MEDICAL COVERAGE POLICY	
SERVICE: Esketamine (Spravato®)	
Policy Number:	**257**
Effective Date:	**05/01/2021**
Last Review:	**04/22/2021**
Next Review Date:	**04/22/2022**

Important note:
Unless otherwise indicated, this policy will apply to all lines of business.
Even though this policy may indicate that a particular service or supply may be considered medically necessary and thus covered, this conclusion is not based upon the terms of your particular benefit plan. Each benefit plan contains its own specific provisions for coverage and exclusions. Not all benefits that are determined to be medically necessary will be covered benefits under the terms of your benefit plan. You need to consult the Evidence of Coverage (EOC) or Summary Plan Description (SPD) to determine if there are any exclusions or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and your plan of benefits, the provisions of your benefits plan will govern. However, applicable state mandates will take precedence with respect to fully insured plans and self-funded non-ERISA (e.g., government, school boards, church) plans. Unless otherwise specifically excluded, Federal mandates will apply to all plans. With respect to Medicare-linked plan members, this policy will apply unless there are Medicare policies that provide differing coverage rules, in which case Medicare coverage rules supersede guidelines in this policy. Medicare-linked plan policies will only apply to benefits paid for under Medicare rules, and not to any other health benefit plan benefits. CMS's Coverage Issues Manual can be found on the CMS website. Similarly, for Medicaid-linked plans, the Texas Medicaid Provider Procedures Manual (TMPPM) supersedes coverage guidelines in this policy where applicable.

SERVICE: Esketamine (Spravato®)

PRIOR AUTHORIZATION: Required.

POLICY:

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

For Medicaid plans, please confirm coverage as outlined in the Texas Medicaid TMPPM.

SWHP/FirstCare may consider esketamine (Spravato®) nasal spray medically necessary for treatment of treatment-resistant depression (TRD) or major depression disorder (MDD) with acute suicidal ideation or behavior when the following criteria are met:

For initial requests:

1) A diagnosis of either:
   a) Treatment of treatment-resistant depression (TRD) with:
      i) documentation of failure of or intolerance to FOUR medication trials with adequate dose and duration for depression (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
      ii) Esketamine to be used in combination with an oral antidepressant (e.g., duloxetine, escitalopram, sertraline, venlafaxine

   OR

   b) Treatment of major depression disorder (MDD) with acute suicidal ideation or behavior with:
      i) Documentation of current suicidal ideation with intent or need for acute psychiatric hospitalization due to imminent risk of suicide; AND
      ii) Esketamine to be used in combination with a new standard-of-care oral antidepressant(s) treatment (either monotherapy or antidepressant + augmentation therapy) or optimizing current regimen; AND

2) Member has a confirmed diagnosis of severe major depressive disorder documented by standardized rating scales (e.g., Beck Depression Scale [BDI], Hamilton Depression Rating Scale [HDRS], Montgomery-Asberg Depression Rating Scale [MADRS], etc.); AND
3) Esketamine is prescribed by or in consultation with a psychiatrist; AND
4) Member is 18 years of age or older; AND
5) Member does not have contraindication to therapy, such as aneurysmal vascular disease, arteriovenous malformation, or intracerebral hemorrhage; AND
6) Member does not have a current or recent history (i.e., within the last 6 months) of moderate or severe substance or alcohol use disorder; AND
7) Esketamine to be administered under the direct supervision of a healthcare provider; AND
8) Member will be monitored by a health care provider for at least 2 hours after administration; AND
9) There is written confirmation that all Risk Evaluation and Mitigation Strategy (REMS) requirements have been met; AND

For renewal requests, documentation must be submitted showing:

1) Continued use of the drug is consistent with criteria above; AND
2) Documentation of improvement in depression symptoms using one of the standardized rating scales above; AND
3) Manageable or no side effects

Approval duration is for six months.

SWHP considers esketamine experimental and investigational for all other indications.

OVERVIEW: 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

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.

On August 3rd, 2020, the Food and Drug Administration (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.

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

- Healthcare settings must be certified in the program and ensure that esketamine is only dispensed in healthcare settings and administered to patients who are enrolled in the program;
- Esketamine is administered by patients under the direct observation of a healthcare provider;
- Patients are monitored by a healthcare provider for at least 2 hours after administration of esketamine;
- Pharmacies must be certified in the REMS and must only dispense esketamine to healthcare settings that are certified in the program.
- REMS details can be found of FDA website: https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=386

MANDATES:

CODES:

Important note:
CODES: 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:	
CPT Not Covered:	
HCPCS Codes	J3490 and C9399
ICD10 codes:	F33.0- F33.9 Major depressive disorder [treatment-resistant depression] R45.851 Suicidal ideations
ICD10 Not covered:	

CMS:

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

REFERENCES:

The following scientific references were utilized in the formulation of this medical policy. SWHP 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 SWHP 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. 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)
7. 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
8. 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.
9. Practice guideline for the assessment and treatment of patients with suicidal behaviors. Am J Psychiatry. 2003;160(11 Suppl):1–60.