

## Corporate Medical Policy

### Esketamine (Spravato™) Nasal Spray

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<b>Last Review:</b>	1/2021

#### Description of Procedure or Service

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Esketamine (Spravato™) nasal spray is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist that is indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (TRD) in adult patients and the treatment of depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior.

Major depressive disorder (MDD) is a common but serious psychiatric condition that can lead to a variety of disabling emotional and physical problems. It is a chronic illness that typically requires long-term treatment. Depressive symptoms can vary and may include persistent depressed mood, lack of pleasure (anhedonia), insomnia or hypersomnia, appetite or weight change, psychomotor agitation or retardation, decreased energy, poor concentration, feelings of hopelessness or worthlessness, and recurrent thoughts of suicide or death. Treatment typically includes a combination of pharmacotherapy and psychotherapy, and can lead to improvement in many patients. There are several classes of first-line oral antidepressant drugs available such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants; however, choice of pharmacological agent is usually patient-specific. TRD refers to when a patient has a major depressive episode with an inadequate response to therapy of adequate dose and duration. While the definition of TRD has not been standardized, it is generally indicated by an unsatisfactory response to at least two trials of antidepressant monotherapies in a current depressive episode. Patients with TRD often do not respond to subsequent pharmacotherapy trials and frequently experience chronic depression, impaired psychosocial functioning, and poor overall health. Subsequent treatment strategies may include augmentation therapy (adding a treatment to the oral antidepressant) with second generation antidepressants and/or switching treatment (e.g., psychotherapy, electroconvulsive therapy or repetitive transcranial magnetic stimulation).

Esketamine (Spravato), the S-enantiomer of racemic ketamine, is a non-selective, non-competitive antagonist of the NMDA receptor that was approved by the U.S. Food and Drug Administration (FDA) in March 2019 in conjunction with an oral antidepressant for the treatment of TRD in adults, and in July 2020 in conjunction with an oral antidepressant for the treatment of MDD with acute suicidal ideation or behavior. The mechanism by which esketamine exerts its antidepressant effect is unknown.

***\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

# Esketamine (Spravato™) Nasal Spray

## Policy

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**BCBSNC will provide coverage for esketamine (Spravato™) nasal spray when it is determined to be medically necessary because the medical criteria and guidelines noted below are met.**

## Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

## When Esketamine (Spravato) Nasal Spray is covered

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### Initial Therapy

Esketamine (Spravato) nasal spray may be considered medically necessary for the treatment of adult patients ( $\geq 18$  years old) when the following criteria are met:

1. The patient has been diagnosed with treatment-resistant depression (TRD); AND
  - a. The patient has a confirmed diagnosis of major depressive disorder (MDD) to include one of the following:
    - i. If single-episode MDD, the duration has been  $\geq 2$  years, OR
    - ii. Recurrent MDD without psychotic features; AND
  - b. In the current depressive episode, the patient has had an inadequate response ( $\leq 25\%$  improvement) to at least two different oral antidepressants of adequate dose and duration (typically 6 weeks); OR
2. The patient has been diagnosed with major depressive disorder (MDD) with suicidal ideation or behavior; AND
  - a. The suicidal ideation and intent are imminent and warrant potential hospitalization; AND
3. At initiation of esketamine nasal spray, the patient has a depression symptom severity of  $\geq 28$  on the Montgomery-Asberg Depression Rating Scale (MADRS), or as scored by a comparable standardized rating scale that reliably measures depressive symptoms (see Policy Guidelines); AND
4. The patient is receiving esketamine nasal spray in conjunction with an oral antidepressant agent (i.e., esketamine will not be used as monotherapy); AND
5. The patient does not have any clinical contraindications to esketamine therapy (i.e., aneurysmal vascular disease or intracerebral hemorrhage); AND
6. Esketamine nasal spray is:
  - a. Prescribed by a psychiatrist, AND
  - b. There is physician attestation that it will be administered under direct supervision of a healthcare professional at a treatment facility that is certified through the Spravato (esketamine) REMS program (see Policy Guidelines).

Initial authorization: 3 months

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## **Continuation (Maintenance) Therapy**

Continuation of treatment with esketamine (Spravato) nasal spray beyond 3 months after initiation of therapy, and every 6 months thereafter, is considered medically necessary for the treatment of treatment-resistant depression (TRD) or major depressive disorder (MDD) with acute suicidal ideation or behavior when the following criteria are met:

1. The patient is currently using esketamine nasal spray and continues to meet initial criteria; AND
2. The patient will continue therapy with an oral antidepressant agent in conjunction with esketamine nasal spray; AND
3. Using the MADRS scale or a comparable standardized rating scale that reliably measures depressive symptoms, the patient has demonstrated at least a 50% reduction in depressive symptoms compared to baseline while on esketamine nasal spray therapy.

## **When Esketamine (Spravato) Nasal Spray is not covered**

Esketamine (Spravato) nasal spray is considered **investigational** and therefore not covered when the above criteria are not met.

Esketamine nasal spray is considered **investigational** when used as an anesthetic agent.

## **Policy Guidelines**

Spravato nasal spray is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) due to the risk of serious adverse outcomes from sedation, dissociation, and abuse and misuse. Healthcare settings must be certified in the Spravato REMS program to be able to dispense and administer Spravato nasal spray to patients who are also enrolled in the program. In addition, pharmacies must be certified in the REMS program in order to dispense Spravato nasal spray to certified healthcare settings. If Spravato nasal spray is dispensed and administered in a healthcare setting separate from that of the prescribing provider, the healthcare facility must be certified by the Spravato REMS program.

The FDA has issued the following black box warnings for patients receiving intranasal esketamine (Spravato): risk for sedation and dissociation after administration, potential for abuse and misuse, availability only through a restricted program called the Spravato REMS, and increased risk of suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants.

Spravato nasal spray must be administered intranasally under direct supervision of a healthcare provider, including the administration period and the post-administration supervised 2-hour observation period. Spravato nasal spray should be administered in conjunction with an oral antidepressant.

Each Spravato device contains 28 mg of esketamine, and each nasal spray device delivers two sprays containing a total of 28 mg of esketamine. The recommended dosing regimen for Spravato for treatment-resistant depression includes an induction phase and a maintenance phase, see Table 1. Dosing adjustments should be made based on efficacy and tolerability, and the patient should be evaluated for evidence of therapeutic benefit at the end of the induction phase in order to determine the need for continuation of treatment.

### **Table 1: Spravato Recommended Dosage for TRD**

# Esketamine (Spravato™) Nasal Spray

	Frequency	Dose
<b>Induction Phase</b>	<b><u>Weeks 1 to 4:</u></b> Twice weekly	Day 1 initial dose: 56 mg Subsequent doses: 56 mg or 84 mg
<b>Maintenance Phase</b>	<b><u>Weeks 5 to 8:</u></b> Once weekly	56 mg or 84 mg
	<b><u>Week 9 and after:</u></b> Every 2 weeks or once weekly*	56 mg or 84 mg

\*Dosing frequency should be individualized to the least frequent dosing necessary to maintain remission/response

The recommended dosing regimen for depressive symptoms in patients with MDD with acute suicidal ideation or behavior is 84 mg twice weekly for 4 weeks in conjunction with an oral antidepressant. The dose may be reduced to 56 mg twice weekly based on tolerability. Therapeutic benefit should be evaluated after 4 weeks of treatment to determine need for continuation of therapy. The use of Spravato nasal spray, in conjunction with an oral antidepressant, beyond 4 weeks has not been systematically evaluated in the treatment of depressive symptoms in MDD patients with acute suicidal ideation or behavior.

The patient's blood pressure (BP) should be assessed prior to and after administration of Spravato nasal spray. If the baseline BP is elevated (e.g., >140 mmHg systolic, >90 mmHg diastolic), the risks of short-term BP increases should be assessed compared to the benefit of Spravato treatment for the patient. Spravato should not be administered if an increase in BP or intracranial pressure poses a serious risk for the patient. BP should be reassessed approximately 40 minutes after Spravato administration, and if decreasing and the patient is clinically stable for at least 2 hours post-administration, the patient may be discharged.

Spravato is contraindicated in patients for whom an increase in BP or intracranial pressure poses a serious risk, such as aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels) or arteriovenous malformation, or history of intracerebral hemorrhage.

Esketamine (Spravato) nasal spray is not approved as an anesthetic agent, as the safety and efficacy of esketamine nasal spray have not been established for use as an anesthetic agent. Esketamine nasal spray is not approved for use in pediatric patients.

The effectiveness of Spravato in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use of Spravato nasal spray does not preclude the need for hospitalization if clinically warranted, even if the patient experiences improvement after an initial Spravato dose.

The Montgomery-Asberg Depression Rating Scale (MADRS) is commonly used to evaluate the efficacy of antidepressant therapy by assessing the severity of depression. The MADRS scoring system consists of a ten-item, clinician-rated scale that is used to evaluate the severity of core depressive symptoms. The total score on the MADRS scale ranges from 0 to 60, with higher scores indicating more severe depression.

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

# Esketamine (Spravato™) Nasal Spray

## Clinical Trial Evidence

The efficacy and safety of esketamine (Spravato) nasal spray in conjunction with an oral antidepressant (AD) for the treatment of treatment-resistant depression (TRD) has been evaluated in both short-term and long-term studies.

The efficacy and safety of intranasal esketamine (Spravato) plus an oral AD for the treatment of adult patients with TRD was evaluated in a randomized, placebo-controlled, double-blind, multicenter, short-term (4-week), phase 3 study (TRANSFORM-2 trial; NCT02418585). Patients included in the trial (n=236) met DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) diagnostic criteria for major depressive disorder (MDD) and, in the current depressive episode, had not responded adequately ( $\leq 25\%$  improvement) to at least two different oral ADs of adequate dose and duration. Patients enrolled in the trial must also have a current major depressive episode depression symptom severity defined by a MADRS total score of  $\geq 28$  at week 1. Following discontinuation of prior AD treatments, study participants were randomized to receive twice weekly dosing of Spravato nasal spray (flexible dose; 56 mg or 84 mg) or intranasal placebo. Additionally, all patients also received open-label concurrent treatment with a newly initiated daily oral AD (duloxetine, escitalopram, sertraline, or extended-release venlafaxine). The Spravato dose could be titrated up to 84 mg per investigator discretion beginning with the second dose. The primary efficacy endpoint was change from baseline in MADRS total score at the end of the 4-week double-blind induction phase. The least-squares mean difference in MADRS score between the two treatment groups was 4.0 (95% CI, -7.3; -0.6). Treatment with Spravato plus a newly initiated oral AD showed statistical superiority for the primary efficacy endpoint compared to intranasal placebo plus a newly initiated oral AD.

The efficacy of intranasal esketamine (Spravato) plus an oral AD in delaying relapse of depressive symptoms in TRD was also evaluated in a long-term randomized, double-blind, parallel-group, multicenter, maintenance-of-effect trial of 703 adult patients who were known remitters and responders to Spravato (SUSTAIN-1 trial; NCT02493868). Patients enrolled in Study 2 were either responders in one of two short-term controlled trials (Study 1 and another 4-week study) or in an open-label direct-enrollment study in which they received flexible dosing of Spravato (56 mg or 84 mg twice weekly) plus a daily oral AD in an initial 4-week phase. Within the study, stable remission was defined as a MADRS total score of  $\leq 12$  for at least 3 of the last 4 weeks, and stable response was defined as a MADRS total score reduction of  $\geq 50\%$  for the last 2 weeks of optimization and not in remission. Following at least 16 initial weeks of Spravato treatment plus an oral AD, stable remitters and stable responders were randomized separately to continue receiving Spravato nasal spray or to switch to intranasal placebo, with each group continuing concomitant therapy with an oral AD. The primary efficacy endpoint was time to relapse in patients with stable remission. Relapse was defined within the study as a MADRS total score of  $\geq 22$  for 2 consecutive weeks or hospitalization for worsening depression or any other clinically relevant event indicating relapse. Patients in stable remission who continued treatment with Spravato nasal spray plus an oral AD demonstrated a statistically significant longer time to relapse of depressive symptoms than patients receiving intranasal placebo plus an oral AD.

## **Billing/Coding/Physician Documentation Information**

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcsnc.com](http://www.bcsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable codes: G2082, G2083, S0013*

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BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## Scientific Background and Reference Sources

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Janssen Pharmaceuticals, Inc. Spravato (esketamine) nasal spray. Highlights of prescribing information. May 2019. Available at: <http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/SPRAVATO-pi.pdf>. Last accessed May 2019.

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American Psychiatric Association. Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Third Edition, 2010. Available at: [https://psychiatryonline.org/pb/assets/raw/sitewide/practice\\_guidelines/guidelines/mdd.pdf](https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf). Last accessed May 2019.

Medical Director review 5/2019

Specialty Matched Consultant Advisory Panel 6/2019

Medical Director review 12/2019

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*. 2019 Sep; 76(9): 893-903.

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* 2019; 176:428-438.

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Janssen Pharmaceuticals, Inc. Spravato (esketamine) nasal spray. Highlights of prescribing information. July 2020. Available at: <http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/SPRAVATO-pi.pdf>. Last accessed September 2020.

Medical Director review 9/2020

Blue Cross NC Pharmacy and Therapeutics Committee 1/2021

## Policy Implementation/Update Information

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5/28/19 New policy developed. Spravato nasal spray is considered medically necessary for the treatment of adult patients (≥18 years old) with treatment-resistant depression. Added HCPCS code J3490 to Billing/Coding section. References added. Medical Director review 5/2019. (krc)

7/30/19 Added the following statement to criterion #3 for initial and continuation (maintenance) criteria within “When Covered” section, “or a comparable standardized

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rating scale that reliably measures depressive symptoms.” Specialty Matched Consultant Advisory Panel review 6/19/2019. (krc)

- 12/31/19 Added additional REMS program specifications within Policy Guidelines section for clarity. No change to policy intent. Added HCPCS codes G2082 and G2083 to Billing/Coding section effective 1/1/2020. Medical Director review 12/2019. (krc)
- 8/11/20 Added score descriptions to MADRS scoring description in Policy Guidelines. References added. Specialty Matched Consultant Advisory Panel review 6/17/2020. (krc)
- 10/1/20 Added the following new indication within “When Covered” section: “the patient has been diagnosed with major depressive disorder (MDD) with suicidal ideation or behavior and the suicidal ideation and intent are imminent and warrant potential hospitalization.” Updated Description and Policy Guidelines sections to reflect addition of new indication. Reference added. Medical Director review 9/2020. (krc)
- 12/31/20 Added HCPCS code S0013 to Billing/Coding section effective 1/1/2021. (krc)
- 5/4/21 Blue Cross NC Pharmacy and Therapeutics Committee 1/5/2021. Removed HCPCS code J3490 from Billing/Coding section for clarity. (krc)

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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.