Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCCNS054.0825	**CENTRAL NERVOUS SYSTEM DRUGS** **SPRAVATO®** (esketamine nasal spray)
Effective Date: 10/1/2025	**Review/Revised Date**: 06/19, 08/19, 5/20, 08/20, 10/20, 07/21, 11/21, 06/22, 07/23, 06/24, 04/25, 06/25 (JWL)
Original Effective Date: 08/19	**P&T Committee Meeting Date**: 06/19, 08/19, 8/20, 12/20, 08/21, 12/21, 08/22, 08/23, 08/24, 04/25, 08/25
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
For initiation of therapy, all the following criteria (1-4) must be met:

1. Confirmed diagnosis of one of the following:
    a. For treatment-resistant depression (TRD), clinical documentation must be provided that outlines the patient evaluation. TRD is defined as use of the following regimens (i and ii) for the current depressive episode:
        i. Inadequate response to at least three oral antidepressants in two different therapeutic classes for at least eight weeks of treatment at a therapeutic dose for major depressive disorder (MDD).
        ii. Inadequate response to augmentation therapy (i.e., two antidepressants with different mechanisms of action used concomitantly or an antidepressant and a second-generation antipsychotic, lithium, thyroid hormone, or anticonvulsant used concomitantly).
    b. For MDD with acute suicidal ideation or behavior, documentation must be provided that patient has current suicidal ideation with intent defined as both of the following:
        i. Patient has thoughts, even momentarily, of self-harm with at least some intent or awareness that they may die as a result, or patient thinks about suicide, and

ii. Patient intends to act on thoughts of killing themselves.

2. Baseline score from one of the following standardized depression rating scales confirming severe depression:
    a. Patient Health Questionnaire-9 (PHQ-9) score of at least 20
    b. Hamilton Depression Scale (HAMD17) score of at least 24
    c. Quick Inventory of Depressive Symptomatology, Clinician-Rated (QIDS-C16) score of at least 16
    d. Montgomery Asberg Depression Rating Scale (MADRS) total score of at least 28
3. For MDD with acute suicidal ideation or behavior: Documentation that esketamine (Spravato®) will be used in combination with oral antidepressant therapy
4. Dosing is in accordance with the United States Food and Drug Administration approved labeling

For patients established on therapy for MDD, **all** the following criteria must be met:
1. Documentation of sustained clinical improvement from baseline in depression symptoms, documented by depression rating scores
2. Dosing is in accordance with the United States Food and Drug Administration approved labeling

Reauthorization requests for MDD with acute suicidal ideation or behavior will not be covered. Patient must meet criteria for initiation of therapy in TRD.

EXCLUSION CRITERIA:
- Concomitant use with ketamine
- Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels) or arteriovenous malformation
- History of intracerebral hemorrhage

AGE RESTRICTIONS:
Approved for 18 years and older

PRESCRIBER RESTRICTIONS:
Prescribed by a psychiatrist or a psychiatric nurse practitioner.

COVERAGE DURATION:
For TRD, initial authorization will be approved for three months. Reauthorization will be approved for six months

For MDD with suicidal ideation or behavior, initial authorization will be approved for four weeks.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Spravato® 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.

FDA APPROVED INDICATIONS:

Spravato® is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist indicated for the treatment of:

- Treatment-resistant depression (TRD) in adults, as monotherapy or in conjunction with an oral antidepressant.
- Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior in conjunction with an oral antidepressant.
- Limitations of Use:
    - The effectiveness in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose
    - This is not approved as an anesthetic agent. The safety and effectiveness as an anesthetic agent have not been established

POSITION STATEMENT:

Major depressive disorder (MDD) is one of the most common mental disorders in the United States. In 2017, the NIH estimated 17 million adults in the United States had at least one major depressive episode. It is estimated that about 30–40% of patients with MDD fail to respond to first-line therapies including oral antidepressants and/or

psychotherapy. To date, effective therapies for treatment resistant depression (TRD) is an unmet medical need.

Although the definition of TRD has not been standardized, the generally accepted definition is based on failure of two trials of antidepressant monotherapy for an adequate duration of therapy and at an adequate dose. This definition is based on data from the Sequenced Treatment Alternatives to Relieve Depression (STAR-D) Study that showed evidence of declining rates of remission as sequential therapies were added in patients not responding to their prior therapy. In this study, 3671 patients with unipolar major depression were treated with up to four sequential trials of antidepressant medication. The rate of remission for the initial and second courses of treatment were comparable (37% and 31%) while the remission rate was substantially lower for patients receiving a third or fourth therapy (14% and 13%).

Esketamine efficacy was established in a 4-week study in 224 adult patients with TRD. Participants were randomized to receive twice weekly doses of intranasal Spravato® or intranasal placebo. All patients also had concomitant treatment with a newly initiated daily oral antidepressant (AD). The primary outcome was change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at the end of the 4-week double-blind induction phase. Statistical superiority of the primary outcome measure vs. placebo (least-squares mean difference: -4.0; 95% CI: -7.3, -0.6) was demonstrated by esketamine.

Long-term efficacy of esketamine was also demonstrated in a long-term, maintenance-of-effect study in adults. Participants were responders in one of two short-term controlled studies or in an open-label direct-enrollment study in an initial 4-week phase. At the completion of 16 weeks of treatment with esketamine and oral AD, stable remitters and stable responders were randomized separately to continue intranasal treatment with esketamine or switch to placebo nasal spray, both groups continued taking their oral AD. The primary outcome was time to relapse in the stable remitter group. Patients in stable remission who continued treatment with esketamine plus oral AD experienced a statistically significant longer time to relapse of depressive symptoms than did patients on placebo nasal spray plus an oral AD (Hazard Ratio [HR]: 0.49; 95% CI: 0.29, 0.84). Time to relapse was also significantly delayed in the stable responder population (HR: 0.30; 95% CI: 0.16, 0.55).

Esketamine efficacy in major depressive disorder with acute suicidal ideation or behaviors was demonstrated in two identical phase 3 trials with 224 and 226 patients, respectively. Participants were randomized to receive treatment with esketamine 84 mg or placebo nasal spray twice weekly for four weeks. All patients were receiving standard of care treatment and at least one antidepressant. The primary efficacy measure was the change from baseline in the MADRS total score at

24 hours after first dose (Day 2). In Study 3 and Study 4, esketamine plus standard of care demonstrated statistical superiority (least square means difference: -3.8; 95% CI -6.56; -1.09 and -3.9; 95% CI -6.60; -1.11) on the primary efficacy measure compared to placebo nasal spray plus standard of care.

Esketamine contains a boxed warning to alert health care professionals and patients about the increased risk of sedation and dissociation, abuse/misuse, and suicidal thoughts and behaviors. In addition, healthcare settings and dispensing pharmacies must be certified in the Spravato® REMS program.

BILLING GUIDELINES AND CODING◊:

If You Buy and Bill for SPRAVATO®	
G2082*	Office or other outpatient visit for the evaluation and management of an established patient that requires the supervision of a physician or other qualified health care professional and provision of up to 56 mg of esketamine nasal self-administration, includes 2 hours post-administration observation
G2083*	Office or other outpatient visit for the evaluation and management of an established patient that requires the supervision of a physician or other qualified health care professional and provision of greater than 56 mg esketamine nasal self-administration, includes 2 hours post-administration observation
Bundled G codes may only be billed when the product is acquired by an office through a specialty distributor. They may not be used if the product is acquired from a specialty pharmacy. ***Buy and Bill is required for Medicare.***	
If You Acquire Spravato® Through a REMS-certified Pharmacy	
Administration Evaluation and Management Only billing:	
99415	Prolonged clinical staff service (the service beyond the highest time in the range of total time of the service) during an evaluation and management service in the office or outpatient setting, direct patient contact with physician supervision; first hour (list separately in addition to code for outpatient E/M service)
99416	Each additional 30 minutes (list separately in addition to code for outpatient E/M service)
99417	Prolonged office or other outpatient E/M service(s) beyond the minimum required time of the primary procedure that has been selected using total time, requiring total time with or without direct patient contact beyond the usual service, on the date of the primary service, each 15 minutes of total time (list separately in addition to codes 99205 or 99215 for office or other outpatient E/M services)

If You are a REMS-certified Pharmacy Billing for SPRAVATO® ONLY	
S0013	Esketamine, nasal spray, 1 mg

◊ Coding/Administration Notes:
• The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
• HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

REFERENCE/RESOURCES:

1. [Spravato] package insert. Titusville, NJ; Janssen Pharmaceuticals; January 2025.
2. A Study to Evaluate the Efficacy, Safety, and Tolerability of Flexible Doses of Intranasal Esketamine Plus an Oral Antidepressant in Adult Participants With Treatment-resistant Depression (TRANSFORM-2). 2019. Retrieved from https://www.clinicaltrials.gov/ct2/show/NCT02418585 (Identification No. NCT02418585).
3. Daly EJ, Trivedi MH, Janik A, et al. Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients With Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA Psychiatry. Published online June 05, 2019.
4. American Psychiatry Association. Practice Guidelines for the Treatment of Patients with Major Depressive Disorder: Third Edition. https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf [Accessed June 30, 2025].
5. Fu DJ, 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). J Clin Psychiatry. 2020 May 12;81(3).