MEDICAL MUTUAL®

# Drug Policy

| | | |
|---|---|---|
| **Policy:** | **201911 – MRx** | **Initial Effective Date: 03/21/2019** |
| **Code(s):** | **HCPCS J3490, S0013, G2082, G2083** | **Annual Review Date: 02/20/2025** |
| **SUBJECT:** | **Spravato™ (esketamine nasal spray)** | **Last Revised Date: 02/20/2025** |

Subject to: ☐Site of Care
☐Medication Sourcing

**Prior approval is required for some or all procedure codes listed in this Corporate Drug Policy.**

## POLICY STATEMENT

This policy involves the use of Spravato. Prior authorization is recommended for medical benefit coverage of Spravato. Approval is recommended for those who meet the conditions of coverage in the **Initial Approval and Renewal Criteria, Preferred Drug (when applicable), Dosing/Administration, Length of Authorization, and Site of Care (when applicable)** for the diagnosis provided. The requirement that the patient meet the Criteria and Preferred Drug for coverage of the requested medication applies to the initial authorization only. All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is allowed, a response to therapy is required for continuation of therapy.

### I. Length of Authorization

Initial coverage will be provided for 6 months and may be renewed annually thereafter.

### II. Dosing Limits

**Max Units (per dose and over time) [HCPCS Unit]:**

**[G2082/G2083]**

- **Treatment Resistant Depression (TRD)**
  - Induction (weeks 1 to 4): 1 billable unit twice weekly
  - Maintenance (weeks 5 and after): 1 billable unit weekly
- **Depressive Symptoms In Patients With Major Depressive Disorder (MDD) With Acute Suicidal Ideation/Behavior:** 1 billable unit twice weekly

**[S0013]**

- **Treatment Resistant Depression (TRD)**
  - Induction (weeks 1 to 4): 56 billable units on Day 1, then 84 billable units twice weekly
  - Maintenance (weeks 5 and after): 84 billable units weekly
- **Depressive Symptoms In Patients With Major Depressive Disorder (MDD) With Acute Suicidal Ideation/Behavior:** 168 billable units weekly

## III. Initial Approval Criteria [1,15]

Coverage is provided in the following conditions:

- Patient is at least 18 years old; **AND**
- Patient must have a baseline assessment using any validated depression rating scale (e.g., Montgomery-Asberg Depression Rating Scale [MADRS], Hamilton Depression Rating Scale [HAM-D], Patient Health Questionnaire Depression Scale [PHQ-9], Beck Depression Inventory [BDI], Quick Inventory of Depressive Symptomatology [QIDS], etc.); **AND**

**Universal Criteria [1,11]**

- Patient has a diagnosis of major depressive disorder (MDD) according to the current version of the Diagnostic and Statistical Manual of Mental Disorders (e.g., DSM-5-TR); **AND**
- Patient must not have any of the following:
  - Aneurysmal vascular disease
  - Arteriovenous malformation
  - History of intracerebral hemorrhage
  - Known hypersensitivity to ketamine; **AND**
- Patient is not receiving concomitant ketamine therapy; **AND**

**Treatment-Resistant Depression (TRD) † [1,7,8,12-13,16]**

- Used as monotherapy or in conjunction with an oral antidepressant; **AND**
- Patient has tried psychotherapy alone or in combination with an oral antidepressant, if psychotherapy resources are available; **AND**
- Patient is NOT receiving concomitant electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS), or deep brain stimulation (DBS); **AND**
- Patient has failed a trial of at least 2 antidepressants of *different* classes for a duration of at least 6 weeks each with adequate adherence at generally accepted doses in the current depressive episode, unless contraindicated or

clinically significant adverse effects are experienced *('Failed trial' is defined as less than or equal to 25% reduction in symptom severity using any validated depression rating scale)*

**Depressive Symptoms In Patients With Major Depressive Disorder (MDD) With Acute Suicidal Ideation/Behavior † [1,9,10]**

- Must be used in conjunction with an oral antidepressant; **AND**
    - Patient is experiencing acute suicidal ideation or behavior; **OR**
    - Patient has recently been discharged from a hospital in which treatment with esketamine has been initiated

† FDA Approved Indication(s); ‡ Compendia Recommended Indication(s); **Φ** Orphan Drug

## IV. Renewal Criteria [1,15]

Coverage can be renewed based upon the following criteria:

- Patient continues to meet the universal and indication specific criteria as identified in section III; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: sedation, dissociation, respiratory depression, signs of abuse/dependance, severe cognitive impairment, ulcerative/interstitial cystitis, suicidal thoughts/behavior, severe hypertension, etc.; **AND**
- Patient has demonstrated disease improvement and/or stabilization as evidenced by a reduction in symptom severity, compared to baseline, using any validated depression rating scale.

## V. Dosage/Administration [1]

| Indication | Dose |
|---|---|
| Treatment-resistant depression (TRD) | Induction Phase:<br>• Weeks 1 to 4: Administer 56 mg or 84 mg intranasally twice per week<br>Maintenance Phase:<br>• Weeks 5 to 8: Administer 56 mg or 84 mg intranasally once weekly<br>• Weeks 9 and after: Administer 56 mg or 84 mg intranasally once every 2 weeks or once weekly*****<br>*******Dosing frequency should be individualized to the least frequent dosing to maintain remission/response.* |
| Depressive Symptoms in Major Depressive Disorder (MDD) with Acute Suicidal Ideation/Behavior | Administer 84 mg intranasally twice per week for 4 weeks.<br>• Dosage may be reduced to 56 mg twice per week based on tolerability.<br>• After 4 weeks of treatment with Spravato, evidence of therapeutic benefit should be evaluated to determine need for continued treatment. |

| | |
|---|---|
| | • The use of Spravato, in conjunction with an oral antidepressant, beyond 4 weeks has not been systematically evaluated in the treatment of depressive symptoms in patients with MDD with acute suicidal ideation or behavior. |
| • Spravato must be administered under the direct supervision of a healthcare provider. A treatment session consists of nasal administration of Spravato and post-administration observation under supervision.<br>• Spravato is for nasal use only. The nasal spray device delivers a total of 28 mg of esketamine. To prevent loss of medication, do not prime the device before use. Use 2 devices (for a 56 mg dose) or 3 devices (for an 84 mg dose), with a 5-minute rest between use of each device. | |

## VI. Billing Code/Availability Information

HCPCS(s):

- J3490 – Unclassified drugs
- C9399 – Unclassified drugs or biologicals
- S0013 – Esketamine, nasal spray, 1 mg; 1 billable unit = 1 mg
- *****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 health care 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 health care professional and provision of greater than 56 mg esketamine nasal self-administration, includes 2 hours post-administration observation

****** *Required for Medicare part B claims. For non-Medicare, those that do not accept the G Codes, providers may continue to report separate codes for the drug and service using the unclassified drug codes (J3490 or C9399) for Spravato and the most appropriate E/M CPT® code for the service.*

NDC(s):

- 56 mg Dose Kit: Unit-dose carton containing two 28 mg nasal spray devices (56 mg total dose): 50458-0028-xx
- 84 mg Dose Kit: Unit-dose carton containing three 28 mg nasal spray devices (84 mg total dose): 50458-0028-xx

## VII. References

1. Spravato [package insert]. Titusville, NJ; Janssen Pharmaceuticals., Inc.; January 2025. Accessed January 2025.
2. Papakostas GI. Incidence, impact, and current management strategies for treatment-resistant major depressive disorder. Medscape. Available at: https://www.medscape.org/viewarticle/574817_1. Accessed July 3, 2024.

3. American Psychiatric Association Work Group on Major Depressive Disorder. Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. October 2010. Available at: https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Accessed July 3, 2024.
4. Major Depression. National Institute of Mental Health. Available at: https://www.nimh.nih.gov/health/statistics/major-depression.shtml. Accessed July 3, 2024.
5. Johnston KM, Powell LC, Anderson IM, et al. The burden of treatment-resistant depression: a systematic review of the economic and quality of life literature. J Affect Disord. 2019; 242: 195-210. DOI: 10.1016/j.jad.2018.06.045.
6. Socci C, Medda P, Toni C, et al. Electroconvulsive therapy and age: age-related clinical features and effectiveness in treatment resistant major depressive episode. J Affect Disord. 2018; 227:627-632.
7. Starr HL, Abell J, Larish A, et al. Self-reported review of the value of esketamine in patients with treatment-resistant depression: Understanding the patient experience in the STRIVE Study. Psychiatry Res. 2020 Nov;293:113376. doi: 10.1016/j.psychres.2020.113376. Epub 2020 Aug 8. PMID: 32818917.
8. Jha MK, Williamson DJ, Magharehabed G, et al. Intranasal esketamine effectively treats treatment-resistant depression in adults regardless of baseline irritability. J Affect Disord. 2023 Jan 15;321:153-160. doi: 10.1016/j.jad.2022.10.020. Epub 2022 Oct 20. PMID: 36273682.
9. Fu D-J, Ionescu DF, Li X, et al. Esketamine nasal spray for rapid reduction of major depressive disorder symptoms in patients who have active suicidal ideation with intent: double-blind, randomized study (ASPIRE I). J Clin Psychiatry. 2020;81(3):19m13191.
10. Rozjabek, H., Li, N., Hartmann, H. *et al.* Assessing the meaningful change threshold of Quality of Life in Depression Scale using data from two phase 3 studies of esketamine nasal spray. *J Patient Rep Outcomes* 6, 74 (2022). https://doi.org/10.1186/s41687-022-00453-y
11. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR), 2022.
12. Reif A, Bitter I, Buyze J, et al. Esketamine Nasal Spray versus Quetiapine for Treatment-Resistant Depression. N Engl J Med 2023; 389:1298.
13. McIntyre RS, Rosenblat JD, et al. Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation. Am J Psychiatry. 2021 May 1;178(5):383-399. doi: 10.1176/appi.ajp.2020.20081251. Epub 2021 Mar 17. PMID: 33726522; PMCID: PMC9635017.
14. Qaseem A, Owens DK, Etxeandia-Ikobaltzeta I, Tufte J, et al. Nonpharmacologic and Pharmacologic Treatments of Adults in the Acute Phase of Major Depressive Disorder: A Living Clinical Guideline From the American College of Physicians. Ann Intern Med. 2023;176(2):239. Epub 2023 Jan 24.

15. American Psychological Association. Depression Assessment Instruments. January 2023. Available at: https://www.apa.org/depression-guideline/assessment. Accessed on July 3, 2024.
16. Rush AJ, Thase ME. Improving Depression Outcome by Patient-Centered Medical Management. Am J Psychiatry. 2018 Dec 1;175(12):1187-1198. doi: 10.1176/appi.ajp.2018.18040398. Epub 2018 Sep 17. PMID: 30220219.
17. Janik A, Qiu X, Lane R, et al. Efficacy and Safety of Esketamine Nasal Spray as Monotherapy in Adults with Treatment-Resistant Depression: A Randomized, Double-Blind, Placebo-Controlled Study. Janssen Research & Development, LLC, San Diego, CA, USA; Janssen Research & Development, LLC, Raritan, NJ, USA; Janssen Research & Development, LLC, Titusville, NJ, USA; Janssen Pharmaceutica NV, Beerse, Belgium. efficacy-and-safety-of-esketamine-nasal-spray-as-monotherapy-in-adults-with-treatmentresistant-depre.pdf
18. 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 Jun 1;176(6):428-438. doi: 10.1176/appi.ajp.2019.19020172. Epub 2019 May 21. Erratum in: Am J Psychiatry. 2019 Aug 1;176(8):669. doi: 10.1176/appi.ajp.2019.1768correction1. PMID: 31109201.
19. 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 1;76(9):893-903. doi: 10.1001/jamapsychiatry.2019.1189. PMID: 31166571; PMCID: PMC6551577.
20. Ionescu DF, Fu DJ, Qiu X, et al. 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). Int J Neuropsychopharmacol. 2021 Jan 20;24(1):22-31. doi: 10.1093/ijnp/pyaa068. PMID: 32861217; PMCID: PMC7816667.
21. Novitas Solutions, Inc. Local Coverage Article: Billing and Coding: Esketamine (A59249). Centers for Medicare & Medicaid Services, Inc. Updated on 09/13/2024 with effective date 09/19/2024. Accessed January 2025.
22. First Coast Service Options, Inc. Local Coverage Article: Billing and Coding: Esketamine (A59250). Centers for Medicare & Medicaid Services, Inc. Updated on 09/13/2024 with effective date 09/19/2024. Accessed January 2025.

**Appendix 1 – Covered Diagnosis Codes**

| ICD-10 | ICD-10 Description |
|---|---|
| F32.0 | Major depressive disorder, single episode, mild |
| F32.1 | Major depressive disorder, single episode, moderate |
| F32.2 | Major depressive disorder, single episode, severe without psychotic features |
| F32.3 | Major depressive disorder, single episode, severe with psychotic features |

| | |
|---|---|
| F32.4 | Major depressive disorder, single episode, in partial remission |
| F32.5 | Major depressive disorder, single episode, in full remission |
| F32.9 | Major depressive disorder, single episode, unspecified |
| F33.0 | Major depressive disorder, recurrent, mild |
| F33.1 | Major depressive disorder, recurrent, moderate |
| F33.2 | Major depressive disorder, recurrent severe without psychotic features |
| F33.3 | Major depressive disorder, recurrent, severe with psychotic symptoms |
| F33.40 | Major depressive disorder, recurrent, in remission, unspecified |
| F33.41 | Major depressive disorder, recurrent, in partial remission |
| F33.42 | Major depressive disorder, recurrent, in full remission |
| F33.8 | Other recurrent depressive disorders |
| F33.9 | Major depressive disorder, recurrent, unspecified |
| R45.851 | Suicidal ideations |

**Appendix 2 – Centers for Medicare and Medicaid Services (CMS)**

The preceding information is intended for non-Medicare coverage determinations. Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determinations (NCDs) and/or Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. Local Coverage Articles (LCAs) may also exist for claims payment purposes or to clarify benefit eligibility under Part B for drugs which may be self-administered. The following link may be used to search for NCD, LCD, or LCA documents: https://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications, including any preceding information, may be applied at the discretion of the health plan.

| Medicare Part B Covered Diagnosis Codes | | |
|---|---|---|
| **Jurisdiction** | **NCD/LCA/LCD Document (s)** | **Contractor** |
| H, L | A59249 | Novitas Solutions, Inc. |
| N | A59250 | First Coast Service Options, Inc. |

| Medicare Part B Administrative Contractor (MAC) Jurisdictions | | |
|---|---|---|
| **Jurisdiction** | **Applicable State/US Territory** | **Contractor** |
| E (1) | CA, HI, NV, AS, GU, CNMI | Noridian Healthcare Solutions, LLC |
| F (2 & 3) | AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ | Noridian Healthcare Solutions, LLC |
| 5 | KS, NE, IA, MO | Wisconsin Physicians Service Insurance Corp (WPS) |
| 6 | MN, WI, IL | National Government Services, Inc. (NGS) |
| H (4 & 7) | LA, AR, MS, TX, OK, CO, NM | Novitas Solutions, Inc. |
| 8 | MI, IN | Wisconsin Physicians Service Insurance Corp (WPS) |
| N (9) | FL, PR, VI | First Coast Service Options, Inc. |
| J (10) | TN, GA, AL | Palmetto GBA |
| M (11) | NC, SC, WV, VA (excluding below) | Palmetto GBA |
| L (12) | DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA) | Novitas Solutions, Inc. |
| K (13 & 14) | NY, CT, MA, RI, VT, ME, NH | National Government Services, Inc. (NGS) |
| 15 | KY, OH | CGS Administrators, LLC |

**Documentation Requirements:**

The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the drug provided or services performed were not medically necessary, investigational or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

MEDICAL MUTUAL®

# Drug Policy

**FOR MEDICAL BENEFIT COVERAGE REQUESTS:**

**Prior approval is required for HCPCS Codes S0013, G2082, andG2083**