Regence Oregon and Utah

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Medication Policy Manual

Policy No: dru605

Topic: Spravato, esketamine

Date of Origin: August 15, 2019

Committee Approval Date: January 22, 2026

Next Review Date: 2027

Effective Date: April 1, 2026

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Spravato (esketamine) is a nasal medication administered under the supervision of a healthcare provider. It is used for the management of treatment-resistant depression (TRD) or depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior.

Policy/Criteria

Most contracts require pre-authorization approval of Spravato (esketamine) prior to coverage.

I. Continuation of therapy (COT): Spravato (esketamine) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1, 2 and 3 below must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. Spravato (esketamine) is prescribed by or in consultation with a board-certified psychiatric-mental health (PMH) provider, including a psychiatrist, PMH nurse practitioner (PMHNP), or psychologist.

PLEASE NOTE: Attestation of previous PMH evaluation, at the initiation of Spravato (esketamine), may be used to establish medical necessity of this criterion.

AND

3. There is documentation of clinical benefit, such as disease stability or improvement of depression symptoms over pretreatment baseline (e.g., improvement in PHQ-9 or MADRS).

OR

C. Spravato (esketamine) was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Spravato (esketamine) may be considered medically necessary when there is clinical documentation (such as chart notes) that criteria A and B below are met:

A. Spravato (esketamine) is prescribed by or in consultation with a board-certified psychiatric-mental health (PMH) provider, including a psychiatrist, PMH nurse practitioner (PMHNP), or psychologist with prescribing authority (subject to state prescribing laws).

AND

B. Attestation that one of the following (criterion 1 or 2) are met:

1. Depressive symptoms in patients with a diagnosis of major depressive disorder (MDD) with acute suicidal ideation or behavior (R45.851).

OR

2. A diagnosis of treatment-resistant MDD (F33.1, F33.2).

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Spravato (esketamine) coverable only under the medical benefit (as a provider-administered medication).

B. **Quantity Limits**: When pre-authorization is approved, Spravato (esketamine) will be authorized in quantities as follows:

1. **Initial authorization (induction phase)**: Up to 12 dose kits (56 mg or 84 mg per dose kit) in 8 weeks.

2. **Continued authorization (maintenance phase)**: Up to 48 dose kits (56 mg or 84 mg per dose kit) in 48 weeks.

C. Authorization shall be reviewed as follows to confirm that medical necessity criteria are met, and that the medication is effective (criteria 1 and 2 below).

1. Authorization shall be reviewed as follows:

a. Initial authorization: Authorization shall be reviewed after 8 weeks.

b. Continued authorization (after the initial 8-week induction period): Authorization shall be reviewed at least every 48 weeks.

2. Clinical documentation (such as chart notes) must be provided to confirm all of the following (a and b):

a. Spravato (esketamine) is providing clinical benefit, as evidenced by disease stability or improvement in depression symptoms over pretreatment baseline (e.g., improvement in PHQ-9 or MADRS).

b. The current dose and frequency of Spravato (esketamine) is within the Quantity Limits listed above. Doses above Quantity Limits are not coverable.

IV. Spravato (esketamine) is considered investigational when used for all other conditions, including but not limited to:

A. Depression other than listed in the coverage criteria above.

B. As an anesthetic agent.

Position Statement

Summary

- Spravato (esketamine) nasal spray is a non-competitive N-methyl-D-aspartate receptor antagonist indicated for the treatment of treatment-resistant depression (TRD), as well as depressive symptoms in patients with major depressive disorder (MDD) with acute suicidal ideation (SI) or behavior. [1]
- The intent of the policy is to cover Spravato (esketamine) for the treatment of TRD or depressive symptoms in patients with MDD with acute SI or behavior, the indications where it has been studied and shown to be safe and effective, as detailed in coverage criteria.
- TRD: The efficacy of Spravato (esketamine) for TRD was evaluated in four late phase randomized controlled trials in patients with MDD. The primary endpoint in all trials was change from baseline in the MADRS total score. One trial evaluated Spravato (esketamine) monotherapy, which was found to be superior to placebo. Of the three remaining trials, one trial demonstrated a significant difference between treatment with Spravato (esketamine) plus an oral antidepressant compared to the oral antidepressant alone. [1,2]
- Depressive symptoms with MDD and SI: In two double-blind phase 3 studies, Spravato (esketamine) plus standard of care demonstrated statistical superiority on the primary efficacy measure of the change from baseline in the MADRS total score at 24 hours after first dose compared to placebo. [2]
- Guidelines recommend psychotherapy in combination with an oral antidepressant for the initial treatment for MDD. If there is no adequate response after optimizing the antidepressant dose for an adequate duration of time, switching to another antidepressant (from the same or different class), or combination with another antidepressant (from a different class) or non-antidepressant medication (lithium, thyroid hormone, a second-generation antipsychotic, or a stimulant) are recommended treatment options. [3]
- Spravato (esketamine) is dosed at 56 mg or 84 mg twice per week during the induction phase (weeks 1 to 4). Evidence of therapeutic benefit is evaluated at the end of the induction phase (at week 4) to determine the need for continued treatment. During the maintenance phase (beyond week 4), treatment is administered once weekly or every two weeks. [1]
- Because of the risk for sedation and dissociation after administration, Spravato (esketamine) must be administered under direct supervision of a healthcare provider, including a post-administration 2-hour observation period. [1,5] In addition, because the medication is for administration only by a REMS-certified provider, Spravato (esketamine) is not considered a self-administered medication. Therefore, Spravato (esketamine) is coverable only under the medical benefit.
- The safety and effectiveness of Spravato (esketamine) in conditions other than TRD and depressive symptoms in patients with MDD with acute SI or behavior have not been established.

Clinical Efficacy

- The efficacy of Spravato (esketamine) for TRD was evaluated in three phase 3, randomized, controlled trials in patients with MDD. [4-6]
    * Patients were required to have a MADRS total score ≥28 and failed therapy with at least two other antidepressants.
    * The trials compared treatment with Spravato (esketamine) plus a newly assigned oral antidepressant to an oral antidepressant alone for four weeks.
    * The primary endpoint in all three trials was the change from baseline in the MADRS total score.
    * Of the three trials, one trial demonstrated a significant difference between treatment with Spravato (esketamine) plus an oral antidepressant compared to the oral antidepressant alone.
- A long-term randomized, double-blind, maintenance study was also conducted in patients with TRD and determined that the time to relapse was delayed in patients treated with Spravato (esketamine) plus an oral antidepressant compared to an oral antidepressant alone. [1]
- The efficacy of Spravato (esketamine) monotherapy for TRD was evaluated in a Phase 4, randomized, controlled trial in patients with MDD. [1-2]
    * All participants met DSM-5 criteria for MDD and in the current depressive episode had not responded adequately to at least two different antidepressants.
    * The trial compared treatment with Spravato (esketamine) monotherapy to a placebo nasal spray for 28 days.
    * The primary endpoint was the change from baseline in the MADRS total score.
    * Spravato (esketamine) monotherapy demonstrated statistical superiority on the primary efficacy measure compared to placebo nasal spray.
- The efficacy of Spravato (esketamine) for <u>depressive symptoms with moderate-to-severe MDD and active SI</u> was evaluated in two phase 3, 4-week randomized, double-blind, placebo-controlled studies. [7,8]
    * Patients were required to have a MADRS total score ≥28 and active SI and intent.
    * All patients received comprehensive standard of care treatment, including an initial inpatient psychiatric hospitalization and a newly initiated or optimized oral antidepressant. Patients were on antidepressant monotherapy or antidepressant plus augmentation therapy.
    * Spravato (esketamine) plus standard of care demonstrated statistical superiority on the primary efficacy measure of the change from baseline in the MADRS total score at 24 hours after first dose (Day 2) compared to placebo nasal spray plus standard of care.
- There is insufficient evidence to establish the safety or efficacy of dose escalation of Spravato (esketamine) beyond the doses in the FDA approved labeling (up to a maximum dose of 84 mg weekly). In addition, given the short half-life of Spravato (esketamine), the use of a repeat loading (full or partial) is not recommended for dose escalation. No published evidence was identified for higher doses or use of reloading. Therefore, the use of higher doses and/or a repeat loading dose is not coverable.

- MDD guidelines have not been updated for more than a decade. The 2010 American Psychiatric Association (APA) Guidelines recommend a stepwise approach to treatment of MDD with the following: [3]
    * For initial treatment for MDD, use of psychotherapy in combination with an oral antidepressant.
    * If inadequate response after optimizing the antidepressant dose for an adequate duration of time, switch to another antidepressant, from the same or different class.
    * Alternatively, use of the initial antidepressant in combination with another antidepressant (from a different class) or non-antidepressant medication (lithium, thyroid hormone, a second-generation antipsychotic, or a stimulant) are recommended treatment options.
    * Neither ketamine nor Spravato (esketamine) are included in the most recent guidelines (2010).

Investigational Uses

- The safety and effectiveness of Spravato (esketamine) in conditions other than those listed above (TRD or depressive symptoms with MDD with SI as detailed in the coverage criteria) have not been established.

Safety [1]

- The most common adverse reactions associated with Spravato (esketamine) are dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, increased blood pressure, vomiting, and feeling drunk.
- Because of the possibility of delayed or prolonged sedation and dissociation, Spravato (esketamine) must be administered under the direct supervision of a healthcare provider, including the administration period and the post-administration 2-hour observation period with each treatment session.
- Patients are not to engage in potentially hazardous activities, such as driving a motor vehicle or operating machinery, until the next day after a restful sleep.
- Spravato (esketamine) is only available through a restricted program under a REMS due to the serious adverse outcomes from sedation, dissociation, and abuse and misuse. [5]

<table>
<tr><th colspan="5">Appendix 1: Antidepressants and Augmentation Medications [3,9]</th></tr>
<tr><td>TCAs</td><td>SSRIs</td><td>SNRIs</td><td>Serotonin Modulators</td><td>Augmentation Medications</td></tr>
<tr><td rowspan="6">amitriptyline
desipramine
doxepin
clomipramine
imipramine
maprotiline
nortriptyline
protriptyline
trimipramine</td><td rowspan="6">citalopram
escitalopram
fluoxetine
fluvoxamine
paroxetine
sertraline
vilazodone</td><td>desvenlafaxine
duloxetine
levomilnacipran
milnacipran
venlafaxine</td><td>nefazodone
trazodone
vortioxetine</td><td rowspan="6">- lithium
- liothyronine (Cytomel)
- Atypical antipsychotics: aripiprazole, brexpiprazole, quetiapine, olanzapine, risperidone
- AEDs: carbamazepine, valproic acid, lamotrigine
- Stimulants: methylphenidate, modafinil</td></tr>
<tr><td>NE-Serotonin</td><td>MAOIs</td></tr>
<tr><td>mirtazapine</td><td rowspan="3">isocarboxazid
phenelzine
selegiline
tranylcypromine</td></tr>
<tr><td>DNRI</td></tr>
<tr><td>bupropion</td></tr>
</table>

Key: AED=antiepileptic drug; DNRI=dopamine norepinephrine reuptake inhibitor; MAOI=monoamine oxidase inhibitor; NE=norepinephrine; SNRI=serotonin norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant

Cross References
BlueCross BlueShield Association Medical Policy, 5.01.34 - Esketamine Nasal Spray for Depression. [November 2024]
Transcranial Magnetic Stimulation as a Treatment of Depression and Other Disorders, Medical Policy Manual. Medicine, Policy No. 148.

Codes	**Number**	**Description**
HCPCS	G2082	Visit esketamine (Spravato) 56 mg or less
HCPCS	G2083	Visit esketamine (Spravato) > 56 mg
HCPCS	S0013	Esketamine (Spravato), nasal spray, 1 mg

References

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2. Spravato (esketamine) Dossier, data on file. Titusville, NJ: Janssen. February 2025.
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4. 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. PMID: 31166571
5. 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 Oct 1;22(10):616-630. PMID: 31290965.
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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 May 12;81(3):19m13191. PMID: 32412700.
9. Facts & Comparisons 4.0 (electronic version). Wolters Kluwer Health, Inc. Updated periodically.
10. Spravato REMS enrollment form. [Accessed 8/31/2022]. Available online at: https://www.spravatorems.com/
11. SPRAVATO Treatment Centers. [Accessed 8/31/2022]. Available online at: https://www.spravato.com/find-a-center#YTk4MDQw

Revision History

Revision Date	Revision Summary
1/22/2026	Clarified that a psychologist must have prescribing authority to meet criterion IIA (no change to intent).
7/10/2025	• Removed requirements for concurrent antidepressant use and step therapy. • Simplified prescriber and continuation of therapy verbiage.
12/12/2024	• Expanded prescriber requirement criterion to include licensed prescribing psychologists in states where legal. • For operational consistency: Simplified *Appendix 1* and clarified that low antidepressant doses used primarily for non-MDD indications do not meet intent of policy.
12/7/2023	No criteria changes with this annual review.
12/9/2022	• Updated COT criteria to include PMH provider requirement. • Expanded prescriber requirement criterion to include PMHNP and reworded PMH provider assessment. • For operational consistency: Simplified antidepressant step therapy criterion, Updated *Appendix 1* alternatives to align with guidelines. • Reworded reauthorization review criteria.
04/21/2021	Updated COT language wording (no change to intent). No other criteria changes with this annual update.
10/28/2020	Added coverage criteria for major depressive disorder (MDD) with acute suicidal ideation or behavior, a newly approved FDA indication. Clarified intent of other coverage criteria for MDD.
01/22/2020	Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).
07/24/2019	New policy (effective 8/15/2019). Limits coverage to patients with treatment-resistant depression, the setting in which it was studied and has a labeled indication.

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