Spravato® (Esketamine)

Policy Number: PHARMACY 318.9 T2
Effective Date: June 1, 2021

Coverage Rationale

This policy refers to the following ketamine products:
- Spravato (esketamine)

Spravato (Esketamine) Nasal Spray
Spravato is proven for the treatment of treatment-resistant depression (TRD) when all of the following criteria are met:

Initial Therapy
- Diagnosis of major depressive disorder (treatment-resistant) 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 of 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
- Reauthorization will be for no longer than 6 months.
Spravato is medically necessary for the treatment of treatment-resistant depression (TRD) when all of the following criteria are met:

### Initial Therapy
- Diagnosis of major depressive disorder (treatment-resistant), according to the current DSM (i.e., DSM-5), by a mental health professional; and
- Prescribed by or in consultation with a psychiatrist; and
- Submission of medical records (e.g., chart notes, laboratory values) documenting baseline scoring (prior to starting Spravato) on at least one of the following clinical assessments has been completed:
  - Baseline score on the 17-item *Hamilton Rating Scale for Depression (HAMD17)*
  - Baseline score on the 16-item *Quick Inventory of Depressive Symptomatology (QIDS-C16)*
  - Baseline score on the 10-item *Montgomery-Asberg Depression Rating Scale (MADRS)*
- Patient has not experienced a clinically meaningful improvement after treatment with at least three different antidepressants or treatment regimens of adequate dose (maximally tolerated), duration (at least 8 weeks), and adherence in the current depressive episode
  - An antidepressant or treatment regimen would include any of the following classes or combinations (document medication, dose, and duration):
    - Selective serotonin reuptake inhibitors (e.g., citalopram, fluoxetine, paroxetine, sertraline)
    - Serotonin norepinephrine reuptake inhibitors (e.g., duloxetine, venlafaxine, etc.)
    - Bupropion
    - Tricyclic antidepressants (e.g., amitriptyline, clomipramine, nortriptyline, etc.)
    - Mirtazapine
    - Monoamine oxidase inhibitors (e.g., selegiline, tranylcypromine, etc.)
    - Serotonin modulators (e.g., nefazodone, trazodone, etc.)
    - Augmentation with lithium, Cytomel (liothyronine), antipsychotics, or anticonvulsants
- Spravato will be initiated at the same time the member starts a new daily oral antidepressant (one that has not previously been tried); 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 (FDA) approved labeling; and
- Initial authorization will be for no longer than 12 weeks.

### Continuation of Therapy
- Patient has previously been treated with Spravato; and
- Documentation of remission or a positive clinical response to Spravato; and
- Submission of medical records (e.g., chart notes, laboratory values) documenting baseline and recent (within the last month) scoring on at least one of the following assessments demonstrating remission or clinical response (e.g., score reduction from baseline) as defined by the:
  - *Hamilton Rating Scale for Depression (HAMD17)*, remission defined as a score of ≤7
  - *Quick Inventory of Depressive Symptomatology (QIDS-C16)*, remission defined as a score of ≤5
  - *Montgomery-Asberg Depression Rating Scale (MADRS)*, remission defined as a score of ≤12
- Patient is to receive Spravato therapy in conjunction with an oral antidepressant; and
- Provider and/or the provider’s healthcare setting is certified in the Spravato REMS program; and
- Prescribed by or in consultation with a psychiatrist; and
- Spravato dosing is in accordance with the United States FDA approved labeling, not to exceed 84 mg (3 devices) per week; and
- Reauthorization will be for no longer than 6 months.

Spravato is proven for the treatment of depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior when all of the following criteria are met:
**Initial Therapy**

- Diagnosis for major depressive disorder according to the current DSM (i.e., DSM-5), by a mental health professional; and
- Patient is experiencing an acute suicidal ideation or behavior; 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 4 weeks.

Spravato is medically necessary for the treatment of depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior when all of the following criteria are met:

**Initial Therapy**

- Diagnosis for major depressive disorder according to the current DSM (i.e., DSM-5), by a mental health professional; and
- Patient is experiencing an acute suicidal ideation or behavior; and
- Patient is to receive Spravato therapy in conjunction with a newly initiated or optimized 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 4 weeks.

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

**Prior Authorization Requirements**

Prior authorization is required in all sites of service.

Notes:

- Participating providers in the office setting: Prior authorization is required for services performed in the office of a participating provider.
- Non-participating/out-of-network providers in the office setting: Prior authorization is not required but is encouraged for out-of-network services. If prior authorization is not obtained, Oxford will review for out-of-network benefits and medical necessity after the service is rendered.
- Spravato must be administered in the presence of a certified healthcare provider and is covered under the medical benefit.
- 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.

**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.

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<tr>
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<th>Description</th>
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<tr>
<td>J3490</td>
<td>Unclassified drugs</td>
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<tr>
<td>S0013</td>
<td>Esketamine, nasal spray, 1 mg</td>
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<table>
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<tr>
<th>Diagnosis Code</th>
<th>Description</th>
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<tbody>
<tr>
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### 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.\(^\text{16,17}\) 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).\(^\text{18}\) 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.\(^\text{19}\) 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).\(^\text{20}\)

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.\(^\text{14}\)

### Clinical Evidence

#### Chronic Pain

Schwartzman et al conducted a randomized double-blind placebo controlled trial to evaluate the effectiveness of intravenous ketamine in the treatment of complex regional pain syndrome (CRPS).\(^\text{2}\) Patients were evaluated for 2 weeks or longer before treatment and for 3 months after. All subjects received normal saline with or without ketamine intravenously for 4h (25ml/h) daily for 10 days. The results showed that intravenous ketamine administered in an outpatient setting resulted in statistically significant (p<0.05) reductions in many pain parameters. It also showed that subjects in the placebo group did not experience treatment effect in any parameter. The authors conclude that the results of this study warrant a larger randomized placebo controlled trial using higher doses of ketamine and a longer follow-up period.

Noppers et al performed a randomized double blind, active placebo-controlled trial to evaluate the analgesic efficacy of ketamine on fibromyalgia pain.\(^\text{3}\) Twenty-four fibromyalgia patients were randomized to receive either ketamine or the active placebo, midazolam by intravenous infusion. Visual Analogue Pain Scores (VAS) and ketamine plasma samples were collected after the infusion. In addition, an 8 week follow up collected pain scores derived from the fibromyalgia impact questionnaire (FIQ) were collected weekly. Fifteen minutes after infusion completion, the number of patients showing a reduction in pain scores >50% was 8 vs. 3 (P<0.05), at t=180min 6 vs. 2 (ns), at the end of week<1, 2 vs. 0 (ns), and at end of week8, 2 vs. 2 in the ketamine and midazolam groups, respectively. For VAS and FIQ scores no significant differences in treatment effects were

### Diagnosis Code

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<tr>
<td>F33.2</td>
<td>Major depressive disorder, recurrent severe without psychotic features</td>
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<tr>
<td>F33.3</td>
<td>Major depressive disorder, recurrent, severe with psychotic symptoms</td>
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<td>F33.42</td>
<td>Major depressive disorder, recurrent, in full remission</td>
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<tr>
<td>F33.8</td>
<td>Other recurrent depressive disorders</td>
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<td>F33.9</td>
<td>Major depressive disorder, recurrent, unspecified</td>
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</table>
observed in the 2.5-h following infusion or during the 8-week follow-up. Adverse events were mild to moderate in both study groups. The authors conclude that a short-term infusion of ketamine is insufficient to induce long-term analgesic effects in fibromyalgia patients.

Psychiatric Disorders

Esketamine

Esketamine is indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (TRD) in adults. Esketamine is also indicated for depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior. Spravato is not approved as an anesthetic agent. The safety and effectiveness of Spravato as an anesthetic agent have not been established.14

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.20

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.20

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 ≥ 2years) without psychotic features, which was verified by the structured Mini International Neuropsychiatric Interview (MINI).8 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 ≤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).20

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 ≥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.20

In a phase 3, randomized, double-blind, active controlled, multicenter study, Popova et al compared the efficacy and safety of switching patients with treatment-resistant depression from an ineffective antidepressant to a flexible dosed esketamine nasal

Spravato® (Esketamine)
UnitedHealthcare Oxford Clinical Policy

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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. 14

Important requirements of the Spravato REMS include the following:14
- 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 those 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.

Esketamine was evaluated in two identical Phase 3 short-term (4-week) randomized, double-blind, multicenter, placebo controlled studies, ASPIRE I and ASPIRE II, in adults with moderate-to-severe MDD (MADRS total score >28) who had active suicidal ideation and intent. In these studies, patients received treatment with esketamine 84 mg or placebo nasal spray twice weekly for 4 weeks. All patients 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 primary efficacy measure was the change from baseline in the MADRS total score at 24 hours after first dose (Day 2). In ASPIRE I and II, 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 a patient’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 ASPIRE I and II, 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 ASPIRE I and II, 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. 31,32

**U.S. Food and Drug Administration (FDA)**

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

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  - Administered by patients under the direct observation of a healthcare provider and those 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](http://www.Spravatorems.com) or 1-855-382-6022.

## References

The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealth Group National Pharmacy & Therapeutics Committee. [2021D0069IJ]


32. 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), International Journal of Neuropsychopharmacology, pyaa068
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.

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