

## Prior Authorization Update: Esketamine

**Date of Review:** February 2024

**Generic Name:** esketamine

**PDL Class:** Antidepressants

**Date of Last Review:** December 2023

**Brand Name (Manufacturer):** Spravato (Janssen Pharmaceuticals, Inc.)

See **Appendix 1** for Prescribing Information Highlights

### Purpose for Class Update:

Evaluate evidence for the effectiveness and safety of esketamine in people with suicidal ideation or behavior to establish a policy for outpatient initiation of therapy in people with depression and acute risk for suicide. This document provides a summary of previous reviews and recent guidelines from the Veterans Administration.

### Plain Language Summary:

- Suicide is a common cause of death in the United States. Guidelines recommend risk evaluation for people who have suicidal thoughts or behavior.
- Studies show that some types of talk therapy (like cognitive behavior therapy, dialectical behavior therapy, and/or problem-solving based psychotherapy) decrease risk of suicide. Some medicines also may decrease risk of suicidal thoughts for some groups of people. Medicines with some benefit include:
  - Ketamine infusion for people with depression,
  - Lithium for people with bipolar disorder or depression, and
  - Clozapine for people with psychosis.
- Esketamine is a medicine that the Food and Drug Administration approved for depression in people at risk for suicide. Studies show that esketamine improves depression symptoms but may not change suicide risk compared to placebo (e.g., sugar pill).
- We recommend the Oregon Health Authority pay for esketamine for people with suicidal thoughts and depression when:
  - they have been referred to psychotherapy and
  - the doctor has re-evaluated the medicine they take by mouth for depression.

### Research Questions:

1. What is the evidence for esketamine in improving symptoms, function, or quality of life in patients with depression and suicidal ideation?
2. What is the evidence for safety of esketamine in people with depression and suicidal ideation or behavior?
3. Are there specific subpopulations for which esketamine may be specifically indicated, more effective, or associated with less harm?

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**Conclusions:**

- Guidelines updated in 2019 from the Veterans Administration/Department of Defense (VA/DOD) recommend several treatments with evidence for reduction in suicidal ideation and behavior.<sup>1</sup> Non-pharmacologic treatment includes cognitive behavioral therapy (strong recommendation), a crisis response plan, dialectical behavior therapy, and/or problem-solving based psychotherapy for suicide prevention (weak recommendations).<sup>1</sup> Short-term use of intravenous ketamine was suggested for people with major depressive disorder, lithium was suggested for people with bipolar disorder or unipolar depression, and clozapine was suggested for people with schizophrenia or schizoaffective disorder (weak recommendation for all therapies).<sup>1</sup> Esketamine was approved by the Food and Drug Administration (FDA) after the literature search was completed for this guideline.
- The VA/DOD also recommends management of co-occurring conditions for all people with suicidal ideation or behavior.<sup>1</sup> Evidence shows that patients with psychiatric conditions (e.g., substance use disorder, mood disorders), and psychiatric symptoms (e.g., hopelessness, insomnia, agitation) have increased risk for suicide.<sup>1</sup>
- Two randomized controlled trials (RCTs) evaluated use of esketamine in patients with major depressive disorder (MDD) at high risk for suicide.<sup>2,3</sup> Over 60% of people in these RCTs had a prior suicide attempt, 45-61% were prescribed an oral antidepressant plus oral augmentation therapy, and 67-75% were prescribed a benzodiazepine.<sup>2,3</sup> There is low quality evidence that esketamine does not decrease suicidality, but has a slight improvement in depression symptoms compared to placebo with a mean difference [MD] in the Montgomery-Asberg Depression Rating Scale (MADRS) of -3.8 (95% CI -6.56 to -1.09) and -3.9 (95% CI -6.6 to -1.11) for each study.<sup>2,3</sup> A 2 point improvement on MADRS may be associated with a clinically significant improvement.<sup>4</sup>
- There is insufficient evidence for other outcomes including suicide attempts, hospitalizations, or hospital length-of-stay in patients with MDD and risk for suicide.

**Recommendations:**

- Update the safety edit for esketamine to include outpatient initiation of esketamine for people with suicidal ideation who have optimized alternative treatments for depression.

**Summary of Prior Reviews and Current Policy:**

- Esketamine was approved by the Food and Drug Administration (FDA) for people with major depressive disorder and acute suicidal ideation or behavior in 2020. Evidence supporting approval for this indication was reviewed by the Pharmacy and Therapeutics Committee in 2021. Esketamine is also FDA-approved as adjunct therapy for treatment-resistant depression.
- The current safety edit for esketamine allows continuation of therapy when esketamine is initiated in a hospital setting for acute suicidal ideation or behavior because studies evaluated for FDA approval were conducted in the inpatient setting.
- Esketamine is carved-out of CCO plans and is paid for by FFS when billed as a pharmacy claims. Medical claims for esketamine are not carved-out and can be covered by CCOs for their members.

**Background:**

In the United States in 2017, suicide was the 10<sup>th</sup> leading cause of death (with a death rate of 14 deaths per 100,000 individuals).<sup>5</sup> Epidemiologic studies show that suicidal ideation is higher in women than men, but completed suicides are more common in men.<sup>5</sup> In the United States, the most common means of suicide include use of firearms (for men) and poisoning (for women).<sup>1</sup> Age-adjusted death rates from 2013 to 2015 also indicate that suicide is highest in rural areas and increases with age.<sup>5</sup> Risk factors for suicide include prior suicide attempts, current suicidal ideation, current psychosocial stressors, availability of firearms, prior

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psychiatric hospitalization, psychiatric conditions (e.g., substance use disorder, mood disorders), and psychiatric symptoms (e.g., hopelessness, insomnia, agitation).<sup>1</sup>

Recent guidelines from the VA/DOD suggest against the use of a single instrument or method to evaluate suicide risk.<sup>1</sup> Instead, they recommend a comprehensive risk assessment to evaluate risk for suicide based on individual patient factors and circumstances.<sup>1</sup> While risk stratification is routinely done in clinical practice, authors found insufficient information to recommend for or against the use of risk stratification to evaluate the level of suicide risk.<sup>1</sup> Risk stratification usually includes assessment for risk based on intent, preparatory behaviors or a current suicidal plan and the ability of the person to independently maintain their safety with coping skills and social supports.<sup>1,5</sup>

Treatment is generally recommended in the least restrictive setting that is likely to be safe and effective.<sup>5</sup> For people with high acute risk, recommended treatment typically includes psychiatric hospitalization.<sup>1</sup> For people with intermediate acute risk, 2019 VA/DOD guidelines recommend hospitalization if related factors driving risk are responsive to inpatient treatment or intensive outpatient management including frequent contact, regular re-assessment of risk, and a well-articulated safety plan.<sup>1</sup> For people with low acute risk, primary care management is reasonable with outpatient mental health treatment for co-occurring conditions. For all categories of risk, treatment should include management of co-occurring conditions.<sup>1</sup> For people with high chronic risk of suicide, routine mental health follow-up is recommended. These people are considered to be at chronic risk for becoming acutely suicidal, particularly in the context of unpredictable psychosocial changes (e.g., job or relationship loss, relapse on drugs). Routine care should include a well-articulated safety plan, lethal means safety (e.g., no access to guns, limited medication supply), routine suicide risk screening, building coping skills, and management of co-occurring conditions.<sup>1</sup> Similar recommendations are made for people at intermediate chronic risk including routine mental health care, a well-articulated safety plan including lethal means safety, and management of co-occurring conditions.<sup>1</sup> For people at low chronic risk, primary care management or mental health care when needed for successful treatment is usually reasonable.<sup>1</sup>

Goals for people with suicidal ideation or suicide risk include reduction of immediate risk and prevention of recurrent symptoms for people with chronic suicide risk. Goals of treatment for depression typically focus on improvement in symptoms, function, remission, and relapse prevention. A wide variety of rating scales are used to evaluate symptom improvement, quality of life, and function in patients treated with antidepressants. Scales vary depending on the condition. Some of the most commonly used rating-scales and thresholds include the Montgomery-Asberg Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HAM-D). The MADRS is a 10-item scale which assesses depression symptoms (range 0 to 60) with higher scores indicating more severe depression.<sup>4</sup> The HAM-D is a clinician-rated, 17-item scale to assess symptoms (range 0 to 52).<sup>4</sup> Values associated with remission and minimum clinically important differences for each of these scales vary. A 2 point improvement on MADRS may be associated with a clinical improvement and HAM-D scores of 3 to 7 points may be clinically significant.<sup>4</sup> Typically, a 50% improvement in symptom score from baseline is used to evaluate response to therapy.<sup>4</sup>

#### **Methods:**

A Medline literature search for new randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Oregon Mental Health Clinical Advisory Group (MHCAG), the Scottish Intercollegiate Guidelines Network (SIGN), and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for recent high quality systematic reviews.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

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## Guidelines:

In 2019, the Veterans Administration/Department of Defense updated guidelines for the assessment and management of people at risk for suicide.<sup>1</sup> Recommendations were based on a systematic literature search through April 2018.<sup>1</sup> Literature for esketamine, which was approved by the Food and Drug Administration (FDA) in 2019, was not included. An update of this guideline is currently in progress. Guideline authors used “suggest” to describe recommendations based on weak evidence and “recommend” to describe recommendations with strong evidence. Recommendations were divided into the following categories:

- **Screening:** A validated screening tool, such as the Patient Health questionnaire-9 (PHQ-9), was suggested to identify suicide-related behavior and risk (weak recommendation).<sup>1</sup>
- **Evaluation:** Include an assessment of risk factors as part of a comprehensive evaluation for suicide risk (strong recommendation).<sup>1</sup> They suggest against the use of a single instrument or method to evaluate suicide risk (weak recommendation). While risk stratification is routinely done in clinical practice, authors found insufficient information to recommend for or against the use of risk stratification to evaluate the level of suicide risk.<sup>1</sup>
- **Non-pharmacologic therapy:** Cognitive behavioral therapy for suicide prevention was recommended for people with a recent history of self-directed violence to reduce risk of suicide (strong recommendation).<sup>1</sup> Completion of a crisis response plan is suggested for all patients with suicidal ideation (weak recommendation). Dialectical behavioral therapy was suggested for people with borderline personality disorder or recent self-directed violence (weak recommendation).<sup>1</sup> They suggest offering problem-solving based psychotherapies for people with a history of more than one prior incident of self-directed violence, people with a recent history of self-directed violence, or people with hopelessness and a history of moderate to severe traumatic brain injury (weak recommendation).<sup>1</sup>
- **Pharmacotherapy:** For all patients at risk of suicide, treatment should include management of co-occurring conditions. For people with comorbid major depressive disorder, ketamine infusion was suggested for short-term reduction in suicidal ideation (weak recommendation).<sup>1</sup> Lithium was suggested to reduce the risk of death by suicide as monotherapy in people with bipolar disorder or add-on therapy for people with unipolar depression or bipolar disorder (weak recommendation).<sup>1</sup> For people with comorbid schizophrenia or schizoaffective disorder, clozapine was suggested to reduce risk of death (weak recommendation).<sup>1</sup>
- **Post-acute care:** In addition to usual care after a psychiatric hospitalization, there were weak recommendations to support sending periodic caring communications (e.g., postcards) for 12-24 months, offering home visits to support reengagement for people not presenting for outpatient visits, and offering the World Health Organization brief intervention and contact treatment modality following an ER visit.<sup>1</sup>
- **Technology-based treatments:** There was insufficient evidence to recommend for or against self-directed or provider-driven technology-based, virtual interventions.<sup>1</sup>
- **Population/community-based interventions:** They suggest reducing access to lethal means to decrease suicide rates at a population level (weak recommendation). There was insufficient data to recommend for or against other community-based interventions.<sup>1</sup>

Recommendations for pharmacotherapy were based on the following evidence:

- **Ketamine:** Evidence for this recommendation was based on a meta-analysis of trials evaluating intravenous ketamine infusion which report that 55% of patients at 24 hours post-infusion and 66% of patients at 7 days post-infusion reported no suicidal ideation (moderate quality evidence).<sup>1</sup> Trials were primarily based in the inpatient hospital setting, and there is limited long-term evidence following discharge.<sup>1</sup> Repeated administration is not recommended because of the potential risk of addiction and known dissociative effects which may exacerbate psychotic symptoms.<sup>1</sup> Authors found no data to support ketamine’s effect on suicide attempts or deaths.<sup>1</sup>

- **Lithium:** Recommendations for lithium were based on several cohort studies and systematic reviews which demonstrated reduced suicidal behavior and deaths associated with lithium in patients with bipolar depression.<sup>1</sup> Despite these benefits, discontinuations due to adverse events contributed to large variation in adherence across studies.<sup>1</sup> Adverse events related to discontinuations included gastrointestinal effects, polyuria, polydipsia, weight gain, hypothyroidism, and leukocytosis. Lithium has a low therapeutic index and caution is recommended in elderly people and people with comorbidities (e.g, seizure disorders and chronic kidney disease).<sup>1</sup>
- **Clozapine:** Evidence from systemic reviews and meta-analyses show that clozapine can lower death by suicide, suicide attempts, and suicidal behaviors with long-term treatment.<sup>1</sup> While evidence is most favorable for clozapine, evidence suggests that any antipsychotic may protect against suicide risk.<sup>1</sup> Clozapine is only available through a Risk Evaluation and Mitigation Strategy (REMS) program which mandates frequent follow-up visits to monitor for adverse events.<sup>1</sup>

### **New Indications:**

In July 2020, esketamine nasal spray received an expanded indication for depressive symptoms in adults (18-64 years of age) with MDD and acute suicidal ideation or behavior. Esketamine was previously approved for treatment-resistant depression. Approval was based on 2 identical, double-blind, 4-week, multicenter RCTs in adults (ASPIRE I and II).<sup>3</sup> These trials enrolled a total of 456 patients (n=226 in ASPIRE I and n=230 in ASPIRE II) from the United States, Europe, Asia, South Africa, South America, and Canada.<sup>2,3</sup> Participants had a diagnosis of MDD without psychotic features, suicidal ideation within the 24 hours prior to randomization with need for hospitalization due to imminent suicide risk, and a MADRS score greater than 28 indicating at least moderate depression.<sup>2,3</sup> Imminent suicide risk was defined based on affirmative answers to the Mini-International Neuropsychiatric Interview questions B3 (“Did you think about suicide [killing yourself]?”) and B10 (“Intend to act on thoughts of killing yourself in the past 24 hours?”) upon screening in the emergency department or on inpatient psychiatric admission.<sup>2</sup> Patients received comprehensive standard of care treatment including an initial 5 to 14 day hospitalization in a psychiatric unit.<sup>2,3</sup> Esketamine, administered twice weekly, was initiated upon enrollment with standard antidepressant optimization during the first 2 weeks of each trial.<sup>2,3</sup> Pharmacotherapy standards of care could include either antidepressant monotherapy or an antidepressant plus augmentation therapy (second antidepressant, atypical antipsychotic or mood stabilizer).<sup>2</sup> Patients with clinically significant comorbidities were excluded from the studies (e.g., bipolar disorder, obsessive compulsive disorder [OCD], personality disorder, moderate to severe substance use disorder, psychotic disorder, renal or liver insufficiency, uncontrolled hypertension, history of malignancy, or clinically significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic or metabolic disease).<sup>2,3</sup> The primary endpoint was change in depressive symptom severity evaluated with the MADRS score from baseline to 24 hours.<sup>2,3</sup> The key secondary outcome was symptom severity using the Clinical Global Impression of Severity of Suicidality - Revised scale (CGI-SS-r; range 0 to 6) which is a one-item, clinician-rated assessment of suicide severity.<sup>2,3</sup>

Overall, 78-89% of patients receiving esketamine and 82-83 % of patients receiving placebo completed 4 weeks of treatment, and about 72% of patients in each study completed the 90 day follow-up.<sup>2,3</sup> Baseline mean MADRS score was 40-41 indicating severe depressive symptoms, clinician-rated suicidality based on CGI-SS-r was moderate to extremely suicidal for 90-91% of patients.<sup>2,3</sup> Over 60% of patients in each study had a prior suicide attempt. In ASPIRE I, 28% had a recent attempt in the past month.<sup>2</sup> Common therapy included venlafaxine, escitalopram, duloxetine, quetiapine (as adjunct therapy), mirtazapine, and sertraline.<sup>2,3</sup> On average, an antidepressant plus oral augmentation therapy was prescribed to 45% and 61% of people in ASPIRE I and II, respectively. About 67-75% of patients received concomitant benzodiazepines, though use was not permitted within 8 hours of esketamine dosing.<sup>2,3</sup> Most baseline characteristics were balanced between groups. However, in ASPIRE I, more males were randomized to esketamine compared to placebo (42% vs. 34%) and a slightly higher proportion of patients randomized to esketamine were prescribed antidepressant plus oral augmentation therapy compared to placebo (47% vs. 42%).<sup>2</sup> In ASPRE II, the proportion of patients with a recent suicide attempt within the past 28 days at baseline differed between groups with more patients in the esketamine group

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with a recent suicide (31.6%) compared to placebo (21.2%).<sup>3</sup> A prior suicide attempt is a known risk factor for subsequent attempts which may indicate that patients randomized to treatment had more severe suicidality than those given placebo.

There was a substantial difference in MADRS from baseline to 24 hours for both esketamine and placebo groups. Patients given esketamine had mean improvements in MADRS of 16.4 (SD 11.95) and 15.7 (SD 11.56) points while patients randomized to placebo improved by 12.8 (SD 10.73) and 12.4 (SD 10.43) points in each study.<sup>2,3</sup> The mean difference from placebo at 24 hours was -3.8 (95% CI -6.56 to -1.09) and -3.9 (95% CI -6.6 to -1.11) for ASPIRE I and II, respectively. A 2-point change in MADRS may correspond with clinically meaningful improvements in symptoms. The difference from placebo was maintained at 4 weeks. Both placebo and esketamine groups had a decrease in acute suicidality (median 1 point improvement on CGI-SS-r from baseline to 24 hours), and there was no statistical difference compared to placebo indicating that hospitalization and standard therapy had a greater impact on acute suicidality than esketamine.<sup>2,3</sup> In general, subgroup analyses for the primary outcome based on baseline MADRS score, prior suicide attempts, oral antidepressant therapy, sex and age showed similar treatment effects.<sup>2,3</sup>

The overall rate of suicide attempts during and after the study was low compared to current epidemiological data which authors attribute to the comprehensive clinical care and frequent follow-up required as part of the study. The mean length of hospital stay in ASPIRE II was 21.6 days (SD 20.6) for patients receiving esketamine and 19.1 days (SD 19.6) for placebo indicating that the majority of the trial occurred during an inpatient stay.<sup>3</sup> Hospital duration was not reported in ASPIRE I. Psychotherapy was permitted, but less than 5% of patients received psychotherapy during the 4-week treatment phase.<sup>3</sup>

Nineteen percent (n=21) and 11% (n=13) of patients had a dose reduction due to intolerance in ASPIRE I and II, respectively.<sup>2,3</sup> In total, suicide-related adverse events (including suicidal ideation) occurred in 12 patients in the 4-week treatment period and were generally balanced between groups.<sup>2,3</sup> Eight suicide attempts occurred during therapy (4 in each group) on treatment.<sup>2,3</sup> During the 90 day follow-up period while on standard therapy, 10 patients had suicide attempts (7 with prior esketamine and 3 with prior placebo) during the follow-up period.<sup>2,3</sup> One patient, previously randomized to esketamine, completed suicide.<sup>2</sup> In most cases, patients with a suicide attempt after enrollment also had an attempt prior to enrollment.<sup>2,3</sup>

In these studies, depression symptoms (evaluated with MADRS score) were improved with esketamine compared to placebo. However, there is no evidence to suggest that esketamine decreases suicidal thoughts, suicide attempts, hospitalizations, or hospital length-of-stay in patients with MDD and risk for suicide. These studies evaluated inpatient initiation of esketamine, and there is limited applicability to outpatient treatment. Both groups had a decrease in acute suicidality with no difference from placebo indicating that standard therapy, including hospitalization and greater clinical follow-up, likely continues to be the most effective treatment for suicidal symptoms.

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## References:

1. VA/DOD Clinical Practice Guideline for the Assessment and Management of Patients at Risk for Suicide. May 2019. Available at: <https://www.healthquality.va.gov/guidelines/MH/srb/VADoDSuicideRiskFullCPGFinal5088212019.pdf>. Accessed December 29, 2023.
2. Fu D-J, Ionescu DF, Li X, et al. Esketamine Nasal Spray for Rapid Reduction of Major Depressive Disorder Symptoms in Patients Who Have Active Suicidal Ideation With Intent: Double-Blind, Randomized Study (ASPIRE I). *The Journal of clinical psychiatry*. 2020;81(3).
3. Ionescu DF, Fu DJ, Qiu X, et al. Esketamine Nasal Spray for Rapid Reduction of Depressive Symptoms in Patients with Major Depressive Disorder Who Have Active Suicide Ideation with Intent: Results of a Phase 3, Double-Blind, Randomized Study (ASPIRE II). *Int J Neuropsychopharmacol*. 2020.
4. Aripiprazole (Abilify): Depression, Major Depressive Disorder (MDD) [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2016 Nov. APPENDIX 5, VALIDITY OF OUTCOME MEASURES. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK409740/> Accessed December 2, 2020.
5. DynaMed. Suicidal Ideation and Behavior. EBSCO Information Services. Accessed January 2, 2024. <https://www-dynamed-com.liboff.ohsu.edu/condition/suicidal-ideation-and-behavior>.

## Appendix 1: Prescribing Information Highlights

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SPRAVATO® safely and effectively. See full prescribing information for SPRAVATO®.

SPRAVATO® (esketamine) nasal spray, CIII

Initial U.S. Approval: 1970 (ketamine)

#### WARNING: SEDATION; DISSOCIATION; ABUSE AND MISUSE; and SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- Risk for sedation and dissociation after administration. Monitor patients for at least two hours after administration. (5.1, 5.2)
- Potential for abuse and misuse. Consider the risks and benefits of prescribing SPRAVATO prior to using in patients at higher risk of abuse. Monitor patients for signs and symptoms of abuse and misuse. (5.3)
- SPRAVATO is only available through a restricted program called the SPRAVATO REMS. (5.4)
- Increased risk of suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. SPRAVATO is not approved for use in pediatric patients. (5.5)

#### RECENT MAJOR CHANGES

Indications and Usage (1)	07/2020
Dosage and Administration (2.3, 2.6)	07/2020
Warnings and Precautions (5.1, 5.2, 5.4, 5.6)	07/2020

#### INDICATIONS AND USAGE

SPRAVATO® is a non-competitive *N*-methyl *D*-aspartate (NMDA) receptor antagonist indicated, in conjunction with an oral antidepressant, for the treatment of:

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

#### 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 an initial dose of SPRAVATO. (1)
- SPRAVATO is not approved as an anesthetic agent. The safety and effectiveness of SPRAVATO as an anesthetic agent have not been established. (1)

#### DOSAGE AND ADMINISTRATION

- Administer SPRAVATO intranasally under the supervision of a healthcare provider. (2.1)

- Assess blood pressure prior to and after administration. (2.1)
- TRD: Evidence of therapeutic benefit should be evaluated at the end of the 4-week induction phase to determine need for continued treatment. (2.2)
- Depressive symptoms in MDD with acute suicidal ideation or behavior: Evidence of therapeutic benefit should be evaluated after 4 weeks to determine need for continued treatment. Treatment beyond 4 weeks has not been systematically evaluated. (2.3)
- See Full Prescribing Information for recommended dosage. (2.2, 2.3)
- See Full Prescribing Information for important administration instructions. (2.4)

#### DOSAGE FORMS AND STRENGTHS

Nasal Spray: 28 mg of esketamine per device. Each nasal spray device delivers two sprays containing a total of 28 mg of esketamine. (3)

#### CONTRAINDICATIONS

- Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation. (4)
- Intracerebral hemorrhage. (4)
- Hypersensitivity to esketamine, ketamine, or any of the excipients. (4)

#### WARNINGS AND PRECAUTIONS

- *Increases in Blood Pressure*: Patients with cardiovascular and cerebrovascular conditions and risk factors may be at an increased risk of associated adverse effects. (5.6)
- *Cognitive Impairment*: SPRAVATO may impair attention, judgment, thinking, reaction speed and motor skills. (5.7)
- *Impaired Ability to Drive and Operate Machinery*: Do not drive or operate machinery until the next day after a restful sleep. (5.8)
- *Embryo-fetal Toxicity*: May cause fetal harm. Consider pregnancy planning and prevention in females of reproductive potential. (5.10, 8.1, 8.3)

#### ADVERSE REACTIONS

The most commonly observed adverse reactions (incidence  $\geq 5\%$  and at least twice that of placebo plus oral antidepressant):

- TRD: dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk. (6)
- Treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior: dissociation, dizziness, sedation, blood pressure increased, hypoesthesia, vomiting, euphoric mood, and vertigo. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### USE IN SPECIFIC POPULATIONS

- Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 07/2020



## Appendix 2: Key Inclusion Criteria

<b>Population</b>	People with major depressive disorder and suicidal ideation or behavior
<b>Intervention</b>	Esketamine
<b>Comparator</b>	Placebo, another antidepressant, or standard of care
<b>Outcomes</b>	Symptoms of depression or suicidal ideation, function or quality of life, hospitalizations or urgent care visits, attempted or completed suicides, all-cause mortality
<b>Setting</b>	Outpatient treatment

## Appendix 3: Prior Authorization Criteria

### Esketamine (Spravato)

#### Goal(s):

- To ensure safe and appropriate use of esketamine in patients with treatment resistant depression or suicidal ideation.

#### Length of Authorization:

- Up to 6 months

#### Requires PA:

- Esketamine requires a prior authorization approval due to safety concerns (pharmacy and physician administered claims).

#### Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at [www.orpdl.org](http://www.orpdl.org)
- Searchable site for Oregon FFS Drug Class listed at [www.orpdl.org/drugs/](http://www.orpdl.org/drugs/)

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPh. Deny; medical appropriateness
3. Is the request for maintenance dosing of esketamine (for determining response to therapy) OR for continuation after initiation during a recent hospitalization?	<b>Yes:</b> Go to <b>Renewal Criteria</b>	<b>No:</b> Go to #4

<b>Approval Criteria</b>		
4. Is the patient 65 years or older?	<b>Yes:</b> Pass to RPh. Deny; medical appropriateness.	<b>No:</b> Go to #5
5. Is the member currently engaged in or been referred for psychotherapy?	<b>Yes:</b> Go to #6	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
6. Is the patient currently on an FDA approved dose of an oral antidepressant?	<b>Yes:</b> Go to #7	<b>No:</b> Pass to RPh. Deny; medical appropriateness.  Esketamine is indicated for use with an oral antidepressant.
7. Does the patient have treatment resistant depression (failure of two separate antidepressant trials which were each given for at least 6 weeks at therapeutic doses)?	<b>Yes:</b> Go to #10	<b>No:</b> Go to #8
8. Is the request for treatment of major depressive disorder in the setting of acute suicidal ideation or behavior?	<b>Yes:</b> Go to #9	<b>No:</b> Pass to RPh. Deny; medical appropriateness.  Recommend an adequate trial (minimum of 6-8 weeks) of 2 or more antidepressants.
9. Is there a documented plan to optimize oral antidepressant treatment in one of the following ways: a. Titrating the dose of the current antidepressant to a therapeutic level b. Switching to a different antidepressant OR c. Adding oral augmentation therapy (e.g., a second antidepressant, an atypical antipsychotic, or mood stabilizer)?	<b>Yes:</b> Go to #10	<b>No:</b> Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
<p>10. Does the patient have documentation of any of the following:</p> <ul style="list-style-type: none"> <li>• Current Aneurysmal vascular disease or arterial venous malformation OR</li> <li>• History of Intracerebral hemorrhage OR</li> <li>• Current Pregnancy OR</li> <li>• Current Uncontrolled hypertension (e.g., &gt;140/90 mmHg)</li> </ul>	<p><b>Yes:</b> Pass to RPh. Deny; medical appropriateness.</p>	<p><b>No:</b> Approve up to 28 days for induction (either 56 mg and/or 84 mg for titration) not to exceed 24 units total to be covered within the approved time window.</p> <p>The approved time window typically spans 60 days to accommodate scheduling visits.</p>

Renewal Criteria		
<p>1. Is there documentation that the patient demonstrated an adequate response during the 4-week induction phase (an improvement in depressive symptoms)?</p>	<p><b>Yes:</b> Go to #2</p>	<p><b>No:</b> Go to #4</p>
<p>2. Is the request for administration of esketamine once weekly or every 2 weeks?</p>	<p><b>Yes:</b> Go to #3</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness.</p>
<p>3. Has the patient been adherent to oral antidepressant therapy?</p>	<p><b>Yes:</b> Approve for up to 6 months (maximum of 12 per 28 days)</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness.</p>
<p>4. Has the patient been on therapy for at least 4 weeks?</p>	<p><b>Yes:</b> Pass to RPh. Deny; medical appropriateness.</p>	<p><b>No:</b> Approve for completion of induction phase (total 28 days of treatment with a maximum of 24 nasal spray devices (each device contains 28 mg of esketamine))</p>

P&T/DUR Review: 2/24; 12/23 (KS); 2/23, 10/21; 2/21; 7/19  
Implementation: 4/1/24; 1/1/22; 3/1/21; 8/19/19