



Medical Policy

Esketamine Nasal Spray (Spravato™) and Intravenous Ketamine for Mental Health Conditions

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Policy Number: 087

BCBSA Reference Number: N/A

Related Policies

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Policy

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

Overview of covered services:

An initial, acute trial of Esketamine nasal spray or ketamine IV infusion for Treatment resistant depression or major depressive disorder with suicidal ideation may be considered **medically necessary** when the criteria below are met.

Subsequent trials, reinitiation of Esketamine or Ketamine, or continuation therapy beyond 12 months for treatment resistant depression or 4 weeks for major depressive disorder with suicidal ideation is considered **investigational and non-covered**.

Any other preparations of ketamine (oral or inhaled) are considered **not medically necessary**.

- Esketamine Nasal Spray is FDA approved and comes with a Black Box warning for risk of sedation, dissociation, abuse and misuse. The FDA requires all patients and providers register in the Risk Evaluation and Mitigation Strategy program and requires all patients receive Spravato under the supervision of a licensed provider.
- Intravenous Ketamine was FDA approved in 1970 and is approved for off-label use. The use of intravenous ketamine in treatment resistant depression and reduction of suicidal ideation has been studied extensively.

Esketamine (Spravato™) Nasal Spray or IV ketamine for Treatment Resistant Depressionⁱ

An acute trial of Esketamine (Spravato™) nasal spray or IV 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 any of the following:
 - a. Montgomery-Asberg Depression Rating Scale (MADRS) $\geq 28^*$
 - b. Hamilton Rating Scale for Depression (HAM-D) score $\geq 17^{**}$
4. Individual has tried and had an inadequate response to four antidepressant agents from at least two 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 $\geq 80\%$ adherent to the agent during the trial; **AND**,
5. Individual is to receive Esketamine (Spravato™) nasal spray or IV 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. For Esketamine (Spravato™) nasal spray only, the individual must NOT have any Food and Drug Administration (FDA) labeled contraindications. Esketamine (Spravato™) 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™) or IV 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). If medication is received from a Retail Specialty Pharmacy it must be shipped to the providers office.

Authorization for Continuation Phase

An acute trial for Esketamine (Spravato™) or IV Ketamine will be authorized for up to 28 days.

Continuation phase treatment of Esketamine (Spravato™) nasal spray or IV Ketamine may be authorized 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 (Spravato™) or IV Ketamine in conjunction with an oral antidepressant **AND**,
3. Individuals with substance use disorder have remained in remission (complete abstinence) **AND**,
4. For Esketamine Individual does NOT develop any FDA labeled contraindications to the requested agent

5. Administration of Esketamine (Spravato™) nasal spray or IV 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). If medication is received from a Retail Specialty Pharmacy it must be shipped to the providers office.

Subsequent trials or maintenance treatment (continuation treatment beyond the initial trial) of Esketamine (Spravato™) nasal spray or IV Ketamine is considered [INVESTIGATIONAL](#).

Esketamine (Spravato™) or IV Ketamine for Major Depressive Disorder with Acute Suicidal Ideation or Behavior

An acute trial of Esketamine (Spravato™) nasal spray or IV Ketamine may be considered [MEDICALLY NECESSARY](#) for a treatment period of **28 days** if all of the following conditions are met:

1. Individual is 18 years of age or older,
2. Individual is currently hospitalized and is at a imminent risk for suicide as documented by:
 - a. Individual response to a structured assessment for suicidal ideation indicative of imminent risk of suicide (see policy guidelines) AND,
 - b. Confirmation of imminent risk of suicide by clinical assessment by a mental health professional/psychiatrist (see policy guidelines)
3. 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,
4. Individual current depressive episode is moderate or severe based on either of the following scales:
 - a. Montgomery-Asberg Depression Rating Scale (MADRS) $\geq 28^*$ OR,
 - b. Hamilton Rating Scale for Depression (HAM-D) score $\geq 17^{**}$
5. Individual is to receive Esketamine (Spravato™) nasal spray or IV Ketamine in conjunction with standard-of-care treatment based on clinical judgment and practice guidelines that may be comprised of oral antidepressant(s), an atypical antipsychotic, or a mood stabilizer.
6. Individual does NOT have any U.S. 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 (see policy guidelines) including meeting Spravato Risk Evaluation and Mitigation Strategy (REMS) program requirements (see policy guidelines).
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. If medication is received from a Retail Specialty Pharmacy it must be shipped to the providers office.

Subsequent trials or maintenance treatment of Esketamine (Spravato™) nasal spray or IV Ketamine for major depressive disorder with suicidal ideation or behavior is considered [INVESTIGATIONAL](#).

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

Esketamine (Spravato™) nasal spray or IV Ketamine are considered [INVESTIGATIONAL](#) in all other situations.

FDA Dosing recommendations for Esketamine or IV Ketamine:

Treatment Resistant Depression:

FDA Dosing and administration guidelines for Esketamine

The recommended adult dosage of Esketamine (Spravato™) nasal spray are as follows:

- Induction phase (initial acute trial) (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 (initial acute trial) to determine need for continued treatment.
- Maintenance phase (weeks 5-8): Administer once weekly, doses at 56 mg or 84 mg. Starting week 9 and after, administer every 2 weeks or once weekly doses at 56mg or 84 mg. Dosing

frequency should be individualized to the least frequent dosing to maintain remission/response.

Major Depression with Suicidal Ideation or Behavior:

The recommended adult dosage of Esketamine (Spravato™) nasal spray is 84 mg twice per week for 4 weeks. Dosage may be reduced to 56 mg twice per week based on tolerability. The use of esketamine nasal spray beyond 4 weeks has not been systematically evaluated.

Dosing recommendations for IV ketamine*

The recommended adult dosage of intravenous ketamine are as follows:

- Induction phase (initial acute trial) (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.

*IV Ketamine is approved for off label use.

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 SM	Prior authorization is required.*
Medicare PPO Blue SM	Prior authorization is required.*

Requesting Prior Authorization Using Authorization Manager

Providers will need to use [Authorization Manager](#) to submit initial authorization requests for services. Authorization Manager, available 24/7, is the quickest way to review authorization requirements, request authorizations, submit clinical documentation, check existing case status, and view/print the decision letter. For commercial members, the requests must meet medical policy guidelines.

All requests will be reviewed by the behavioral health department. To ensure the request is processed accurately and quickly:

- Enter the facility's NPI or provider ID for where services are being performed.
- Enter the appropriate surgeon's NPI or provider ID as the servicing provider, *not* the billing group.

Authorization Manager Resources

- Refer to our [Authorization Manager](#) page for tips, guides, and video demonstrations.

Complete Prior Authorization Request Form for Esketamine Nasal Spray (Spravato) and Intravenous Ketamine (094) using [Authorization Manager](#).

For out of network providers: Requests should still be faxed to 1-888-641-5199.

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:

HCPSC Codes

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

HCPSC 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.

Major Depressive Disorder and Suicidal Ideation/Behavior

In a community survey conducted in 21 countries with over 100,000 individuals by World Health Organization, 12-month prevalence of suicidal ideation (thoughts) was approximately 2 percent⁵, and that the lifetime prevalence was 9 percent.⁶ Reported annual prevalence of suicidal ideation in US adults is 4 percent⁷. Psychiatric illness is strongly associated with risk of suicide⁸ and major depressive disorder is the psychiatric diagnosis most commonly associated with suicide.⁹ The reported prevalence of suicidal ideation in adult patients with MDD is as high as 60%, and the lifetime incidence of attempted suicide in this population ranges between 10% and 20%.^{10,11} Further, the lifetime risk of completed suicide has been estimated to be 3.4% in this population.¹²

Patients with major depressive disorder who have active suicidal ideation with intent constitute a psychiatric emergency as the time between the onset of suicidal ideation and suicide attempt is often very short.¹³ These patients are often hospitalized to protect them from self-harm, although the benefits of hospitalization are often temporary. Moreover, while standard antidepressants effectively treat depressive symptomatology, including suicidal ideation,¹⁴ they require 4–6 weeks to exert their full effect,^{15,16} limiting their utility in crisis situations. Currently, there is no approved medication for emergency treatment of patients with depression who have active suicidal ideation with intent.¹⁷

***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

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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

No further clinical trials have been published evaluating the effects of maintenance treatment beyond 12 months or evaluating the long term safety effects. In a four year safety analysis of patients from the SUSTAIN trial, many patients experienced significant side effects including increased sedation (48%-61% of patients and 0.3%-0.4% experienced loss of consciousness requiring medical intervention. In a short term analysis evaluating cognitive impairment, patients administered with Spravato demonstrated a cognitive performance decline 40 minutes post dose compared to the placebo treated patients 61%-84% of patients treated with Spravato experienced dissociative or perceptual changes and increase in blood pressure post dosing. 8-19% of patients experienced clinically significant increases in blood pressure within the first 4 weeks of administration. Limited studies are available evaluating long term effects on cognitive impairment, dissociation, and cardiovascular health however, the significant treatment related adverse events should be monitored closely. Spravato is considered a schedule III controlled substance and should only be administered to patients according to the FDA labelling and administration guidelines. The evidence is insufficient to determine the net health outcomes for maintenance/continuation or repeat administration of Spravato beyond the initial acute trial.

Major Depressive Disorder with Acute Suicidal Ideation or Behavior

For individuals with major depressive disorder with acute suicidal ideation or behavior who receive esketamine, the evidence includes 2 randomized, double-blind, placebo-controlled trials. Relevant outcomes are change in disease status, quality of life, treatment-related mortality and treatment-related morbidity. The 2 identical randomized controlled trials (ASPIRE-1 and -2) with placebo comparators enrolled 449 adult patients with moderate-to-severe major depressive disorder who had active suicidal ideation. The primary objective was to assess short-term (24-hour after first dose) efficacy of esketamine. Results showed that both trials met the primary endpoint with approximately a 4 point difference in least square mean difference of MADRS total score in favor of esketamine. As per the FDA, statistically significant response results on the MADRS can likely be considered clinically meaningful. The magnitude of treatment effect observed in trials 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 and remained fairly consistent through day 25 with no further separation between groups after day 2. Limitations included possibility of unblinding due to patients 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 major depressive disorder with acute suicidal ideation or behavior who receive IV Ketamine, the evidence includes multiple randomized, controlled, double blinded trials, meta-analysis and case studies. Primary outcomes include reduction of suicidal ideation or behavior using the Montgomery Asberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale for Depression (Ham-D), Beck Depression Inventory (BDI), Beck Scale for Suicide Ideation (BSS) and Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR). In all of the clinical trials, patients received baseline depression and suicidality screening and were randomized to receive a dose of ketamine or placebo Midazolam. In all of the studies, patients who received ketamine demonstrated a clinically significant reduction in depression and suicidality on post screen measures compared to control groups. Documented treatment effect, compared to control groups, was evident by the 24 and 48 hour marks as well as 7 days post treatment. IV ketamine was not associated with major adverse events and was well tolerated by patients. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

No further clinical trials have been published evaluating the clinical and health outcomes for patients who receive Esketamine or IV Ketamine for major depressive disorder with suicidal ideation or behavior. In a four year safety analysis of patients from the SUSTAIN trial, many patients experienced significant side effects including increased sedation (48%-61% of patients and 03%-0.4% experienced loss of consciousness requiring medical intervention. In a short term analysis evaluating cognitive impairment, patients administered with Spravato demonstrated a cognitive performance decline 40 minutes post dose compared to the placebo treated patients. 61%-84% of patients treated with Spravato experienced dissociative or perceptual changes and increase in blood pressure post dosing. 8%-19% of patients experienced clinically significant increases in blood pressure within the first 4 weeks of administration. Limited studies are available evaluating long term effects on cognitive impairment, dissociation, and cardiovascular health however, the significant treatment related adverse events should be monitored closely. Spravato is considered a schedule III controlled substance and should only be administered to patients according to the FDA labelling and administration guidelines. The evidence is insufficient to determine the net health outcomes for maintenance/continuation or repeat administration of Spravato beyond the initial acute trial.

Policy History

Date	Action
1/2025	Annual policy review. References, description and summary reviewed. No changes to policy statements made. 1/1/2025.
9/2024	Policy clarified to indicate that medication must be shipped to providers office when obtained through specialty pharmacy. 9/1/2024.
9/2023	Policy clarified to include prior authorization requests using Authorization Manager.
1/1/2023	Policy criteria updated and reformatted. Maintenance/continuation therapy or repeat treatment of Esketamine or IV ketamine is investigational. Description and Summary updated. References added. 1/1/2023.
3/1/2022	Annual policy review. References, description and summary reviewed. No changes to policy statements made. 3/1/2022.
3/1/2021	New medically necessary indications added. Description, Summary and references updated. 3/1/2021.
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](#)

References

1. Thase ME, Rush AJ. When at first you don't succeed: sequential strategies for antidepressant nonresponders. *J Clin Psychiatry*. 1997;58 Suppl 13:23-29. PMID 9402916
2. Institute for Clinical and Economic Review, Final Evidence Report. Esketamine for the Treatment of Treatment-Resistant Depression: Effectiveness and Value. 2019; https://icer-review.org/wp-content/uploads/2018/10/ICER_TRD_Final_Evidence_Report_062019.pdf. Accessed Sep 5, 2019.
3. Gaynes BN, Asher G, Gartlehner G, et al. Definition of Treatment-Resistant Depression in the Medicare Population. Rockville, MD2018.
4. American Psychiatric Association. DSM 5. Diagnostic and statistical manual of mental disorders. American Psychiatric Press Inc, (5th edition). 2013; Washington, DC: American Psychiatric Association.
5. Borges G, Nock MK, Haro Abad JM, et al. Twelve-month prevalence of and risk factors for suicide attempts in the World Health Organization World Mental Health Surveys. *J Clin Psychiatry*. Dec 2010; 71(12): 1617-28. PMID 20816034
6. Nock MK, Borges G, Bromet EJ, et al. Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. *Br J Psychiatry*. Feb 2008; 192(2): 98-105. PMID 1824502.
7. Piscopo K, Lipari RN, Cooney J, et al. Suicidal thoughts and behavior among adults: Results from the 2015 National Survey on Drug Use and Health. NSDUH; <http://www.samhsa.gov/data/>. Accessed Sep 30, 2020.
8. Tidemalm D, Langstrom N, Lichtenstein P, et al. Risk of suicide after suicide attempt according to coexisting psychiatric disorder: Swedish cohort study with long term follow-up. *BMJ*. Nov 18 2008; 337: a2205. PMID 19018040
9. Kessler RC, Berglund P, Borges G, et al. Trends in suicide ideation, plans, gestures, and attempts in the United States, 1990-1992 to 2001-2003. *JAMA*. May 25 2005; 293(20): 2487-95. PMID 1591474.
10. Hasin DS, Sarvet AL, Meyers JL, et al. Epidemiology of Adult DSM-5 Major Depressive Disorder and Its Specifiers in the United States. *JAMA Psychiatry*. Apr 01 2018; 75(4): 336-346. PMID 2945046.
11. Holma KM, Melartin TK, Haukka J, et al. Incidence and predictors of suicide attempts in DSM-IV major depressive disorder: a five-year prospective study. *Am J Psychiatry*. Jul 2010; 167(7): 801-8. PMID 20478879
12. Blair-West GW, Cantor CH, Mellsop GW, et al. Lifetime suicide risk in major depression: sex and age determinants. *J Affect Disord*. Oct 1999; 55(2-3): 171-8. PMID 10628886
13. Deisenhammer EA, Ing CM, Strauss R, et al. The duration of the suicidal process: how much time is left for intervention between consideration and accomplishment of a suicide attempt?. *J Clin Psychiatry*. Jan 2009; 70(1): 19-24. PMID 19026258
14. Montgomery SA, Dunner DL, Dunbar GC. Reduction of suicidal thoughts with paroxetine in comparison with reference antidepressants and placebo. *Eur Neuropsychopharmacol*. Mar 1995; 5(1): 5-13. PMID 7613102
15. Simon GE, Savarino J. Suicide attempts among patients starting depression treatment with medications or psychotherapy. *Am J Psychiatry*. Jul 2007; 164(7): 1029-34. PMID 17606654

16. Wasserman D, Rihmer Z, Rujescu D, et al. [The European Psychiatric Association (EPA) guidance on suicide treatment and prevention]. *Neuropsychopharmacol Hung*. Jun 2012; 14(2): 113-36. PMID 22710852
17. Valenstein M, Kim HM, Ganoczy D, et al. Higher-risk periods for suicide among VA patients receiving depression treatment: prioritizing suicide prevention efforts. *J Affect Disord*. Jan 2009; 112(1-3): 50-8. PMID 18945495
18. Alphs L, Fu D-J, Williamson D, et al. Validation and mapping of the Suicidal Ideation and Behavior Assessment Tool (SIBAT). (abstract W88) *Neuropsychopharmacology*. 2018;43:S427S428.
19. Popova V, Daly EJ, Trivedi M, et al. Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study. *Am J Psychiatry*. Jun 01 2019; 176(6): 428-438. PMID 31109201
20. Janssen Pharmaceuticals, Inc. Prescribing Information Spravato (esketamine) nasal spray. July 2020. <http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/SPRAVATO-pi.pdf> Accessed Sep 11, 2020.
21. 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*. May 12 2020; 81(3). PMID 32412700
22. 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*. Aug 29 2020. PMID 32861217
23. Practice Guideline for the Treatment of Patients With Major Depressive Disorder Third Edition: AMERICAN PSYCHIATRIC ASSOCIATION. 2010; https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Accessed Sep 11, 2020.
24. Singh JB, Fedgchin M, Daly EJ, et al. A Double-Blind, Randomized, Placebo-Controlled, Dose-Frequency Study of Intravenous Ketamine in Patients With Treatment-Resistant Depression. *Am J Psychiatry*. Aug 01 2016; 173(8): 816-26. PMID 27056608
25. Ionescu DF, Rosenbaum JF, Alpert JE. Pharmacological approaches to the challenge of treatment-resistant depression. *Dialogues Clin Neurosci*. Jun 2015;17(2):111-126. PMID 26246787
26. Papadimitropoulou K, Vossen C, Karabis A, et al. Comparative efficacy and tolerability of pharmacological and somatic interventions in adult patients with treatment-resistant depression: a systematic review and network meta-analysis. *Curr Med Res Opin*. Apr 2017;33(4):701-711. PMID 28035869
27. FDA Briefing Document Psychopharmacologic Drugs Advisory Committee (PDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee Meeting February 12, 2019. <https://www.fda.gov/media/121376/download>. Accessed Sep 9, 2019.
28. Zimmerman M, Chelminski I, Posternak M. A review of studies of the Montgomery-Asberg Depression Rating Scale in controls: implications for the definition of remission in treatment studies of depression. *Int Clin Psychopharmacol*. Jan 2004;19(1):1-7. PMID 15101563
29. Zimmerman M, Martinez JH, Young D, et al. Severity classification on the Hamilton Depression Rating Scale. *J Affect Disord*. Sep 5 2013;150(2):384-388. PMID 23759278
30. Center for Drug Evaluation and Research Application Number: 211243Orig1s000 Summary Review https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211243Orig1s000SumR.pdf. Accessed Sep 11, 2019.
31. FDA Presentations for the February 12, 2019 Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. <https://www.fda.gov/media/121378/download>. Accessed Sep 11, 2019.
32. Janssen Briefing Information for the February 12, 2019 Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. <https://www.fda.gov/media/121377/download>. Accessed Sep 11, 2019.
33. Janssen Presentations for the February 12, 2019 Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. <https://www.fda.gov/media/121379/download>. Accessed Sep 11, 2019.

34. 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*. Feb 1 2018;75(2):139-148. PMID 29282469
35. 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*. Jun 5 2019. PMID 31166571
36. Fedgchin M, Trivedi M, Daly EJ, et al. Efficacy and Safety of Fixed-Dose Esketamine Nasal Spray Combined With a New Oral Antidepressant in Treatment-Resistant Depression: Results of a Randomized, Double-Blind, Active-Controlled Study (TRANSFORM-1). *Int J Neuropsychopharmacol*. Jul 10 2019. PMID 31290965
37. Practice Guideline for the Treatment of Patients With Major Depressive Disorder Third Edition: AMERICAN PSYCHIATRIC ASSOCIATION. 2010; https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Accessed Sep 11, 2019.
38. Murrough, J.W., Losifescu, D.V., Chang, L.C. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. *Am J Psychiatry*. 2013 Oct;170(10):1134-42.
39. Murrough, J.W., Burdick, K.E., Levitch, C.F. Neurocognitive effects of ketamine and association with antidepressant response in individuals with treatment-resistant depression: a randomized controlled trial. *Neuropsychopharmacology*. 2015 Mar 13;40(5):1084-90.
40. Zanos, P., Gould, T.D. Mechanisms of ketamine action as an antidepressant. *Mol Psychiatry*. 2018 Mar 13.
41. Serafini, G., Howland, R.H., Rovedi, F. The role of ketamine in treatment-resistant depression: a systematic review. *Curr Neuropharmacol*. 2014 Sep;12(5):444-61.
42. Zarate, C., Niciu, M. Ketamine for depression: evidence, challenges and promise. *World Psychiatry*. 2015 Oct; 14(3): 348–350. Published online 2015 Sep 25.
43. Sanacora, G., Frye, M., McDonald, W. A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders. American Psychological Association. *JAMA Psychiatry*. 2017;74(4):399-405.
44. Zorumski, C.F., Conway, C.R. Use of Ketamine in Clinical Practice: A Time for Optimism and Caution. *JAMA Psychiatry*. 2017;74(4):405-406.
45. Gao, M., Rejaei, D., Liu, H. Ketamine use in current clinical practice. *Acta Pharmacol Sin*. 2016 Jul; 37(7): 865–872.
46. Canusco, C.M., Ionescu, D.F., Li, X, et al, Esketamine Nasal Spray for the Rapid Reduction of Depressive Symptoms in Major Depressive Disorder with Acute Suicidal Ideation of Behavior. *Journal of Clinical Psychopharmacology*. 2021. 41(5). 516-524.
47. Turkoz, I., Daly, E., Singh, J, et al. Treatment Response with Esketamine Nasal Spray Plus an Oral Antidepressant in Patients with Treatment- Resistant Depression Without Evidence of Early Response: A Pooled Post Hoc Analysis of the TRANSFORM studies. *Journal Clinical Psychiatry*. 2021. 82(4).
48. Zaki, N., Fu, D.J., Daly, E., et al. Long Term Safety of Esketamine Nasal Spray in Adults with Treatment Resistant Depression: a subgroup analysis of the ongoing Sustain-3 study. Neuroscience Education Institute (NEI) Congress. November 4-7 2021.
49. Jeon HJ, Ju PC, Sulaiman AH, Aziz SA, Paik JW, Tan W, Bai D, Li CT. Long-term Safety and Efficacy of Esketamine Nasal Spray Plus an Oral Antidepressant in Patients with Treatment-resistant Depression- an Asian Sub-group Analysis from the SUSTAIN-2 Study. *Clin Psychopharmacol Neurosci*. 2022 Feb 28;20(1):70-86. doi: 10.9758/cpn.2022.20.1.70. PMID: 35078950; PMCID: PMC8813327.
50. Wajs, E., Aluisio, L., Holder, R., et al. Esketamine Nasal Spray Plus Oral Antidepressant in Patients With Treatment-Resistant Depression: Assessment of Long-Term Safety in a Phase 3, Open-Label Study (SUSTAIN-2). *J Clin Psychiatry*. 2020 Apr 28;81(3):19m12891.

ⁱ Based on expert opinion