VHA Office of Integrated Veteran Care
Clinical Determination and Indication
Intranasal Esketamine for Treatment Resistant Depression

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I. Disclaimer

This document is currently in draft and is intended to be used as a reference for non-VA providers and not intended to replace clinical judgment when determining care pathways. These guidelines do not guarantee benefits or constitute medical advice.

II. Clinical Determinations and Indications

a. Indications for Intranasal Esketamine

Intranasal esketamine is considered **medically necessary**, in conjunction with an oral antidepressant, for the following indications:

- Treatment-resistant depression (TRD)
- Hospitalization with major depressive disorder (MDD) complicated by acute suicidal ideation or behavior

Note: This document is in alignment with the VA National Formulary. Please visit the VA Formulary Advisor to access VA Pharmacy Benefits Management Services' resources and additional information on clinical criteria.

- *Criteria for Use:* Esketamine (SPRAVATO) Criteria for Use
- *National Protocol Guidance:* Intranasal Esketamine for Depression

Note: Due to the risk of serious adverse outcomes, Risk Evaluation and Mitigation Strategies (REMS) requirements must be met before esketamine may be administered. For more information, please refer to the Approved Risk Evaluation and Mitigation Strategies (REMS) from the FDA.

b. Limitations/Exclusions

For all conditions/indications not listed in section II.a. of this document, intranasal esketamine is considered **not medically necessary** due to insufficient evidence of efficacy and safety.

c. Description of Treatment

Esketamine is a N-methyl-D-aspartate glutamate (NMDA) receptor antagonist that enhances glutamine release in the brain. This increase in glutamate affects mood regulation and emotional behaviors. Esketamine is for intranasal use only. Each intranasal device contains a total of 28 mg of esketamine per 0.2 mL spray and is to be administered with a 5-minute rest between each administration. A treatment session includes nasal administration of esketamine, and a post-administration supervised observation period. Treatment can be administered in either an inpatient or outpatient facility.

Veterans should be instructed not to engage in potentially hazardous activities (e.g., driving a motor vehicle or operating machinery) until the following day after a period of restful sleep. Because of the high risk of sedation and dissociation, esketamine must be administered under the direct supervision of a healthcare provider and Veterans must be monitored for at least 2 hours after receiving esketamine prior to leaving treatment session.

III. Background and Supporting Information

The following information is for reference purposes only in accordance with the medical benefits package outlined in 38 C.F.R. § 17.38 (b). Each subsection supports VA's determination for medical necessity and is in alignment with generally accepted standards of medical practice.

a. Background Information

Major depressive disorder (MDD) can become resistant to treatments with pharmacological products, resulting in treatment-resistant depression (TRD). There are a variety of treatment options for MDD and TRD including antidepressants, antipsychotics, mood stabilizers, psychotherapy, electroconvulsive therapy, transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS) and esketamine. During a clinical study on low dose ketamine for the treatment of pain, researchers observed mood improvements in patients with TRD. This led to additional research and the development of intranasal esketamine, which eventually received FDA approval for the treatment of TRD and depressive symptoms in adults with MDD with acute suicidal ideation or behavior.

Major Depressive Disorder

The World Health Organization (WHO) predicts that MDD will be the leading cause of disease burden by 2030. Diagnosis of MDD is based on the presence of the following symptoms: persistently low or depressed mood, anhedonia or decreased interest in pleasurable activities, feelings of guilt or worthlessness, lack of energy, poor concentration, changes in appetite,

psychomotor retardation or agitation, sleep disturbances, or suicidal thoughts. Esketamine, used in conjunction with an oral antidepressant, is a treatment option for patients with MDD with acute suicidal ideation or behavior when treatment with other antidepressant medications has failed.

Treatment-resistant depression

Treatment-resistant depression is a type of MDD that has not responded adequately to multiple antidepressant regimens of adequate dose and duration (six to eight weeks). Despite treatment attempts with standard protocols, about 30% of patients diagnosed with MDD do not achieve remission and are considered treatment resistant. For people who have not responded to other antidepressants, esketamine used in conjunction with an oral antidepressant, is an available treatment option.

b. Research, Clinical Trials, and Evidence Summaries

Esketamine is made from a drug called ketamine, an anesthetic that has been used for many years. Treatment with esketamine may relieve the symptoms of depression. Studies have shown esketamine to be an effective treatment option for patients with TRD.

Fedgchin et al. (2019) conducted a randomized, double-blind, active-controlled study across multiple centers. The study compared the efficacy and safety of fixed doses of esketamine paired with a newly initiated oral antidepressant, against a newly initiated oral antidepressant (active comparator) paired with a placebo nasal spray in adult patients with TRD. Between September 2015 and February 2018, 346 patients were divided into three study groups: patients receiving esketamine 56 mg with an oral antidepressant, esketamine 84 mg with an oral antidepressant, or a placebo nasal spray with an oral antidepressant. Eligible participants were 18 to 64 years old with recurrent MDD (as defined by the Diagnostic and Statistical Manual of Mental Disorders) or single-episode MDD (≥ two years), without psychotic features. The primary efficacy endpoint was the change from baseline to day 28 in the Montgomery-Asberg Depression Rating Scale (MADRS) total score. Statistical significance was not achieved with esketamine 84 mg/antidepressant compared with antidepressant/placebo. Esketamine 56 mg/antidepressant could not be formally tested based on the predefined statistical testing sequence. The most common adverse events reported for esketamine/antidepressant were nausea, dissociation, dizziness, vertigo, and headache. No meaningful differences in safety and tolerability between doses were observed. The study provided supportive evidence for the safety and efficacy of esketamine nasal spray as a rapid-acting antidepressant for patients with TRD.

Popova et al. (2019) conducted a study comparing the efficacy and safety of switching patients with TRD from an unsuccessful antidepressant to either esketamine nasal spray plus a newly initiated antidepressant or to a newly initiated antidepressant (active comparator) plus placebo nasal spray. Eligible patients were between 18 and 64 years of age with confirmed single-episode or recurrent MDD without psychotic features per Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria. Patients also had to have a score ≥34 on the Inventory of Depressive Symptomatology, Clinician Rating (IDS-C), meet the study definition of TRD, be medically stable and be able to self-administer intranasal medication to participate in the study. This double blind, active controlled, multicenter controlled study included 197 patients who completed the 28-day treatment phase. Patients received either esketamine (56 mg or 84 mg) nasal spray or placebo nasal spray twice weekly combined with a newly initiated open-label oral antidepressant taken daily. The primary efficacy endpoint was the change from baseline to day 28 in the MADRS. The change in MADRS with esketamine plus antidepressant was significantly greater than with antidepressant plus placebo at day 28. Common adverse events included dissociation, nausea, vertigo, dysgeusia, and dizziness. The study supports the efficacy and safety of esketamine nasal spray as a rapid acting antidepressant for patients with treatment-resistant depression.

Ochs-Ross et al conducted a phase 3 randomized, double-blind study in patients with TRD who were > 65 years old. Subjects were randomly assigned (1:1) to flexibly dosed esketamine nasal spray and new oral antidepressant (esketamine/antidepressant) or new oral antidepressant and placebo nasal spray (antidepressant/placebo). The primary endpoint was change in the MADRS from baseline to day 28. Esketamine/antidepressant did not achieve statistical significance for the primary endpoint. The median-unbiased estimate of the treatment difference (95% CI) was -3.6 (-7.20, 0.07); p = 0.06.

Ionescu et al. (2021) performed a phase 3, double-blind study (ASPIRE II) including randomized adults with MDD and active suicidal ideation with intent. Patients were treated with esketamine 84 mg or placebo nasal spray twice weekly for 4 weeks, given with comprehensive standard of care. A total of 230 patients were randomized of which 227 received the study drug and were included in efficacy/safety analyses; 184 completed double-blind treatment. The primary efficacy endpoint was the change from baseline to 24 hours after first dose in the MADRS using ANCOVA (analysis of covariance). Clinical Global Impression Severity of Suicidality (key secondary endpoint) was analyzed using ANCOVA on ranks of change. Patients receiving esketamine demonstrated greater improvement in MADRS versus patients receiving placebo, each with standard of care, at 24 hours. The most common adverse events among esketamine-treated patients were dizziness, dissociation,

nausea, dysgeusia, somnolence, headache, and paresthesia. Patients in both treatment groups experienced rapid reduction in Clinical Global Impression - Severity of Suicidality score; the between-group difference was not statistically significant. The study confirmed rapid and robust reduction of depressive symptoms with esketamine nasal spray in severely ill patients with MDD who have active suicidal ideation with intent. This was also noted at the earlier (4-hour) timepoint.

c. U.S. Food & Drug Administration (FDA) Information

Esketamine has received FDA approval for the treatment of adult patients with TRD and depressive symptoms in individuals with MDD with acute suicidal ideation or behavior.

To search for more FDA-approved pharmaceutical agents, please visit the FDA-approved drugs website.

Information	Description
NDA Number	NDA 211243
Drug Name	Spravato nasal spray, 28 mg (esketamine)
Active Ingredients	Esketamine Hydrochloride
Company Name	Janssen Pharmaceuticals, Inc.
Approval Date	March 5, 2019
FDA Site	NDA Approval

d. Medicare Coverage Determinations

Currently, there are no available Medicare coverage determinations available for esketamine for depression. VA and Medicare are governed by separate laws and regulations; thus, VA coverage determinations may be different.

e. TRICARE Policy Manual

Available TRICARE coverage determinations are listed below as a resource. VA and TRICARE are governed by separate laws and regulations; thus, VA coverage determinations may be different.

TRICARE Policy Manual 6010.63-M, Chapter 7, Section 3.7

- Spravato (esketamine) nasal spray is a covered treatment for treatment-resistant depression and other US Food and Drug Administration (FDA) approved indications, which is available to providers from the FDA's Spravato Risk Evaluation and Mitigation Strategy (REMS) Program

IV. Definitions

Term	Definition
Anhedonia	A psychological condition characterized by the inability to experience pleasure in normally pleasurable acts
Dissociation	A break in how the mind handles information, disconnecting from thoughts, feelings, memories, surroundings, and sense of identity
Dopamine	Chemical that acts on areas of the brain to give feelings of pleasure, satisfaction, and motivation; considered a feel-good chemical that rewards the brain for actions
Enantiomer	Each of a pair of molecules that are mirror images of each other
Ester	A group of chemical compounds which are formed by bonding of an alcohol group with a group of organic acids, by losing water molecules
Glutamate	A salt or ester of levorotatory glutamic acid that functions as an excitatory neurotransmitter
Hypoesthesi	A reduced sense of touch or sensation, or a partial loss of sensitivity to sensory stimuli
Lethargy	The state of feeling drowsy, unusually tired, or not alert
Montgomery–Åsberg Depression Rating Scale (MADRS)	Widely used clinician-rated measure of depressive severity
Norepinephrine	A chemical that affects energy and concentration levels (high levels of this neurotransmitter can cause euphoria and a spike in blood pressure)
Neurotransmitters	Chemicals in the body that carry messages from one nerve cell across a space to the next nerve, muscle, or gland cell
Psychomotor retardation	The slowing down or hampering of mental or physical activities
Racemic Mixture	A mixture containing two enantiomers in equal proportions
Sedation	The inducing of a relaxed easy state especially using sedatives
S-enantiomer	One of the two enantiomers of ketamine
Serotonin	A chemical in the brain that regulates emotions like anxiety, happiness, and general mood
Vertigo	A sensation of motion or spinning that is often described as dizziness

V. References

Bains N, Abdijadid S. (2023). Major Depressive Disorder. StatPearls Publishing. Retrieved January 15, 2024, from: https://www.ncbi.nlm.nih.gov/books/NBK559078/

Canuso, C. M., Singh, J. B., Fedgchin, M., Alphs, L., Lane, R., Lim, P., Pinter, C., Hough, D., Sanacora, G., Manji, H., & Drevets, W. C. (2018). Efficacy and Safety of Intranasal Esketamine for the Rapid Reduction of Symptoms of Depression and Suicidality in Patients at Imminent Risk for Suicide: Results of a Double-Blind, Randomized, Placebo-Controlled Study. The American journal of psychiatry, 175(7), 620–630. https://doi.org/10.1176/appi.ajp.2018.17060720

Cleveland Clinic, (n.d.). Treatment-Resistant Depression. Retrieved December 12, 2023 from https://my.clevelandclinic.org/health/diseases/24991-treatment-resistant-depression

Fedgchin, M., Trivedi, M., Daly, E. J., Melkote, R., Lane, R., Lim, P., Vitagliano, D., Blier, P., Fava, M., Liebowitz, M., Ravindran, A., Gaillard, R., Ameele, H. V. D., Preskorn, S., Manji, H., Hough, D., Drevets, W. C., & Singh, J. B. (2019). Efficacy and Safety of Fixed-Dose Esketamine Nasal Spray Combined With a New Oral Antidepressant in Treatment-Resistant Depression: Results of a Randomized, Double-Blind, Active-Controlled Study (TRANSFORM-1). The international journal of neuropsychopharmacology, 22(10), 616–630. https://doi.org/10.1093/ijnp/pyz039

Harmer B, Lee S, Duong TvH, et al. (2024). Suicidal Ideation. StatPearls Publishing. Retrieved January 15, 2024, from: https://www.ncbi.nlm.nih.gov/books/NBK565877/

Ochs-Ross R, Daly EJ, Zhang Y, Lane R, Lim P, Morrison RL, Hough D, Manji H, Drevets WC, Sanacora G, Steffens DC, Adler C, McShane R, Gaillard R, Wilkinson ST, Singh JB. Efficacy and Safety of Esketamine Nasal Spray Plus an Oral Antidepressant in Elderly Patients With Treatment-Resistant Depression-TRANSFORM-3. Am J Geriatr Psychiatry. 2020 Feb;28(2):121-141. https://pubmed.ncbi.nlm.nih.gov/31734084/

Ionescu, D. F., Fu, D. J., Qiu, X., Lane, R., Lim, P., Kasper, S., Hough, D., Drevets, W. C., Manji, H., & Canuso, C. M. (2021). Esketamine Nasal Spray for Rapid Reduction of Depressive Symptoms in Patients with Major Depressive Disorder Who Have Active Suicide Ideation with Intent: Results of a Phase 3, Double-Blind, Randomized Study (ASPIRE II). The international journal of neuropsychopharmacology, 24(1), 22–31. https://doi.org/10.1093/ijnp/pyaa068

Popova, V., Daly, E. J., Trivedi, M., Cooper, K., Lane, R., Lim, P., Mazzucco, C., Hough, D., Thase, M. E., Shelton, R. C., Molero, P., Vieta, E., Bajbouj, M., Manji, H., Drevets, W. C., & Singh, J. B. (2019). 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. The American journal of psychiatry, 176(6), 428–438. https://doi.org/10.1176/appi.ajp.2019.19020172

U.S. Food & Drug Administration. (n.d.). *Drugs @ FDA: FDA-approved drugs.* Retrieved October 11, 2023, from https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211243Orig1s000Approv.pdf

U.S. Food & Drug Administration. (n.d.). FDA Label for Spravato. Retrieved February 13, 2024, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/211243s012lbl.pdf

VA Pharmacy Benefits Management Services (2022). Intranasal Esketamine for Depression. National Protocol Guidance. Retrieved October 23, 2023, from https://www.va.gov/formularyadvisor/DOC_PDF/CRE_Intranasal_Esketamine_for_Depression_National_Protocol_Rev_FEB2022.pdf

VI. CDI History/Revision Information

- Explanation of changes to the CDI

Revision Type	Date of Revision	Update(s) Made to CDI
	MM/DD/YYYY	
	MM/DD/YYYY	