Ascension
Personalized Care

Ascension

Esketamine Nasal Spray

(Spravato®) J3490 (NOC) (1unit/device = 28 mg)

Covered with prior authorization

In order to enter authorizations correctly, **please** submit the J code provided at the top of this document. G codes **may not** allow for proper authorization of the request. For Spravato®, the S code is S0013 and the agent is documented as esketamine, nasal spray, (1 mg) for this corresponding code.

Requests for Spravato® (esketamine) nasal spray for **treatment resistant depression** may be approved if the following criteria are met:

- Individual is 18 years of age or older; **AND**
- Individual has been diagnosed with moderate to severe major depressive disorder; **AND**
- Individual has had an inadequate response to the maximum tolerated dose of two antidepressant therapies during the current major depressive episode (MDE) as defined by less than 50% reduction in symptom severity using a standard rating scale that reliably measures depressive symptoms; **AND**
- Individual will use Spravato® in addition to antidepressant therapy.

Continuation of Spravato® (esketamine) nasal spray for **treatment resistant depression** may be approved if the following criteria are met:

- Individual has had at least a 50% reduction in symptoms of depression compared to baseline using a standard rating scale that reliably measures depressive symptoms; **AND**
- Individual will use Spravato® in addition to antidepressant therapy.

Requests for Spravato® (esketamine) nasal spray for **depressive symptoms in individuals with major depressive disorder with acute suicidal ideation or behavior** may be approved if the following criteria are met:

- Individual is 18 years of age or older; **AND**
- Individual has a diagnosis of major depressive disorder (MDD) without psychotic features according to DSM-5 (Fu 2020, Ionescu 2020); **AND**
- Individual is judged to be at risk for suicide by a clinician based on consideration of suicidal behavior, expressed suicidal ideation, or overall clinical assessment consistent with significant continuing risk of suicide; **AND**
- Individual must use Spravato® in addition to antidepressant therapy.

Initial authorizations for **treatment resistant depression** are for up to 3 months.
Reauthorizations for **treatment resistant depression** are for up to 12 months.

Initial and **Reauthorizations** for depressive symptoms in individuals with major depressive disorder with acute suicidal ideation or behavior are limited to **4 weeks only**.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Requests for Spravato® (esketamine) may **not** be approved if the above criteria are not met and for all other indications not included above.

Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Exclusion criteria:

- Individual has aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation.
- Individual has intracerebral hemorrhage.
- Individual is using in combination with intravenous ketamine.
- Individual has severe hepatic impairment (Child-Pugh Class C).
- Doses, durations, or dosing intervals that exceed FDA maximum limits for any FDA-approved indication or are not supported by industry-accepted practice guidelines or peer-reviewed literature for the relevant off-label use.
- Individuals with significant known risk factors unless the record provides an assessment of clinical benefit that outweighs the risk.

U.S. Food and Drug Administration:
This section is to be used for informational purposes. FDA approval alone is not a basis for coverage). Spravato® is FDA approved for those with treatment resistant depression when used concomitantly with antidepressant therapy. Relevant clinical trials cited in the label were TRANSFORM 2 and SUSTAIN 1. Other trials completed include TRANSFORM 1 and TRANSFORM 3. In these trials, Spravato® plus an antidepressant (AD) was compared to placebo plus an antidepressant. The TRANSFORM trials, while short in duration (4 weeks), demonstrated a decrease in Montgomery-Asberg Depression Rating Scale (MADRS) total score compared to placebo of between -3.6 and -4.2. Response and, in some cases, remission of depressive symptoms was noted to occur in more Spravato®plus AD patients than placebo plus AD patients. The SUSTAIN I trial was longer in duration and was done to determine time to relapse during the maintenance phase in those who had achieved stable remission or response to Spravato® plusAD compared to placebo plus AD. Fewer Spravato® plus AD patients experienced a relapse compared to placebo plus AD.

Spravato® for **treatment resistant depression** is administered intranasally twice weekly for 4 weeks, then once weekly for four weeks, then weekly or every other week thereafter. The recommended dosing schedule is as follows:

Induction Phase	Weeks 1-4: Twice weekly	Day 1: 56 mg (2 devices) Subsequent doses: 56 mg or 84 mg (3 devices)
Maintenance Phase	Weeks 5-8: Once weekly	56 mg (2 devices) or 84 mg (3 devices)
	Week 9 and after: every 2 weeks OR once weekly*	56 mg (2 devices) or 84 mg (3 devices)

*Dosing frequency should be individualized to the least frequent dosing to maintain remission/response.

Spravato® is also FDA approved for the treatment of depressive symptoms with major depressive disorder (MDD) with acute suicidal ideation or behavior. The effectiveness of Spravato® in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of Spravato. Approval was based on the results of the ASPIRE I and ASPIRE II studies. Change from baseline to 24- hour post-dose Montgomery-Asberg Depression Rating Scale (MADRS) total score showed a mean difference with use of Spravato® plus standard of care antidepressant (SOC AD) of -3.8 (ASPIRE I) and -3.9 (ASPIRE II) when compared to placebo plus standard of care antidepressant. However, there was no superiority of Spravato® plus SOC AD over placebo plus SOC AD when evaluating suicidality scores but both groups did improve.

The recommended dosage of Spravato® for the **treatment of depressive symptoms with major depressive disorder (MDD) with acute suicidal ideation or behavior** is 84 mg intranasally twice per week for 4 weeks; dose may be reduced to 56 mg twice weekly based on tolerability. Per label, after 4 weeks of treatment, evidence of therapeutic benefit should be evaluated to determine need for continued treatment; however, the use of Spravato®, in addition to an oral antidepressant, for more than 4 weeks has not been systematically evaluated in the treatment of depressive symptoms in patients with MDD with acute suicidal ideation or behavior.

Because of the risk of increased blood pressure, blood pressure should be assessed prior to dosing and after dosing Spravato®. If predose blood pressure is elevated (> 140 mmHg systolic, >90 mmHg diastolic), a risk-benefit evaluation must be done to determine if the risk of short term blood pressure increase outweighs the potential benefits of treatment with Spravato®. Spravato® should be given on an empty stomach (avoidance of food at least 2 hours before administration) due to the increased risk for nausea and vomiting. Because there have been cases of ulcerative or interstitial cystitis reported in individuals with long-term, off-label use or misuse of ketamine, and clinical trials with esketamine have shown an increased rate of lower urinary tract symptoms, it is recommended that individuals be monitored for urinary tract and bladder symptoms. In clinical trials, the mean AUC and half-life of Spravato® were increased in those with 2 moderate hepatic impairment, and, therefore, increased

monitoring is recommended in these individuals. Spravato® was not studied in those with severe hepatic impairment; however, use is not recommended in this population per label.

Spravato® has a **Risk Evaluation and Mitigation Strategy (REMS)** due to the increased risk for sedation as well as abuse and misuse. Healthcare settings **must be certified** to provide Spravato®; administration must be under direct observation of a healthcare provider and the individual must be monitored for at least 2 hours after administration. Pharmacies must also be certified and will only dispense Spravato® to certified healthcare settings.

Spravato® has a **black box warning** for sedation and dissociation, potential for misuse and abuse, and increased risk of suicidal thoughts and behaviors. Spravato® is not approved for use in pediatric individuals.

Key References Accessed 8/2022:

1. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2022; Updated periodically.
2. Canuso CM, Singh JB, Fedgchin M, et al. 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. Am J Psychiatry. 2018;175:620-630.
3. Daly EJ, Singh JB, Fedgchin M, et al. Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA Psychiatry. 2018;75:139-148.
4. Nierenberg AA, DeCecco LM. Definitions of antidepressant treatment response, remission, nonresponse, partial response, and other relevant outcomes: A focus on treatment-resistant depression. J Clin Psychiatry. 2001;62[Suppl16]:5-9.
5. Spravato® [package insert]. Titusville, NJ: Janssen Pharmaceutical Companies; 2020.
6. Fedgchin M, Trivedi M, Daly EJ, et al. 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). Int J Neuropsychopharmacol. 2019; 22:616-630.
7. Ochs-Ross R, Daly EJ, Zhang Y, et al. 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; 28:121-141.
8. Fu DJ, 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.
9. 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. 2020 Aug 29;pyaa068. doi: 10.1093/ijnp/pyaa068. Epub ahead of print. Available from: https://pubmed.ncbi.nlm.nih.gov/32861217/.

Date	Summary of Changes
August 2022	Criteria for use summary developed by the Ascension Medical Specialty Prior Authorization Team.
September 2022	Criteria for use summary approved by the Ascension Ambulatory Care Expert Review Panel.
October 2022	Criteria for use summary approved by the Ascension Therapeutic Affinity Group.

If you have questions, call 833-980-2352 to speak to a member of the Ascension Rx prior authorization team.

PDF created for upload: 6.23.2023