Corporate Medical Policy: Esketamine (Spravato®) Nasal Spray **"Notification"** **POLICY EFFECTIVE JANUARY 1, 2026**

Restricted Product(s):

- esketamine (Spravato®) intranasal spray for administration under supervision of healthcare professional

FDA Approved Use:

- For the treatment of treatment-resistant depression in adults, as monotherapy or in conjunction with an oral antidepressant
- For the treatment of depressive symptoms in adults with major depressive disorder with acute suicidal ideation or behavior in conjunction with an oral antidepressant
- Limitations of use:
    - The effectiveness in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated; the use of this product does not preclude the need for hospitalization if clinically warranted, even if improvement is observed following initial dosing
    - This product is not approved as an anesthetic agent, as safety and effectiveness for this use have not been established

Criteria for Medical Necessity:

The restricted product(s) may be considered medically necessary when the following criteria are met:

Initial Criteria for Approval:

1. The patient is 18 years of age or older; **AND**
2. ONE of the following:
    a. The patient has a diagnosis of **treatment-resistant depression (TRD)**; **AND**
        i. The patient has a confirmed diagnosis of major depressive disorder (MDD) to include one of the following:
            1. Single-episode MDD and the duration has been ≥ 2 years; **OR**
            2. Recurrent MDD without psychotic features; **AND**
        ii. In the current depressive episode, the patient has had an inadequate response (≤ 25% improvement) to at least two antidepressants from at least two different classes (different mechanisms of action) (e.g., selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], tricyclic antidepressants [TCAs], bupropion, mirtazapine) of adequate dose and duration (typically 6 weeks); **OR**
    b. The patient has a diagnosis of **major depressive disorder (MDD)** with suicidal ideation or behavior; **AND**
        i. The suicidal ideation and intent are imminent and warrant potential hospitalization; **AND**

   ii. The patient is receiving esketamine nasal spray in conjunction with an oral antidepressant agent (i.e., esketamine will not be used as monotherapy); **AND**
3. At initiation of treatment with esketamine nasal spray, the patient has a depression symptom severity of ≥ 28 on the Montgomery-Asberg Depression Rating Scale (MADRS), or as scored by a comparable standardized rating scale that reliably measures depressive symptoms; **AND**
4. The patient will NOT receive esketamine nasal spray in combination with ketamine of any formulation or route of administration used for the same indication; **AND**
5. The patient does NOT have any clinical contraindications to esketamine nasal spray therapy (i.e., aneurysmal vascular disease or intracerebral hemorrhage); **AND**
6. The prescriber is a specialist in the area of the patient's diagnosis (i.e., psychiatrist); **AND**
7. The prescribed dose of esketamine nasal spray will be administered under direct supervision of a healthcare professional at a treatment facility that is certified through the Spravato (esketamine) REMS program; **AND**
   a. The requested product will be administered to the individual patient for whom it has been specifically prescribed and ordered, and within 14 days after receipt by the REMS-certified treatment facility; **AND**
8. The requested dose is within FDA labeled dosing for the requested indication, and the requested quantity does NOT exceed the maximum units allowed for the duration of approval (see table below).

   Duration of Approval: 90 days (3 months)

Continuation Criteria for Approval:

1. The patient was approved through Blue Cross NC initial criteria for approval; **OR**
2. The patient would have met initial criteria for approval at the time they started therapy; **AND**
3. ONE of the following:
   a. The patient has a diagnosis of **treatment-resistant depression (TRD)**; **OR**
   b. The patient has a diagnosis of **major depressive disorder (MDD)** with suicidal ideation or behavior; **AND**
      i. The patient will continue therapy with an oral antidepressant agent in conjunction with esketamine nasal spray; **AND**
4. Using the MADRS scale or a comparable standardized rating scale that reliably measures depressive symptoms, the patient has demonstrated at least a 50% reduction in depressive symptoms compared to baseline while on esketamine nasal spray therapy; **AND**
5. The patient will NOT receive esketamine nasal spray in combination with ketamine of any formulation or route of administration used for the same indication; **AND**
6. The patient does NOT have any clinical contraindications to esketamine therapy (i.e., aneurysmal vascular disease or intracerebral hemorrhage); **AND**

7. The prescriber is a specialist in the area of the patient's diagnosis (i.e., psychiatrist) or has consulted with a specialist in the area of the patient's diagnosis, **AND**
8. The prescribed dose of esketamine nasal spray will be administered under direct supervision of a healthcare professional at a treatment facility that is certified through the Spravato (esketamine) REMS program; **AND**
    a. The requested product will be administered to the individual patient for whom it has been specifically prescribed and ordered, and within 14 days after receipt by the REMS-certified treatment facility; **AND**
9. The requested dose is within FDA labeled dosing for the requested indication, and the requested quantity does NOT exceed the maximum units allowed for the duration of approval (see table below).

Duration of Approval: 180 days (6 months)

FDA Label Reference				
Medication	**Indication**	**Dosing**	**HCPCS**	**Maximum Units***
esketamine (Spravato®) nasal spray	Treatment Resistant Depression (TRD)	**Induction (Weeks 1-4):** Administer twice weekly starting Day 1 with 56mg dose, may increase to 84mg subsequently **Maintenance (Weeks 5-8):** Administer once weekly (56mg or 84mg) **Maintenance (Weeks 9 and after):** Administer every 2 weeks or once weekly (56mg or 84mg). Dosing frequency should be individualized to the least frequent dosing to maintain remission/response. Note: Evidence of therapeutic benefit should be evaluated at the end of the 4-week induction phase to determine need for continued treatment.	S0013 G2082** G2083**	**Initial: 2,016** **Continuation: 4,032**

FDA Label Reference				
Medication	**Indication**	**Dosing**	**HCPCS**	**Maximum Units***
	Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior	84 mg twice per week for 4 weeks, may be reduced to 56mg twice per week based on tolerability Note: Evidence of therapeutic benefit should be evaluated after 4 weeks to determine need for continued treatment. Treatment beyond 4 weeks has not been systematically evaluated.		

***Maximum units allowed for duration of approval**

**Please note the following applicable HCPCS codes:

- G2082 – Office or other outpatient visit for the evaluation and management of an established patient that requires the supervision of a physician or other qualified healthcare professional and provision of **up to 56 mg of esketamine** nasal self-administration, includes 2 hours post-administration observation
- G2083 – Office or other outpatient visit for the evaluation and management of an established patient that requires the supervision of a physician or other qualified healthcare professional and provision of **greater than 56 mg of esketamine** nasal self-administration, includes 2 hours post-administration observation
- For requests where the drug is supplied/dispensed AND administered with monitoring at the same site, only G codes combining both the drug and service should be submitted (i.e., G2082 or G2083)
- For requests where the drug is supplied/dispensed by a different site (e.g., specialty pharmacy) than where the drug is administered with monitoring (e.g., physician office), separate codes for the drug and service should be submitted (i.e., S0013 and the most appropriate E/M CPT code for the service)

References: all information referenced is from FDA package insert unless otherwise noted below.

1. American Psychiatric Association. Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Third Edition, 2010.
2. Daly EJ, Trivedi MH, Janik A, et al. Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry*. 2019 Sep;76(9):893-903.

3. 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;176:428-438.
4. 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):1905-17.

Policy Implementation/Update Information: Criteria and treatment protocols are reviewed annually by the Blue Cross NC P&T Committee, regardless of change. This policy is reviewed in Q2 annually.

January 2026: Criteria change: Added requirement that the requested product be administered to the individual patient for whom it has been specifically prescribed and ordered, and within 14 days after receipt by the REMS-certified treatment facility. Minor adjustments made to dosing table and coding description for clarity according to FDA label. **Policy notification given 11/1/2025 for effective date 1/1/2026**.
January 2025: Criteria change: Expanded treatment-resistant depression (TRD) indication to allow for use as monotherapy according to updated FDA label.
October 2024: Criteria change: For treatment-resistant depression indication, adjusted requirement of inadequate response to at least two antidepressants to specify from at least two different drug classes (different mechanisms of action). **Policy notification given 8/2/2024 for effective date 10/1/2024**.
October 2023: Criteria change: Added requirement for no use in combination with ketamine of any formulation or route of administration used for the same indication within initial and continuation criteria sections. Added requirement within maximum units criteria that the requested dose is within FDA labeled dosing for the requested indication. Updated maximum units for clarity. Minor adjustments made to formatting throughout policy for clarity. **Policy notification given 8/2/2023 for effective date 10/1/2023**.
June 2021: Coding change: Added applicable HCPCS codes G2082 and G2083, and description of billing scenarios.
June 2021: Criteria change: Added maximum units; medical policy formatting change. **Policy notification given 4/16/2021 for effective date 6/16/2021**.
*Further historical criteria changes and updates available upon request from Medical Policy and/or Corporate Pharmacy.