Clinical Policy: Esketamine (Spravato)

Reference Number: PA.CP.PMN.199
Effective Date: 4.17.19
Last Review Date: 04.19

Revision Log

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 health plans affiliated with PA Health & Wellness® that Spravato is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

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

1. Diagnosis of treatment-resistant depression;
2. Age ≥ 18 years;
3. For members currently receiving Spravato, members will not be required to try and fail other agents;
4. For members not currently treated with Spravato (must meet a and b):
   a. Failure of two antidepressants (e.g., selective serotonin reuptake inhibitor [SSRI], serotonin-norepinephrine reuptake inhibitor [SNRI], tricyclic antidepressant [TCA], bupropion, mirtazapine) from at least two different classes at up to maximally indicated doses but no less than the commonly recognized minimum therapeutic doses, each used for ≥ 8 weeks, unless contraindicated or clinically significant adverse effects are experienced;
   b. Failure of two of the following antidepressant augmentation therapies, each used for ≥ 4 weeks, unless contraindicated or clinically significant adverse effects are experienced: second-generation antipsychotic, lithium, thyroid hormone;
5. Currently on an oral antidepressant for at least two weeks (must not be one of the aforementioned agents previously failed);
6. Dose does not exceed 168 mg (6 nasal spray devices) per week.

Approval duration: 4 weeks

B. Other diagnoses/indications

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

II. Continued Therapy

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

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
2. Member is responding positively to therapy;
3. Spravato is being used in combination with an oral antidepressant;
4. 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. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

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 policy – refer to PA.CP.PMN.53

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration
SNRI: serotonin norepinephrine reuptake inhibitor
SSRI: selective serotonin reuptake inhibitor
TCA: tricyclic antidepressant

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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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
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
TCAs		
amitriptyline (Elavil®)	25 to 50 mg/day PO QD or divided doses	150 mg/day
amoxapine	25 to 300 mg/day PO in divided doses	400 mg/day (300 mg/day if geriatric)
clomipramine* (Anafranil®)	12.5 to 150 mg/day PO QD	250 mg/day (200 mg/day if pediatric)
desipramine (Norpramin®)	25 to 300 mg/day PO QD	300 mg/day (100 mg/day if pediatric)
doxepin (Sinequan®)	25 to 300 mg/day PO QD	300 mg/day
imipramine HCl (Tofranil®)	25 to 200 mg/day PO QD or divided doses	200 mg/day (150 mg/day if geriatric or pediatric)
imipramine pamoate (Tofranil PM®)	25 to 200 mg/day PO QD or divided doses	200 mg/day (100 mg/day if geriatric or pediatric)
nortriptyline (Pamelor®)	25 to 150 mg/day PO QD	150 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
protriptyline (Vivactil®)	10 to 60 mg/day PO in divided doses	60 mg/day (30 mg/day if geriatric or pediatric)
trimipramine (Surmontil®)	25 to 200 mg/day PO QD	200 mg/day (100 mg/day if geriatric or pediatric)
Second Generation Antipsychotics		
aripiprazole (Abilify®)	2 to 15 mg PO QD	15 mg/day
Rexulti® (brexpiprazole)	0.5 to 3 mg PO QD	3 mg/day
Vraylar® (cariprazine)*	0.5 to 4.5 mg PO QD	4.5 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
ziprasidone (Geodon®)*	20 to 80 mg PO BID	160 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
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

- 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.
- Healthcare settings must be certified in the REMS 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.
  - Further information, including a list of certified pharmacies is available at www.Spravatorems.com or 1-855-382-6022.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Treatment-resistant depression	Administer in conjunction with an oral antidepressant. **Induction Phase** <u>Weeks 1 to 4:</u> Administer nasally twice per week Day 1 starting dose: 56 mg Subsequent doses: 56 mg or 84 mg **Maintenance Phase** <u>Weeks 5 to 8:</u> Administer 56 mg or 84 mg nasally once weekly <u>Week 9 and after:</u> Administer 56 mg or 84 mg every 2 weeks or once weekly	84 mg/dose

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; March 2019. Available at: http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/SPRAVATO-pi.pdf. Accessed March 7, 2019.
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 March 7, 2019.
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
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