POLICY: Psychiatry – Spravato Utilization Management Medical Policy
- Spravato® (esketamine nasal spray – Janssen)

EFFECTIVE DATE: 1/1/2021
LAST REVISION DATE: 01/29/2025

COVERAGE CRITERIA FOR: All Aspirus Medicare Plans

OVERVIEW

Spravato, a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist, is indicated in conjunction with an oral antidepressant for the treatment of:[1]

- Depressive symptoms in **major depressive disorder (MDD) with acute suicidal ideation or behavior** in adults in conjunction with an oral antidepressant.
- **Treatment-resistant depression** (TRD) in adults as monotherapy or in conjunction with an oral antidepressant.

Limitation of Use: The effectiveness of Spravato in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use of Spravato 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.

For MDD with acute suicidal ideation or behavior, the recommended dosage is 84 mg twice weekly for 4 weeks.[1] The dosage may be reduced to 56 mg twice weekly based on tolerability. Spravato should be administered in conjunction with an oral antidepressant. After 4 weeks of treatment, evidence of therapeutic benefit should be evaluated to determine the need for continued treatment. The use of Spravato, in conjunction with an oral antidepressant, beyond 4 weeks has not been systematically evaluated in the treatment of depressive symptoms in patients with MDD with acute suicidal ideation or behavior. For treatment-resistant depression, the recommended dose as monotherapy or in conjunction with an oral antidepressant is 56 mg or 84 mg intranasally twice weekly for Weeks 1 through 4. On Weeks 5 to 8, Spravato should be administered once weekly at a dose of 56 mg or 84 mg intranasally. On Week 9 and thereafter, the dosing frequency should be individualized to the least frequent dosing to maintain remission/response (either every 2 weeks or once weekly) at a dose of 56 mg or 84 mg. Spravato must be administered under the direct supervision of a healthcare provider.

Disease Overview

Major depressive disorder is a serious, life-threatening condition with high rates of morbidity and a chronic disease course.[2] Major depressive disorder is considered the leading cause of disability worldwide and is also associated with increased mortality rates.[3,4] About 30% to 40% of patients with major depressive disorder fail to respond to first-line treatments including oral antidepressant medications of all classes (e.g., selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], tricyclic antidepressants [TCAs], bupropion) and/or psychotherapy.[2,5] In addition, the onset of treatment response for these modalities, even when effective, often takes ≥ 4 weeks, leading to greater suffering, expense, and risk. For regulatory purposes, the FDA considers patients to have treatment-resistant depression if they have MDD and they have not responded to treatment despite trials of at least two antidepressants given at adequate doses for an adequate duration in the current episode.[2]

The available treatments for treatment-resistant depression are limited.[2] Prior to the approval of Spravato, only one medication was FDA-approved for treatment-resistant depression, Symbyax® (olanzapine and fluoxetine capsules). Symbyax is indicated for treatment-resistant depression (major depressive disorder in patients who do not respond to two separate trials of different antidepressants of adequate dose and duration in the current episode) and acute depressive episodes in bipolar I disorder.[6]

Guidelines

In 2022, the U.S. Department of Veterans Affairs (VA) and U.S. Department of Defense (DoD) published a guideline for the management of MDD.[7] The guideline divides treatment into uncomplicated MDD and MDD that is severe or has a partial or limited response to initial treatment. For uncomplicated MDD, the guideline recommends that MDD be treated with either psychotherapy (i.e., acceptance and commitment therapy, behavioral therapy/behavioral activation, cognitive behavioral therapy, interpersonal therapy, mindfulness-based cognitive therapy, problem-solving therapy, or short-term psychodynamic psychotherapy) or pharmacotherapy (i.e., bupropion, mirtazapine, SSRIs, SNRIs, trazodone, vilazodone, or vortioxetine) as monotherapy, based on patient preference. Factors including treatment response, severity, and chronicity may lead to other treatment strategies, such as augmentation, combination treatment, switching of treatments, or use of non-first-line treatments. When choosing an initial pharmacotherapy, the guideline suggests against using esketamine, ketamine, monoamine oxidase inhibitors (MAOIs), nefazodone, or TCAs. For the treatment of MDD that is severe or has a partial or limited response to initial treatment, the guideline recommends offering a combination of pharmacotherapy and evidence-based psychotherapy for MDD characterized as severe (e.g., nine-item patient health questionnaire [PHQ-9] score > 20), persistent (duration > 2 years), or recurrent (≥ two episodes). For patients with MDD who have shown partial or no response to an adequate trial of initial pharmacotherapy, the guideline suggests switching to another antidepressant, switching to psychotherapy, augmenting with psychotherapy, or augmenting with a second-generation antipsychotic. For patients who have shown partial or no response to ≥ two adequate pharmacologic treatment trials, the guideline suggests offering repetitive transcranial magnetic stimulation for treatment. For patients with MDD who have not responded to several adequate pharmacologic trials, the guideline suggests ketamine or esketamine for augmentation. For patients with MDD who achieve remission with antidepressants, the guideline recommends continuation of antidepressants at the therapeutic dose for ≥ 6 months to decrease risk for relapse. For patients with MDD at high risk for relapse or recurrence (e.g., ≥ two prior episodes, unstable remission status), the guideline suggests offering a course of cognitive behavioral therapy, interpersonal therapy, or mindfulness-based cognitive therapy during the continuation phase of treatment (i.e., after remission is achieved).

Abuse and Misuse

Spravato contains esketamine, a Schedule III controlled substance (CIII), which may be subject to abuse and diversion.[1] Assess each patient's risk for abuse or misuse prior to prescribing Spravato. All patients receiving Spravato should be monitored for the development of these behaviors or conditions, including drug-seeking behavior, while on therapy. Patients with a history of drug abuse or dependence are at greater risk. Careful consideration should be given prior to prescribing Spravato to individuals with a history of substance use disorder.

Safety

Spravato labeling includes a Boxed Warning regarding sedation, dissociation, respiratory depression, abuse and misuse, and suicidal thoughts and behaviors in pediatric and young adult patients.[1] The most common psychological effects of Spravato were dissociative or perceptual changes (including distortion of time, space, and illusions), derealization and depersonalization (61% to 84% of patients treated with Spravato developed dissociative or perceptual changes based on the Clinician-Administered Dissociative States

Scale). Given its potential to induce dissociative effects, carefully assess patients with psychosis before administering Spravato; treatment should be initiated only if the benefit outweighs the risk.

Because of the risks of serious adverse outcomes resulting from sedation, dissociation, respiratory depression, and abuse and misuse, Spravato is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) program.[1] Healthcare settings must be certified in the program and ensure that Spravato is only dispensed in healthcare settings and administered to patients who are enrolled in the program, administered by patients under the direct observation of a healthcare provider, and that patients are monitored by a healthcare provider for at least 2 hours after administration of Spravato. Pharmacies must be certified in the REMS and must only dispense Spravato to healthcare settings that are certified in the program.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Spravato. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Spravato as well as the monitoring required for adverse events and efficacy, approval requires Spravato to be prescribed by a physician who specializes in the condition being treated.
Note: A 2-month approval duration is applied for the indication of MDD with Acute Suicidal Ideation or Behavior to allow time for the scheduling and administration of a 4-week course of therapy at a certified healthcare setting. If after completing the 4-week course of therapy for MDD with Acute Suicidal Ideation or Behavior, another request for Spravato is submitted and the patient meets the approval criteria, then another 4-week course of treatment (with a 2-month approval duration to complete the course of therapy) could be approved.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Spravato is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Major Depressive Disorder with Acute Suicidal Ideation or Behavior.** Approve for 2 months if the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has major depressive disorder that is considered to be severe, according to the prescriber; AND
   - **C)** Patient is concomitantly receiving at least one oral antidepressant; AND
     Note: Antidepressants may include, but are not limited to, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), mirtazapine, and bupropion.
   - **D)** Patient has ONE of the following (i or ii):
     - **i.** No history of psychosis; OR

ii. History of psychosis and the prescriber believes that the benefits of Spravato outweigh the risks; AND

E) The medication is prescribed by a psychiatrist.

Dosing. Approve the following dosing regimen (A and B):

A) Maximum single dose: 84 mg intranasally; AND

B) Twice weekly dosing for 4 weeks.

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2. Treatment-Resistant Depression. Approve for 6 months if the patient meets ALL of the following (A, B, C, D, and E):

A) Patient is ≥ 18 years of age; AND

B) Patient meets BOTH of the following (i and ii):

i. Patient has demonstrated nonresponse (≤ 25% improvement in depression symptoms or scores) to at least two different antidepressants, each from a different pharmacologic class; AND
Note: Different pharmacologic classes of antidepressants include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), bupropion, mirtazapine, etc.

ii. Each antidepressant was used at therapeutic dosages for at least 6 weeks in the current episode of depression, according to the prescriber; AND

C) Patient has ONE of the following (i or ii):

i. No history of psychosis; OR

ii. History of psychosis and the prescriber believes that the benefits of Spravato outweigh the risks; AND

D) The patient's history of controlled substance prescriptions has been checked using the state prescription drug monitoring program (PDMP), according to the prescriber; AND

E) The medication is prescribed by a psychiatrist.

Dosing. Approve the following dosing regimen (A, B, and C):

A) Maximum single dose: 84 mg intranasally; AND

B) Induction phase (Weeks 1 through 4): twice weekly dosing; AND

C) Maintenance phase (Weeks 5 and after): up to once weekly dosing.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Spravato is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Spravato® nasal spray [prescribing information]. Titusville, NJ: Janssen; January 2025.
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3. National Institute of Mental Health. Major Depression. Last updated: July 2023. Available at: https://www.nimh.nih.gov/health/statistics/major-depression.shtml. Accessed on January 22, 2025.
4. World Health Organization. Depressive disorder (depression). Last updated: March 31, 2023. Available at: Depressive disorder (depression) (who.int) . Accessed on January 22, 2025.
5. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006;163(11):1905-17.

6. Symbyax® capsules [prescribing information]. Indianapolis, IN: Lilly; August 2023.
7. McQuaid JR, Buelt A, Capaldi V, et al. The management of major depressive disorder: synopsis of the 2022 U.S. Department of Veterans Affairs and U.S. Department of Defense clinical practice guideline. *Ann Intern Med*. 2022;175(10):1440-1451.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Treatment-Resistant Depression:** Removed "unless unavailable in the state" from criterion requiring the "patient's history of controlled substance prescriptions has been checked using the state prescription drug monitoring program (PDMP)." Removed Note regarding Missouri not having a statewide PDMP (legislation was enacted in 2021). **Policy Statement:** A Note was added to the Policy Statement to clarify that a 2-month approval duration is applied for the indication of MDD with Acute Suicidal Ideation or Behavior to allow time for the scheduling and administration of a 4-week course of therapy at a certified healthcare setting. Additionally, if after completing the 4-week course of therapy for MDD with Acute Suicidal Ideation or Behavior, another request for Spravato is submitted and the patient meets the approval criteria, then another 4-week course of treatment (with a 2-month approval duration to complete the course of therapy) could be approved.	05/31/2023
Annual Revision	No criteria changes.	05/22/2024
Aspirus P&T Review	Policy reviewed and approved by Aspirus P&T committee. Annual review process	09/16/2024
Early Annual Revision	**Treatment-Resistant Depression:** Removed criterion requiring "Patient is concomitantly receiving at least one oral antidepressant" due to the new indication for use as monotherapy in adults with treatment-resistant depression.	01/29/2025