BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 5/16/19**
SECTION: DRUGS	**LAST REVIEW DATE: 5/16/19**
	LAST CRITERIA REVISION DATE:
	ARCHIVE DATE:

SPRAVATO™ (esketamine Hcl) nasal solution

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

SPRAVATO™ (esketamine Hcl) nasal solution (cont.)

SPRAVATO IS AVAILABLE ONLY THROUGH RESTRICTED DISTRIBUTION UNDER A RISK EVALUATION AND MITIGATION STRATEGY (REMS) PROGRAM CALLED SPRAVATO REMS PROGRAM.

Criteria:

- **Criteria for initial therapy:** Spravato (esketamine) nasal spray is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in Psychiatry or is a Psychiatrist

2. Individual is 18 years of age or older

3. A confirmed diagnosis of major depressive disorder that is treatment resistant defined as not having responded adequately to at least **two** different antidepressants and **BOTH** of the following:
   - Each antidepressant treatment trial used the highest tolerable dose or the FDA-approved maximum for the medication
   - Each antidepressant treatment trial lasted at least 4-6 weeks

4. Individual has failed after at least 4 weeks of using the highest tolerable dose or the FDA-approved maximum, or is intolerant to, or has a contraindication such that the individual is unable to use **TWO** the following:
   - Augmentation strategy with **any** of the following:
     - Aripiprazole + antidepressant
     - Qeutiapine + antidepressant
     - Risperidone + antidepressant
     - Ziprasidone + antidepressant
     - Olanzapine + Fluoxetine or other antidepressant
     - Thyroid hormone + antidepressant
     - Lithium + antidepressant
   - Use of combination antidepressants from different classes
   - Switching failed antidepressant monotherapy to another antidepressant monotherapy

5. Individual has a low risk for abuse or misuse of Controlled Substances defined as a score of 3 or less using Substance Abuse Risk Assessment Tool (see Definitions section) before administration and during treatment

6. Individual has failed or is intolerant to intravenous ketamine

7. If approved, individual will continue use of an oral antidepressant concurrently with Spravato (esketamine)

8. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
   - Blood pressure, before administration and during the observation period
   - Patient has arranged for transportation home following each treatment

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- Montgomery-Asberg Depression Rating Scale (MADRS) baseline score of at least 35 (MADRS score must be submitted with request)
- A woman of child bearing potential is counselled on methods to prevent pregnancy during treatment

9. Will not be used in severe hepatic impairment (Child-Pugh Class C)

10. Will not be used in patients on renal dialysis

11. There are **NO** contraindications
    - Contraindications include:
      - Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels) or arteriovenous malformations
      - History of intracerebral hemorrhage
      - Hypersensitivity to esketamine, ketamine, or any of the excipients of the product

Initial approval duration: 4 weeks

- **Criteria for continuation of coverage (renewal request):** Spravato (esketamine) nasal spray is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be seen by a physician specializing in Psychiatry or is a Psychiatrist

2. Individual's condition responded and has not worsened while on therapy
   - Response is defined as:
     - Achieved and maintains a therapeutic benefit defined as **ONE** of the following:
       - At least a 4 point reduction in Montgomery-Asberg Depression Rating Scale (MADRS) after 4 weeks
       - Individual is in stable remission, defined as MADRS total score ≤ 12 for at least 3 of the last 4 weeks
       - Individual has a stable response, defined as MADRS total score reduction ≥ 50% for at least 3 of the last 4 weeks and not in remission
   - Worsening is defined as:
     - Individual has not relapsed, defined as **ANY** of the following:
       - MADRS total score ≥ 22 for 2 consecutive weeks
       - Hospitalization for worsening depression
       - Any other clinically relevant event indicative of relapse

3. Individual has been adherent with REMS requirements and is adherent with oral antidepressant therapy

4. individual will continue use of an oral antidepressant concurrently with Spravato (esketamine)

5. A woman of child bearing potential is not pregnant or has been counselled on methods to prevent pregnancy during treatment

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6. A woman of child bearing potential is not breast feeding an infant or child

7. Will not be used in severe hepatic impairment (Child-Pugh Class C)

8. Will not be used in patients on renal dialysis

9. Individual has a low risk for abuse or misuse of Controlled Substances defined as a score of 3 or less using Substance Abuse Risk Assessment Tool (see Definitions section)

10. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
    - Contraindications as listed in the criteria for initial therapy section
    - Significant adverse effect such as:
        - Persistent, prolonged or delayed sedation after treatment
        - Persistent dissociative or perceptual changes, derealization, or depersonalization
        - No evidence of clinical worsening or emergence of suicidal thoughts and behaviors
        - No evidence of persistent elevations in blood pressure, hypertensive crisis, or hypertensive encephalopathy
        - No evidence of cognitive and memory impairment

11. There are no significant interacting drugs

Renewal duration: 6 months

- Spravato (esketamine) nasal spray for all other indications not previously listed or if above criteria is not met, use is considered ***experimental or investigational*** based upon:

1. Lack of final approval from the Food and Drug Administration, and
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
3. Insufficient evidence to support improvement of the net health outcome, and
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, *but are not limited to:*

- Treatment with dosing or frequency outside the FDA-approved dosing and frequency

SPRAVATO™ (esketamine Hcl) nasal solution (cont.)

Description:

Spravato (esketamine) is indicated for treatment-resistant depression (TRD) in adults. It used in conjunction with an oral antidepressant. Because of the risks of serious adverse outcomes resulting from sedation, dissociation, and abuse and misuse, Spravato (esketamine) is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the SPRAVATO REMS. Spravato (esketamine) is a schedule III controlled substance.

Spravato (esketamine) must be given under the direct supervision of a healthcare provider. A treatment session consists of nasal administration and post-administration observation under supervision for a minimum of 2 hours to determine if the patient is clinically stable.

TRD refers to the occurrence of a major depressive episode resulting from an inadequate response to therapy after using adequate dosing and used for an adequate duration. The failure of at least two trials of antidepressant monotherapies in the current episode may indicate TRD, but the number of treatment trials is not standardized. The common definition of inadequate response to two or more antidepressants does not take into account adjunctive strategies and those with varying levels of response to therapy. Factors that may contribute to inadequate treatment include: early discontinuation of treatment, insufficient dosage of medication, patient noncompliance, misdiagnosis, and concurrent psychiatric disorders. Initial treatment may not work or may cause unacceptable side effects and switching to a different therapy is common occurrence in treating depressed patients. A trial of a therapy may require dose adjustments and 6-12 weeks to assess response.

Patients with major depressive disorder (MDD) may have other co-existing psychiatric illnesses such as bipolar disorder (termed depression with mixed features), substance use disorders and anxiety disorders. Patients with TRD who have such other psychiatric conditions may not respond as well to antidepressant treatments. It is unclear how esketamine may work in such patients, as patients with co-existing disorders including psychosis, mania, and moderate or severe substance use were excluded from the clinical trials of esketamine.

Several therapeutic options for individuals with TRD are available, such as switching to an antidepressant from the same pharmacological class (e.g., from one SSRI to another) or switching to a different pharmacological class of antidepressants (e.g., from an SSRI to a SNRI or a tricyclic antidepressant). Combination therapy with an antidepressant from another pharmacological class, or augmentation with a non-antidepressant medication (e.g., an antipsychotic or lithium). There is limited evidence comparing these different strategies

In three meta-analyses of double-blind, randomized, controlled trials evaluating the role of ketamine for depressive disorders, the use of a single infusion of ketamine has been shown to produce a rapid antidepressant response that lasts approximately seven days. This effect has been seen when ketamine is used as monotherapy and as an antidepressant augmentation strategy. Repeated infusions have been assessed in a limited number of patients in open-label and blinded studies with positive results; however, relapse rates were high within the 2-3 weeks following treatment in the open-label studies.

Despite positive studies for depressive episodes, there are currently no guidelines recommending the use of ketamine in major depressive disorder. Due to a lack of long-term data in patients with depressive episodes without psychotic features associated with major depressive disorder, the American Psychiatric Association's Council of Research Task Force on Novel Biomarkers and Treatments recommends balancing the risk of each infusion with the risk of long-term exposure, including neurotoxicity, cystitis, and abuse potential.

SPRAVATO™ (esketamine Hcl) nasal solution (cont.)

Esketamine, the S-enantiomer of racemic ketamine, is a non-selective, non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor. The mechanism by which esketamine exerts its antidepressant effect is unknown. The major circulating metabolite of esketamine (noresketamine) demonstrated activity at the same receptor but with less affinity.

Definitions:

Major depressive disorder (MDD):
Also known as, Unipolar Major Depression is diagnosed in patients who suffer at least one major depressive episode and have no history of mania or hypomania

Major depressive episode:
Is a period lasting at least two weeks, with *five or more* of the following symptoms: depressed mood, anhedonia, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, low energy, poor concentration, thoughts of worthlessness or guilt, and recurrent thoughts about death or suicide

Treatment-resistant depression (**TRD**):
A term used to describe a condition that affects people with major depressive disorder (MDD) who do not respond adequately to a course of appropriately dosed antidepressant medication within a certain time

A major depressive episode that does not respond satisfactorily to at least two trials of antidepressant monotherapy; however, the definition has not been standardized

Substance Abuse Risk Assessment Tool:
Adapted from Opioid Risk Tool by Webster LR, Webster R. Predicting aberrant behaviors in Opioid-treated patients: preliminary validation of the Opioid risk tool. Pain Med. 2005; 6 (6):432

Circle each that applies	Female	Male
Family history of substance abuse		
Alcohol	1	3
Illegal drugs	2	3
Rx drugs	4	4
Personal history of substance abuse		
Alcohol	3	3
Illegal drugs	4	4
Rx drugs	5	5
Age between 16-45 years	1	1
History of preadolescent sexual abuse	3	0
Psychological disorders		
ADD,OCD, Bipolar, Schizophrenia	2	2
Depression	1	1
Score total		

SPRAVATO™ (esketamine Hcl) nasal solution (cont.)

Assessment of risk	
Low risk for abuse	≤ 3
Moderate risk for abuse	4-7
High risk for abuse	≥ 8
Definitions of risk	
Low = unlikely to abuse Moderate = as likely will as will not abuse High = likely to abuse	

Montgomery-Asberg Depression Rating Scale (MADRS):

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones that allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5) and then report the appropriate number. The items should be rated with regard to the state of the patient over the past week. Score can range from 0 to 60, with higher scores indicating more severe depression. Total score can range from 0 to 60, with higher scores indicating more severe depression. Usual cut-points are: score 0-6 = no depression; score 7-19 = mild depression; score 20-34 = moderate depression; and score 35-60 = severe depression.

1 - APPARENT SADNESS - *Representing despondency, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.*

0 No sadness
1
2 Looks dispirited but does brighten up without difficulty
3
4 Appears sad and unhappy most of the time
5
6 Looks miserable all the time. Extremely despondent.

2 - REPORTED SADNESS - *Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.*

0 Occasional sadness in keeping with the circumstances.
1
2 Sad or low but brightens up without difficulty.
3
4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
5
6 Continuous or unvarying sadness, misery or despondency.

3 - INNER TENSION - *Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.*

0 Placid. Only fleeting inner tension.
1
2 Occasional feelings of edginess and ill-defined discomfort
3
4 Continuous feelings of inner tension or intermittent panic that the patient can only master with some difficulty.

5
6 Unrelenting dread or anguish. Overwhelming panic.

4 - REDUCED SLEEP - *Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.*

0 Sleeps as usual.
1
2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep
3
4 Sleep reduced or broken by at least two hours.
5
6 Less than two or three hours sleep.

5 - REDUCED APPETITE - *Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.*

0 Normal or increased appetite.
1
2 Slightly reduced appetite
3
4 No appetite. Food is tasteless.
5
6 Needs persuasion to eat at all.

6 - CONCENTRATION DIFFICULTIES - *Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.*

0 No difficulties in concentrating.
1
2 Occasional difficulties in collecting one's thoughts.
3
4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
5
6 Unable to read or converse without great difficulty.

7 - LASSITUDE - *Representing a difficulty getting started or slowness initiating and performing everyday activities.*

0 Hardly any difficulties in getting started. No sluggishness.
1
2 Difficulties in starting activities.
3
4 Difficulties in starting simple routine activities, that are carried out with effort.
5
6 Complete lassitude. Unable to do anything without help.

8 - INABILITY TO FEEL - *Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure.The ability to react with adequate emotion to circumstances or people is reduced.*

0 Normal interest in the surroundings and in other people.
1
2 Reduced ability to enjoy usual interests.
3
4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
5
6 The experience of being emotionally paralyzed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

9 - PESSIMISTIC THOUGHTS - *Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.*

0 No pessimistic thoughts.

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1
2 Fluctuating ideas of failure, self-reproach or self-depreciation.
3
4 Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.
5
6 Delusions of ruin, remorse and unredeemable sin. Self-accusations which are absurd and unshakable.

10 - SUICIDAL THOUGHTS - *Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.*

0 Enjoys life or takes it as it comes.
1
2 Weary of life. Only fleeting suicidal thoughts.
3
4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
5
6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

Risk Evaluation and Mitigation Strategies (REMS):

Use of Spravato (esketamine) is subject to a Risk Evaluation and Mitigation Strategies (REMS) program that requires provider, patient, and dispensing pharmacy be enrolled into the program. Only providers and Pharmacies enrolled into the REMS may prescribe and dispense the drug, respectively, to individuals who are also in the program. A REMS program attempts to manage known or potentially serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) for some drugs to ensure that the benefits of a drug outweigh its risks.
The requirements of the SPRAVATO REMS include the following:

- Healthcare settings must be certified in the program and ensure that Spravato is:
  - Only dispensed in healthcare settings and administered to patients who are enrolled in the program.
  - Administered by patients under the direct observation of a healthcare provider and that patients are monitored by a healthcare provider for at least 2 hours after administration of Spravato.
- Pharmacies must be certified in the REMS and must only dispense Spravato to healthcare settings that are certified in the program

Resources:

Spravato (esketamine) nasal spray product information accessed 04-02-19 at DailyMed: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d81a6a79-a74a-44b7-822c-0dfa3036eaed

UpToDate: Unipolar depression in adults: Treatment of resistant depression. Current through Feb 2019.

Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. *Pain Med*. 2005;6(6):432-442. PMID: 16336480

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:	Dosage Form:
Directions for Use:	Quantity: / Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.