

**POLICY:** Psychiatry – Spravato™ (esketamine nasal spray – Janssen)

**DATE REVIEWED:** 03/25/2020

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## OVERVIEW

Spravato, a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist, is indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (TRD) in adults.<sup>1</sup> Limitation of Use: Spravato is not approved as an anesthetic agent. The safety and effectiveness of Spravato as an anesthetic agent have not been established. Esketamine, the S-enantiomer of racemic ketamine, is a non-selective, non-competitive antagonist of the NMDA receptor, an ionotropic glutamate receptor. The mechanism by which Spravato exerts its antidepressant effect is unknown.

Spravato should be administered in conjunction with an oral antidepressant.<sup>1</sup> The recommended dose is 56 mg intranasally on Day 1, followed by 56 mg or 84 mg intranasally twice weekly for Weeks 1 to 4. On Weeks 5 to 8, Spravato should be administered once weekly at a dose of 56 mg or 84 mg intranasally. On Week 9 and thereafter, the dosing frequency should be individualized to the least frequent dosing to maintain remission/response (either every 2 weeks or once weekly) at a dose of 56 mg or 84 mg. If a patient misses treatment sessions and there is worsening of depression symptoms, consider returning to the patient's previous dosing schedule (i.e., every two weeks to once weekly, weekly to twice weekly). Spravato must be administered under the direct supervision of a healthcare provider. A treatment session consists of nasal administration of Spravato and post-administration observation under supervision. The nasal spray device delivers a total of 28 mg of esketamine (two sprays of 14 mg each). Do not prime the device before use. Use two devices (56 mg) or three devices (84 mg), with a 5-minute rest between use of each device to allow the medication to absorb. During and after Spravato administration at each treatment session, observe the patient for at least 2 hours until the patient is safe to leave.

## Disease Overview

Major depressive disorder (MDD) is a serious, life-threatening condition with high rates of morbidity and a chronic disease course.<sup>2</sup> Over 17 million people in the US and over 300 million people worldwide have depression.<sup>3,4</sup> For some individuals, MDD can result in severe impairments that interfere with work, relationships, self-care, and in severe cases, may lead to hospitalization or suicide. MDD is considered the leading cause of disability worldwide and is also associated with increased mortality rates. About 30% to 40% of patients with MDD fail to respond to first-line treatments including oral antidepressant medications of all classes (e.g., selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], tricyclic antidepressants [TCAs], bupropion) and/or psychotherapy.<sup>2,5</sup> In addition, the onset of treatment response for these modalities, even when effective, often takes at least four weeks, leading to greater suffering, expense, and risk. For regulatory purposes, the FDA considers patients to have TRD if they have MDD and they have not responded to treatment despite trials of at least two antidepressants given at adequate doses for an adequate duration in the current episode.<sup>2</sup>

The available treatments for TRD are limited.<sup>2</sup> Prior to the approval of Spravato, only one medication was FDA-approved for TRD, Symbyax® (olanzapine and fluoxetine capsules). Symbyax is indicated for treatment-resistant depression (major depressive disorder [MDD]) in patients who do not respond to

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two separate trials of different antidepressants of adequate dose and duration in the current episode) and acute depressive episodes in bipolar I disorder.<sup>6</sup> The only other FDA-approved interventions for TRD are device related and include electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and vagus nerve stimulator (VNS).<sup>2</sup> These treatments can be associated with significant adverse events and interventional concerns, such as the use of general anesthesia, seizure induction, and memory loss with ECT; or surgical intervention and infection risk with VNS implantation. Additionally, TMS is associated with inconvenient daily office visits.

### **Guidelines**

According to the American Psychiatric Association (APA) practice guideline for the treatment of patients with MDD (2010), the effectiveness of antidepressants is generally comparable between classes and within classes.<sup>7</sup> Therefore, the initial selection of antidepressant will largely be based on the anticipated side effects, the safety or tolerability of these side effects for the individual patient, pharmacological properties of the medication (e.g., half-life, drug interactions), and additional factors such as medication response in prior episodes, cost, and patient preference. In patients with depression who either have not responded or have had trouble tolerating one SSRI agent, a trial of another SSRI (or another antidepressant) may be effective and/or better tolerated. Patients who have had a partial response to antidepressant monotherapy can be augmented with another antidepressant from a different pharmacological class or with another non-antidepressant medication, such as lithium, thyroid hormone, an anticonvulsant, a psychostimulant, or an atypical antipsychotic.

### **Abuse and Misuse**

Spravato contains esketamine, a Schedule III controlled substance (CIII), which may be subject to abuse and diversion. Assess each patient's risk for abuse or misuse prior to prescribing Spravato. All patients receiving Spravato should be monitored for the development of these behaviors or conditions, including drug-seeking behavior, while on therapy. Patients with a history of drug abuse or dependence are at greater risk. Careful consideration should be given prior to prescribing Spravato to individuals with a history of substance use disorder.

### **Safety**

Spravato is contraindicated in patients with aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels) or arteriovenous malformation; history of intracerebral hemorrhage; or hypersensitivity to esketamine, ketamine, or any of the excipients.<sup>1</sup> Spravato labeling includes a Boxed Warning regarding sedation, dissociation, abuse and misuse, and suicidal thoughts and behaviors in pediatric and young adult patients.

Because of the risks of serious adverse outcomes resulting from sedation, dissociation, and abuse and misuse, Spravato is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS).<sup>1</sup> Healthcare settings must be certified in the program and ensure that Spravato is only dispensed in healthcare settings and administered to patients who are enrolled in the program, administered by patients under the direct observation of a healthcare provider, and that patients are monitored by a healthcare provider for at least 2 hours after administration of Spravato. Pharmacies must be certified in the REMS and must only dispense Spravato to healthcare settings that are certified in the program.

### **POLICY STATEMENT**

Prior authorization is recommended for medical benefit coverage of Spravato. Because of the specialized skills required for evaluation and diagnosis of patients treated with Spravato as well as the monitoring required for adverse events and long-term efficacy, approval requires Spravato to be prescribed by or in consultation with a physician who specializes in the condition being treated. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

### **RECOMMENDED AUTHORIZATION CRITERIA**

Coverage of Spravato is recommended in those who meet the following criteria:

#### **FDA-Approved Indications**

- 1. Treatment-Resistant Depression.** Approve for 6 months if the patient meets the following criteria (A, B, C, D, E, and F):
  - A)** Patient is  $\geq 18$  years of age; AND
  - B)** Patient has demonstrated nonresponse ( $\leq 25\%$  improvement in depression symptoms or scores) to at least two different antidepressants, each from a different pharmacologic class (e.g., selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], tricyclic antidepressants [TCAs], bupropion, mirtazapine, etc.) and each used at therapeutic dosages for at least 6 weeks in the current episode of depression, according to the prescribing physician; AND
  - C)** Patient is concomitantly receiving at least one oral antidepressant; AND
  - D)** Patient has one of the following (i or ii):
    - i.** No history of psychosis; OR
    - ii.** History of psychosis and the prescriber believes that the benefits of Spravato outweigh the risks; AND
  - E)** The patient's history of controlled substance prescriptions has been checked using the state prescription drug monitoring program (PDMP), unless unavailable in the state (see note below), according to the prescribing physician; AND
  - F)** Spravato is being prescribed by a psychiatrist.

Note: Antidepressants may include, but are not limited to, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), mirtazapine, and bupropion.

Note: As of 03/25/2020, the state of Missouri is the only state in the US that does not have a PDMP program in place.

**Dosing.** Approve the following dosing regimen (A, B, and C):

- A)** Maximum single dose: 84 mg intranasally; AND
  - B)** Induction phase (Weeks 1 to 4): twice weekly dosing; AND
  - C)** Maintenance phase (Weeks 5 and after): up to once weekly dosing.
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**CONDITIONS NOT RECOMMENDED FOR APPROVAL**

Spravato has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

**REFERENCES**

1. Spravato™ nasal spray [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; February 2020.
2. FDA briefing document for Spravato. Psychopharmacologic Drugs Advisory Committee (PDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee Meeting on February 12, 2019. Available at: <https://www.fda.gov/advisory-committees/february-12-2019-joint-meeting-psychopharmacologic-drugs-advisory-committee-pdac-and-drug-safety-and>. Accessed on March 20, 2020.
3. National Institute of Mental Health. Major Depression. Last updated: February 2019. Available at: <https://www.nimh.nih.gov/health/statistics/major-depression.shtml>. Accessed on March 20, 2020.
4. Depression and Other Common Mental Disorders: Global Health Estimates. Geneva: World Health Organization; 2017. Available at: <https://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf;jsessionid=A566BCE2138CF7D2CA9F1E283F2F4E71?sequence=1>. Accessed on March 20, 2020.
5. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR\*D report. *Am J Psychiatry*. 2006;163(11):1905-17.
6. Gelenberg A, Freeman MP, Markowitz JC, et al. Practice guideline for the treatment of patients with major depressive disorder, third edition. American Psychiatric Association, November 2010. Available at: [http://www.psychiatryonline.com/pracGuide/pracGuideTopic\\_7.aspx](http://www.psychiatryonline.com/pracGuide/pracGuideTopic_7.aspx). Accessed on March 20, 2020.
7. Symbyax® capsules [prescribing information]. Indianapolis, IN: Lilly USA, LLC; March 2018.

**HISTORY**

| Type of Revision  | Summary of Changes  | Date Reviewed |
|-------------------|---|---------------|
| New Policy        | --  | 03/11/2019    |
| Selected revision | Addition of the following language to the criterion requiring trials of two different antidepressants: each from a different pharmacologic class (e.g., selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], tricyclic antidepressants [TCAs], bupropion, mirtazapine, etc.). No other changes to criteria. | 03/20/2019    |
| Annual revision   | No change to criteria.  | 03/25/2020    |