Clinical Policy: Esketamine (Spravato)

Reference Number: AZ.CP.PMN.199
Effective Date: 05.19.20
Last Review Date: 07.20
Line of Business: Arizona Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Esketamine (Spravato™) is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist.

FDA Approved Indication(s)

Spravato is indicated for the treatment of treatment-resistant depression (TRD) in adults, in conjunction with an oral antidepressant.

Limitation(s) of use: Spravato is not approved as an anesthetic agent. The safety and effectiveness of Spravato as an anesthetic agent have not been established.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of Arizona Complete Health that Spravato is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Treatment-Resistant Depression (must meet all)**:**

1. Member has a confirmed diagnosis of major depressive disorder as defined by the DSM-V criteria and is treatment resistant;
2. Age ≥ 18 years;
3. Spravato is prescribed by or in consultation with a psychiatric provider;
4. Member does not have an active substance use disorder (SUD) or if SUD is not in remission, member is currently receiving therapy;
5. Member has experienced an inadequate response during the current depressive episode with each of the following therapies (a and b) or (a and c):
   a. **Two** antidepressants from at least **two** different classes (must include one of each AHCCCS preferred agents: SSRI, SNRI, and bupropion) having different mechanisms of action at the maximally tolerated labeled dose, each used for at least 4-6 weeks AND
   b. At least **two** augmentation therapies below for at least 4 weeks:
      i. SSRI or SNRI and a second-generation antipsychotic used concomitantly (aripiprazole, quetiapine, risperidone, olanzapine);
      ii. SSRI or SNRI and lithium used concomitantly;
      iii. SSRI or SNRI and liothyronine (T3) used concomitantly;

iv. SSRI or SNRI and mirtazapine;
v. SSRI and bupropion and buspirone;
OR

c. Member has active suicidal ideation and urgent symptom control is necessary;

6. Esketamine is used in combination with an oral antidepressant (e.g., duloxetine, escitalopram, sertraline, venlafaxine);
7. Esketamine is administered under the direct supervision of a healthcare provider;
8. Provider is certified in the Spravato REMS program;
9. Member must be monitored by a health care provider for at least 2 hours after administration;
10. Dose does not exceed the following (must met all):
    a. 84 mg intranasally twice per week during the induction phase, (weeks 1-4);
    b. 84 mg intranasally once per week during the maintenance phase, (weeks 5-8);
    c. 56mg or 84mg every two weeks or once weekly (during week 9 and thereafter).

Approval duration: 3 months

B. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): AZ.CP.PMN.53 for Arizona Medicaid.

II. Continued Therapy

A. Treatment-Resistant Depression (must meet all)**:**

1. Provider attests that the member has documented improvement or sustained improvement in depressive symptoms from baseline;
2. Member use of esketamine is in combination with an oral antidepressant;
3. Member administers esketamine under the direct supervision of a healthcare provider;
4. Provider is certified in the Spravato REMS Program;
5. Member must continue to be monitored by a health care provider certified by the Spravato REMS Program for at least 2 hours after administration;
6. If request is for a dose increase, new dose does not exceed 84 mg (3 nasal spray devices) per week.

Approval duration: 6 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): AZ.CP.PMN.53 for Arizona Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – AZ.CP.PMN.53 for Arizona Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration
NMDA: non-competitive N-methyl D aspartate
SNRI: serotonin norepinephrine reuptake inhibitor
SSRI: selective serotonin reuptake inhibitor
TCA: tricyclic antidepressant
TRD: treatment-resistant depression

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
SSRI		
citalopram (Celexa®)	20 mg PO QD; may increase to 40 mg PO QD after one week	40 mg/day (≤ 60 years) 20 mg/day (> 60 years)
escitalopram (Lexapro®)	10 mg PO QD; may increase to 20 mg PO QD after 1 week	20 mg/day
fluoxetine (Prozac®, Prozac Weekly®)	Prozac: 20 mg PO QD; may increase by 10-20 mg after several weeks Prozac Weekly: 90 mg PO q week beginning 7 days after the last daily dose	Prozac: 80 mg/day Prozac Weekly: 90 mg/week
paroxetine (Paxil®, Paxil CR®, Pexeva®)	Paxil, Pexeva: 20 mg PO QD; may increase by 10 mg every week as needed Paxil CR: 25 mg PO QD; may increase by 12.5 mg every week as needed	Paxil, Pexeva: 50 mg/day Paxil CR: 62.5 mg/day
sertraline (Zoloft®)	50 mg PO QD; may increase every week as needed	200 mg/day
SNRIs		
duloxetine (Cymbalta®)	20 mg PO BID or 30 mg PO BID or 60 mg PO QD	120 mg/day
venlafaxine (Effexor®, Effexor XR®)	Effexor: 75 mg/day PO in 2-3 divided doses; may increase by 75 mg every 4 days as needed Effexor XR: 75 mg PO QD; may increase by 75 mg every 4 days as needed	Effexor: 225 mg/day (outpatient) or 375 mg/day (inpatient) Effexor XR: 225 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
desvenlafaxine (Pristiq®, Khedezla®)	50 mg PO QD	400 mg/day
Fetzima® (levomilnacipran)	20 mg PO QD for 2 days, then 40 mg PO QD; may increase by 40 mg every 2 days	120 mg/day
Second Generation Antipsychotics		
aripiprazole (Abilify®)	2 to 15 mg PO QD	15 mg/day
olanzapine (Zyprexa®)*	5 to 20 mg PO QD	20 mg/day
quetiapine (Seroquel®)*	25 to 400 mg PO QD	400 mg/day
risperidone (Risperdal®)*	0.25 to 3 mg PO QD	3 mg/day
Other Antidepressants		
bupropion (Aplenzin®, Budeprion SR®, Budeprion XL®, Forfivo XL®, Wellbutrin®, Wellbutrin SR®, Wellbutrin XL®)	Varies	Immediate-release: 450 mg/day (300 mg/day if pediatric) Sustained-release: 400 mg/day Extended-release (HCl): 450 mg/day Extended-release (HBr): 522 mg/day
buspirone*	15 to 20 mg/day PO in 2 divided doses	60 mg/day
mirtazapine (Remeron®)	15 to 15 mg PO QD	45 mg/day
lithium*	300 mg PO QD or BID; up to 600 to 1,200 mg PO daily in divided doses	1,200 mg/day
thyroid hormone*	25 to 50 mcg/day PO	50 mcg/day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
**Off-label*

Appendix C: Contraindications/Boxed Warnings

- Spravato is not indicated for the treatment of bipolar depression.
- Contraindication(s):
  - Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels) or arteriovenous malformation
  - History of intracerebral hemorrhage
  - Hypersensitivity to esketamine, ketamine, or any of the excipients
- Boxed warning(s):
  - Risk for sedation and dissociation after administration. Monitor patients for at least two hours after administration.
  - Potential for abuse and misuse. Consider the risks and benefits of prescribing Spravato prior to using in patients at higher risk of abuse. Monitor patients for signs and symptoms of abuse and misuse.

- Spravato is only available through a restricted program called the Spravato REMS.
- Increased risk of suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. Spravato is not approved for use in pediatric patients. Spravato is available only through a restricted program under a REMS called the Spravato REMS because of the risks of serious adverse outcomes from sedation, dissociation, and abuse and misuse.

- Spravato is available only through a restricted program called the SPRAVATO REMS. Important requirements of the SPRAVATO REMS include the following:
  - Pharmacies must be certified in the REMS and must only dispense Spravato to healthcare providers and settings that are certified for the REMS Program and to the provider's address that is listed on the provider's certification. Further information, including a list of certified pharmacies is available at www.SPRAVATOrems.com or 1-855- 382-6022.
  - SPRAVATO as part of the REMS Program, must be dispensed to a certified Health Care Setting operating under a DEA number for the overall management and storage elements related to a controlled substance. When a healthcare setting is registered, they must designate an authorized representative to be responsible for ensuring compliance with all REMS requirements.
  - Each provider who prescribes and oversees SPRAVATO administration must have a DEA number.
  - A provider can enroll his/her own DEA # as a Healthcare setting as long as the location/address of the physician's DEA registration is the same as the Healthcare Setting where SPRAVATO will be administered.
  - Healthcare practitioners must be certified in the program and ensure that Spravato is:
    - Only dispensed in healthcare settings to patients who are enrolled in the Spravato REMS 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.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Treatment-resistant depression	Administer in conjunction with an oral antidepressant. **Induction Phase** Weeks 1 to 4: Administer nasally twice per week Day 1 starting dose: 56 mg Subsequent doses: 56 mg or 84 mg **Maintenance Phase** Weeks 5 to 8: Administer 56 mg or 84 mg nasally once weekly	84 mg/dose

Indication	Dosing Regimen	Maximum Dose
	Week 9 and after: Administer 56 mg or 84 mg every 2 weeks or once weekly	

VI. Product Availability

Nasal Spray: 28 mg of esketamine per device. Each nasal spray device delivers two sprays containing a total of 28 mg esketamine.

VII. References

1. Spravato Prescribing Information. Titusville, NJ: Janssen Pharmaceuticals; November 2019. Available at: http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/SPRAVATO-pi.pdf. Accessed May 19, 2020.
2. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder, third edition. November 2010. Available at: http://psychiatryonline.org/guidelines.aspx. Accessed May 19, 2020.
3. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2019. Available at: http://www.clinicalpharmacology-ip.com/.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created per AHCCCS approved policy.	05.19.20	05.20

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.