Medication Policy Manual | **Policy No:** dru605

Topic: Spravato, esketamine | **Date of Origin:** August 15, 2019

Committee Approval Date: December 7, 2023 | **Next Review Date:** 2024

Effective Date: March 1, 2024

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 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. It is used in combination with an oral antidepressant. Spravato (esketamine) is administered under the supervision of a healthcare provider.

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. Attestation of evaluation by, or in consultation with, a board-certified psychiatric-mental health (PMH) prescriber [psychiatrist or PMH nurse practitioner (PMHNP)], and agreement with the use of Spravato (esketamine).

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 as detailed in the reauthorization criteria.

OR

C. Spravato (esketamine) was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission, AND attestation of an evaluation by, or in consultation with, a board-certified psychiatric-mental health (PMH) prescriber [psychiatrist or PMH nurse practitioner (PMHNP)] and agreement with the use of Spravato (esketamine).

***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 (including, but not limited to chart notes) that criteria A, B, and C below are met:

A. Mental health provider assessment - One of the following is met (criteria 1 or 2):

1. The prescriber is a psychiatrist.

OR

2. The prescriber is not a psychiatrist, and both of the following are met (criteria a and b):

a. The patient is managed by, or in consultation with, a board-certified psychiatric-mental health (PMH) provider [psychiatrist or nurse practitioner (PMHNP)].

AND

b. The board-certified PMH provider completes both of the following (criteria i and ii):

i. Establishes the coverable diagnosis [attestation].

AND

ii. Has evaluated the suitability of the patient for the use of and agrees with the treatment plan for Spravato (esketamine) [attestation].

AND

B. Diagnostic criteria - One of the following (criteria 1 or 2) are met, as outlined in clinical documentation (in chart notes):

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

OR

2. A diagnosis of **treatment resistant major depressive disorder** (MDD), when all the following are met (criteria a and b):

a. Documentation that at least three different antidepressants from two classes were ineffective or not tolerated (see *Appendix 1*).

AND

b. Documentation of non-pharmacologic treatments (including but not limited to cognitive behavioral therapy (see *Appendix 2*).

AND

C. Use in combination with an antidepressant: Spravato (esketamine) will be used in combination with an oral antidepressant.

III. Administration, Quantity Limitations, and Authorization Period

A. Bridgespan 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 (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, including all of the following (a through d):

a. Spravato (esketamine) continues to be used in conjunction with an oral antidepressant.

b. The patient has been re-evaluated and Spravato (esketamine) is providing clinical benefit evidenced by documented improvement or sustained improvement of depression symptoms.

PLEASE NOTE: Patient-specific symptoms must be provided, both current depression symptoms. Use of a depression symptom score (such as PHQ-9 or MADRS) may be used in the efficacy assessment.

c. Documentation that the current dose and frequency of Spravato (esketamine) is within the Quantity Limits (as stated above).

d. Use of doses of Spravato (esketamine) in excess of those listed above in the 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 that is used in combination with an oral antidepressant for the treatment of treatment-resistant depression (TRD), as well as depressive symptoms in patients with major depressive disorder (MDD) with acute suicidal ideation or behavior. [1]
- The intent of the policy is to cover Spravato (esketamine) for the treatment of TRD, as well as for depressive symptoms in patients with MDD with acute suicidal ideation (SI) or behavior, the indications where it has been studied and shown to be safe and effective, as detailed in coverage criteria.
- The efficacy of Spravato (esketamine) plus an oral antidepressant was evaluated as follows:

    * TRD: In three phase 3, randomized, controlled acute efficacy trials, as well as one maintenance trial. Patients had moderate to severe MDD and failed therapy with at least two other oral antidepressants. Once enrolled in the trial, patients received treatment with esketamine plus a newly assigned oral antidepressant or an oral antidepressant alone. [2]
- Depressive symptoms with MDD and SI: In two Phase 3, 4-week randomized, double-blind, placebo-controlled studies in adults with moderate-to-severe MDD (MADRS total score >28) who had active SI and intent. [2] In clinical trials, Spravato (esketamine) has only been studied as an adjunct therapy to oral antidepressants. The use of Spravato (esketamine) as a monotherapy is not coverable. [1]
- 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 (see *Appendix 1*). [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.
    * Patients failed therapy with at least two other antidepressants.
    * In the trial, patients had used an average of two prior antidepressants.
    * The trials compared treatment with Spravato (esketamine) plus a newly assigned oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine) 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) for depressive symptoms with moderate-to-severe MDD and active SI 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 suicidal ideation 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 (see *Appendix 1*).
    * 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.
- In clinical trials, Spravato (esketamine) has only been studied as an adjunct therapy to oral antidepressants. The use of Spravato (esketamine) as a monotherapy is not coverable. [1]
- 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.
- There are various available antidepressant options, with several different mechanisms of action for treatment of MDD. There is no conclusive evidence that one antidepressant (within a class or between classes) is superior to other antidepressants, including use of augmentation medications (see *Appendix 1*) or Spravato (esketamine). However, Spravato (esketamine) is significantly more costly than other antidepressants, including many generics. Therefore, Spravato (esketamine) for TRD is coverable only when at least three antidepressant options, from at least two therapeutic classes, are ineffective or not a treatment option, when given as scheduled adequate therapeutic antidepressant doses. Of note: Some antidepressants (and augmentation therapies) may be used at much lower doses for sleep, management of pain, and other conditions. Therefore, the step therapy with lower-cost antidepressant treatment alternatives is met only when there is documented use of symptoms refractory to therapeutic antidepressant doses.
- 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 (See *Appendix 1*).
    * 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] REMS certified pharmacies and distributors include, but are not limited to, facility (such as hospital) or specialty pharmacies such as home infusion pharmacies. Once REMS certified, providers should call 1-855-382-6022 to access information on how to obtain Spravato for their patient(s). [10]
    * A REMS-certified pharmacy will dispense (in person or ship) Spravato (esketamine) for a patient directly to the administering provider's office for storage and administration.
    * All REMS-certified providers must have a facility DEA number and the ability to "Maintain records on all shipments of SPRAVATO received and dispensing information including the patient name, dose, number of devices and date administered."

<table>
<tr><th colspan="5">Appendix 1: An antidepressant (or treatment regimen) would include any of the following classes or combination of classes, given as scheduled adequate therapeutic antidepressant doses [3,9]</th></tr>
<tr><td>TCAs [a]</td><td>SSRIs</td><td>SNRIs</td><td>Serotonin Modulators</td><td>Augmentation Medications</td></tr>
<tr><td rowspan="8">amitriptyline [b]
desipramine
doxepin
imipramine
nortriptyline
protriptyline
trimipramine</td><td rowspan="8">citalopram
escitalopram
fluoxetine
fluvoxamine
paroxetine
sertraline
vilazodone</td><td>desvenlafaxine
duloxetine
levomilnacipran
milnacipran
venlafaxine</td><td>nefazodone
trazodone [b]
vortioxetine</td><td rowspan="8">- lithium
- liothyronine (Cytomel)
- Atypical antipsychotics: aripiprazole, brexpiprazole, quetiapine, [b] 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 [b]</td></tr>
</table>

[a] Less frequently used, due to adverse event profile: clomipramine, maprotiline

[b] Antidepressant usual doses (mg/day): bupropion 300-450; trazodone 150-600; quetiapine 300. Lower doses are used for non-MDD indications, such as sleep.

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

NOTE: Documentation of duration of treatment and outcome of therapy to scheduled use of an adequate therapeutic dose for depression must be met.

Appendix 2: Psychotherapy methods to treat major depressive disorder may include, but are not limited to the following:

- Cognitive behavioral therapy (CBT)
- Interpersonal therapy (IPT)
- Psychodynamic therapy
- Problem-solving therapy (in individual and group formats)

Cross References

BlueCross BlueShield Association Medical Policy, 5.01.34 - Esketamine Nasal Spray for Depression. [November 2023]

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

1. Spravato [Prescribing Information]. Titusville, NJ: Janssen. October 2023.
2. Spravato (esketamine) Dossier, data on file. Titusville, NJ: Janssen. March 2019.
3. Gelenberg, A, Freeman, M, et al.. The American Psychiatric Association Practice Guideline for the Treatment of Patients with Major Depressive Disorder (updated May 2010) [Accessed 8/31/2022]. https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd-1410197717630.pdf
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.
6. Popova V, Daly EJ, Trivedi M, et al. Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study. Am J Psychiatry. 2019 Jun 1;176(6):428-438. PMID: 31109201
7. 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. 2021 Jan 20;24(1):22-31. PMID: 32861217.
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
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.

Drug names identified in this policy are the trademarks of their respective owners.