For adults with major depressive disorder:

If it feels like you're going in circles after trying two or more oral antidepressants...

Turn to a different treatment

Spravato® (esketamine) CIII
28 mg nasal spray

What is SPRAVATO® (esketamine) CIII nasal spray?

SPRAVATO® is a prescription medicine, used along with an antidepressant taken by mouth to treat:

- Adults with treatment-resistant depression (TRD)
- Depressive symptoms in adults with major depressive disorder (MDD) with suicidal thoughts or actions

SPRAVATO® is not for use as a medicine to prevent or relieve pain (anesthetic). It is not known if SPRAVATO® is safe or effective as an anesthetic medicine.

It is not known if SPRAVATO® is safe and effective for use in preventing suicide or in reducing suicidal thoughts or actions. SPRAVATO® is not for use in place of hospitalization if your healthcare provider determines that hospitalization is needed, even if improvement is experienced after the first dose of SPRAVATO®.

It is not known if SPRAVATO® is safe and effective in children.

Please see Boxed WARNINGS related to sedation, dissociation, respiratory depression, abuse and misuse, and suicidal thoughts and behavior on the following pages. To learn more about these and other risks, please read the Important Safety Information in this brochure and Medication Guide for SPRAVATO® and discuss any questions you may have with your healthcare provider.

IMPORTANT SAFETY INFORMATION

What is the most important information I should know about SPRAVATO®?

SPRAVATO® can cause serious side effects, including:

- **Sedation and dissociation.** SPRAVATO® may cause sleepiness (sedation), fainting, dizziness, spinning sensation, anxiety, or feeling disconnected from yourself, your thoughts, feelings, space and time (dissociation).
  - Tell your healthcare provider right away if you feel like you cannot stay awake or if you feel like you are going to pass out.
  - Your healthcare provider must monitor you for serious side effects for at least 2 hours after taking SPRAVATO®. Your healthcare provider will decide when you are ready to leave the healthcare setting.
- **Respiratory depression** was observed with the use of SPRAVATO®; additionally, there were rare reports of respiratory arrest.
  - Your healthcare provider must monitor you for serious side effects for at least 2 hours (including pulse oximetry) after taking SPRAVATO®. Your healthcare provider will decide when you are ready to leave the healthcare setting.
- **Abuse and misuse.** There is a risk for abuse and physical and psychological dependence with SPRAVATO® treatment. Your healthcare provider should check you for signs of abuse and dependence before and during treatment with SPRAVATO®.
  - Tell your healthcare provider if you have ever abused or been dependent on alcohol, prescription medicines, or street drugs.
  - Your healthcare provider can tell you more about the differences between physical and psychological dependence and drug addiction.
- **SPRAVATO® Risk Evaluation and Mitigation Strategy (REMS).** Because of the risks for sedation, dissociation, respiratory depression, and abuse and misuse, SPRAVATO® is only available through a restricted program called the SPRAVATO® Risk Evaluation and Mitigation Strategy (REMS) Program. SPRAVATO® can only be administered at healthcare settings certified in the SPRAVATO® REMS Program. Patients treated in outpatient healthcare settings (e.g., medical offices and clinics) must be enrolled in the program.
- **Increased risk of suicidal thoughts and actions.** Antidepressant medicines may increase suicidal thoughts and actions in some people 24 years of age and younger**, especially within the first few months of treatment or when the dose is changed. SPRAVATO® is not for use in children.**
  - Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a higher risk of having suicidal thoughts or actions. These include people who have (or have a family history of) depression or a history of suicidal thoughts or actions.
- **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
  - Pay close attention to any changes, especially sudden changes, in mood, behavior, thoughts, or feelings, or if you develop suicidal thoughts or actions.
  - Tell your healthcare provider right away if you have any new or sudden changes in mood, behavior, thoughts, or feelings.
  - Keep all follow-up visits with your healthcare provider as scheduled. Call your healthcare provider between visits as needed, especially if you have concerns about symptoms.
- **Tell your healthcare provider right away if you or your family member have any of the following symptoms, especially if they are new, worse, or worry you:**
  - suicide attempts
  - thoughts about suicide or dying
  - worsening depression
  - other unusual changes in behavior or mood

Please see Important Safety Information in this brochure and see full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO® and discuss any questions you may have with your healthcare provider.

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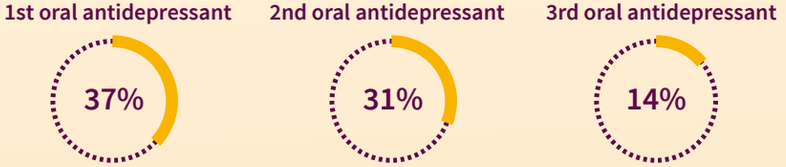
An oral antidepressant alone may not be the best option

Success Rate of Oral Antidepressants Alone

1 in 3 people did not experience a reduction in their depressive symptoms when taking oral antidepressants alone.

After inadequate response to 2 oral antidepressants, the chance to see benefit from a third oral antidepressant alone **dropped to 14%.**

Percentage of people who saw results after treatment:



If you've taken 2 or more oral antidepressants and still experience symptoms of depression, you may have treatment-resistant depression (TRD)

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SPRAVATO® offers a different approach

SPRAVATO® is an FDA-approved nasal spray indicated for people who've taken 2 or more oral antidepressants and still experience symptoms of depression

- SPRAVATO® works differently by acting on a pathway in the brain where glutamate, a brain chemical, works with other brain chemicals to balance well-being and depression
- The exact way SPRAVATO® works is not fully understood

Scan here to watch a video about using SPRAVATO® nasal spray

Visit SPRAVATO.com/howtouse

Scan here to watch top healthcare providers answer questions about SPRAVATO®

Visit SPRAVATO.com/asktheexperts

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Is there proof that SPRAVATO® can help?

Short-Term Study Results

In a 4-week clinical study, patients who had an inadequate response to 2 or more oral antidepressants were given either a nasal esketamine spray, the active ingredient in SPRAVATO®, or a placebo spray, which showed:

More patients using SPRAVATO® plus oral antidepressants **demonstrated rapid and superior reduction in depressive symptoms** at 4 weeks compared to patients who received placebo plus an oral antidepressant.*

Most of the reduction in depressive symptoms was seen at 24 hours.

Between 24 hours and 4 weeks, both groups continued to improve; the difference in improvement between the groups remained but did not appear to increase through 4 weeks.

*Based on an overall score on a standardized rating scale.

Long-Term Study Results

An 18-month SPRAVATO® study to see if the effect of treatment was maintained over time showed:

Patients who stayed on SPRAVATO® were less likely to experience a return of depressive symptoms (known as relapse) compared to patients who stopped therapy.

The trial compared patients who stayed on SPRAVATO® and an oral antidepressant to patients on a placebo spray and oral antidepressant long term.

Scan here to see answers to FAQs about SPRAVATO®

Visit SPRAVATO.com/faqs

Please see Important Safety Information in this brochure and see full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO® and discuss any questions you may have with your healthcare provider.

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What are the possible side effects of SPRAVATO®?

SPRAVATO® may cause serious side effects, including increased blood pressure, problems with thinking clearly, and bladder problems.

Scan QR code for Important Safety Information.

Visit SPRAVATO.com/importantsafetyinformation

The most common side effects of SPRAVATO®
when used along with an antidepressant taken by mouth include:

- feeling disconnected from yourself, your thoughts, feelings and things around you
- dizziness
- nausea
- feeling sleepy
- spinning sensation
- decreased feeling of sensitivity (numbness)
- feeling anxious
- lack of energy
- increased blood pressure
- vomiting
- feeling drunk
- feeling very happy or excited

If these common side effects occur, they usually happen right after taking SPRAVATO® and go away the same day

SPRAVATO® plus an oral antidepressant offers a minimal risk for sexual dysfunction compared to placebo plus oral antidepressant in clinical studies

Sexual dysfunction was not seen in more than 2% of patients in the SPRAVATO® clinical trials.

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You've decided to try SPRAVATO®. What's next?

After you and your healthcare provider have decided SPRAVATO® is right for you — and you understand the benefits and risks — you can start planning for treatment at a certified treatment center.

1: Treatment Plan

SPRAVATO® is taken with an oral antidepressant.

SPRAVATO® is taken twice a week for the first 4 weeks. After the first 4 weeks, you and your healthcare provider will discuss how often you'll receive SPRAVATO®.

SPRAVATO® is administered under the supervision of a healthcare provider at a treatment center that is certified in the SPRAVATO® Risk Evaluation and Mitigation Strategy (REMS) Program. This could be at a different location than your usual healthcare provider's office. **Work with your healthcare provider to locate a treatment center that is right for you.**

Scan here to locate certified SPRAVATO® treatment centers

Visit SPRAVATO.com/treatmentcenter

Your First Visit to a Treatment Center

Your first visit to a certified SPRAVATO® treatment center will be a consultation. The treatment center will:

Receive your medical information from your healthcare provider.

Conduct its own assessment to determine if SPRAVATO® may be right for you.

Verify your insurance information as part of the eligibility confirmation.

REMS

Build a treatment plan with you and enroll you in the SPRAVATO® REMS program if SPRAVATO® is recommended.

REMS=Risk Evaluation and Mitigation Strategy.

REMEMBER

Make sure to follow up with your healthcare provider after your treatment plan is built if you have questions

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What happens on your first day of treatment?

2: Treatment Days

You may start treatment as soon as your second visit to the SPRAVATO® treatment center.

You will administer SPRAVATO® nasal spray yourself under the supervision of a healthcare provider at a certified SPRAVATO® treatment center.

After you administer SPRAVATO®, there will be an observation period of at least 2 hours, during which you will rest comfortably while a healthcare provider at the treatment center monitors you for possible side effects.

Because of possible side effects affecting mental alertness and motor coordination, you won't be able to drive, operate machinery, or do anything where you need to be completely alert until the next day.

You'll need to plan for rides on treatment days.

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Tips to Prepare for Treatment Days

Avoid eating 2 hours before, and drinking liquids 30 minutes before, the treatment session. Some patients taking SPRAVATO® may experience nausea or vomiting.

If you take a nasal corticosteroid or nasal decongestant medicine, take these medicines at least 1 hour before taking SPRAVATO®.

Look at your visit as "me time." Bring a book or playlist to enjoy for the 2 hours after treatment when a healthcare provider at the treatment center will monitor you.

Keep in mind, your referring healthcare provider will continue to be involved with your care during SPRAVATO® treatment even if they are not present during your treatment. They will still be available to answer questions or address concerns as you start and progress through treatment.

Watch these stories to hear about the SPRAVATO® patient experience

Visit SPRAVATO.com/patientstories

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What should you know about ongoing visits to the treatment center?

3: Ongoing Treatment

After 4 weeks on SPRAVATO®, you and your healthcare provider will discuss your progress and any appropriate treatment changes going forward.

Patients who stayed on SPRAVATO® were less likely to relapse.

In a long-term clinical study, patients on SPRAVATO® had consistent effects through 5 years of follow-up.

Treatment Timeline

WEEKS 1-4
Induction
Two times per week

WEEKS 5-8
Maintenance
Once per week

WEEKS 9+
Maintenance
Ongoing

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Is support available for people who take SPRAVATO®?

Spravato withMe

Once you and your healthcare provider have decided that SPRAVATO® is right for you, ask your healthcare provider about enrolling in SPRAVATO withMe—the support program that's by your side from the start

Get started by getting in touch with a SPRAVATO withMe Care Navigator at **1-844-4S-WITHME** (1-844-479-4846), Monday through Friday, from 8:00 AM to 8:00 PM ET. Multilingual phone support is available.

Pay as little as $10 per treatment for your SPRAVATO® medication with the SPRAVATO withMe Savings Program

If you're commercially insured and eligible, our Savings Program could help you pay as little as $10 per treatment for SPRAVATO® medication costs. There are quantity limits and a maximum program benefit per calendar year. The program does not cover the cost of treatment observation. You may participate without sharing your income information.

See program requirements at SPRAVATO.com/SavingsRequirements.

Please see Important Safety Information in this brochure and see full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO® and discuss any questions you may have with your healthcare provider.

Observation Rebate Program for eligible commercially insured patients

Pay $0 after rebate for observation of each treatment

Eligible patients using commercial or private insurance can save on out-of-pocket treatment observation costs for SPRAVATO®.

If you're eligible, you can pay $0 after rebate for this observation period for each SPRAVATO® treatment session with the SPRAVATO withMe Observation Rebate Program. There is a limit to savings each year. Terms expire at the end of each calendar year and may change. Not valid for residents of MA, MI, MN, or RI. See program requirements at **SPRAVATO.com/Observation**.

If you have government insurance, or if you're currently uninsured, SPRAVATO withMe can point you to cost support options that may be able to help. To learn about support options available for all SPRAVATO® patients, call **1-844-4S-WITHME** (1-844-479-4846).

Scan here to learn more about support offerings from SPRAVATO withMe

Visit SPRAVATO.com/patientsupport

The patient support and resources provided by SPRAVATO withMe are not intended to provide medical advice, replace a treatment plan from the patient's doctor or nurse, provide case management services, or serve as a reason to prescribe SPRAVATO®.

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Can SPRAVATO® help with the depressive symptoms in adults with MDD with suicidal thoughts or actions (MDSI)?

In clinical studies of adults with MDSI, those who took SPRAVATO® and an oral antidepressant experienced a greater reduction of depressive symptoms at 24 hours compared to those who received a placebo plus 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®.

Help is available 24/7. If you're struggling with suicidal thoughts, call 988 Suicide & Crisis Lifeline

*Based on an overall score on a standardized rating scale.

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IMPORTANT SAFETY INFORMATION

What is the most important information I should know about SPRAVATO®?

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- **Sedation and dissociation.** SPRAVATO® may cause sleepiness (sedation), fainting, dizziness, spinning sensation, anxiety, or feeling disconnected from yourself, your thoughts, feelings, space and time (dissociation).
  - Tell your healthcare provider right away if you feel like you cannot stay awake or if you feel like you are going to pass out.
  - Your healthcare provider must monitor you for serious side effects for at least 2 hours after taking SPRAVATO®. Your healthcare provider will decide when you are ready to leave the healthcare setting.
- **Respiratory depression** was observed with the use of SPRAVATO®; additionally, there were rare reports of respiratory arrest.
  - Your healthcare provider must monitor you for serious side effects for at least 2 hours (including pulse oximetry) after taking SPRAVATO®. Your healthcare provider will decide when you are ready to leave the healthcare setting.
- **Abuse and misuse.** There is a risk for abuse and physical and psychological dependence with SPRAVATO® treatment. Your healthcare provider should check you for signs of abuse and dependence before and during treatment with SPRAVATO®.
  - Tell your healthcare provider if you have ever abused or been dependent on alcohol, prescription medicines, or street drugs.
  - Your healthcare provider can tell you more about the differences between physical and psychological dependence and drug addiction.
- **SPRAVATO® Risk Evaluation and Mitigation Strategy (REMS).** Because of the risks for sedation, dissociation, respiratory depression, and abuse and misuse, SPRAVATO® is only available through a restricted program called the SPRAVATO® Risk Evaluation and Mitigation Strategy (REMS) Program. SPRAVATO® can only be administered at healthcare settings certified in the SPRAVATO® REMS Program. Patients treated in outpatient healthcare settings (e.g., medical offices and clinics) must be enrolled in the program.

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IMPORTANT SAFETY INFORMATION (Continued)

- **Increased risk of suicidal thoughts and actions.** Antidepressant medicines may increase suicidal thoughts and actions in some people 24 years of age and younger, **especially within the first few months of treatment or when the dose is changed. SPRAVATO® is not for use in children.**
  - Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a higher risk of having suicidal thoughts or actions. These include people who have (or have a family history of) depression or a history of suicidal thoughts or actions.
- **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
  - Pay close attention to any changes, especially sudden changes, in mood, behavior, thoughts, or feelings, or if you develop suicidal thoughts or actions.
  - Tell your healthcare provider right away if you have any new or sudden changes in mood, behavior, thoughts, or feelings.
  - Keep all follow-up visits with your healthcare provider as scheduled. Call your healthcare provider between visits as needed, especially if you have concerns about symptoms.
- **Tell your healthcare provider right away if you or your family member have any of the following symptoms, especially if they are new, worse, or worry you:**
  - suicide attempts
  - thoughts about suicide or dying
  - worsening depression
  - other unusual changes in behavior or mood

Do not take SPRAVATO® if you:

- have blood vessel (aneurysmal vascular) disease (including in the brain, chest, abdominal aorta, arms and legs)
- have an abnormal connection between your veins and arteries (arteriovenous malformation)
- have a history of bleeding in the brain
- are allergic to esketamine, ketamine, or any of the other ingredients in SPRAVATO®.

If you are not sure if you have any of the above conditions, talk to your healthcare provider before taking SPRAVATO®.

Before you take SPRAVATO®, tell your healthcare provider about all of your medical conditions, including if you:

- have heart or brain problems, including:
  - high blood pressure (hypertension)
  - slow or fast heartbeats that cause shortness of breath, chest pain, lightheadedness, or fainting
  - history of heart attack
  - history of stroke
  - heart valve disease or heart failure
  - history of brain injury or any condition where there is increased pressure in the brain
- have liver problems
- have ever had a condition called “psychosis” (see, feel, or hear things that are not there, or believe in things that are not true).
- are pregnant or plan to become pregnant. SPRAVATO® may harm your baby. You should not take SPRAVATO® if you are pregnant.
  - Tell your healthcare provider right away if you become pregnant during treatment with SPRAVATO®.
  - If you are able to become pregnant, talk to your healthcare provider about methods to prevent pregnancy during treatment with SPRAVATO®.
  - There is a pregnancy registry for women who are exposed to SPRAVATO® during pregnancy. The purpose of the registry is to collect information about the health of women exposed to SPRAVATO® and their baby. If you become pregnant during treatment with SPRAVATO®, talk to your healthcare provider about registering with the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or online at https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/.
- are breastfeeding or plan to breastfeed. You should not breastfeed during treatment with SPRAVATO®.

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IMPORTANT SAFETY INFORMATION (Continued)

Tell your healthcare provider about all the medicines that you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Taking SPRAVATO® with certain medicine may cause side effects.

Especially tell your healthcare provider if you take central nervous system (CNS) depressants, psychostimulants, or monoamine oxidase inhibitors (MAOIs) medicine. Keep a list of them to show to your healthcare provider and pharmacist when you get a new medicine.

How will I take SPRAVATO®?

- You will take SPRAVATO® nasal spray yourself, under the supervision of a healthcare provider in a healthcare setting. Your healthcare provider will show you how to use the SPRAVATO® nasal spray device.
- Your healthcare provider will tell you how much SPRAVATO® you will take and when you will take it.
- Follow your SPRAVATO® treatment schedule exactly as your healthcare provider tells you to.
- During and after each use of the SPRAVATO® nasal spray device, you will be checked by a healthcare provider who will decide when you are ready to leave the healthcare setting.
- You will need to plan for a caregiver or family member to drive you home after taking SPRAVATO®.
- If you miss a SPRAVATO® treatment, your healthcare provider may change your dose and treatment schedule.
- Some people taking SPRAVATO® get nausea and vomiting. You should not eat for at least 2 hours before taking SPRAVATO® and not drink liquids at least 30 minutes before taking SPRAVATO®.
- If you take a nasal corticosteroid or nasal decongestant medicine take these medicines at least 1 hour before taking SPRAVATO®.

What should I avoid while taking SPRAVATO®?

Do not drive, operate machinery, or do anything where you need to be completely alert after taking SPRAVATO®. **Do not** take part in these activities until the next day following a restful sleep. See **"What is the most important information I should know about SPRAVATO®?"**

What are the possible side effects of SPRAVATO®?

SPRAVATO® may cause serious side effects including:

See **"What is the most important information I should know about SPRAVATO®?"**

Increased blood pressure. SPRAVATO® can cause a temporary increase in your blood pressure that may last for about 4 hours after taking a dose. Your healthcare provider will check your blood pressure before taking SPRAVATO® and for at least 2 hours after you take SPRAVATO®. Tell your healthcare provider right away if you get chest pain, shortness of breath, sudden severe headache, change in vision, or seizures after taking SPRAVATO®.

Problems with thinking clearly. Tell your healthcare provider if you have problems thinking or remembering.

Bladder problems. Tell your healthcare provider if you develop trouble urinating, such as a frequent or urgent need to urinate, pain when urinating, or urinating frequently at night.

The most common side effects of SPRAVATO® when used along with an antidepressant taken by mouth include:

- feeling disconnected from yourself, your thoughts, feelings and things around you
- dizziness
- nausea
- feeling sleepy
- spinning sensation
- decreased feeling of sensitivity (numbness)
- feeling anxious
- lack of energy
- increased blood pressure
- vomiting
- feeling drunk
- feeling very happy or excited

If these common side effects occur, they usually happen right after taking SPRAVATO® and go away the same day.

These are not all the possible side effects of SPRAVATO®.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Please read full Prescribing Information, including Boxed WARNINGS, and Medication Guide for SPRAVATO® and discuss any questions you may have with your healthcare provider.

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Scan here to locate certified SPRAVATO® treatment centers

Visit SPRAVATO.com/locator

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