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Coverage Policy Number **IP0220**

Esketamine

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Related Coverage Resources

Unassigned Drug or Biologic Code Medical Precertification

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. 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.

Overview

This policy supports medical necessity review for esketamine nasal spray (**Spravato**®).

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

Note: Ketamine (Ketalar) is not covered for psychological conditions. Please refer to the related coverage policy above (Unassigned Drug or Biologic Code Medical Precertification).

Medical Necessity Criteria

Esketamine nasal spray (Spravato) is considered medically necessary when ONE of the following is met (1 or 2):

1. **Major Depressive Disorder with Acute Suicidal Ideation or Behavior.** Individual meets **ALL** of the following criteria (A, B, C, D, and E):

A. Individual is 18 years of age or older
B. Individual has major depressive disorder that is considered to be severe, according to the prescriber
C. Individual is concomitantly receiving at least **ONE** oral antidepressant [for example, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), mirtazapine, bupropion. (Refer to Appendix 1 for examples of products according to pharmacologic class)]
D. Individual has **ONE** of the following (i or ii):
    i. No history of psychosis
    ii. History of psychosis and the prescriber believes that the benefits of esketamine nasal spray (Spravato) outweigh the risks
E. Medication is being prescribed by, or in consultation with, a psychiatrist

2. **Treatment-Resistant Depression.** Individual meets ALL of the following criteria (A, B, C, D, E, and F):
    A. Individual is 18 years of age or older
    B. Individual meets **BOTH** of the following (i and ii):
        i. Individual has demonstrated nonresponse (defined as ≤ 25% improvement in depression symptoms or scores) to at least **TWO** different antidepressants, each from a different pharmacologic class, according to the prescriber [for example, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), mirtazapine, bupropion. (Refer to Appendix 1 for examples of products according to pharmacologic class)]
        ii. Each antidepressant was used at therapeutic dosages for at least 6 weeks in the current episode of depression, according to the prescriber
    C. Individual is concomitantly receiving at least **ONE** oral antidepressant [for example, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), mirtazapine, bupropion. (Refer to Appendix 1 for examples of products according to pharmacologic class)]
    D. Individual has **ONE** of the following (i or ii):
        i. No history of psychosis
        ii. History of psychosis and the prescriber believes that the benefits of esketamine nasal spray (Spravato) outweigh the risks
    E. Individual's risk for abuse of controlled substances has been assessed by the provider (for example, using the state prescription drug monitoring program [PDMP])
    F. The medication is prescribed by, or in consultation with, a psychiatrist

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.

Reauthorization Criteria

Esketamine nasal spray (Spravato) is considered medically necessary for continued use when initial criteria are met AND there is documentation of beneficial response (for example, a 50% or greater reduction in a depression rating scale score from baseline).

Authorization Duration

Initial approval duration:
- Major Depressive Disorder with Acute Suicidal Ideation or Behavior: 1 month
- Treatment-Resistant Depression: 2 months

Reauthorization approval duration:
- Major Depressive Disorder with Acute Suicidal Ideation or Behavior: not applicable for continuation beyond initial approval duration

- Treatment-Resistant Depression: up to 6 months

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

1. **Anesthetic Use**
   Ketamine is indicated as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation, for the induction of anesthesia prior to the administration of other general anesthetic agents, and to supplement low-potency agents, such as nitrous oxide.[8] Ketamine injection has been used for a number of off-label conditions including agitation, delirium, moderate pain, pre-anesthesia, procedural sedation, rapid-sequence intubation, sedation induction, sedation maintenance, severe pain, and status asthmaticus.[9] However, Spravato is not approved as an anesthetic agent. The safety and effectiveness of Spravato as an anesthetic agent have not been established.[1]

2. **Bipolar Disorder**
   Spravato is currently only indicated for treatment-resistant depression in adults and for the treatment of depressive symptoms in adults with major depressive disorder with acute suicidal ideation or behavior.[1] The safety and effectiveness of Spravato for other psychiatric uses has not been established.

3. **Pain Syndromes** (for example fibromyalgia, neuropathic pain, complex regional pain syndrome, reflex sympathetic dystrophy)

4. **Post-traumatic Stress Disorder**
   Spravato is currently only indicated for treatment-resistant depression in adults and for the treatment of depressive symptoms in adults with major depressive disorder with acute suicidal ideation or behavior. The safety and effectiveness of Spravato for other psychiatric uses has not been established.[1]

Coding / Billing Information

Note: 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.

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

HCPCS Codes	Description
S0013	Esketamine, nasal spray, 1 mg

Background

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 adults with **major depressive disorder (MDD) with acute suicidal ideation or behavior**.
- **Treatment-resistant depression** (TRD) in adults.

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.

Spravato should be administered in conjunction with an oral antidepressant.[1] For MDD with acute suicidal ideation or behavior, the recommended dosage is 84 mg twice weekly for 4 weeks. The dosage may be reduced to 56 mg twice weekly based on tolerability. 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 is 56 mg intranasally on Day 1, followed by 56 mg or 84 mg intranasally twice weekly for Weeks 1 to 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
According to the American Psychiatric Association practice guideline for the treatment of patients with major depressive disorder (2010), the effectiveness of antidepressants is generally comparable between classes and within classes.[7] Therefore, the initial selection of antidepressant will largely be based on the anticipated side effects, the safety or tolerability of these side effects for the individual patient, pharmacological properties of the medication (e.g., half-life, drug interactions), and additional factors such as medication response in prior episodes, cost, and patient preference. In patients with depression who either have not responded or have had trouble tolerating one SSRI agent, a trial of another SSRI (or another antidepressant) may be effective and/or better tolerated. Patients who have had a partial response to antidepressant monotherapy can be augmented with another antidepressant from a different pharmacological class or with another non-antidepressant medication, such as lithium, thyroid hormone, an anticonvulsant, a psychostimulant, or an atypical antipsychotic.

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, 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, and abuse and misuse, Spravato is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS).[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.

Appendix 1

Atypical Agents
Bupropion (Aplenzin, Forfivo XL, Wellbutrin, Wellbutrin SR, Wellbutrin XL)
Mirtazapine (Remeron, Remeron SolTab)
Serotonin Modulators
Nefazodone
Trazodone
Vilazodone (Viibryd)
Vortioxetine (Trintellix)
Serotonin-Norepinephrine Reuptake Inhibitors [SNRIs] include the following:
Desvenlafaxine (Khedezla)
Desvenlafaxine succinate (Pristiq)
Duloxetine (Cymbalta)
Levomilnacipran (Fetzima)
Venlafaxine (Effexor XR)
Selective Serotonin Reuptake Inhibitors [SSRIs] include the following:
Citalopram (Celexa)
Escitalopram (Lexapro)
Fluoxetine (Prozac)
Fluvoxamine
Paroxetine hydrochloride (Paxil, Paxil CR)
Paroxetine mesylate (Brisdelle, Pexeva)
Sertraline (Zoloft)
Tricyclic Antidepressants [TCAs] include the following:
Amitriptyline (Elavil)
Amoxapine
Clomipramine (Anafranil)
Desipramine (Norpramin)
Doxepin (Silenor)
Imipramine (Tofranil, Tofranil-PM)
Nortriptyline (Pamelor)
Protriptyline
Trimipramine (Sumontil)

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