

# SPRAVATO™ (ESKETAMINE)

Policy Number: PHARMACY 318.1 T2

Effective Date: May 1, 2019

[Instructions for Use](#) ⓘ

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## Related Policy

- [Review at Launch for New to Market Medications](#)

## CONDITIONS OF COVERAGE

Applicable Lines of Business/Products	This policy applies to Oxford Commercial plan membership.
Benefit Type	General Benefits Package <sup>2</sup> , Pharmacy <sup>3</sup>
Referral Required (Does not apply to non-gatekeeper products)	No
Authorization Required (Precertification always required for inpatient admission)	No <sup>1</sup>
Precertification with Medical Director Review Required	No <sup>1</sup>
Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required)	All
Special Considerations	<p><sup>1</sup>Precertification is not required, however it is strongly recommended for this medication. While no penalty will be imposed for failure to request a pre-service review, if one is not requested, a medical necessity review will be conducted post-service to determine coverage. It is the referring physician’s responsibility to provide medical documentation to demonstrate clinical necessity for the medication. As of <b>Oct. 1, 2019</b>, precertification <b>will</b> be required. Refer to the policy titled <a href="#">Review at Launch for New to Market Medications</a>.</p> <p><sup>2</sup>Spravato must be administered in the presence of a certified healthcare provider and is covered under the medical benefit.</p> <p><sup>3</sup>If a retail pharmacy meets the REMS requirement and dispenses the drug directly to the administering provider, Spravato would be covered under the pharmacy benefit.</p>

## COVERAGE RATIONALE

### **Spravato (Esketamine) Nasal Spray**

**Spravato is proven and/or medically necessary for the treatment of treatment-resistant depression (TRD) when ALL of the following criteria are met:**

### **Initial Therapy**

- Diagnosis for major depressive disorder (MDD) according to the current DSM (i.e., DSM-5), by a mental health professional; **and**
- Patient has not experienced a clinically meaningful improvement after treatment with at least **two** different antidepressants of adequate dose, duration (at least 6 weeks), and adherence in the current depressive episode (**Must document medications, doses, and durations**); **and**
- Patient is to receive Spravato therapy in conjunction with another oral antidepressant; **and**
- Provider and/or the provider's healthcare setting is certified in the Spravato REMS program; **and**
- Spravato dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
- Initial authorization will be for no longer than 12 weeks.

### **Continuation Therapy**

- Patient has previously been treated with Spravato; **and**
- Documentation demonstrating a positive clinical response from baseline (e.g., improved Montgomery-Asberg Depression Rating Scale [MADRS], clinical remission, response, etc.), as defined by the provider; **and**
- Patient is to receive Spravato therapy in conjunction with another oral antidepressant; **and**
- Provider and/or the provider's healthcare setting is certified in the Spravato REMS program; **and**
- Spravato dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
- Authorization will be for no longer than 6 months.

### **Spravato is unproven and not medically necessary for the following:**

- Anesthetic agent
- Chronic pain (including but not limited to nonmalignant pain, Fibromyalgia, neuropathic pain, Complex Regional Pain Syndrome, Reflex Sympathetic Dystrophy)
- Migraine headaches

## **U.S. FOOD AND DRUG ADMINISTRATION (FDA)**

Spravato (esketamine) 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. Spravato is not approved as an anesthetic agent. The safety and effectiveness of Spravato as an anesthetic agent have not been established.<sup>1</sup>

Spravato is available only through a restricted program under a REMS called the Spravato REMS because of the risks of serious adverse outcomes from sedation, dissociation, and abuse and misuse.

Important requirements of the Spravato REMS include the following:<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 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.

Further information, including a list of certified pharmacies is available at <http://www.Spravatorems.com> or 1-855-382-6022.

## **BACKGROUND**

Major depressive disorder (MDD) is a serious and life-threatening condition with high rates of individual and society-level morbidity, and a chronic disease course. Over 16 million people in the United States and over 300 million people worldwide have depression. Patients with MDD may be unable to work, maintain relationships, attend to self-care, and in the most severe cases may become hospitalized or attempt or commit suicide.<sup>3-4</sup> MDD is considered the leading cause of disability worldwide and also is associated with increased mortality rates (at a median rate of 10 years of life lost).<sup>5</sup> About 30 to 40% of patients with MDD fail to respond to first-line treatments including oral antidepressant medications of all classes (selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), etc.) and/or psychotherapy.<sup>6</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.

Patients who have failed at least two trials of antidepressant treatment generally comprise the population with treatment-resistant depression (TRD). Relative to other patients with MDD, patients with TRD can incur even more severe morbidity, with higher rates of hospitalization, suicidal ideation and behavior, and medical complications.

Standard of care measures for TRD include switching to a different antidepressant (of either the same or a different class), adding an adjunctive treatment to an ongoing antidepressant (typically a drug with a different mechanism of action), adding or switching psychotherapy, or referral for a procedure such as electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS).<sup>7</sup>

Spravato (esketamine) is the S-enantiomer of racemic ketamine, and is a non-selective, non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor. The mechanism by which esketamine exerts its antidepressant effect is unknown.<sup>1</sup>

## APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies may apply.

HCPCS Code	Description
J3490	Unclassified drugs

ICD-10 Diagnosis Code	Description
F32.0	Major depressive disorder, single episode, mild
F32.1	Major depressive disorder, single episode, moderate
F32.2	Major depressive disorder, single episode, severe without psychotic features
F32.3	Major depressive disorder, single episode, severe with psychotic features
F32.4	Major depressive disorder, single episode, in partial remission
F32.5	Major depressive disorder, single episode, in full remission
F32.81	Premenstrual dysphoric disorder
F32.89	Other specified depressive episodes
F32.9	Major depressive disorder, single episode, unspecified
F33.0	Major depressive disorder, recurrent, mild
F33.1	Major depressive disorder, recurrent, moderate
F33.2	Major depressive disorder, recurrent severe without psychotic features
F33.3	Major depressive disorder, recurrent, severe with psychotic symptoms
F33.40	Major depressive disorder, recurrent, in remission, unspecified
F33.41	Major depressive disorder, recurrent, in partial remission
F33.42	Major depressive disorder, recurrent, in full remission
F33.8	Other recurrent depressive disorders
F33.9	Major depressive disorder, recurrent, unspecified

## CLINICAL EVIDENCE

### Psychiatric Disorders

#### ***Esketamine***

Esketamine is indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (TRD) in adults. Spravato is not approved as an anesthetic agent. The safety and effectiveness of Spravato as an anesthetic agent have not been established.<sup>1</sup>

The safety and efficacy of esketamine was examined in four phase 3 international randomized controlled trials comparing intranasal esketamine and intranasal placebo. Three studies were of similar short-term parallel group design, and one was a randomized withdrawal maintenance-of-effect design. The majority of subjects in all the studies were women in their 40s and 50s, white, with higher body mass index (BMI >24). Depending on the study, around 33 to 40% of enrolled subjects had failed three or more antidepressant (AD) treatments by the start of screening, and 12 to 17% had failed at least four. Each treatment was added to one of four newly initiated oral antidepressants (duloxetine, venlafaxine XR, escitalopram, or sertraline), each dosed daily beginning at the start of the treatment phase. For the first 4 weeks of treatment, the nasal spray was administered twice weekly. For the

maintenance-of-effect study and for long-term open-label safety studies, the nasal spray was administered weekly for the next 4 weeks post-induction phase, then either weekly or every other week for ongoing maintenance.<sup>7</sup>

The primary outcome measure used for the studies was the Montgomery-Asberg Depression Rating Scale (MADRS). To decrease the introduction of bias, all MADRS score evaluations were performed by independent, remote (via telephone), blinded raters. Scales were administered on study visit days prior to intranasal esketamine (or placebo) dosing and with a few exceptions (shorter-term secondary endpoints) were meant to assess symptoms over the previous 7 days. Baseline mean MADRS total scores for 3 of the studies ranged from 37 to 38 and for the geriatric study, the mean was 35. These baseline mean scores indicate greater illness severity for the treatment population in the esketamine phase 3 studies than is typical for MDD development programs.<sup>7</sup>

The key inclusion criteria involved the definition of TRD for the patients included: Patients were required to meet DSM-5 diagnostic criteria for recurrent MDD or single-episode MDD (duration  $\geq$  2years) without psychotic features, which was verified by the structured Mini International Neuropsychiatric Interview (MINI).<sup>8</sup> Patients must have been experiencing moderate to severe depressive symptomatology based on specified scores of the Inventory of Depressive Symptomatology-Clinician rated, 30-item (ICD-C30), and MADRS at Weeks 1, 2, and 4 of the screening/observational phase. In all controlled phase 3 studies, treatment resistance was defined in accordance with the regulatory definition, i.e., a lack of clinically meaningful improvement (defined for phase 3 studies as  $\leq$ 25%) in the current episode of depression after treatment with at least 2 different antidepressant (AD) agents prescribed in adequate dosages for an adequate duration (defined for phase 3 studies as at least 6 weeks).<sup>7</sup>

In two studies (one parallel-group study and the randomized withdrawal study), esketamine was statistically superior to placebo on the study's primary efficacy endpoint; in the other two short-term parallel group studies, esketamine was not. In the study, TRANSFORM-2, patients in the esketamine treatment group experienced statistically significantly greater improvement in depressive symptoms, as measured by the CFB to endpoint in the MADRS, than patients in the placebo group. On the MADRS, the mean difference between esketamine and placebo was statistically significant at most time points throughout the 28 days of double-blind treatment (except Day 15). In the SUSTAIN-1, trial, direct entry patients or from TRANSFORM-1 or TRANSFORM-2, were enrolled. All subjects who experienced  $\geq$ 50% reduction from baseline in MADRS total score by the end of acute 4-week treatment were eligible to enter the optimization phase, where they received at least 12 weeks of open-label esketamine treatment with oral antidepressant ongoing. There was a statistically significant difference in time to relapse of depression favoring those patients randomized to continue esketamine versus those who were switched to placebo (with oral antidepressant ongoing in both arms) in the stable remitters group. The secondary endpoint of time to relapse in the stable responders group was also statistically significant.<sup>7</sup>

## REFERENCES

The foregoing Oxford policy has been adapted from an existing UnitedHealthcare Pharmacy, Clinical Pharmacy Program that was researched, developed and approved by the UnitedHealth Group National Pharmacy & Therapeutics Committee. [2019D0069C]

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## POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
05/01/2019	• New policy

## INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting UnitedHealthcare Oxford standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare Oxford reserves the right to modify its Policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice.

The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Oxford Clinical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.