217538. Janssen Pharmaceuticals, Inc. **5.** Data on File. SD-217566. Janssen Pharmaceuticals, Inc. **6.** Zaki N, Fu DJ, Daly E, et al. Long-term efficacy of esketamine nasal spray in adults with treatment-resistant depression: a subgroup analysis of the ongoing SUSTAIN-3 study. Poster presented at: Neuroscience Education Institute (NEI) Congress; November 4-7, 2021; Colorado Springs, CO. **7.** Zajecka J, Zaki N, Fu D, et al. Long-term efficacy of esketamine nasal spray dosed in accordance with US prescribing information in adults with treatment-resistant depression: a subgroup analysis of the SUSTAIN-3 study up to 6.5 years. Poster presented at: Psych Congress; September 6-10, 2023; Nashville, TN. **8.** Kawczak P, Feszak I, Baczek T. Ketamine, esketamine, and arketamine: their mechanisms of action and applications in the treatment of depression and alleviation of depressive symptoms. *Biomedicines.* 2024;12(10):2283. doi:10.3390/biomedicines12102283 **9.** Cleveland Clinic. Glutamate. Accessed January 12, 2025. https://my.clevelandclinic.org/health/articles/22839-glutamate **10.** Popova V, Daly EJ, Trivedi M, et al. Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized double blind active-controlled study. *Am J Psychiatry.* 2019;176(6):428-438. Published online May 21, 2019. doi:10.1176/appi.ajp.2019.19020172

05/25 cp-517924v1