MASSACHUSETTS

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Medical Policy

Esketamine Nasal Spray (Spravato™) and Intravenous Ketamine for Treatment-Resistant Depression

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Policy Number: 087

BCBSA Reference Number: N/A

Related Policies

- Repetitive transcranial magnetic stimulation (rTMS), #297
- Anesthetics for the Treatment of Chronic Pain, #291

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue℠ and Medicare PPO Blue℠ Members

Esketamine Nasal Spray (Spravato™)[i]

Esketamine nasal spray may be considered **MEDICALLY NECESSARY** if **all** of the following conditions are met:

Initial Authorization for 28 Days:

1. Individual is 18 years of age or older **AND**,
2. Individual meets the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria for a major depressive episode (See Table 1) by a structured clinical interview for DSM-5 disorders **AND**,
3. Current depressive episode is severe depression based on either any of the following:
    a. Montgomery-Asberg Depression Rating Scale (MADRS) ≥ 28*
    b. Hamilton Rating Scale for Depression (HAM-D) score ≥ 17**
4. Individual has tried and had an inadequate response to four antidepressant agents from at least 2 or more different antidepressant classes (i.e. selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, bupropion, or mirtazapine) and at least one trial of augmenting agent (i.e. atypical antipsychotic, lithium, or thyroid hormone T3. An adequate trial of an antidepressant is defined by **BOTH** of the following:
    a. The trial length was at least 6 weeks at generally accepted doses or of sufficient duration as determined by the treating physician at the generally accepted doses; and
    b. Individual was ≥80% adherent to the agent during the trial; **AND**,
5. Individual is to receive esketamine nasal spray in conjunction with an oral antidepressant **AND**,
6. Individual must not have any of the following:

a. current substance use disorder unless in remission (for example, complete abstinence for one month),
b. hypersensitivity to esketamine, ketamine, or any of the excipients.
c. Previous treatment that was determined not to reduce symptoms or be efficacious
d. Current episode of delirium,
e. Not currently pregnant or breastfeeding,
f. aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation,
g. intracerebral hemorrhage,

7. Individual does NOT have any Food and Drug Administration (FDA) labeled contraindications to the requested agent and esketamine nasal spray is intended to be used consistently with the FDA approved label including meeting Spravato Risk Evaluation and Mitigation Strategy (REMS) program requirements **AND**,
8. The prescriber is a specialist in the area of the patient's diagnosis (e.g. psychiatrist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis AND,
9. Administration of Esketamine (Spravato™) is to occur in a provider's office or hospital setting and must be monitored by a specialist in the area of a patient's diagnosis (e.g., psychiatrist).

Reauthorization
Initial requests for Esketamine will be authorized for up to 28 days. Esketamine nasal spray may be reauthorized for up to 1 year if **all** of the following conditions are met:

1. Individual has had improvement in depression symptoms as evaluated with an appropriate depression rating scale (e.g. Patient Health Questionnaire -9, Clinically Useful Depression Outcome Scale, Quick Inventory of Depressive Symptomatology-Self Report 16 Item, MADRS, HAM-D). **AND**,
2. Individual is to receive esketamine nasal spray in conjunction with an oral antidepressant **AND**,
3. Individuals with substance use disorder have remained in remission (complete abstinence) **AND**,
4. Individual does NOT develop any FDA labeled contraindications to the requested agent and esketamine nasal spray is intended to be used consistently with the FDA approved label including meeting Spravato REMS program requirement,
5. Administration of Esketamine (Spravato™) is to occur in a provider's office or hospital setting and must be monitored by a specialist in the area of a patient's diagnosis (e.g., psychiatrist).

Esketamine nasal spray (Spravato™) is considered **INVESTIGATIONAL** in all other situations.

Additional Information
The recommended adult dosage of esketamine nasal spray during the induction and maintenance phases are as follows:

- Induction phase (weeks 1-4): Administer twice per week with day 1 starting dose at 56 mg and subsequent doses at 56 mg or 84 mg. Evidence of therapeutic benefit should be evaluated at the end of the induction phase to determine need for continued treatment.
- Maintenance phase (weeks 5-8): Administer once weekly doses at 56mg or 84mg. Starting week 9 and after, administer every 2 weeks or once weekly doses at 56mg or 84mg. Dosing frequency should be individualized to the least frequent dosing to maintain remission/response.

Esketamine nasal spray has a black box warning because of 1) risk for sedation and dissociation after administration 2) potential for abuse and misuse. In order to mitigate these risks, it is available only through a restricted program called the SPRAVATO REMS. The essential features of this program include:

- Esketamine nasal spray is only dispensed and administered to patients in a medically supervised healthcare setting that monitors these patients.
- Pharmacies and healthcare settings that dispense esketamine nasal spray are certified.
- Ensuring that each patient is informed about the serious adverse outcomes resulting from sedation and dissociation and need for monitoring.
- Enrollment of all patients in a registry to further characterize the risks and support safe use

Intravenous Ketamine[ii]

Intravenous Ketamine may be considered **MEDICALLY NECESSARY** if **all** of the following conditions are met:

Initial Authorization for 28 Days

1. Individual is 18 years of age or older **AND**,
2. Individual meets the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria for a major depressive episode (See Table 1) by a structured clinical interview for DSM-5 disorders **AND,**
3. Current depressive episode is severe depression based on either of the following:
    a. Montgomery-Asberg Depression Rating Scale (MADRS) ≥ 28* **OR**
    b. Hamilton Rating Scale for Depression (HAM-D) score ≥ 17** **AND,**
4. Individual has tried and had an inadequate response to four antidepressant agents from at least 2 or more different antidepressant classes (i.e. selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, bupropion, or mirtazapine) and at least one trial of augmenting agent (i.e. atypical antipsychotic, lithium, or thyroid hormone T3. An adequate trial of an antidepressant is defined by **BOTH** of the following:
    a. The trial length was at least 6 weeks at generally accepted doses or of sufficient duration as determined by the treating physician at the generally accepted doses; and
    b. Individual was ≥80% adherent to the agent during the trial; **AND**,
5. Individual is to receive intravenous ketamine in conjunction with an oral antidepressant **AND,**
6. Individual must not have any of the following:
    a. current substance use disorder unless in remission (for example, complete abstinence for one month),
    b. hypersensitivity to esketamine, ketamine, or any of the excipients.
    c. Previous treatment that was determined not to reduce symptoms or be efficacious
    d. Current episode of delirium,
    e. Not currently pregnant or breastfeeding,
    f. aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation,
    g. intracerebral hemorrhage,
7. The prescriber is a specialist in the area of the patient's diagnosis (e.g. psychiatrist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND,**
8. Administration of intravenous ketamine is to occur in a provider's office or hospital setting and must be monitored by a specialist in the area of a patient's diagnosis (e.g., psychiatrist).

Reauthorization for up to 1 Year

Initial requests for Intravenous ketamine will be authorized for up to 28 days. Intravenous ketamine may be reauthorized for up to 1 year if **all** of the following conditions are met:

1. Individual has had improvement in depression symptoms as evaluated with an appropriate depression rating scale (e.g. Patient Health Questionnaire -9, Clinically Useful Depression Outcome Scale, Quick Inventory of Depressive Symptomatology-Self Report 16 Item, MADRS, HAM-D) **AND,**
2. Individual is to receive intravenous ketamine in conjunction with an oral antidepressant **AND,**
3. Individual does not have current substance use disorder unless in remission (complete abstinence for one month) **AND,**
4. Administration of intravenous ketamine is to occur in a provider's office or hospital setting and must be monitored by a specialist in the area of a patient's diagnosis (e.g., psychiatrist).

Intravenous ketamine is considered **INVESTIGATIONAL** in all other situations.

Additional Information

The recommended adult dosage of intravenous ketamine during the induction and maintenance phases are as follows:

- Induction phase (weeks 1-4): Administer 2-3 times per week with a standard dose of 0.5mg/kg per 40 minutes IV. Evidence of therapeutic benefit should be evaluated at the end of the induction phase to determine need for continued treatment.

- Maintenance or discontinuation of treatment is followed by a taper period and/or continued treatment based on empirically determined duration of responses for each patient.

Inhaled Ketamine (Ketanest™), and oral ketamine for the treatment of major depressive disorder (MDD), including treatment resistant depression (TRD) is **INVESTIGATIONAL**.[1]

***Montgomery–Asberg Depression Rating Scale (MADRS)**
MADRS is commonly used to evaluate the efficacy of antidepressant by assessing the severity of depression. It contains 10 items and the total score ranges from 0 to 60. The following cut-offs were proposed to classify the level of depression severity:

- 0-6: No depression (absence of symptoms)
- 7-19: Mild depression
- 20-34: Moderate depression
- 35-60: Severe depression

****Hamilton Rating Scale for Depression (HAM-D)**
HAM-D is a 17-item rating scale to determine the severity level of depression in a patient before, during, and after treatment. The total score ranges from 0 to 52, with the score corresponding to the following classifications:

- 0-7: No depression (normal)
- 8-16: Mild depression
- 17-23: Moderate depression
- ≥24: Severe depression

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization **is required.***
Commercial PPO and Indemnity	Prior authorization **is required.***
Medicare HMO Blue℠	Prior authorization **is required.***
Medicare PPO Blue℠	Prior authorization **is required.***

Prior Authorization Request Form: Esketamine Nasal Spray (Spravato™) and Intravenous Ketamine for Treatment-Resistant Depression

*This form must be completed and faxed to: Behavioral Health: 1-888-641-5199

Click here for Esketamine Nasal Spray (SpravatoTM) and Intravenous Ketamine for Treatment-Resistant Depression prior authorization request form, #094.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

HCPCS Codes

HCPCS codes:	Code Description
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

ICD-10 Procedure Codes

ICD-10-PCS codes:	Code Description
XW097M5	Introduction of Esketamine Hydrochloride into Nose, Via Natural or Artificial Opening, New Technology Group 5

The following HCPCS code is considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

HCPCS codes:	Code Description
S0013	Esketamine, nasal spray, 1 mg

Description

Treatment-resistant depression

Patients with either major depressive disorder or bipolar disorder can manifest depressive episodes (See Table 1). Patients whose depressive disorder does not respond satisfactorily to adequate treatment have harder-to-treat depression, generally referred to as treatment-resistant depression.[1] Overall, approximately one in three patients with depression are considered treatment-resistant.[2] While there is no standardized definition of treatment-resistant depression, generally accepted definition is failure of two or more antidepressant treatment attempts with an adequate dose and duration.[3] Majority of systematic reviews and guidelines or consensus statements report that the commonly used definitions were based on treatment of patients whose depression failed to respond (a decrease in depressive severity of at least half) or did not go into remission (complete recovery as measured by a score on a depressive severity instrument below a threshold) following two or more treatment attempts of an adequate dose and duration. Experts do not agree on how to define adequate dose and adequate duration, although the minimum duration cited is typically 4 weeks.

Lack of consensus on definition of treatment-resistant depression limit the ability of systematic reviewers or other experts to synthesize information and generalize treatment-resistant depression findings to the array of patient populations encountered in daily practice. According to the Technology Assessment by Agency for Healthcare Research and Quality (AHRQ) on defining treatment-resistant depression in the Medicare population, lack of clear definition for treatment-resistant depression have made translating research findings or systematic reviews into clinical practice guidelines challenging and inconsistent. As a

result, guideline definitions of treatment-resistant depression differ, agreement on what constitutes prior treatment adequacy is lacking, and recommended “next step” interventions can diverge.[3]

According to the AHRQ Report, there are no validated, standard diagnostic tools for treatment-resistant depression. Diagnosis of a major depressive episode or bipolar disorder can be made through a standard clinical evaluation using Diagnostic and Statistical Manual of Mental Disorders (DSM), International Classification of Diseases (ICD), or through a structured clinical assessment tool. Subsequently, treatment history may be elicited by a clinical interview (e.g., the number of prior pharmacologic attempts of adequate dose and duration that did not produce remission) or administering a structured, staging tool (Antidepressant Treatment Response Questionnaire, Thase Rush Staging Model, Massachusetts General Hospital Staging Model, or the Maudsley Staging Model) to confirm treatment resistance. No preferred approach exists, and careful history has not been compared directly with a structured tool.[3]

Table 1. Diagnostic Criteria for a Major Depressive Episode

	Criteria	
A	Five or more symptoms for 2 weeks (one of which must be either depressed mood or anhedonia)	1. Depressed mood most of the day nearly every day 2. Anhedonia most of the day nearly every day 3. Significant weight loss or gain 4. Insomnia or hypersomnia 5. Psychomotor agitation or retardation 6. Fatigue or loss of energy 7. Feelings of worthlessness or excessive guilt 8. Diminished ability to think or concentrate; indecisiveness 9. Recurrent thoughts of death; suicidal ideation or attempt
B	Symptoms cause clinically significant distress or functional impairment	
C	The episode is not attributable to the physiological effects of a substance or another medical condition	
D	The episode is not better explained by a psychotic illness	
E	There has never been a manic or hypomanic episode	

Adapted from Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed., American Psychiatry Association, 2013.[4]

Current Treatment

Prior to the approval of esketamine, olanzapine-fluoxetine combination was the only U.S. Food and Drug Administration (FDA) approved drug for treatment resistant depression. Strategy for managing treatment resistant depression generally involves modifying current antidepressant therapy or augmenting existing therapies with non-antidepressant medications (such as atypical antipsychotics).[5,2] Modification strategies include use of higher dose, switching to a new antidepressant, or adding on to an existing therapy. The adequate duration of antidepressant therapy is usually minimum of 6 weeks. Additional 4 to 6 weeks may be required for patients who show partial response.[6]

For patients with long-standing treatment-resistant depression who do not benefit from treatment modification or augmentation strategies are referred to as refractory depression. For these patients, other strategies such as electroconvulsive therapy, repetitive transcranial magnetic stimulation, vagus nerve stimulation techniques have been used with limited success.[7,8] Depression-focused psychotherapy may be added to pharmacotherapy but is generally not considered stand-alone therapy for refractory depression. Off-label treatments include drugs from multiple classes (antipsychotics, lithium, thyroid hormone, ketamine), often in combination with antidepressants.

Summary

Treatment-resistant depression is chronic depression that does not improve despite the adequate use of multiple antidepressants. The poor response to multiple antidepressants limits additional treatment options. Esketamine targets the N-methyl-D-aspartate receptor, an ionotropic glutamate receptor in nerve

cells. However, the mechanism by which esketamine exerts its antidepressant effect is unknown. Esketamine is administered intranasally under the supervision of a healthcare provider while the patient is still taking daily oral antidepressants.

For individuals with treatment-resistant depression who receive esketamine, the evidence includes 4 randomized, double-blind, placebo-controlled trials. The relevant outcomes are change in disease status, quality of life, treatment-related mortality and treatment-related morbidity. The 4 randomized controlled trials (TRANSFORM-1, -2 and -3 and SUSTAIN-1) with placebo comparators enrolled more than 700 patients across studies. Of the 4 randomized controlled trials, TRANSFORM-2 and SUSTAIN-1 were the basis for regulatory approval in the United States. While both trials used flexible esketamine dosing, the objective of TRANSFORM-2 was to assess short-term (4 week) efficacy of esketamine while SUSTAIN-1 aimed to assess durability of treatment effect over the long-term (event-driven study with no fixed duration). Results of TRANSFORM-2 showed that trial met the primary endpoint with a 4-point difference (95% CI -7.3 to 0.6) in least square mean difference of Montgomery-Asberg Depression Rating Scale (MADRS) total score in favor of esketamine. The magnitude of treatment effect observed in TRANSFORM-2 was within the range observed in clinical trials for other approved antidepressants currently on the market. Assessment of time course of response showed that treatment effect was apparent at 24 hours, remained consistent through end of 4 week with no further separation between groups after day 2. Results of the SUSTAIN trial showed that patients who received at least 16 initial weeks of treatment with esketamine and achieved clinical remission or response were less likely to relapse if they continued esketamine vs being switched to placebo (hazard ratio=0.49 for remitters and hazard ratio=0.30 for responders respectively). Results of TRANSFORM-1 (a fixed-dose study) and TRANSFORM-3 (flexible-dose study in patient's ≥ 65 years of age) did not reach statistical significance for the primary endpoint. Limitations included possibility of unblinding due to patient's perception of treatment assignment influenced by acute subjective dissociative effects of esketamine that could bias the results. Further, there is limited generalizability of trials results. More than 90% of patients enrolled in the trials were Caucasians while it is known that depression is also common among other racial and ethnic minorities. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with treatment-resistant depression who receive intravenous ketamine, the evidence includes multiple randomized, double blind, placebo-controlled trials. The relevant outcomes are changes in disease status, quality of life, and treatment related mortality and morbidity. The studies assess the rapid effects of Ketamine in reducing depressive symptoms compared with placebo. The combined studies enrolled 370 patients who were given an oral antidepressant in conjunction with intravenous ketamine treatment. In most cases, patients were given a dose of intravenous ketamine in an office setting under the care of a licensed psychiatrist every 3 to 4 weeks. Patients reported reductions in symptoms lasting a period of 3 or 4 weeks when given intravenous infusion. Multiple randomized controlled trials are available evaluating the safety and tolerability of IV ketamine for chronic pain, migraines, neuropathic pain, treatment resistant depression and obsessive-compulsive disorder.

Policy History

Date	Action
1/2021	Clarified coding information
10/2020	Clarified coding information
5/2020	Policy clarified to state that Esketamine nasal spray or Intravenous ketamine must be administered in a providers office or hospital setting. Formatting and bulletting restructured. HCPCS code J2001 removed. This code is not specific to Ketamine. 5/1/2020.
4/2020	New medical policy describing medically necessary and investigational indications. Effective 4/1/2020.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use

Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

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[i] Based on expert opinion.

[ii] Based on expert opinion.