MEDICAL COVERAGE POLICY	
SERVICE:	**Esketamine (Spravato®)**
Policy Number:	**257**
Effective Date:	**07/01/2025**
Last Review:	**06/09/2025**
Next Review:	**06/09/2026**

Important note: *Unless otherwise indicated, medical policies will apply to all lines of business. Medical necessity as defined by this policy does not ensure the benefit is covered. This medical policy does not replace existing federal or state rules and regulations for the applicable service or supply. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan documents. See the member plan specific benefit plan document for a complete description of plan benefits, exclusions, limitations, and conditions of coverage. In the event of a discrepancy, the plan document always supersedes the information in this policy.*

SERVICE: Esketamine (Spravato®)

PRIOR AUTHORIZATION: Required.

POLICY: Please review the plan's EOC (Evidence of Coverage) or Summary Plan Description (SPD) for details.

For Medicare plans, please refer to appropriate Medicare NCD (National Coverage Determination) or LCD (Local Coverage Determination). If there are no applicable NCD or LCD criteria, use the criteria set forth below.

For Medicaid plans, please confirm coverage as outlined in the Texas Medicaid Provider Procedures Manual | TMHP (TMPPM). Texas Mandate HB154 is applicable for Medicaid plans.

BSWHP may consider esketamine (Spravato®) nasal spray medically necessary when documentation is submitted showing the following criteria are met:

Universal criteria:

1) Member has a diagnosis of treatment-resistant depression (TRD); **AND**
2) Member has a confirmed diagnosis of severe major depressive disorder at baseline documented by standardized rating scales (e.g., PHQ9, Beck Depression Scale [BDI], Hamilton Depression Rating Scale [HDRS], Montgomery-Asberg Depression Rating Scale [MADRS], etc.); **AND**
3) Member is 18 years of age or older; **AND**
4) Esketamine is prescribed by or in consultation with a psychiatrist; **AND**
5) Provider attests that all Risk Evaluation and Mitigation Strategy (REMS) requirements have been met; **AND**
6) Member does not have any of the following:
   a) Contraindication to therapy, such as aneurysmal vascular disease, arteriovenous malformation, or history of intracerebral hemorrhage; **OR**
   b) Current or recent history (i.e., within the last 6 months) of moderate or severe substance or alcohol use disorder

Initial requests:

1) Member meets all universal criteria; **AND**

2) Documentation of failure of or intolerance to FOUR medication trials of minimum 6 weeks each for depression within the past five years (examples: four antidepressant agents, including 2 different agent classes; or two antidepressant agents from different agent classes with 2 augmentation trials), during the current depressive episode; **AND**
3) Pharmacotherapy must be in combination with psychotherapy [e.g. cognitive behavioral therapy (CBT) or interpersonal psychotherapy (IPT) or other] weekly for at least 8 weeks of treatment to yield improvement. If no improvement, the clinician should review and reappraise the treatment plan.

Renewal requests:

1) Member meets all universal criteria; **AND**
2) Provider submits documentation of improvement or sustained improvement from baseline in depression symptoms using one of the standardized rating scales above; **AND**
3) Member has manageable or no side effects; **AND**
4) Pharmacotherapy must be in combination with psychotherapy (e.g. CBT or ITP or other) weekly for at least 8 weeks of treatment to yield improvement.

Authorization duration – 6 months

BSWHP considers esketamine for the treatment of all other indications to be experimental and investigational because the effectiveness of this strategy has not been established.

BACKGROUND:

Major depressive disorder (MDD) is a serious and life-threatening condition with high rates of morbidity and a chronic disease course. Over 16 million people in the U.S. and over 300 million people worldwide have depression. The lifetime prevalence of MDD in the U.S. is approximately 20%. 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. MDD is considered the leading cause of disability worldwide and also is associated with increased mortality rates. Approximately 30% to 40% of patients with MDD fail to respond to first-line treatments, including oral antidepressant medications of all classes and/or psychotherapy. In addition, the onset of treatment response for these modalities often takes at least 4 weeks.

Depression with suicidal ideation typically has more severe depressive symptoms and is tougher to treat pharmacologically. In adult patients with MDD the reported prevalence of suicide ideation is as high as 60%. Of that population with suicidal ideation, 10%-20% have a lifetime incidence of attempted suicide and an estimated 3.4% have a lifetime risk of completed suicide. Since the time between suicide ideation and suicide attempt is often very short and the fact that nearly all patients with MDD who attempt or complete suicide have suicidal ideation prior to the event, there is a need for immediate intervention.

Esketamine (S-enantiomer of racemic ketamine) is a nonselective, noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist. The mechanism by which it exerts its antidepressant effect is

unknown. The major circulating metabolite noresketamine demonstrated activity at the same receptor with less affinity

On March 5th, 2019, the United States Food and Drug Administration (FDA) approved Spravato (esketamine nasal spray) for the treatment of treatment-resistant depression (TRD) based on two phase 3 clinical trials. Prior to approval, the FDA granted the esketamine application Breakthrough Therapy designation. TRANSFORM-2 was a randomized, placebo-controlled, double-blind, multicenter, short-term (4-week), phase 3 short-term study in adult patients 18 to <65 years old with treatment-resistant depression (TRD) evaluating change in Montgomery-Asberg Depression Rating Scale (MADRS). Patients who met DSM-5 criteria for MDD and had not adequately responded to two different antidepressants of adequate dose and duration were randomized to receive esketamine or placebo for the first four weeks concurrently with a newly initiated oral antidepressant (AD), referred to as a new AD control. Both groups experienced improvement, but the esketamine group experienced greater improvement in depressive symptoms based on MADRS change in baseline compared to AD control. SUSTAIN-1 was a long-term randomized, double-blind, parallel-group, multicenter maintenance-of-effect study in adults 18 to <65 years of age who were known remitters and responders to esketamine. The intent of the long-term study was to determine how long patients that experienced remission of their depressive symptoms after 16 weeks would maintain their remission with continuation of intranasal esketamine therapy versus patients that received continuation therapy with intranasal placebo. Patients in stable remission who continued treatment with esketamine plus oral AD experienced a statistically significantly longer time to relapse. Time to relapse was also significantly delayed in the stable responder population. These patients experienced a statistically significantly longer time to relapse of depressive symptoms than patients on placebo nasal spray plus oral AD.

On August 3rd, 2020, the FDA approved the expanded use of esketamine for the treatment of MDD with acute suicidal ideation or behavior. While esketamine does reduce depressive symptoms in conjunction with oral antidepressant therapy, there is no evidence that it is proven to prevent suicide or reduce suicidal ideation. In the two identical Phase 3 clinical trials, ASPIRE I and ASPIRE II, the primary outcome examined was change in MADRS scale 24 hours after the first dose. For esketamine plus standard of care MARDS score at 24 hours after the first dose decreased by 15.9 (ASPIRE I) and 16.0 (ASPIRE II) compared to the placebo group decreasing 12.0 (ASPIRE I) and 12.2 (ASPIRE II). However, as stated before, the two trials did not show that the treatment had any superiority over placebo in preventing suicidal ideation. A systemic review and meta-analysis published January 2025 finds esketamine's efficacy as add-on to antidepressants is modest in TRD and absent against suicidality itself.

On January 25, 2025, the FDA approved esketamine as monotherapy for treatment of MDD in adults who have had an inadequate response to at least two oral antidepressants. A randomized, double-blind, placebo-controlled, multicenter study in adult patients with TRD evaluated the efficacy, safety, and tolerability of esketamine as monotherapy. The monotherapy group demonstrated statistical superiority in change from baseline in the MADRS score at Day 28 compared to placebo.

Esketamine (Spravato®) is available only via a Risk Evaluation and Mitigation Strategy (REMS), which requires the following:

- Ensuring that esketamine is only dispensed and administered to patients in a medically supervised healthcare setting that monitors these patients
- Ensuring pharmacies and healthcare settings that dispense esketamine are certified
- Ensuring that each patient is informed about the serious adverse outcomes resulting from sedation and dissociation and need for monitoring
- Enrolling all patients who receive treatment in an outpatient healthcare setting in a registry to further characterize the risks and support safe use
- REMS details can be found of FDA website: https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=386

CODES:

Important note: *Due to the wide range of applicable diagnosis codes and potential changes to codes, an inclusive list may not be presented, but the following codes may apply. Inclusion of a code in this section does not guarantee that it will be reimbursed, and patient must meet the criteria set forth in the policy language.*

CPT Codes:	
HCPCS Codes:	J3490 and C9399 – unclassified drugs or biologicals S0013 - Esketamine, nasal spray, 1 mg
ICD10 codes:	F33.0- F33.9 Major depressive disorder [treatment-resistant depression]
ICD10 Not covered:	

POLICY HISTORY:

Status	Date	Action
New	07/25/2019	New policy
Revised	06/29/2020	Logo and language changed to include FC
Updated	11/19/2020	Updated policy to add new indication and renewal criteria
Updated	04/22/2021	Added Medicaid instructions
Reviewed	04/21/2022	No changes
Reviewed	04/27/2023	No changes
Updated	09/28/2023	Updated Medicare and Medicaid instructions, HCPCS code
Updated	08/12/2024	Applied new format and layout, updated background information
Updated	06/09/2025	Restructured criteria to universal, initial, and renewal sections. Updated criteria to allow for monotherapy in alignment with new FDA indication and specified 6 week trials of medications within past 5 years. Added PHQ9 to list of scales. Added requirement for CBT or IPT or other therapy. Specified criteria for continuation of therapy. Removed criteria for suicidal ideation or behavior. Added authorization duration. Updated background information. Updated ending note sections to align with CMS requirements and business entity changes.
Update	8/11/2025	Removed, Medicare NCD/LCD Interqual statement for clarity.

REFERENCES:

The following scientific references were utilized in the formulation of this medical policy. BSWHP will continue to review clinical evidence related to this policy and may modify it at a later date based upon the evolution of the published clinical evidence. Should additional scientific studies become available, and they are not included in the list, please forward the reference(s) to BSWHP so the information can be reviewed by the Medical Coverage Policy Committee (MCPC) and the Quality Improvement Committee (QIC) to determine if a modification of the policy is in order.

1. Fond G, Loundou A, Rabu C, et al. Ketamine administration in depressive disorders: A systematic review and metaanalysis. Psychopharmacology (Berl). 2014;231(18):3663-3676.
2. U.S. Food and Drug Administration (FDA). Spravato® (esketamine) nasal spray. Prescribing Information. Reference ID: 4399464.
3. Canuso CM, Singh JB, Fedgchin M, et al. Efficacy and Safety of Intranasal Esketamine for the Rapid Reduction of Symptoms of Depression and Suicidality in Patients at Imminent Risk for Suicide: Results of a Double-Blind, Randomized, Placebo-Controlled Study. Am J Psychiatry. 2018;175(7):620-630.
4. Daly EJ, Singh JB, Fedgchin M, et al. Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA Psychiatry. 2018;75(2):139-148.
5. Lapidus KA, Levitch CF, Perez AM, et al. A randomized controlled trial of intranasal ketamine in major depressive disorder. Biol Psychiatry. 2014;76(12):970-6.
6. Fountoulakis, Konstantinos N et al. “Esketamine Treatment for Depression in Adults: A PRISMA Systematic Review and Meta-Analysis.” *The American journal of psychiatry* vol. 182,3 (2025): 259-275. doi:10.1176/appi.ajp.20240515
7. 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; 12;81(3)
8. 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
9. Pompili M. Intranasal Esketamine and Current Suicidal Ideation with Intent in Major Depression Disorder: Beat the Clock, save a Life, Start a Strategy. Front. Psychiatry. 2020; 11:325.
10. Practice guideline for the assessment and treatment of patients with suicidal behaviors. Am J Psychiatry. 2003;160(11 Suppl):1–60.