UM Clinical Guidelines — Spravato® (esketamine nasal spray) PAM–021

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Iowa Medicaid program:	Prior authorization	**Effective date:**	
Revision number:	4	**Last Rev date:**	6/27/2024
Reviewed by:	Medicaid Medical Director	**Next rev date:**	
Approved by:		**Approved date:**	

Overview

Medication:[1]	esketamine
Brand name:	Spravato®
Pharmacologic category:	N-methyl-D-aspartate (NMDA) receptor antagonist.
FDA-approved indication(s):	Indicated, in conjunction with an oral antidepressant, for the treatment of: 1. Treatment-resistant depression (TRD) in adults. or 2. Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior. **Limitations of use:** • 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. • Spravato is not approved as an anesthetic agent. The safety and effectiveness of Spravato as an anesthetic agent have not been established.
How supplied:	Available in a stoppered glass vial within a nasal spray device. Each nasal spray device delivers two sprays containing a total of 28 mg of esketamine: • 56 mg dose kit: unit-dose carton containing two 28 mg nasal spray devices. • 84 mg dose kit: unit-dose carton containing three 28 mg nasal spray devices.
Benefit category:	Medical

Treatment-resistant depression (TRD)			
Treatment phase	**Time frame**	**Administration frequency**	**Dosage**
Induction	Weeks 1 to 4	Twice per week	Day 1 starting dose: 56 mg Subsequent doses: 56 mg or 84 mg
Maintenance	Weeks 5 to 8	Once weekly	56 mg or 84 mg
Maintenance	Week 9 and after	Every two weeks or once weekly*	56 mg or 84 mg

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

Major depressive disorder (MDD) with acute suicidal ideation or behavior			
Treatment Phase	**Time Frame**	**Administration Frequency**	**Dosage**
Treatment	Weeks 1 to 4 ‡	Twice per week	Day 1 starting dose: 84 mg Subsequent doses: 56 mg or 84 mg

‡
After four weeks of treatment with Spravato , evidence of therapeutic benefit should be evaluated to determine need for continued treatment. The use of Spravato beyond four weeks has not been systematically evaluated in the treatment of depressive symptoms in patients with major depressive disorder (MDD) with acute suicidal ideation or behavior.

Descriptive narrative/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) were compared to placebo plus an antidepressant. The TRANSFORM trials, while short in duration (four 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 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.
Spravato (esketamine) is an N-methyl-D-aspartate (NMDA)-receptor antagonist. The efficacy of esketamine in treatment resistant depression (TRD) is mediated through antagonism of NMDA receptor, which produces a transient increase in glutamate release, leading to increases in postsynaptic alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors stimulation and subsequently to increases in neurotrophic signaling that restore synaptic function in these brain regions.

Black box warnings

- Potential for misuse and abuse — Monitor patients for signs and symptoms.
- Potential for sedation and dissociation — Monitor patients for signs and symptoms.
- Increased risk of suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants —Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors.
- Spravato is not approved for use in pediatric members.
- Spravato is available only through a Risk Evaluation and Mitigation Strategy (REMS) program. Members self-administer the drug in the office and are then monitored for at least two hours by clinicians in the office (due to risk of sedation and dissociation after administration).

Clinical management

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 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 two 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 two hours

after administration. Pharmacies must also be certified and will only dispense Spravato to certified healthcare settings.

Tools for measuring depression

Evaluation of depression and response to treatment is accomplished utilizing a standard rating scale 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)

Guidelines

Clinical practice guidelines for the treatment of depression were last updated prior to FDA approval of Spravato in 2019.

Clinical Criteria

Prior authorization is required.

Use of ketamine as an intravenous (IV) infusion is not FDA-approved and is not a covered benefit.

Treatment resistant depression (TRD)

Spravato is considered medically necessary when **all** of the following are met:

1. Diagnosis of moderate to severe major depressive disorder (MDD; meets DSM-5 criteria within the previous four weeks); **and**
2. Member is 18 years of age or older; **and**
3. Member 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**
4. Member will continue to use oral antidepressant therapy in addition to Spravato®; **and**
5. Member has **not** been diagnosed with any of the following:
    a. Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation; **and/or**

   b. Intracerebral hemorrhage; **or**
   c. Member is using in combination with ketamine; **or**
   d. Member has severe hepatic impairment (Child-Pugh Class C); **or**
   e. When the above criteria are not met and for all other indications.

and

6. Prescribed by, or in consultation with, a psychiatrist or a psychiatric or mental health nurse practitioner; **and**
7. Treatment will be administered at a facility that is certified under the Spravato® Risk Evaluation and Mitigation Strategy (REMS) program; **and**
8. Dose does not exceed 84 mg (three nasal spray devices) twice weekly during the four-week induction phase or 84 mg (three nasal spray devices) per week during the maintenance phase.

Spravato is considered medically necessary for continuation of therapy when ALL of the following are met:

1. Member has a diagnosis of moderate to severe major depressive disorder (MDD) and is currently receiving medication through the Iowa Medicaid benefit or has previously met initial approval criteria; **and**
2. Member 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**
3. Member will continue oral antidepressant therapy in conjunction with Spravato®; **and**
4. Prescribed by, or in consultation with, a psychiatrist or a psychiatric or mental health nurse practitioner; **and**
5. Treatment will be administered at a facility that is certified under the Spravato® Risk Evaluation and Mitigation Strategy (REMS) program; **and**
6. Dose does not exceed 84 mg (three nasal spray devices) per week.

Approval duration for treatment resistant depression:

- Initial approval: three months
- Maintenance approval: 12 months

Major Depressive Disorder (MDD) with Acute Suicidal Ideation or Behavior

Spravato is considered medically necessary when **ALL** of the following are met:

1. Diagnosis of major depressive disorder (MDD; meets DSM-5 criteria within the previous four weeks); **and**
2. Member 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**
3. Member is 18 years of age or older; **and**
4. Prescribed in combination with initiation or optimization of oral antidepressant therapy; **and**
5. Member has **not** been diagnosed with any of the following:
   a. Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation; **and/or**

b. Intracerebral hemorrhage; **or**
c. Member is using in combination with ketamine; **or**
d. Member has severe hepatic impairment (Child-Pugh Class C); **or**
e. When the above criteria are not met and for all other indications.

and

6. Prescribed by, or in consultation with, a psychiatrist or a psychiatric or mental health nurse practitioner; **and**
7. Treatment will be administered at a facility that is certified under the Spravato Risk Evaluation and Mitigation Strategy (REMS) program; **and**
8. Dose does not exceed 84 mg (three nasal spray devices) twice weekly for a total of four weeks.*

* The use of Spravato in conjunction with an oral antidepressant beyond four weeks has not been systematically evaluated in the treatment of depressive symptoms in patients with major depressive disorder (MDD) with acute suicidal ideation or behavior.

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

Approval duration and quantity limits

Diagnosis	Initial	Continuation
Treatment resistant depression (TRD)	3 months 8 kits† per first 28 days, then 4 kits per 28 days	12 months 4 kits per 28 days
Major depressive disorder (MDD) with acute suicidal ideation or behavior	4 weeks 8 kits† for 28-day course of therapy	Not applicable

† Spravato is available in two formulations:
56 mg kit (containing two nasal spray devices, each containing 28 mg of esketamine).
84 mg kit (containing three nasal spray devices, each containing 28 mg of esketamine).

Coding and product information

The following list(s) of codes and product information are provided for reference purposes only and may not be all inclusive. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment, nor does the exclusion of a code imply that its association to the HCPCS code is inappropriate.

HCPCS	Description
S0013	Esketamine, nasal spray, 1 mg (Medicaid)
E&M	Use appropriate evaluation and management (E&M) codes when billing for healthcare provider services required for Spravato administration and post-administration observation. (Medicaid)

G2082	Bundled service code for esketamine drug and visit 56 m or less (Medicare cross over)
G2083	Bundled service code for esketamine drug and visit >56 m (Medicare cross over)

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
F32.4	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
F33.40	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
F33.9	Major depressive disorder, recurrent, unspecified

NDC	Labeler	Dosage	Pkg size	Pkg qty	Units/pkg
50458-0028-02 (56 mg kit)	Janssen Pharmaceuticals, Inc.	1 mg	1	2	56
50458-0028-03 (84 mg kit)	Janssen Pharmaceuticals, Inc.	1 mg	1	3	84

Compliance

1. Should conflict exist between this policy and applicable statute, the applicable statute shall supersede.
2. Federal and state law, as well as contract language, including definitions and specific contract provisions or exclusions, take precedence over medical policy and must be considered first in determining eligibility for coverage.
3. Medical technology is constantly evolving, and Wellpoint reserves the right to review and update medical policy on an annual or as-needed basis.

Medical necessity guidelines have been developed for determining coverage for member benefits and are published to provide a better understanding of the basis upon which coverage decisions are made. Medical necessity guidelines are developed for selected physician-administered medications found to be safe and proven to be effective in a limited, defined population or clinical circumstances. They include concise clinical coverage criteria based on current literature review, consultation with practicing physicians in the service area who are medical experts in the particular field, FDA and

other government agency policies, and standards adopted by national accreditation organizations. Criteria are revised and updated annually, or more frequently if new evidence becomes available that suggests needed revisions.

References

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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.