Medical Drug Clinical Criteria

Subject:	Spravato (esketamine) Nasal Spray		
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Overview

This document addresses the use of Spravato (esketamine nasal spray). 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 + AD patients than placebo + AD patients. The SUSTAIN I trial was longer in duration and was done to determine time to relapse during maintenance phase in those who had achieved stable remission or response to Spravato + AD compared to placebo + AD. Fewer Spravato + AD patients experienced a relapse compared to placebo + 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 + SOC AD over placebo + 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 pre-dose blood pressure is elevated (> 140 mmHg systolic, >90 mmHg diastolic), a risk-benefit evaluation must be done to determine if 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 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.

Evaluation of depression and response to treatment is accomplished utilizing a standard rating scale in order to survey the type and severity of symptoms. There are several standardized rating scales available including the following:

- Beck Depression Inventory (BDI)
- Geriatric Depression Scale (GDS)
- Hamilton Depression Rating Scale (HAM-D)
- Inventory of Depressive Symptomatology-Systems Review (IDS-SR)
- Montgomery-Asberg Depression Rating Scale (MADRS)
- Personal Health Questionnaire Depression Scale (PHQ-9)
- Quick Inventory of Depressive Symptomatology (QIDS)

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Spravato (esketamine) Nasal Spray

Initial requests for Spravato (esketamine) nasal spray for treatment resistant depression may be approved if the following criteria are met (Daly 2018):

I. Individual is 18 years of age or older; **AND**
II. Individual has been diagnosed with moderate to severe major depressive disorder; **AND**
III. 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**
IV. 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:

I. 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**
II. Individual will use Spravato in addition to antidepressant therapy.

Approval duration for treatment resistant depression:

- Initial approval: 3 months
- Maintenance approval: 12 months

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:

I. Individual is 18 years of age or older; **AND**
II. Individual has a diagnosis of major depressive disorder (MDD) without psychotic features according to DSM-5 (Fu 2020, Ionescu 2020); **AND**
III. 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**
IV. Individual must use Spravato in addition to antidepressant therapy.

Approval duration for depressive symptoms in individuals with major depressive disorder with acute suicidal ideation or behavior: 4 weeks

Requests for Spravato (esketamine) nasal spray may not be approved for the following criteria:

I. Individual has aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation; **OR**
II. Individual has intracerebral hemorrhage; **OR**
III. Individual is using in combination with ketamine; **OR**

IV. Individual has severe hepatic impairment (Child-Pugh Class C); **OR**
V. When the above criteria are not met and for all other indications.

Quantity Limits

Spravato (esketamine) nasal spray Quantity Limits

Drug	Limit
Spravato (esketamine) nasal spray 56 mg Dose Kit, 84 mg Dose Kit	4 kits per 28 days
Override Criteria	
*Initiation of therapy for Spravato: May approve up to 4 additional kits in the first month (28 days) of treatment.	

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

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
S0013	Esketamine, nasal spray, 1 mg [Spravato] is for the drug itself, CANNOT be combined with HCPCS G2082 and G2083

ICD-10 Diagnosis

F33.0-F33.9	Major depressive disorder, recurrent
F32.0-F32.9	Major depressive disorder, single episode, mild
R45.850-R45.851	Homicidal and suicidal ideations

Document History

Revised: 02/24/2023
Document History:

- 12/18/2023 – Add quantity limit.
- 02/24/2023 – Annual Review: Update non-approvable criteria to clarify restriction with ketamine. Wording and formatting changes. Coding Reviewed: No changes. Effective 7/1/2023 Removed HCPCS S0013, J3490. Effective 9/1/2023 Added HCPCS S0013.
- 02/25/2022 – Annual Review: Update non-approvable criteria to restrict use in severe hepatic impairment per label. Wording and formatting changes. Coding Reviewed: No changes.
- 02/19/2021 – Annual Review: Updated may not be approved criteria to include concomitant use with IV ketamine; added statement that Spravato would not be approved for non-listed indications. Coding Reviewed: Added HCPCS S0013. 2/9/2022 Added HCPCS J3490 back into policy.
- 09/14/2020 – Select Review: Updated clinical criteria to include treatment of depressive symptoms in individuals with major depressive disorder with acute suicidal ideation or behavior per label and clinical trial inclusion criteria. Coding Reviewed: Added ICD-10-CM R45.850-R45.851. Effective 1/1/21 Added HCPCS S0013. Removed HCPCS J3490.
- 2/21/2020 – Annual Review: No Changes. Coding Reviewed: No changes. 7/31/2020: Added HCPCS G2082, G2083
- 3/6/2019 – Select Review: Add new clinical criteria document for Spravato (esketamine) nasal spray; Coding update: add J3490 HCPCs and F33.0-F33.9, F32.0-F32.9 ICD-10.

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Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.