Drug Coverage Policy

Effective Date……04/01/2025
Coverage Policy Number……IP0220
Policy Title…… Spravato

Psychiatry – Spravato

- Spravato® (esketamine nasal spray – Janssen)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Cigna Healthcare Coverage Policy

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.

Medical Necessity Criteria

Documentation: Documentation is required for use of Spravato as noted in the criteria. Documentation may include, but is not limited to chart notes, laboratory tests, claims records, and/or other information.

Spravato is considered medically necessary when the following criteria are met:

FDA-Approved Indications

1. **Major Depressive Disorder with Acute Suicidal Ideation or Behavior.** Approve for 2 months if the patient meets the following criteria (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Documentation is provided that the patient has major depressive disorder that is considered to be severe, according to the prescriber; AND
   - **C)** Documentation is provided that the 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.

2. **Treatment-Resistant Depression.** Approve for 6 months if the patient meets the following criteria (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.** Documentation is provided that the 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.** Documentation is provided that 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 to 4): twice weekly dosing; AND
   - **C)** Maintenance phase (Weeks 5 and after): up to once weekly dosing.

Spravato post administration patient monitoring is considered medically necessary when ONE of the above criteria has been met (1 or 2).

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven (criteria will be updated as new published data are available).

Coding Information

1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

For Commercial Plans ONLY:

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
S0013	Esketamine, nasal spray, 1 mg

For Medicare Advantage Plans ONLY:

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
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

References

1. Spravato® nasal spray [prescribing information]. Titusville, NJ: Janssen; January 2025.
2. FDA news release. FDA approves new nasal spray medication for treatment-resistant depression; available only at a certified doctor's office or clinic. March 5, 2019. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-new-nasal-spray-medication-treatment-resistant-depression-available-only-certified. Accessed on January 22, 2025.

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.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	**Policy Name Change: Updated** Policy Name from "Esketamine" to "Psychiatry – Spravato." **Updated** initial approval duration to 2 months for Major Depressive Disorder with Acute Suicidal Ideation or Behavior and 6 months for Treatment-Resistant Depression. **Added** dosing indication for all FDA Approved Indications. **Conditions Not Covered: Removed** Anesthetic Use, Bipolar Disorder, Pain Syndromes, and Post-traumatic Stress Disorder.	08/15/2024
Selected Revision	**Added "<u>Documentation</u>:** Documentation is required for use of Spravato as noted in the criteria. Documentation may include, but is not limited to chart notes, laboratory tests, claims records, and/or other information" **Major Depressive Disorder with Acute Suicidal Ideation or Behavior.** **Updated from "**Patient has major depressive disorder that is considered to be severe, according to the Prescriber" **to** "Documentation is provided that the Patient has major depressive disorder that is considered to be severe, according to the Prescriber" **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. **Updated from** "Patient has demonstrated nonresponse (≤ 25% improvement in depression symptoms or	04/01/2025

	scores) to at least two different antidepressants, each from a different pharmacologic class" **to** "Documentation is provided that the Patient has demonstrated nonresponse (≤ 25% improvement in depression symptoms or scores) to at least two different antidepressants, each from a different pharmacologic class" **Updated from** "Each antidepressant was used at therapeutic dosages for at least 6 weeks in the current episode of depression, according to the prescriber" **to** "Documentation is provided that each antidepressant was used at therapeutic dosages for at least 6 weeks in the current episode of depression, according to the prescriber"	

The policy effective date is in force until updated or retired.