Spravato (esketamine) Nasal Spray

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This medical policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the Spravato drug policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines and clinical studies. Spravato (esketamine) is the S-enantiomer of racemic ketamine, and is a non-selective, non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor. The mechanism by which esketamine exerts its antidepressant effect is unknown. The indications below including FDA-approved indications and compendial uses are considered covered benefits provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

Spravato is indicated, in conjunction with an oral antidepressant, for the treatment of:

1. Treatment-resistant depression (TRD) in adults.
2. Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation of behavior.

Limitations 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 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.

POLICY

Documentation

Submission of the following information is necessary to initiate the prior authorization review:

A. For initial requests:
    1. Pretreatment depression severity score(s) from standardized rating scale(s) that reliably measure depressive symptoms (i.e.., Beck Depression Scale [BDI], Hamilton Depression Rating Scale [HDRS], Montgomery-Asberg Depression Rating Scale [MADRS])
    2. Medical records documenting inadequate response with antidepressant and augmentation agents for the current depressive episode (if applicable)
    3. Medical records documenting urgent need for treatment negating the step through antidepressant and augmentation agents (if applicable)
    4. Medical records documenting current suicidal ideation with intent (if applicable)
    5. Medical records documenting diagnosis and consultation, if not prescribed by a psychiatrist or a psychiatric or mental health nurse practitioner
B. For continuation of therapy:
    1. Current and baseline depression severity score(s) from standardized rating scale(s) that reliably measure depressive symptoms
    2. Medical records documenting consultation, if not prescribed by a psychiatrist or a psychiatric or mental health nurse practitioner

Exclusion

Coverage will not be provided for members with current or recent history (i.e., within the last 6 months) of moderate or severe substance or alcohol use disorder.

Criteria for Initial Approval

A. Treatment-resistant depression (TRD)/Major depressive disorder (MDD) with acute suicidal ideation or behavior

Authorization of 1 month may be granted for treatment of TRD/MDD with acute suicidal ideation or behavior when all of the following criteria are met:

1. Member has a confirmed diagnosis of severe major depressive disorder (single or recurrent episode), documented by standardized rating scales that reliably measure depressive symptoms (i.e., Beck Depression Scale [BDI], Hamilton Depression Rating Scale [HDRS], Montgomery-Asberg Depression Rating Scale [MADRS]).
2. Diagnosis is verified by a psychiatrist or a psychiatric or mental health nurse practitioner.
3. Must be prescribed by, or in consultation with, a psychiatrist or prescribed by a psychiatric or mental health nurse practitioner
4. Member is 18 years of age or older.
5. Requested drug will be administered under the direct supervision of a healthcare provider.
6. Member will be monitored by a health care provider for at least 2 hours after administration.
7. Member meets either of the following criteria:
    a). Member must meet all of the following:
        i. Member has treatment-resistant depression (TRD) as defined by experiencing an inadequate response during the current depressive episode with two antidepressants (e.g., selective serotonin reuptake inhibitor [SSRI], serotonin-norepinephrine reuptake inhibitor [SNRI], tricyclic antidepressant [TCA], bupropion, mirtazapine) from at least two different classes (different mechanisms of action) at the maximally tolerated labeled dose, each used for at least 8 weeks;
            - Aminoketone (Wellbutrin/SR/XL [bupropion])
            - Monoamine oxidase inhibitors (MAOIs) (e.g., Marplan, Nardil, Parnate, phenelzine, tranylcypromine)
            - Noradrenaline and specific serotoninergic antidepressants (NASSAs) (e.g., amoxapine, maprotiline, mirtazapine/ODT, Oleptro ER, Remeron/Solutab, trazodone)

- Selective serotonin reuptake inhibitors (SSRIs) (e.g., Celexa, citalopram, escitalopram, fluoxetine, fluvoxamine, Lexapro, Luvox/CR, paroxetine, Paxil/CR, Pexeva, Prozac/Weekly, sertraline, Zoloft)
- Serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g., Cymbalta, desvenlafaxine/ER, duloxetine, Effexor/XR, Fetzima, Irenka, Khedezla, Pristiq, venlafaxine/ER)
- Tricyclic antidepressants (TCAs) (e.g., amitriptyline, desipramine, doxepin, Elavil, imipramine, Norpramin, nortriptyline, Pamelor, Surmontil, Tofranil, trimipramine)

ii. Member has experienced an inadequate response with an adequate trial of augmentation therapy OR cognitive behavioral therapy during the current depressive episode
- Augmentation therapy is defined as:
  - Two antidepressants with different mechanisms of action used concomitantly
  - An antidepressant and a second-generation antipsychotic used concomitantly
  - An antidepressant and lithium used concomitantly
  - An antidepressant and thyroid hormone used concomitantly
  - An antidepressant and buspirone used concomitantly

b). Member has major depressive disorder with both of the following:
i. Member has current suicidal ideation with intent defined as both of the following:
a. Member has thoughts, even momentarily, of self-harm with at last some intent or awareness that they may die as a result, or member thinks about suicide
b. Member intends to act on thoughts of killing themselves
ii. The prescriber represents that, in the absence of the requested drug, within the next 24 to 48 hours the member will require confinement in an acute care psychiatric institution.

8. Requested drug will be used in combination with an oral antidepressant (e.g., duloxetine, escitalopram, sertraline, venlafaxine).

Continuation of Therapy

A. Treatment-resistant depression (TRD)

1. Authorization of 3 months may be granted for the continuation of treatment of TRD when ALL of the following criteria are met:
   a) There is an improvement or sustained improvement from baseline in depressive symptoms documented by standardized rating scales that reliably measure depressive symptoms (i.e., Beck Depression Scale [BDI], Hamilton Depression Rating Scale [HDRS], Montgomery-Asberg Depression Rating Scale [MADRS])
   b) The member will continue therapy with an oral antidepressant agent in conjunction with Spravato nasal spray
   c) If duration of use is greater than 4 months, the dosing frequency has been individualized to the least frequent dosing to maintain remission/response
   d) Requested drug will continue to be administered under the direct supervision of a healthcare provider
   e) Requested drug must be prescribed by, or in consultation with, a psychiatrist or prescribed by a psychiatric or mental health nurse practitioner

B. Major depressive disorder (MDD) with acute suicidal ideation or behavior

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.

Spravato is considered **not medically necessary** for members who do not meet the criteria set forth above.

Dosage and Administration

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

Quantity Limits

Trade Name	Generic Name	Quantity Limit
Spravato nasal spray 56 mg Dose Kit, 84 mg dose Kit	esketamine	Treatment-resistant depression (TRD) Initiation of therapy: 8 kits per first 28 days Maintenance: 4 kits per 28 days Major depressive disorder (MDD) with acute suicidal ideation or behavior 8 kits per 28-day course of therapy

CLINICAL RATIONALE

Approximately 300 million people suffer from depression worldwide, making it the leading cause of disability according to the World Health Organization (WHO). Depression can be classified into major depressive disorder (MDD), disruptive mood dysregulation disorder, persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, and depressive disorder due to another medical condition. MDD, the most common and disabling form of depression, affects close to 30% of patients in the United States during their lifetime.

Despite pharmacologic treatment for MDD, over half of patients have an inadequate response, leading to a prolonged loss of functioning and higher risk of unemployment than those who do respond. Almost 30% of patients with MDD do not achieve remission from available treatments and are considered to have treatment-resistant depression. Patients are considered to have treatment-resistant depression when they do not respond to multiple therapeutic courses of antidepressant medications, but definitions range from not responding to a single treatment to not responding to eight treatments. Failure of two adequate therapeutic courses of antidepressants or psychotherapy from different classes either in combination or succession in a current episode has been proposed as a definition of treatment-resistant depression since it predicts a poor prognosis in terms of efficacy. When patients have an inadequate response to an optimal dose of antidepressant therapy, options include switching to another antidepressant, combining the initial antidepressant with a second antidepressant with a different mechanism of action, or augmenting the antidepressant with a non-antidepressant. There is the most evidence to support the use of augmentation with a second-generation antipsychotic.

Spravato (esketamine) was approved in March 2019 and received FDA Breakthrough Therapy designation as the first N-methyl-D-aspartate (NMDA) antagonist indicated, in conjunction with an oral antidepressant, for treatment-resistant depression (TRD) in adults. The mechanism by which esketamine exerts its antidepressant effect is unknown.

Spravato (esketamine) is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the SPRAVATO REMS due to the risks of serious adverse outcomes resulting from sedation, dissociation, abuse and misuse, and suicidal thoughts and behaviors. Spravato (esketamine) must be given under the direct supervision of a healthcare provider for a minimum of 2 hours.

The safety and efficacy of esketamine in TRD was examined in four phase 3 international randomized controlled trials comparing intranasal esketamine and intranasal placebo. The primary outcome measure used for the studies was the was improvement in symptoms, based on change from baseline Montgomery-Asberg Depression Rating Scale (MADRS) at week four. The secondary outcomes reported in these trials

were clinical response, defined as at least 50% improvement in MADRS scale at week four from baseline; and clinical remission rate, defined as reaching 12 or less on MADRS scale at week four.

In TRANSFORM-2, flexible dosed esketamine plus newly initiated antidepressant resulted in greater improvement in MADRS score compared to placebo plus newly initiated antidepressant at four weeks (mean change from baseline (CFB) -21.4 vs. -17.0; least square mean difference [LSMD] -4.0; 95% CI: –7.31, –0.64; P =0.020). In TRANSFORM-1, both doses of esketamine (56 mg and 84 mg) showed a numerically greater improvement from baseline compared to placebo (mean CFB -19.0 & -18.8 vs. -14.8), however, statistical significance was not demonstrated with the 84 mg esketamine plus a newly initiated antidepressant versus placebo plus newly initiated antidepressant. The 56 mg arm of esketamine experienced a statistically significant improvement compared to the placebo arm (LSMD -4.1;95% CI: -7.67, -0.49; p=0.0114). A greater proportion of patients achieved clinical response and remission at four weeks in the esketamine arms compared to placebo when looking at secondary outcomes, however, statistical significance was not reported.

In TRANSFORM-3, the study was conducted in adults 65 years and older and and found patients on esketamine plus newly initiated antidepressant also experienced numerically greater improvement on the MADRS scale compared to those on placebo plus newly initiated antidepressant at four weeks (mean CFB –10.0 vs –6.3), however this difference was not statistically significant. A greater proportion of elderly patients in the esketamine arm achieved clinical response (23.6% vs. 12.3%) and clinical remission (15.3% vs. 6.2%) although statistical significance was not reported.

The SUSTAIN-1 trial was a randomized withdrawal trial that was designed to assess relapse prevention in patients who achieved stable remission (MADRS ≤ 12 in at least three of four weekly assessment conducted in weeks 12-16) or stable response (but were not in stable remission) following 4 weeks of induction and a 12-week optimization phase of esketamine. All subjects who experienced ≥50% reduction from baseline in MADRS total score by the end of acute 4-week treatment were eligible to enter the optimization phase, where they received at least 12 weeks of open-label esketamine treatment with oral antidepressant ongoing. Out of the 705 patients enrolled in the trial designed to assess relapse, 176 patients achieved stable remission, while an additional 121 patients only achieved stable response. Among the stable remitters, 26.7% of patients on maintenance esketamine plus newly initiated antidepressant experienced a relapse compared to 45.3% among patients switched to placebo plus newly initiated antidepressant. Time to relapse was statistically significantly delayed for patients on esketamine compared to patients on placebo (p=0.003).

The most commonly reported adverse events with esketamine use included nausea/vomiting, dissociation, dizziness, headache, vertigo, dysgeusia (distortion of sense of taste), somnolence, sedation, insomnia, blurry vision, increased blood pressure, paresthesia, hypoesthesia (reduced sense of touch or sensation), and fatigue. The FDA label for esketamine includes a boxed warning for sedation; dissociation; abuse and misuse; and suicidal thoughts and behaviors, and states that patients should be monitored for at least two hours after administration, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting. The FDA label also includes a warning for increased blood pressure with monitoring instructions.

Spravato (esketamine) was approved for a second indication on July 31, 2020, in conjunction with an oral antidepressant, for the treatment of depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior. Spravato has not been proven to prevent suicide or reduce suicidal ideation, and the use of Spravato does not preclude the need for hospitalization if clinically warranted, even if a patient experiences symptom improvement after its initial use.

The safety and efficacy of esketamine in MDD with acute suicidal ideation or behavior was examined in two identical phase 3 randomized controlled trials comparing intranasal esketamine and intranasal placebo in adults 18-64 years of age with moderate-to-severe MDD who had active suicidal ideation and intent and for whom acute psychiatric hospitalization was clinically warranted. In both arms, patients also received standard-of-care treatment, which included an inpatient psychiatric hospitalization and a newly initiated or optimized oral antidepressant. The primary outcome measure used for the studies was the was

improvement in symptoms, based on change from baseline Montgomery-Asberg Depression Rating Scale (MADRS) at 24 hours post-dose. The key secondary outcome reported in these trials was clinical the change in Clinical Global Impression of Severity of Suicidaility Revised version (CGI-SS-r) at 24 hours after the first dose. Data was collected throughout the 4-week treatment period.

In ASPIRE I & ASPIRE II, Spravato plus the standard-of-care treatment demonstrated statistical superiority to placebo in the primary efficacy endpoint, with Spravato reducing the MADRS score at 24 hours after first dose by 15.9 points (ASPIRE I) and 16.0 points (ASPIRE II) and placebo reducing the score by 12.0 (ASPIRE I) and 12.2 (ASPIRE II). This superiority was maintained over the 4-week treatment period, but did not increase with increased length of treatment with Spravato plus standard-of-care. In addition, the key secondary endpoint, which evaluated the severity of patients' suicidal ideation, did not demonstrate superiority of Spravato over placebo. The most commonly reported adverse events with esketamine use in ASPIRE I & ASPIRE II were similar to those experienced in clinical trials for TRD.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- C9399 unclassified drugs or biologicals
- J3490 Unclassified drugs
- J3590 Unclassified biologics

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POLICY HISTORY

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