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. Patients 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 patients 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.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Necessity</th>
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</table>
| Spravato™ (esketamine) Nasal Spray | Spravato™ (esketamine) may be considered medically necessary for the treatment of depression when the following criteria are met:  
• Patient is 18 years of age or older  
AND  
• Patient has medical record documentation of DSM-5 diagnostic criteria for major depressive disorder (unipolar, not bipolar)  
AND  
• Patient’s current episode of depression is moderate to severe  
AND  
• No current or past psychosis  
AND  
• No current substance use disorder unless in remission (complete abstinence for a month)  
AND  
• Tried and failed four antidepressants from at least two different classes  
OR  
• Tried and failed three antidepressants from at least two different classes plus an augmenting agent  
AND  
• Spravato™ is used in conjunction with an oral antidepressant  

Note: Failed trial = not effective, or partially but inadequately effective, or initially effective but then lost effectiveness, or intolerable side effects |

<table>
<thead>
<tr>
<th>Drug</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spravato™ (esketamine) Nasal Spray</td>
<td>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.</td>
</tr>
</tbody>
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### Length of Approval

<table>
<thead>
<tr>
<th>Approval</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Initial authorization</td>
<td>Spravato™ (esketamine) may be approved up to 6 months</td>
</tr>
</tbody>
</table>
| Re-authorization criteria| Future re-authorization of Spravato™ (esketamine) 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  
  - The improvement is being maintained (is not wearing-off)  
  - The patient is not experiencing any serious or dangerous side-effects |

### Documentation Requirements

The patient’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

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>HCPCS</td>
<td></td>
</tr>
<tr>
<td>J3490</td>
<td>Unclassified drugs (use to report Spravato™)</td>
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</tbody>
</table>

**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.

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 patients 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 patients with major depressive disorder found approximately one-third of patients 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 patients who have failed to respond to ≥2 different antidepressants for the current episode of depression.

Summary of Evidence

Efficacy

Esketamine was studied in five Phase 3 studies, none of which are published. The TRANSFORM 1-3 trials were randomized, double-blind, active-controlled studies conducted over 4 weeks which randomized patients 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 patients (≥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 patients 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). Patients 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 outcomes (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 patients with TRD in a 48-week maintenance phase. Patients 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%).
Of note, esketamine was given a breakthrough therapy designation for patients with imminent risk of suicide based on ASPIRE I (Phase 3), ASPIRE II (Phase 3), PERSEVERE (Phase 2), and DIRECTION (Phase 2) studies. The Phase 3 ASPIRE I and II trials are not published and were not provided in the Spravato dossier. Of note, change in MADRS score on Day 2 was assessed in the TRANSFORM-2 trial; however, no significant difference between groups was found.

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. Patients 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 patients (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 patients were considered sedated following esketamine and 0.3% experienced loss of consciousness.

- Dissociation was assessed with a Clinical Administered Dissociative States Scale (CADSS) which found 61%-75% of patients 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 patients 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 patients (<24 years) in a pooled analysis of placebo-controlled, randomized controlled trials (RCTs) across classes of antidepressants. Esketamine is not approved in pediatric patients. 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 patients 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 patients.
- 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 patients 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 cause fetal harm).

Tolerability

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

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


History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>07/01/19</td>
<td>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.</td>
</tr>
</tbody>
</table>

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  • Written information in other formats (large print, audio, accessible electronic formats, other formats)
• Provides free language services to people whose primary language is not English, such as:
  • Qualified interpreters
  • Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

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Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592. TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir dados importantes neste aviso.

Română (Romanian):

Русский (Russian):
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