Intranasal Esketamine for Depression

National Protocol Guidance
February 2022

VA Pharmacy Benefits Management Services, Medical Advisory Panel, VISN Pharmacist Executives, and Office of Mental Health and Suicide Prevention

Purpose: To provide general guidance on ensuring access to intranasal esketamine for the treatment of major depressive disorder (MDD) under a National VA protocol that will facilitate collection of safety and effectiveness outcomes via a prospective medication use evaluation (MUE).

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 MDD.

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 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 a new indication, depressive symptoms in adults with MDD with acute suicidal ideation or behavior.

Because of the risk of serious adverse outcomes resulting from possible sedation and/or dissociation caused by Spravato® administration, and the potential for abuse and misuse of the drug, it 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®

A summary of the efficacy data for FDA-approved indications is available in the VA PBM Drug Monograph for esketamine (Esketamine (SPRAVATO) monograph). Esketamine provides similar therapeutic effects to ketamine. VA PBM developed a national protocol for the use of intravenous ketamine in treatment resistant depression and severe suicidal ideation which was published in December 2017. (Ketamine Infusion for Treatment Resistant Depression). The national protocol for intravenous ketamine is consistent with the VA PBM Guidance on Off Label Prescribing of drugs that was published in August 2013 and can be accessed at: (Guidance on Off Label Prescribing).

Departments Affected: Pharmacy, Nursing, Mental Health

Procedure:

- Patients can either be treated as outpatients or inpatients

Patient Selection

Inclusion Criteria

The answers to **ALL** of the following must be fulfilled in order 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.
- The patient did not achieve remission from at least four adequate therapeutic trials (dose and duration) of antidepressants, either alone or in combination with evidence-based psychotherapy, and in the current episode of depression is experiencing moderate to severe depressive symptomatology based on a depression rating scale within the last 30 days. At least two trials must include an antidepressant augmented with an additional agent (e.g. antipsychotic, second antidepressant, lithium, or thyroid supplementation) **OR** the patient is hospitalized with MDD complicated by acute suicidal ideation or behavior.
- 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.
- The patient has been considered for electroconvulsive therapy (ECT).
- The patient has started and is currently receiving a new antidepressant that has not previously failed in the current depressive episode.
- A VA psychiatrist or a VA licensed 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 health-care provider (i.e., CPP, NP, PA).
- The patient agrees to stay and be monitored for at least two hours 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 patient were to become pregnant.

Exclusion Criteria

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

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

- History of seizures
- 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, MDD with psychotic symptoms, bipolar disorder, obsessive-compulsive disorder, intellectual disability, autism, **cluster B personality disorder**, or a major neurocognitive disorder diagnosis).
- History of non-response to ketamine, esketamine, or ECT.
- History of VNS or deep brain stimulation in current episode of depression.
- Current or previous abuse of ketamine or esketamine.
- Clinical evidence for current substance abuse except tobacco use (e.g. confirmed UDS).
- Current barbiturate, cannabis or opioid use.
- Current moderate or severe substance use disorder (SUD).
- Pregnancy (known pregnancy or positive pregnancy test).
- Patient is breastfeeding.

Issues for Consideration

- 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 30 days prior to acceptance and administration of the first dose of esketamine.
- Screening will include the following: signed informed consent; inclusion/exclusion criteria; psychiatric examination including a depression rating scale (PHQ-9), evaluation of cognitive status (Mini-Addenbrooke's Cognitive Examination (M-ACE)) and assessment of suicidality (Comprehensive Suicide Risk Evaluation (CSRE; New Evaluation version if first CSRE ever, otherwise, this can be an Update)); and physical examination including vitals (blood pressure, heart rate), relevant laboratory measures, and urine toxicology and pregnancy screens.
    - 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.
    - 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.
- 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 consults 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 CNS depressants and other 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, and a positive urine drug screen 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 and may not be able to give informed consent because of long-lasting brain changes that affect decisions involving 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 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 treatment-resistant depression including monoamine oxidase inhibitors, tricyclic antidepressants, ECT, repetitive transcranial magnetic stimulation, or augmentation with lithium, T_3, atypical antipsychotics, or pramipexole 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.
    - Due to the theoretical potential for benzodiazepines and nonbenzodiazepine, benzodiazepine receptor agonists hypnotics (e.g., zolpidem) to attenuate ketamine's antidepressant effects, patients taking benzodiazepines should be allowed adequate time for the last dose of benzodiazepine 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 a 45 degree 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).
- The facility must also be capable of administering oxygen, medication and restraints to manage potentially dangerous behavioral symptoms.
- 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 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 health-care provider (i.e., CPP, NP, PA) will ensure completion of day of treatment baseline PHQ-9, Clinician-Administered Dissociative States Scale (CADSS) and Columbia Suicide Severity Rating Scale (C-SSRS) Screener.
- Patients self-administer intranasal esketamine under the direct observation of a 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 health-care provider (i.e., CPP, NP, PA) will be physically present during the dosing procedure. The VA psychiatrist or VA licensed 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 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 CADSS and 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.

CADSS.pdf

The REMS Patient Monitoring Form shall be completed after every treatment session and submitted to Janssen. The Esketamine Safety Form shall be submitted to VAMedSAFE online (esketamine safety InfoPath link; https://vaww.cmopnational.va.gov/CR/VAMedSAFEMultiSiteResearch/esketamine/default.aspx

or via fax (1-708-786-7894).

- Esketamine dose administration timeline
  - 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 health-care provider (e.g., CPP, NP, PA, RN) administers PHQ-9, CADSS, and C-SSRS Screener as baseline measures. Patient is instructed to blow nose. 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 are acceptable and urine drug screen and pregnancy tests are negative (see Exclusion Criteria), ordering VA psychiatrist or VA 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 REMS Prescribing Information). The ordering VA psychiatrist or VA 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 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, CADSS, 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 health-care provider (i.e., CPP, NP, PA) confirms the following to assure the patient is safe to leave with a safe method of transport.
    - 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 FDA-approved, recommended dosage for intranasal esketamine for TRD:

Induction Phase	**Weeks 1-4**	**Dosage**
	Administer twice per week	Day 1 starting dose: 56 mg Subsequent doses: 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.
- At present, the time frame for maintenance use in TRD is undefined.
- 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 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. The CSRE should be completed at time of screening (New Evaluation version if first CSRE ever, otherwise, this can be an Update) and at discontinuation of treatment (Update version). On day of esketamine treatments, suicide risk should be evaluated both pre and post treatment administration using the C-SSRS Screener. A positive C-SSRS Screener should result in a CSRE Update with the following considerations:

	Post Admin: Positive C-SSRS	**Post Admin: Negative C-SSRS**
Pre-Admin: Positive C-SSRS	CSRE Update before they leave, include discussion if any item level responses changed between pre and post	CSRE Update before they leave, including discussion about what has changed
Pre-Admin: Negative C-SSRS	CSRE Update before they leave, include assessment of what has changed; potential ADE	No CSRE Update indicated

- Following discontinuation of esketamine treatment for any reason, patients require weekly suicide risk screening for 4 weeks, with an additional suicide risk screen at 3 months after completion of treatment course. These suicide risk screens may occur as part of existing suicide prevention protocols at facilities (e.g. high-risk flag patient outreach).
- The REMS Patient Monitoring Form shall be completed after every treatment session and submitted to Janssen. The Esketamine Safety Form shall be submitted to VAMedSAFE online (esketamine safety InfoPath link;https://vaww.cmopnational.va.gov/CR/VAMedSAFEMultiSiteResearch/esketamine/default.aspx) or via fax (1-708-786-7894).
- All sites providing intranasal esketamine treatment must submit information in accordance with the VA PBM Real-time Medication Use Evaluation (MUE) on Intranasal Esketamine for Treatment Resistant Depression (esketamine MUE InfoPath link; https://vaww.cmopnational.va.gov/CR/VAMedSAFEMultiSiteResearch/esketamine/default.aspx
- MUE data should be submitted:
  - **Each time** a patient returns for an esketamine dose.
  - Any time a patient is hospitalized during or between dosing appointments.
  - Within 180 and 365 days from first dose to assess for diagnosis of substance use disorder (SUD).
  - At completion of a treatment course.
  - If patient dies between doses or within 120 days after final dose.

Esketamine Treatment Failure/Discontinuation

- If the patient does not respond to nasal esketamine after one week, discontinue.
  - An adequate response is defined as a 50% or greater decline in the depression rating scale score from baseline.
- If a woman taking esketamine becomes pregnant, the drug should be stopped, and the patient counseled about the risk to the fetus.
- 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 discontinue esketamine.
- Discontinue if signs/symptoms of new or recurrent substance use disorder emerge and refer to SUD specialty care.