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PHARMACY / MEDICAL POLICY – 5.01.609

Spravato (esketamine) Nasal Spray

BCBSA Ref. Policy: 5.01.34

Effective Date:	Jun. 1, 2025	RELATED MEDICAL POLICIES:
Last Revised:	May 13, 2025	None
Replaces:	N/A	

Select a hyperlink below to be directed to that section.

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Depression is the second leading cause of disability in adults worldwide. There are a number of drug classes used to treat depression. These include monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs). Individuals who do not adequately respond to therapy after trying multiple antidepressants are often referred to as having treatment-resistant depression. Although there is no standard definition of treatment-resistant depression, Spravato (esketamine) Nasal Spray can help some individuals who have not responded to standard antidepressant treatment. This policy describes when Spravato (esketamine) Nasal Spray for the treatment of depression may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity
Spravato (esketamine) Nasal Spray	**Spravato (esketamine) may be considered medically necessary for the treatment of depression when the following criteria are met:** • The individual is aged 18 years or older **AND** • Has medical record documentation of DSM-5 diagnostic criteria for major depressive disorder without psychotic features (unipolar, not bipolar) **AND** • Current episode of depression is moderate to severe as demonstrated by documentation of individual's symptoms and their severity or by one or more standardized depression rating scales **AND** • No current or past psychosis **AND** • No current substance use disorder unless in remission (complete abstinence for at least three months or verification that none of the diagnostic criteria for a substance use disorder in the current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM) have been met for at least 3 months) **OR** • Confined 24/7 in a hospital or residential treatment facility or similar facility where access to alcohol or non-prescribed drugs is not possible and the individual has agreed to not use alcohol or non-prescribed drugs after discharge while continuing treatment with Spravato **AND** • No concurrent use of any hallucinogens/psychedelics **AND** • No concurrent use of any illicit drugs **AND** • No concurrent use of any illicit or non-prescribed stimulants **AND** • No concurrent use of any prescribed stimulants in excess of prescribed doses

Drug	Medical Necessity
	AND • No concurrent use of any prescribed controlled medications that were not prescribed for the individual **AND** • If the individual uses alcohol or marijuana, the individual agrees to either cease use while being treated with Spravato or to not use within 24 hours before and 24 hours after each Spravato treatment **AND** • Tried and failed three antidepressants from at least two different classes **OR** • Tried and failed two antidepressants from two different classes plus an augmenting agent **AND** • Induction dose prescribed (weeks 1 to 4) is limited to 84 mg twice per week, or 56 mg on day 1 followed by no more than 84 mg twice per week for 4 weeks **AND** • Maintenance dose prescribed (week 5 and after) is limited to 84 mg once weekly **Note:** Failed trial = not effective, or partially but inadequately effective, or initially effective but then lost effectiveness, or intolerable side effects **A new course of Spravato (esketamine) starting with an induction dose may be considered medically necessary for the treatment of depression when the following criteria are met:** • The individual previously met criteria for coverage for Spravato and had a course of treatment **AND** • Had a positive response to the previous course of treatment with Spravato **AND** • Previous course of treatment with Spravato was terminated, and the time since the last Spravato treatment is greater than 30 days

Drug	Medical Necessity
	AND • Current episode of depression is moderate to severe as demonstrated by documentation of individual's symptoms and their severity or by one or more standardized depression rating scales **AND** • No current or past psychosis **AND** • No current substance use disorder unless in remission (complete abstinence for at least three months or verification that none of the diagnostic criteria for a substance use disorder in the current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM) have been met for at least 3 months) **OR** • Confined 24/7 in a hospital or residential treatment facility or similar facility where access to alcohol or non-prescribed drugs is not possible and the individual has agreed to not use alcohol or non-prescribed drugs after discharge while continuing treatment with Spravato **AND** • No concurrent use of any hallucinogens/psychedelics **AND** • No concurrent use of any illicit drugs **AND** • No concurrent use of any illicit or non-prescribed stimulants **AND** • No concurrent use of any prescribed stimulants in excess of prescribed doses **AND** • No concurrent use of any prescribed controlled medications that were not prescribed for the individual **AND** • If the individual uses alcohol or marijuana, the individual agrees to either cease use while being treated with Spravato or to not use within 24 hours before and 24 hours after each Spravato treatment

Drug	Medical Necessity
	AND • Induction dose prescribed (weeks 1 to 4) is limited to 84 mg twice per week, or 56 mg on day 1 followed by no more than 84 mg twice per week for 4 weeks **AND** • Maintenance dose prescribed (week 5 and after) is limited to 84 mg once weekly

Drug	Investigational
Spravato (esketamine) Nasal Spray	**All other uses of Spravato (esketamine) for conditions not outlined in this policy are considered investigational, including but not limited to:** • Treatment for chronic pain and bipolar depression • Use in conjunction with any modality of neuromodulation, including but not limited to transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT), and vagus nerve stimulation (VNS) • Use in conjunction with any other formulation of ketamine or with any psychedelic drug **Use of Spravato (esketamine) that does not meet the age or diagnosis requirements within the Medical Necessity section is considered investigational.** **Spravato (esketamine) is subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.**

Drug	Not Medically Necessary
Spravato (esketamine) Nasal Spray	**Spravato (esketamine) with more than one provider/group/clinic at the same time is considered not medically necessary.**

Drug	Not Medically Necessary
	Use of Spravato (esketamine) that meets the age and diagnosis requirements within the Medical Necessity section but does not meet other policy criteria within the Medical Necessity section is considered not medically necessary.
Formulations Other Than Spravato (esketamine) Nasal Spray	**Spravato or esketamine in any formulation other than Spravato nasal spray (e.g., intravenous, intramuscular, sub-cutaneous, oral) is considered investigational for the treatment of any symptom or condition.**

Length of Approval	
Approval	**Criteria**
Initial authorization (first course or a repeat course)	**Spravato (esketamine) may be approved up to 12 months for the treatment of depression.** • If Spravato was started under a non-Company plan, medical necessity criteria must have been met at the time when Spravato was started
Re-authorization criteria	**Spravato (esketamine) for the treatment of depression may be approved up to 12 months in duration when clinical benefit/response at the time of re-authorization show:** • Chart notes documenting improvement in signs and symptoms of major depressive disorder **AND** • No current substance use disorder unless in remission (complete abstinence for at least three months or verification that none of the diagnostic criteria for a substance use disorder in the current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM) have been met for at least 3 months) **OR** • Confined 24/7 in a hospital or residential treatment facility or similar facility where access to alcohol or non-prescribed drugs is not possible and the individual has agreed to not use alcohol or non-prescribed drugs after discharge while continuing treatment with Spravato **AND** • No concurrent use of any hallucinogens/psychedelics

Length of Approval	
Approval	**Criteria**
	AND • No concurrent use of any illicit drugs **AND** • No concurrent use of any illicit or non-prescribed stimulants **AND** • No concurrent use of any prescribed stimulants in excess of prescribed doses **AND** • No concurrent use of any prescribed controlled medications that were not prescribed for the individual **AND** • If the individual uses alcohol or marijuana, the individual agrees to either cease use while being treated with Spravato or to not use within 24 hours before and 24 hours after each Spravato treatment **AND** • Improvement is being maintained (is not wearing-off) **AND** • The individual is not experiencing any serious or dangerous side-effects **AND** • Maintenance dose prescribed (week 5 and after) is limited to 84 mg once weekly

Additional Information

For Major Depressive Disorder:

- A diagnosis code that includes a numeral for severity, or a diagnosis with the descriptor moderate or severe, is not sufficient to establish severity; documentation of symptoms and their severity or score on a standardized rating scale is required.
- Each medication that failed must be individually identified, and the reason or reasons for failure must be specified for each medication.
- Second generation antipsychotics, lithium, and anticonvulsants that are utilized as mood stabilizers are considered to be augmenting agents, not antidepressants.
- Trials of antidepressants that are commonly used for insomnia are considered to be failed trials only if the dose was at minimum antidepressant dose (amitriptyline: 150 mg; doxepin: 150 mg;

Additional Information

mirtazapine: 15 mg; trazodone: 150 mg), not at lower doses that are used for insomnia, or, if titration up to an antidepressant dose was planned but could not be done due to intolerable adverse effects.

Documentation Requirements

The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

- Office visit notes that contain the diagnosis, relevant history, physical evaluation, and medication history.
- For each failed medication trial, documentation of at least 30 continuous days with no or inadequate improvement unless stopped sooner because of intolerable adverse effects.

Coding

Code	Description
HCPCS	
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
S0013	Esketamine, nasal spray (Spravato), 1 mg

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Consideration of Age

Age limits specified in this policy are determined according to the FDA-approved indication.

Benefit Application

Spravato (esketamine) is managed through both the pharmacy and medical benefit. Spravato must be administered under the direct supervision of a healthcare provider and a treatment session consists of nasal administration of Spravato and post-administration observation under supervision.

Montgomery–Asberg Depression Rating Scale

The Montgomery–Asberg Depression Rating Scale is commonly used to evaluate the efficacy of antidepressants by assessing the severity of depression. It contains 10 items and the total score ranges from 0 to 60. The following cut-offs were proposed to classify the level of depression severity:

- 0-6: No depression (absence of symptoms)
- 7-19: Mild depression
- 20-34: Moderate depression
- 35-60: Severe depression

Hamilton Rating Scale for Depression

The Hamilton Rating Scale for Depression is a 17-item rating scale to determine the severity level of depression in an individual before, during, and after treatment. The total score ranges from 0 to 52, with the score corresponding to the following classifications:

- 0-7: No depression (normal)
- 8-16: Mild depression
- 17-23: Moderate depression
- ≥24: Severe depression

Tools for Assessment of Suicidal Ideation/Behavior

There are multiple tools used for assessment of suicidal ideation and behavior. The eligibility criteria in the clinical trials of esketamine required that individuals respond affirmatively to questions B3 ("Think about suicide [killing yourself]?") and B10 ("Intend to act on thoughts of killing yourself in the past 24 hours?") on the Mini-International Neuropsychiatric Interview instrument. Other scales that are commonly used to assess suicidal ideation include the Beck Scale for Suicide Ideation (SSI) and the Columbia-Suicide Severity Rating Scale (C-SSRS). SSI is a 19 item clinician-administered scale querying, among other things, the individual's wish to die, wish to live, and the duration and intensity of thoughts of suicide. Each item is rated on a 3-point scale from 0 to 2, with a total score ranging from 0 to 38. The SSI can be administered at initial evaluation and subsequently repeated to assess improvement. C-SSRS characterizes current thoughts of suicide and past suicidal behaviors. It features a clinician-administered initial evaluation form, a "since last visit" version, and a self-report form. It can be used in many settings, including medical, inpatient, and outpatient behavioral health

Evidence Review

Background

Depression is the second leading cause of disability in adults worldwide. The prevalence of depression is estimated at 13%. It is estimated that 20%-40% of individuals do not respond or respond minimally to antidepressant monotherapy. Of these, 50% do not respond to the addition of a second antidepressant. Similarly, the STAR*D trial which included 3,671 individuals with major depressive disorder found approximately one-third of individuals did not respond to two trials of antidepressants.

There is no standardized definition of treatment resistant depression (TRD). In clinical trials with Spravato, TRD was defined as major depressive disorder in individuals who have failed to respond to ≥2 different antidepressants for the current episode of depression.

Summary of Evidence

Efficacy – Treatment-Resistant Depression

Esketamine was studied in five Phase 3 studies. The TRANSFORM 1-3 trials were randomized, double-blind, active-controlled studies conducted over 4 weeks which randomized individuals with moderate to severe, treatment-resistant depression (TRD) to esketamine plus a new oral antidepressant (AD) or placebo plus a new oral AD. The primary outcome was the change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score at 4 weeks.

- The flexible-dosed TRANSFORM-2 trial (N=223) found esketamine plus an AD significantly improved the primary outcome of MADRS total score compared to placebo (-21.4 vs -17.0, p = 0.02). This was the only trial to find a significant outcome in the primary efficacy measure. The sequentially analyzed initial secondary endpoint found no difference between groups in the proportion with clinical response on day 2; therefore, no further outcomes were analyzed.

- The fixed-dose TRANSFORM-1 trial (N=342) found no difference in the primary outcome of change in MADRS score between groups (19.0, -18.8, -14.8 for esketamine 84 mg, 56 mg, and placebo, respectively, p=0.088). Of note, the criteria for minimum important difference in MADRS score (two points) was met.

- The TRANSFORM-3 trial (N=137) was conducted in elderly individuals (≥65 years) and found no significant difference between the esketamine (28-84 mg) plus AD and placebo plus AD groups (-10.0 vs -6.3, p=0.059). Of note, the criteria for minimum important difference in MADRS score (two points) was met.

Additionally, esketamine was studied in two long-term Phase 3 trials.

- SUSTAIN-1 was a randomized, double-blind, multicenter, Phase 3, withdrawal study in 297 individuals with treatment-resistant, moderate-severe depression with duration ≥2 years who were randomized to esketamine plus a new oral AD or placebo plus a new oral AD. The study continued until a predetermined number of relapses had occurred (5-7 years). Individuals underwent a 4-week induction phase and a 12-week optimization phase before randomization for the maintenance phase. The primary outcome of median time to relapse among stable remitters found the median time was 273 days with placebo and was not estimable with esketamine. The hazard ratio (HR) for risk of relapse was 0.49 (95% confidence interval [CI] 0.29-0.84). All secondary out-comes (change in Patient Health Questionnaire-9 [PHQ-9], Sheehan Disability Scale [SDS], and Clinical Global Impression-Severity [CGI-S] scores) significantly favored esketamine plus AD over placebo plus AD.

- The SUSTAIN-2 trial was a long-term, open-label, Phase 3, safety study which enrolled 603 individuals with TRD in a 48-week maintenance phase. Individuals were treated with esketamine plus a new oral AD. Change in MADRS score seen in the induction phase (-16.4) was maintained throughout the study (maintenance phase change in MADRS score 0.3). Additionally, the responder and remission rates increased over the trial duration (76.5% to 78.4% and 47.2% to 58.2%, respectively). However, the trial discontinuation was quite high (75.2%).

Efficacy – MDD with Acute Suicidal Ideation or Behavior

Esketamine was evaluated in two identical phase 3 short-term (4-week) randomized, double-blind, multicenter, placebo-controlled studies, Study 3 (NCT03039192) and Study 4 (NCT03097133), in adults with moderate-to-severe MDD (MADRS total score >28) who had active suicidal ideation and intent. In these studies, individuals received treatment with esketamine 84 mg or placebo nasal spray twice weekly for 4 weeks. After the first dose, a one-time dose reduction to esketamine 56 mg was allowed for individuals unable to tolerate the 84 mg dose. All individuals received comprehensive standard of care treatment, including an initial inpatient psychiatric hospitalization and a newly initiated or optimized oral antidepressant (AD) (AD monotherapy or AD plus augmentation therapy) as determined by the investigator. After completion of the 4-week treatment period with esketamine/placebo, study follow-up continued through day 90.

The baseline demographic and disease characteristics of individuals in Study 3 and Study 4 were similar between the esketamine plus standard of care or placebo nasal spray plus standard of care treatment groups. The median individual age was 40 years (range 18 to 64 years), 61% were female; 73% Caucasian and 6% Black; and 63% of individuals had at least one prior suicide attempt. Prior to entering the study, 92% of the individuals were receiving antidepressant therapy. During the study, as part of standard of care treatment, 40% of individuals received AD monotherapy, 54% of individuals received AD plus augmentation therapy, and 6% received both AD monotherapy/AD plus augmentation therapy.

The primary efficacy measure was the change from baseline in the MADRS total score at 24 hours after first dose (Day 2). In Study 3 and Study 4, esketamine plus standard of care demonstrated statistical superiority on the primary efficacy measure compared to placebo nasal spray plus standard of care.

The secondary efficacy measure was the change in Clinical Global Impression of Suicidal Severity - Revised (CGI-SS-r) score at 24 hours after first dose (Day 2). The CGI-SS-r is a one-item,

clinician-rated assessment used to rate the current severity of an individual's suicidal ideation and behavior. Scores on the CGI-SS-r range from 0 to 6, with higher scores indicating more severe suicidal ideation and behavior. In Study 3 and Study 4, esketamine plus standard of care did not demonstrate superiority compared to placebo nasal spray plus standard of care in improving CGI-SS-r.

In both Study 3 and Study 4, esketamine's treatment difference compared to placebo was observed starting at 4 hours. Between 4 hours and Day 25, both the esketamine and placebo groups continued to improve; the difference between the groups generally remained but did not appear to increase over time through Day 25.

Safety

Serious Adverse Events

Esketamine carries four black box warnings including the risk of sedation, risk of dissociative or perceptual changes, risk of abuse or misuse, and risk of increased suicidal thoughts and behavior. Based on these warnings, esketamine is available through a risk evaluation and mitigation strategy (REMS) program and must be administered by a health care professional. Individuals must be monitored for 2 hours after each treatment session and must be assessed for clinical stability before departure. In clinical trials, symptoms peaked at 40 min and a majority of individuals (93.2% to ≥ 87%) were considered discharge ready at 1.5 hours.

- Sedation reported with esketamine was assessed on a 5-point modified observer's alertness/sedation scale which found 49%-61% of individuals were considered sedated following esketamine and 0.3% experienced loss of consciousness.
- The dissociation was assessed with a Clinical Administered Dissociative States Scale (CADSS) which found 61%-75% of individuals were considered to have dissociative symptoms the day of administration. Dissociative symptoms included derealization, depersonalization, distortion of time and space, and illusions.
- Esketamine is the s-enantiomer of ketamine, both of which are Schedule III substances. A cross-over, double-blind abuse potential study in 34 individuals found drug-liking and take drug again scores for 84 and 112 mg esketamine were similar to those seen with IV ketamine (0.5 mg/kg over 40 minutes). While misuse of esketamine did not occur during clinical trials, misuse of ketamine is well-documented. Long-term cognitive and memory impairment have been reported with ketamine abuse/misuse.

- Increased risk of suicidal thoughts and behavior has been noted in pediatric and young adult individuals (<24 years) in a pooled analysis of placebo-controlled, randomized controlled trials (RCTs) across classes of antidepressants. Esketamine is not approved in pediatric individuals. Close monitoring of depressive symptoms and suicidality is recommended.

Contraindications to esketamine include aneurysmal vascular disease, arteriovenous malformation, history of intracerebral hemorrhage, and hypersensitivity to esketamine, ketamine, or excipients.

Other Adverse Events

Adverse events occurring in ≥5% of individuals and at least twice as frequently with esketamine than placebo include dissociation (41%), dizziness (29%), nausea (28%), sedation (23%), vertigo (23%), hypoesthesia (18%), anxiety (13%), lethargy (11%), increased BP (10%), vomiting (9%), and feeling drunk (5%).

- The mean placebo-adjusted increase in systolic and diastolic BP (SBP and DBP) seen with esketamine were 7-9 mmHg and 4-6 mm Hg, respectively, at 40 minutes post dose. The long-term SUSTAIN-2 trial found increases of SBP ≥180 mm Hg or DBP ≥110 mm Hg occurred in 4.1% of individuals.
- Nausea and vomiting occurred on the day of administration with a mean duration of 1 hour. These symptoms decreased with subsequent infusions.
- Dysgeusia was reported in three clinical trials (27%, 26.1%, and 10.2-11%).
- Death due to suicide occurred in two individuals across all Phase III trials, both in the SUSTAIN-2 trial.

Warnings include sedation, dissociation, abuse/misuse, REMS program, suicidal thoughts/behaviors in adolescents and young adults, increased BP, cognitive impairment, impaired ability to drive/operate machinery, ulcerative or interstitial cystitis, and embryo-fetal toxicity (may case fetal harm).

Tolerability

The requirement to administer esketamine in a health care setting with 2 hours of monitoring may create adherence issues for individuals. Similarly, the restriction against driving following administration may create compliance difficulties for individuals.

Discontinuation due to AEs with esketamine occurred in 5%-16.4% of individuals in short-term trials and 5%-9.5% in long-term trials.

Ongoing Clinical Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05973851	A Randomized, Controlled Trial to Investigate the Effect of a Four Week Intensified Pharmacological Treatment for Major Depressive Disorder Compared to Treatment as Usual in Subjects Who Had a First-time Treatment Failure on Their First-line Treatment	418	Jun 2026
NCT05554627	VA Aripiprazole vs. Esketamine for Treatment of Depression VAST-D II	940	Nov 2028
NCT04599855	A Randomized, Double-Blind, Multicenter, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Esketamine Nasal Spray, Administered as Monotherapy, in Adult Participants with Treatment-resistant Depression	450	Feb 2024
NCT04829318	Open-label Long-Term Extension Study for Participants with Treatment-resistant Major Depressive Disorder Who Are Continuing Esketamine Nasal Spray Treatment from Study 54135419TRD3013	183	Jul 2024

NCT: national clinical trial.

2020 Update

Reviewed prescribing information for Spravato (esketamine). In July 2020 Spravato received a new indication for the treatment of depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior. Updated the Summary of Evidence information in policy on new indication and References to include ASPIRE I and ASPIRE II trials.

2021 Update

Reviewed prescribing information for Spravato (esketamine) and the use of esketamine for treating depression in adults. Updated the re-authorization criteria to clarify that Spravato must continue to be used in conjunction with an oral antidepressant. Added to policy dosage limits following the FDA approved prescribing information. Added to the investigational table that use of Spravato in conjunction with any modality of neuromodulation, including but not limited to transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT), and vagus nerve stimulation (VNS), is investigational. Added to policy coverage criteria for the Spravato indication for the treatment of major depressive disorder (MDD) with acute suicidal ideation or behavior when criteria are met.

2022 Update

Reviewed prescribing information for Spravato (esketamine) and conducted a literature search from 3/1/21 to 2/28/22 on the use of esketamine for the management of depression and acute suicidal ideation. No new information was identified that would change policy statements. Added coverage criteria for a "new course" of Spravato for the treatment of depression and for MDD with acute suicidal ideation or behavior. Updated criteria for the treatment of depression and for the treatment of MDD with acute suicidal ideation adding additional info to define moderate to severe depression and added that no concurrent use of any mind-altering or mood-altering substances that could interfere with the effectiveness of Spravato, including but not limited to alcohol, marijuana, stimulants, and hallucinogens/psychedelics is allowed. Updated the re-authorization criteria for the treatment of depression and for MDD with acute suicidal ideation or behavior adding that individual has no current substance use disorder unless in remission (complete abstinence for a month) and added that no concurrent use of any mind-altering or mood-altering substances that could interfere with the effectiveness of Spravato, including but not limited to alcohol, marijuana, stimulants, and hallucinogens/psychedelics is allowed.

2023 Update

Reviewed prescribing information for Spravato (esketamine) and conducted a literature search on the use of esketamine for the management of depression and acute suicidal ideation. Updated criteria to clarify that the individual has medical record documentation of DSM-5 diagnostic criteria for major depressive disorder without psychotic features (unipolar, not

bipolar). Updated criteria to clarify that there is a requirement to have no current substance use disorder unless in remission (complete abstinence for three months) or confined 24/7 in a hospital or residential treatment facility or similar facility where access to alcohol or non-prescribed drugs is not possible. Updated criteria to clarify that the member is required to have no concurrent use of any hallucinogens/psychedelics, no concurrent use of any illicit drugs, no concurrent use of any illicit or non-prescribed stimulants, no concurrent use of any prescribed stimulants in excess of prescribed doses, and if the individual uses alcohol or marijuana, the individual agrees to either cease use while being treated with Spravato or to not use within 24 hours before and 24 hours after each Spravato treatment. Added additional information on major depressive disorder. Updated criteria to clarify that members continuing use of Spravato must meet the medical necessity criteria. Added documentation requirement that the oral antidepressant that will be used in conjunction with Spravato must be specifically named. Updated criteria for new course of Spravato which requires individuals to have had a positive response to the previous course of treatment with Spravato.

2024 Update

Reviewed prescribing information for Spravato (esketamine) and conducted a literature search on the use of esketamine for the management of depression and acute suicidal ideation. Removed the stipulation that addition of a second antidepressant to an antidepressant trial is considered to be addition of an augmenting agent, not a separate antidepressant trial. Added the following clarification to the Investigational section of the policy: Use of Spravato (esketamine) that does not meet the age or diagnosis requirements within the Medical Necessity section is considered investigational. Use of Spravato (esketamine) that meets the age and diagnosis requirements within the Medical Necessity section but does not meet other policy criteria within the Medical Necessity section is considered not medically necessary.

2025 Update

Reviewed prescribing information for Spravato (esketamine) and conducted a literature search on the use of esketamine for the management of depression and acute suicidal ideation. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.

The most comprehensive review of Spravato trials published to date, which is the only review that includes all published Spravato trials prior to initial FDA approval, the study used by the

FDA to approve the indication for acute suicidal ideation or behavior, and all published Spravato trials in the 6 years subsequent to initial FDA approval, was published in March 2025. Based on detailed and extensive review of the published trials, this review determined that "The effect size concerning suicidality was not significant at any time point" and "both the individual studies and meta-analysis were negative concerning an effect on suicidality at all time points, even acutely, other than one early study…This finding questions the reason behind the second indication of the product" (i.e., the indication for acute suicidal ideation or behavior). An accompanying editorial states there is "negligible evidence for efficacy against suicidality" and "none of the seven trials reporting on suicidal ideation around week 4 were positive" and "the findings call into question the basis for this indication" and that "there is still no evidence that esketamine nasal spray (or ketamine) actually reduces the risk of suicide attempts or suicide." Based on the findings of this comprehensive review, criteria for coverage of Spravato for major depressive disorder (MDD) with acute suicidal ideation or behavior that are separate from criteria for coverage of Spravato for MDD are determined to not have a sufficient evidence basis and have therefore been removed as separate criteria. Criteria for coverage of Spravato for major depressive disorder (MDD) apply to individuals with or without acute suicidal ideation or behavior.

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History

Date	Comments
07/01/19	New policy, approved June 11, 2019. Add to Prescription Drug section. Spravato (esketamine) Nasal Spray may be considered medically necessary when criteria are met, considered investigational when criteria are not met.
06/01/20	Coding update. Added HCPCS codes G2082 and G2083.
01/01/21	Annual Review, approved December 17, 2020. Removed HCPCS code J3490 and added HCPCS code S0013. No changes to policy statements.
01/01/22	Annual Review, approved December 14, 2021. Added coverage for the treatment of MDD with acute suicidal ideation or behavior when criteria are met. Updated the depression re-authorization criteria to require that Spravato is continued to be used in

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	conjunction with an oral antidepressant. Updated the initial authorization and re-authorization criteria for depression adding dosage limits based on the prescribing information. Added to the investigational table that use of Spravato in conjunction with any modality of neuromodulation is investigational.
06/01/22	Annual Review, approved May 10, 2022. Added coverage criteria for a "new course" of Spravato for the treatment of depression and for MDD with acute suicidal ideation or behavior. Updated criteria for the treatment of depression and for the treatment of acute suicidal ideation or behavior adding additional info to define moderate to severe depression and added that no concurrent use of any mind-altering or mood-altering substances that could interfere with the effectiveness of Spravato, including but not limited to alcohol, marijuana, stimulants, and hallucinogens/psychedelics is allowed. Updated the re-authorization criteria for the treatment of depression and for MDD with acute suicidal ideation or behavior adding that individual has no current substance use disorder unless in remission (complete abstinence for a month) and added that no concurrent use of any mind-altering or mood-altering substances that could interfere with the effectiveness of Spravato, including but not limited to alcohol, marijuana, stimulants, and hallucinogens/psychedelics is allowed. Policy updates become effective for dates of service on or after September 2, 2022.
11/01/22	Interim Review, approved October 11, 2022. Updated criteria for the treatment of depression changing to three antidepressants from at least two different classes or two antidepressants from two different classes plus an augmenting agent. For the treatment of depression updated to define remission as complete abstinence for three months. Added to the Investigational table use in conjunction with any other formulation of ketamine or with any psychedelic drug. Added a Not Medically Necessary table and included that Spravato with more than one provider/group/clinic at the same time is considered not medically necessary. In the Documentation Requirement table added that for failed medication trials, each medication that failed must be individually identified, and the reason or reasons for failure must be specified for each medication. Also added to the Documentation Requirement table that for each failed medication trial, documentation of at least 30 continuous days with no or inadequate improvement unless stopped sooner because of intolerable adverse effects. Policy updates become effective for dates of service on or after February 3, 2023. Changed the wording from "patient" to "individual" throughout the policy for standardization.
05/01/23	Annual Review, approved April 11, 2023. Updated criteria to clarify that the individual has medical record documentation of DSM-5 diagnostic criteria for major depressive disorder without psychotic features (unipolar, not bipolar). Updated criteria to clarify that there is a requirement to have no current substance use disorder unless in remission (complete abstinence for three months) or confined 24/7 in a hospital or residential treatment facility or similar facility where access to alcohol or non-prescribed drugs is not possible. Updated criteria to clarify that the member is required to have no concurrent use of any hallucinogens/psychedelics, no concurrent use of any illicit drugs, no concurrent use of any illicit or non-prescribed stimulants, no

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	concurrent use of any prescribed stimulants in excess of prescribed doses, and if the individual uses alcohol or marijuana, the individual agrees to either cease use while being treated with Spravato or to not use within 24 hours before and 24 hours after each Spravato treatment. Added additional information on major depressive disorder. Updated criteria to clarify that members continuing use of Spravato must meet the medical necessity criteria. Added documentation requirement that the oral antidepressant that will be used in conjunction with Spravato must be specifically named.
08/01/23	Interim Review, approved July 11, 2023. Updated criteria for new course of Spravato which requires individuals to have had a positive response to the previous course of treatment with Spravato.
08/01/24	Interim Review, approved July 9, 2024. Removed the stipulation that addition of a second antidepressant to an antidepressant trial is considered to be addition of an augmenting agent, not a separate antidepressant trial.
09/01/24	Annual Review, approved August 12, 2024. No changes to policy statements.
10/01/24	Interim Review, approved September 9, 2024. Added an option for the induction phase for the treatment of depression of an initial dose of 56 mg on the first day of treatment and then no more than 84 mg twice per week for the first 4 weeks. Added a stipulation that Spravato or esketamine in any formulation other than Spravato nasal spray is considered investigational.
11/01/24	Interim Review, approved October 8, 2024. Added the following clarification to the Investigational section of the policy: Use of Spravato (esketamine) that does not meet the age or diagnosis requirements within the Medical Necessity section is considered investigational. Use of Spravato (esketamine) that meets the age and diagnosis requirements within the Medical Necessity section but does not meet other policy criteria within the Medical Necessity section is considered not medically necessary.
03/01/25	Interim Review, approved February 11, 2025. Removed the requirement that an oral antidepressant must be used in conjunction with Spravato in order to be consistent with the FDA's January 21, 2025, approval of Spravato as monotherapy for Major Depressive Disorder.
04/01/25	Annual Review, approved March 24, 2025. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.
06/01/25	Interim Review, approved May 13, 2025. Added clarification that substance use disorder in remission is complete abstinence for at least three months or verification that none of the current DSM diagnostic criteria for a substance use disorder have been met for at least 3 months. Added "the individual has agreed to not use alcohol or non-prescribed drugs after discharge while continuing to be treated with Spravato" for substance use disorder when confined 24/7 in a hospital or residential treatment facility or similar facility where access to alcohol or non-prescribed drugs is not

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	possible. Added "No concurrent use of any prescribed controlled medications that were not prescribed for the individual" to the criteria. Increased the initial authorization period for Spravato to 12 months. Deleted "Non-formulary exception reviews for Spravato (esketamine) may be approved up to 12 months" for initial authorizations and for re-authorizations because the initial authorization period and the re-authorization period is 12 months regardless of formulary or non-formulary status. Changed "under a different plan" to "under a non-Company plan" for consistency with other policies. Deleted the separate criteria and related items for acute suicidal ideation or behavior. Added "Each medication that failed must be individually identified, and the reason or reasons for failure must be specified for each medication" in the Additional Information section.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2025 Premera All Rights Reserved.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.