Spravato® (esketamine)
(Intranasal)

Document Number: IC-0481

Last Review Date: 06/01/2023
Date of Origin: 05/13/2019
Dates Reviewed: 05/2019, 07/2019, 02/2020, 10/2020, 02/2021, 02/2022, 06/2023

I. Length of Authorization

- Initial: 4 weeks
- Renewal: 4 weeks for first renewal; 3 months for subsequent renewals

II. Dosing Limits

A. Quantity Limit (max daily dose) [Pharmacy Benefit]:

- Induction (weeks 1 to 4): 2 kits/week (84 mg kit); (one 56 mg kit Day 1)
- Maintenance (weeks 5 to 8): 1 kit/week (84 mg kit)

B. Max Units (per dose and over time) [Medical Benefit]:

Treatment Resistant Depression

– Induction (weeks 1 to 4): 84 mg twice weekly (56 mg Day 1)
– Maintenance (weeks 5 to 8): 84 mg weekly

Major Depressive Disorder (MDD)

– 2 kits (84 mg kit) weekly

III. Initial Approval Criteria

- 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]); **AND**
- Prescriber's healthcare setting is certified in the Spravato Risk Evaluation and Mitigation Strategies (REMS) program; **AND**

Universal Criteria

- Patient has been instructed not to engage in potentially hazardous activities (e.g., driving a motor vehicle, operating machinery, etc.) until the next day following a restful sleep; **AND**
- Patient has a Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnosis of major depressive disorder (MDD); **AND**
- Patient must not have a current or prior DSM-5 diagnosis of any of the following:
    - Concomitant psychotic disorder; **OR**
    - MDD with psychosis; **OR**
    - Bipolar or related disorders; **OR**
    - Obsessive compulsive disorder (OCD); **OR**
    - History of moderate to severe substance or alcohol use disorder; **OR**
    - Personality disorder; **AND**
- Patient must not have any of the following conditions:
    - Aneurysmal vascular disease; **OR**
    - Arteriovenous malformation; **OR**
    - History of intracerebral hemorrhage; **OR**
    - Uncontrolled hypertension (i.e., greater than 140/90 mmHg); **AND**
- Patient must not have intellectual disability; **AND**
- Patient does not have known hypersensitivity to ketamine; **AND**
- Patient is not receiving concomitant ketamine therapy; **AND**
- Patient must be taking esketamine in conjunction with an antidepressant medication (esketamine is not to be used as monotherapy); **AND**

Treatment-Resistant Depression (TRD) † [1,8,9]

- Patient has a history of adherence with oral therapy (compliant with at least 80% of their doses as evident by refill history or prescriber attestation during current depressive episode); **AND**
- Patient has failed a trial of antidepressant augmentation therapy for a duration of at least 6 weeks in the *current* depressive episode with at least 1 of the following, unless contraindicated or clinically significant adverse effects are experienced (see 'failed trial' as defined above):
    - An antidepressant from a different class; **OR**
    - An atypical antipsychotic; **OR**
    - Lithium; **AND**
- Patient has tried psychotherapy alone or in combination with oral antidepressants, if psychotherapy resource available; **AND**
- Patient must NOT have failed prior ketamine treatment for MDD; **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 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 † [1,10,11]

- Patient admission for an acute inpatient hospitalization is clinically warranted based on imminent risk of suicide; **OR**
- Patient has recently been discharged from a hospital in which treatment with esketamine has been initiated

† FDA Approved Indication(s); ‡ Literature Supported Indication; Φ Orphan Drug

IV. Renewal Criteria

- Patient continues to meet universal and indication specific criteria as identified in section III; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: dissociation, 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

Indication	Dose
Treatment-resistant depression (TRD)	Induction (administer twice per week): • Day 1: 56 mg • Weeks 1 to 4 subsequent doses: 56 mg or 84 mg Maintenance: • Weeks 5 to 8: 56 mg or 84 mg once weekly • Weeks 9 and after: 56 mg or 84 mg once every 2 weeks or once weekly*

	** Dosing frequency should be individualized to the least frequent dosing to maintain remission/response.*
Major Depressive Disorder (MDD)	Administer Spravato in conjunction with an oral antidepressant (AD). – The recommended dosage of Spravato for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior is 84 mg twice per week for 4 weeks. – Dosage may be reduced to 56 mg twice per week based on tolerability. – 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. - 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:

- J3490 – Unclassified drugs
- 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 miscellaneous drug code (J3490 – unclassified drug) for Spravato and the most appropriate E/M CPT® code for the service.*

NDC:

- 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 Pharm., Inc.; July 2020. Accessed May 2023.
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 May 3, 2019.
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 May 3, 2019.
4. Major Depression. National Institute of Mental Health. Available at: https://www.nimh.nih.gov/health/statistics/major-depression.shtml. Accessed May 3, 2019.
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. 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://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines. Accessed May 3, 2019.
7. 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.
8. 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.
9. 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.
10. 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.
11. 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
12. Novitas Solutions, Inc. - Article: Billing and Coding: Esketamine (A59249). Centers for Medicare & Medicaid Services, Inc. Updated on 09/23/2022 with effective date 11/14/2022. Accessed May 2023.

13. First Coast Service Options, Inc. Local Coverage Article: Billing and Coding: Esketamine (A59250). Centers for Medicare & Medicaid Services, Inc. Updated on 09/23/2022 with effective date 11/14/2022. Accessed May 2023.

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

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

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 Determination (NCD), Local Coverage Determinations (LCDs), and Articles may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/Article):

Jurisdiction(s): H, L	**NCD/LCD/LCA Document(s):** A59249
https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=59249&ver=3&keyword=spravato&keywordType=starts&areaId=all&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=1	

Jurisdiction(s): N	**NCD/LCD/LCA Document(s):** A59250

https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=59250&ver=4&keyword=spravato&keywordType=starts&areaId=all&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=1

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, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
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