Intranasal Esketamine for Depression

National Protocol Guidance
October 2025

VA Pharmacy Benefits Management Services, National Formulary Committee, and Office of Mental Health

Purpose: To provide general guidance on ensuring access to intranasal esketamine for treatment-resistant depression (TRD) or depressive symptoms in major depressive disorder (MDD) with acute suicidal ideation or behavior under a National VA protocol.

Disclaimer: To be consistent with the purpose of this general guidance and not to be overly proscriptive, this guidance allows facilities the flexibility to exercise modifications to the protocol as necessary to operationalize the use of intranasal esketamine for treating TRD or MDD with acute suicidal ideation or behavior. Clinical circumstances for the treatment of individual Veterans may necessitate provider decision making that is outside of this guidance.

Background

Esketamine is the S-enantiomer of racemic ketamine, a non-selective, non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor. The mechanism by which esketamine exerts its antidepressant effect is unknown. Spravato® (esketamine) nasal spray, a DEA schedule III medication, was approved by the Food and Drug Administration (FDA) on March 5, 2019, to be used in conjunction with an oral antidepressant for the treatment of depression in adults who have tried other antidepressants medicines but have not benefited from them. On July 31, 2020, the FDA approved its use for depressive symptoms in adults with MDD with acute suicidal ideation or behavior and in January 2025 it was approved for TRD in adults as monotherapy.

Because of the risk of serious adverse outcomes resulting from possible sedation, dissociation, respiratory depression, abuse and misuse, and suicidal thoughts and behaviors, Spravato® administration is only available through a restricted distribution system, under an FDA approved Risk Evaluation and Mitigation Strategy (REMS).

- The Spravato® REMS can be accessed at www.SPRAVATOrems.com.
- All healthcare settings and pharmacies are required to enroll in the Spravato® REMS via a designated authorized representative before they can purchase product from a distributor, dispense, or supervise administration of Spravato®.
- All patients must be enrolled in the Spravato® REMS before they can receive Spravato®

Departments Affected: Pharmacy, Nursing, Mental Health

Procedure:

- Patients can either be treated as outpatients or inpatients

Patient Selection

Inclusion Criteria

One of the following must be selected to meet criteria for use

- Remission not achieved from 2 antidepressant trials including a trial of an augmentation strategy in the current episode of depression^1 and 4 total adequate antidepressant trials in the patient's lifetime
- Patient is hospitalized with TRD with acute suicidal ideation/behavior

^1 One augmentation trial could be an adequate course of evidence-based psychotherapy (EBP)

Additional Inclusion Criteria

The answers to **ALL** of the following must be fulfilled to meet criteria.

- All REMS requirements have been met
- Adults <65 years of age with current diagnosis of unipolar major depressive disorder by DSM-5
- Patient in current episode of depression is experiencing moderate to severe depressive symptomatology (i.e., PHQ-9 $\geq$15 within the last 30 days)
- Antidepressant treatment trials are considered unsuccessful if the patient has not responded to at least 6 weeks of an antidepressant at half maximum dose or greater
- A VA psychiatrist or a VA licensed Mental Health-care provider (i.e., CPP, NP, PA) has evaluated the patient and determined and documented in the patient's medical records that the patient qualifies for esketamine treatment
- The prescriber is a VA psychiatrist or a VA licensed Mental Health care provider (i.e., CPP, NP, PA)
- The patient agrees to stay and be monitored after esketamine administration and agrees not to drive or operate heavy machinery/equipment and not to make major financial or legal decisions for the remainder of the day in which esketamine is administered
- The patient or their legal representative can provide signed informed consent
- The patient has an adult who can accompany him/her and assist with transportation, or another method of safe transport has been arranged and documented
- For women of childbearing potential
  - Pregnancy should be excluded prior to receiving esketamine and the patient provided contraceptive counseling on potential risks vs. benefits of taking esketamine if the patient were to become pregnant

Exclusion Criteria

If the answer to **ANY** item below is met, then the patient should **NOT** receive esketamine.

- Allergy or previous serious adverse effects to ketamine or esketamine
- Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels) or arteriovenous malformation
- History of intracerebral hemorrhage
- Uncontrolled seizures
- Dementia
- Current or recent (within 30 days) delirium
- Current uncontrolled hypertension (systolic blood pressure >140 mm Hg or diastolic blood pressure > 90 mm Hg)
- Severe cardiac decompensation (Class IV heart failure or unstable angina)
- Severe hepatic impairment (Child-Pugh class C)
- Current or previous interstitial or ulcerative cystitis

- Comorbid psychiatric condition is present (schizophrenia, schizoaffective disorder, bipolar disorder)
- History of non-response to ketamine or esketamine
- Current or previous abuse of ketamine or esketamine
- Clinical evidence for current substance abuse, except tobacco
- Current moderate or severe substance use disorder (SUD)
- Pregnancy (known pregnancy or positive pregnancy test)
- Patient is breastfeeding

Issues for Consideration

- In January 2025 FDA approved esketamine for TRD in adults as monotherapy. However, the use of esketamine as the sole agent for antidepressant treatment is not advisable for most Veterans, especially as long-term treatment. However, starting an antidepressant to simply ensure that Veterans meet criteria for esketamine treatment is not advisable either. Using esketamine in a time-limited fashion to achieve response or remission while also developing a long-term plan for an individual Veteran may represent the best course of action.
- Patients prescribed a benzodiazepine, a non-benzodiazepine sedative hypnotic or a monoamine oxidase inhibitor are eligible to receive esketamine; however, it is advised that concurrent use while receiving esketamine may cause sedation or blood pressure changes.
- Carefully review prior to use of esketamine, patients who are less than 6 months in remission from substance use disorder. Review Prescription Drug Monitoring Program (PDMP).
- May cause fetal harm. Consider pregnancy planning and prevention in females of reproductive potential.

Screening and Referral

- Each facility will be responsible for developing and operationalizing a procedure to screen and refer potential candidates for treatment with esketamine.
- Screening should be completed no more than 60 days prior to acceptance and administration of the first dose of esketamine.
- Screening will include the following:
    - Signed informed consent
    - Psychiatric examination including assessment of inclusion/exclusion criteria
    - The PHQ-9 depression rating scale. The PHQ-9 is required at screening and prior to each treatment. Additional depression rating scales may be used.
    - Evaluation of cognitive status (e.g., Mini-Addenbrooke's Cognitive Examination (M-ACE))
    - Assessment of suicide risk.
        - Minimum requirements for risk identification are Columbia-Suicide Severity Rating Scale (C-SSRS) at the intake or initial evaluation (and within 24 hours of discharge or as clinically indicated any time during treatment.
        - In addition the Comprehensive Suicide Risk Evaluation (CSRE; New Evaluation version) should be completed if it is the first CSRE ever. Otherwise, the CSRE should be updated as clinically indicated.
    - Physical examination including vitals (blood pressure, heart rate)
        - Patients with a SBP >140 mm Hg or a DBP >90 mm Hg at screening should be considered at higher risk and treatment for hypertension should be considered prior to initiating treatment with esketamine. Patients with a

diagnosis of hypertension are to be adequately treated prior to receiving a dose of esketamine. Stimulants may increase blood pressure and heart rate, exacerbating the hypertensive effects of esketamine, increasing the risk of cardiovascular complications. The use of esketamine in individuals receiving a stimulant should be considered on a case-by-case basis.

        - Patients with a history of cardiopulmonary or cerebrovascular disease, recent myocardial infarction, symptomatic ischemic heart disease, dyspnea marked by shortness of breath or wheezing, poor exercise capacity (<6 metabolic equivalent of tasks (METs); bicycling – light effort (10-12 mph) =6.0), or any disease that could be associated with increased risk of acute cardiac demand or blood pressure or respiratory depression should be considered on an individual case basis, considering risk/benefit ratios.
        - Patients with a baseline heart rate of <60 beat per minute (bradycardia) or >100 beats per minute (tachycardia) should be considered on a case-by-case basis for the relative risks of esketamine.
    - Relevant laboratory measures, and urine toxicology and pregnancy screens.
        - Other physical and laboratory screening procedures should be determined according to the patient's individual risk factors based on his/her demographics, medical history and review of systems and is the responsibility of the prescribing provider
- Whether to obtain medical clearance from the patient's primary care provider or consultation from a cardiologist, or other medical specialist should be based on the patient's risk factors and is the responsibility of the prescribing provider.
- Concurrent use or abuse of psychoactive substances
    - Considering esketamine's known addictive potential, a history of substance abuse or dependence including ketamine or esketamine, extent of past and current alcohol use, smoking history, a history of medication misuse, a positive urine drug screen, and length of sobriety are important factors to consider.
    - Patients with a history of SUD are at risk for relapse or development of a new SUD when exposed to psychoactive substances. There are case reports of recent substance abuse associated with the risk of relapse with ketamine, one that resulted in death in a single motor vehicle accident. While the length of sobriety may be considered when making a decision, at a minimum, all patients in recovery from SUD should be warned of the risk of inducing a relapse to previous SUD or a new addiction to esketamine or ketamine with this treatment. Other strategies for managing TRD should be prioritized over strategies involving potentially addictive substances, especially for those with a history of SUD. If esketamine treatment is chosen, close monitoring for signs of substance use including random, monitored urine drug testing is recommended.
- Concurrent use or abuse of CNS depressants
    - Due to the theoretical potential for benzodiazepines, nonbenzodiazepine, benzodiazepine receptor agonists hypnotics (e.g., zolpidem), and naltrexone to attenuate ketamine's antidepressant effects, patients taking these agents should allow adequate time for the last dose to washout prior to receiving esketamine.
- Completion and submission of REMS Patient Enrollment Form.

Location of Administration, Monitoring and Recovery

- The facility is responsible for identifying a physical location for the dosing of esketamine and monitoring the patient during and after the dosing. The place for administration and recovery should be private and large enough to accommodate the patient and required personnel. The space must have available a way for the patient to recline his/her head at 45 degrees during the dosing procedure.
- The treatment setting should be able to provide immediate care if necessary. A crash cart should be readily accessible and rapid access/code team available for response if needed. The facility must have the means to monitor basic cardiovascular functions (including electrocardiogram and blood pressure) and respiratory function (oxygen saturation or end-tidal CO_2). Facilities without these capabilities should provide a process for emergency response arrangements in their local SOP.
- The facility must also be capable of administering oxygen, medication and restraints to manage potentially dangerous behavioral symptoms. Facilities without these capabilities should provide a response plan in their local SOP.
- The facility must have a plan to rapidly address any sustained alterations in cardiovascular function including advanced cardiac life support or transfer to a hospital capable of caring for acute cardiovascular events.
- Patients determined to be at high risk for complications based on pretreatment evaluation should be treated at a facility equipped and staffed to manage any cardiovascular or respiratory events that may occur.

Esketamine Procurement, Dosing, and Day of Administration Monitoring

- The facility is responsible for determining the procedure by which the esketamine is ordered, prepared and transported to the place of administration.
- A VA psychiatrist or a VA licensed Mental Health-care provider (i.e., CPP, NP, PA) will order the intranasal esketamine and follow the facility's policy for ordering/handling schedule III-controlled substances.
- The VA psychiatrist or VA licensed Mental Health-care provider (i.e., CPP, NP, PA) will ensure completion of day of treatment PHQ-9 prior to each treatment. Minimum requirements for risk identification are Columbia-Suicide Severity Rating Scale (C-SSRS) at program intake or initial evaluation and within 24hours of discharge from the program. The CSSRS should be completed as clinically indicated at any time during treatment.
- Patients self-administer intranasal esketamine under the direct observation of a Mental Health care provider in a certified medical facility and patients must be monitored by a health care provider for at least two hours after receiving their esketamine dose. Esketamine cannot be dispensed directly to a patient for use at home.
- The ordering VA psychiatrist or VA licensed Mental Health-care provider (i.e., CPP, NP, PA) will be physically present during the dosing procedure. The VA psychiatrist or VA licensed Mental Health-care provider (i.e., CPP, NP, PA) can leave once the dosing is completed and the patient considered stable based on vital signs and cognitive status. A healthcare provider is to remain with the patient for ongoing monitoring of possible adverse events until discharge evaluation. The VA psychiatrist or VA licensed Mental Health-care provider (i.e., CPP, NP, PA) must return at 120 minutes after the end of the dosing to ensure the administration of the C-SSRS Screener, vital signs, and a readiness for discharge assessment (consider Modified Aldrete or Brief Confusion Assessment Method (bCAM)), to clear the patient for discharge.
- The REMS Patient Monitoring Form shall be completed after every treatment session and submitted to Janssen.

- Esketamine intranasal administration timeline as a general guide
  - T-2 days or sooner: Urine drug screen and pregnancy tests are collected.
  - T-120 minutes: Patient to avoid further food intake.
  - T-60 minutes : Patient to avoid use of intranasal sprays and medications.
  - T-30 minutes : Patient to avoid further fluid intake. The VA psychiatrist or VA licensed Mental Health-care provider (e.g., CPP, NP, PA, RN) administers PHQ-9, and C-SSRS Screener as baseline measures. Patient is instructed to blow their nose. The number of devices needed for dose administration is confirmed, expiration date is checked on all device packaging (if expired, get a new device). Perform vital signs (sitting/standing blood pressure, sitting/standing pulse, respiratory rate, and oxygen saturation). In patients whose BP is elevated prior to esketamine administration (as a general guide: >140/90 mmHg) a decision to delay therapy should consider the balance of benefit and risk in individual patients.
  - T-5 minutes : Time out
  - T-0 minutes : Provided vitals and urine drug screen are acceptable and pregnancy tests are negative (see Exclusion Criteria), ordering VA psychiatrist or VA Mental Health care provider opens blister pack, removes device, DOES NOT PRIME DEVICE, confirms 2 green dots on the device indicator, and hands device to patient. Patient is instructed on how to hold device, reclines head at 45-degree angle and self-administers a spray into each nostril in accordance with the instructions provided by the device manufacturer (see Spravato Prescribing Information). The ordering VA psychiatrist or VA Mental Health care provider takes the device from the patient, checks that the indicator shows no green dots (if you see a green dot, have patient spray a second time in the second nostril). The patient rests in a semi-reclined position for 5 minutes. The procedure is repeated with the next device(s) as needed to achieve appropriate dose delivery (2 total devices = 56 mg, 3 total devices = 84 mg). Ensure the patient waits 5 minutes after each dose to allow medication to absorb. Used device(s) are disposed of per facility procedure for a Schedule III drug product per applicable federal, state, and local regulations.
  - T+1-120 minutes : Monitor for onset and resolution of sedation, dissociation, and other possible adverse events.
  - T+20 minutes : Check vital signs
  - T+40 minutes : Check vital signs and patient's cognitive status if indicated.
  - T+90 minutes : Check vital signs
  - T+120 minutes : Check vital signs, C-SSRS Screener, readiness for discharge assessment (consider Modified Aldrete or bCAM).
- Parameters for dose administration (serial use of multiple devices)
  - The appearance of any of the following necessitates stopping the dosing: 1) pallor, cyanosis, or any symptoms of poor perfusion, 2) respiratory symptoms such as shortness of breath, wheezing, 3) the appearance of chest, jaw or arm pain suggesting cardiac involvement, or 4) the patient's desire to stop.
- Discharge procedures
  - The ordering VA psychiatrist or VA licensed Mental Health-care provider (i.e., CPP, NP, PA) confirms the following to assure the patient is safe to leave with a safe method oftransport.
    - Vital signs are stable (BP <140/90 mmHg) and possible adverse effects (e.g. sedation, dissociation) have resolved by T+120 minutes or a later time point.
    - Follow up assessment of dissociation and suicidality have been completed and are determined to be appropriate for discharge.
    - The patient has an adult who can accompany him/her and assist with transportation, or another method of safe transport has been arranged and

documented.

- The patient agrees not to drive or operate heavy machinery/equipment and not to make major financial or legal decisions for the remainder of the day in which esketamine is administered.

Repeat Dosing Schedule

- The recommended dosage of intranasal esketamine for the treatment of TRD in adults as monotherapy or in conjunction with an oral antidepressant.

Induction Phase	**Weeks 1-4**	**Dosage**
	Administer twice per week	56 mg or 84 mg
Maintenance Phase		
	Weeks 5-8	
	Administer once weekly	56 mg or 84 mg
	Week 9 and after	
	Administer every 2 weeks or once weekly	56 mg or 84 mg

- Dosing frequency in week 9 and after during maintenance phase should be individualized to the least frequent dosing to maintain remission/response. While the time frame for maintenance use in TRD is undefined, long-term maintenance treatment with esketamine may be a reality for some Veterans and is not against guidance. Veterans receiving maintenance treatment should receive regular clinical review and/or re-evaluation for the continued need for treatment or adverse effects.
- The recommended dosage for the management of depressive symptoms in patients with MDD with acute suicidal ideation or behavior is 84 mg twice weekly x 4 weeks. The dosage may be reduced to 56 mg twice weekly based on tolerability. Use beyond 4 weeks has not been evaluated.

Longitudinal Monitoring of Esketamine Patients

- A PHQ-9 should be completed prior to each dose of intranasal esketamine.
- A PHQ-9 and cognitive evaluation (such as M-ACE) should be completed at the end of the induction phase, every 6 months of treatment, and at the end of treatment course.
- Suicide risk should be assessed and monitored using a combination of the Comprehensive Suicide Risk Evaluation (CSRE) and Columbia-Suicide Severity Rating Scale (C-SSRS) Screener.
    - Minimum requirements for risk identification are Columbia-Suicide Severity Rating Scale (C-SSRS) at the intake or initial evaluation and within 24hours of discharge or discontinuation from the program for any reason. The CSSRS should be completed as clinically indicated any time during treatment.
    - In addition the Comprehensive Suicide Risk Evaluation (CSRE; New Evaluation version) should be completed at the intake or initial evaluation if it is the first CSRE ever. Otherwise, the CSRE should be updated as clinically indicated.
    - A positive C-SSRS Screener should result in a CSRE
- The REMS Patient Monitoring Form shall be completed after every treatment session and submitted to Janssen.

Esketamine Treatment Failure/Discontinuation

- If the patient does not respond to intranasal esketamine after four weeks, they should not move on to maintenance therapy

  - An adequate response is defined as a 50% or greater decline in the PHQ-9 score from baseline.
- If a woman taking esketamine becomes pregnant, the drug should be stopped, and the patient counseled about the potential risks and benefits of continued treatment.
- If the patient has a positive urine drug screen for specified drugs of abuse (cannabinoids, barbiturates, methadone, opioids, cocaine, phencyclidine, and amphetamine/methamphetamine), while receiving esketamine, then consider discontinuing esketamine.
- Discontinue if signs/symptoms of new or recurrent substance use disorder emerge and refer to SUD specialty care.