RXADVANCE
2 Park Central Drive
Southborough, MA 01772

Clinical Policy Title:	esketamine
Policy Number:	RxA.484
Drug(s) Applied:	Spravato®
Original Policy Date:	03/06/2020
Last Review Date:	12/07/2020
Line of Business Policy Applies to:	All lines of business

Background

Esketamine (Spravato®) is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist. It is indicated, in conjunction with an oral antidepressant, for the treatment of:

- Treatment-resistant depression (TRD) in adults.
- Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior.

Limitation(s) of use:

- The effectiveness of esketamine in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use of esketamine does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of esketamine.
- Esketamine is not approved as an anesthetic agent; the safety and effectiveness of esketamine as an anesthetic agent have not been established.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
esketamine (Spravato®)	Treatment-resistant depression	Administer in conjunction with an oral antidepressant. **Induction Phase** Weeks 1 to 4: Administer intranasally 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 intranasally once weekly Week 9 and after: Administer 56 mg or 84 mg intranasally every 2 weeks or once weekly.	84 mg/dose
	Depressive symptoms in patients with MDD with acute suicidal ideation or behavior	Administer in conjunction with an oral antidepressant. 84 mg intranasally twice per week for 4 weeks.	84 mg/dose

Dosage Forms

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

Clinical Policy

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

I. Initial Approval Criteria

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

1. Diagnosis of treatment-resistant depression;
2. Prescribed by a psychiatrist who is certified in the Spravato® REMS program;
3. Age 18 years or older;
4. Member meets one of the following criteria (a or b):
   a. Member must meet both of the following (i and ii):
      i. Failure of two (2) antidepressants from at least two (2) different classes at up to maximally indicated doses but no less than the commonly recognized minimum therapeutic doses, each used for at least or more than eight (8) weeks, unless contraindicated or clinically significant adverse effects are experienced:
         a) Aminoketone (e.g. bupropion);
         b) Monoamine oxidase inhibitors (MAOIs) (e.g. Marplan, phenelzine, tranylcypromine);
         c) Noradrenaline and specific serotoninergic antidepressants (NASSAs) (e.g. amoxapine, maprotiline, mirtazapine, trazodone);
         d) Selective serotonin reuptake inhibitors (SSRIs) (e.g. citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline);
         e) Serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g. desvenlafaxine, duloxetine, Fetzima®, venlafaxine/XR);
         f) Tricyclic antidepressants (e.g. amitriptyline, desipramine, doxepin, imipramine, nortriptyline, trimipramine);
      ii. Failure of two (2) of the following antidepressant augmentation therapies, each used for at least or more than four (4) weeks, unless contraindicated or clinically significant adverse effects are experienced:
         a) Two (2) antidepressants with different mechanisms of action used concomitantly;
         b) An antidepressant and a second-generation antipsychotic used concomitantly;
         c) An antidepressant and lithium used concomitantly;
         d) An antidepressant and thyroid hormone used concomitantly;
         e) An antidepressant and buspirone used concomitantly;
   b. Member has profound depression and persistent suicidal ideation defined as all of the following:
      i. The prescriber represents that, in the absence of the requested drug, within the next 24 to 48 hours the member will require confinement in an acute care psychiatric institution;
      ii. Member has a depressive episode so acute and so severe that the member is not able to participate in self-care and is unable to participate at all in their usual daily activities;

iii. Member has persistent thoughts of hopelessness and helplessness as well as anhedonia;
iv. Member has thoughts of dying and/or self-harm for at least some part of each day;

5. Must be used in combination with an oral antidepressant;
6. The drug will be administered under the direct supervision of a healthcare provider;
7. Dose does not exceed 168 mg (6 nasal spray devices) per week.

Approval Duration
Commercial: 4 weeks
Medicaid: 4 weeks

II. Continued Therapy Approval

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

1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy (i.e. improvement or sustained improvement from baseline in depressive symptoms);
3. Esketamine 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
Commercial: 3 months
Medicaid: 3 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
BID: Twice Daily
FDA: Food and Drug Administration
PO: By Mouth
SNRI: Serotonin Norepinephrine Reuptake Inhibitor
SSRI: Selective Serotonin Reuptake Inhibitor
TCA: Tricyclic Antidepressant
MDD: Major Depressive Disorder
REMS: Risk Evaluation and Mitigation Strategy
YOA: Years of Age

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
SSRI		
citalopram (Celexa®)	20 mg PO once daily; may increase to 40 mg PO once daily after 1 week	60 yoa or younger:40 mg/day 61 yoa and older: 20 mg/day
escitalopram (Lexapro®)	10 mg PO once daily; may increase to 20 mg PO once daily after 1 week	20 mg/day
fluoxetine	20 mg PO once daily; may increase by 10-20	

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
(Prozac®)	mg after several weeks	80 mg/day
paroxetine (Paxil®, Paxil CR®, Pexeva®)	Paxil®, Pexeva®: 20 mg PO once daily; may increase by 10 mg every week as needed Paxil CR®: 25 mg PO once daily; 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 once daily; 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 once daily	120 mg/day
venlafaxine (Effexor XR®)	Effexor XR®: 75 mg PO once daily; may increase by 75 mg every 4 days as needed	225 mg/day
desvenlafaxine (Pristiq®)	50 mg PO once daily	400 mg/day
Fetzima® (levomilnacipran)	20 mg PO once daily for 2 days, then 40 mg PO once daily; may increase by 40 mg every 2 days	120 mg/day
TCAs		
amitriptyline	25 to 50 mg/day PO once daily 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 once daily	250 mg/day (200 mg/day if pediatric)
desipramine (Norpramin®)	25 to 300 mg/day PO once daily	300 mg/day (100 mg/day if pediatric)
doxepin	25 to 300 mg/day PO once daily	300 mg/day
imipramine HCl	25 to 200 mg/day PO once daily or divided doses	200 mg/day (150 mg/day if geriatric or pediatric)
imipramine pamoate	25 to 200 mg/day PO once daily or divided doses	200 mg/day (100 mg/day if geriatric or pediatric)
nortriptyline (Pamelor®)	25 to 150 mg/day PO once daily	150 mg/day
protriptyline	10 to 60 mg/day PO in divided doses	60 mg/day (30 mg/day if geriatric or pediatric)
trimipramine	25 to 200 mg/day PO once daily	200 mg/day (100 mg/day if geriatric or pediatric)

Drug Name	Dosage Regimen	Dose Limit/Maximum Dose
Second Generation Antipsychotics		
aripiprazole (Abilify®)	2 to 15 mg PO once daily	15 mg/day
Rexulti® (brexpiprazole)	0.5 to 3 mg PO once daily	3 mg/day
Vraylar® (cariprazine)*	0.5 to 4.5 mg PO once daily	4.5 mg/day
olanzapine (Zyprexa®)*	5 to 20 mg PO once daily	20 mg/day
quetiapine (Seroquel®)*	25 to 400 mg PO once daily	400 mg/day
risperidone (Risperdal®)*	0.25 to 3 mg PO once daily	3 mg/day
ziprasidone (Geodon®)*	20 to 80 mg PO BID	160 mg/day
Other Antidepressants		
bupropion (Aplenzin®, 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 once daily	45 mg/day
lithium*	300 mg PO once daily 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 (2) hours after administration.
  - Potential for abuse and misuse. Consider the risks and benefits of prescribing esketamine prior to

using in patients at higher risk of abuse. Monitor patients for signs and symptoms of abuse and misuse.
  - Esketamine 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. Esketamine is not approved for use in pediatric patients.

APPENDIX D: General Information

- Esketamine 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 esketamine 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 two (2) hours after administration of esketamine.
  - Pharmacies must be certified in the REMS and must only dispense esketamine to healthcare settings that are certified in the program.

References

1. Spravato Prescribing Information. Titusville, NJ: Janssen Pharmaceuticals; July 2020. Available at: http://www.janssenlabels.com/package-insert/product-monograph/prescribing- information/SPRAVATO-pi.pdf. Accessed September 28, 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 September 28, 2020.
3. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2019. Available at: http://www.clinicalpharmacology-ip.com/. Accessed September 28, 2020.
4. Janssen announces US FDA approval of Spravato® (esketamine) CIII nasal spray to treat depressive symptoms in adults with major depressive disorder with acute suicidal ideation or behavior. Available at: https://www.prnewswire.com/news-releases/janssen-announces-us-fda-approval-of-spravato-esketamine-ciii-nasal-spray-to-treat-depressive-symptoms-in-adults-with-major-depressive-disorder-with-acute-suicidal-ideation-or-behavior-301104437.html. Accessed September 28, 2020.
5. Koons C. Johnson & Johnson Spray Approved to Treat Suicidal People. Bloomberg. August 3, 2020. Available at: https://www.bloomberg.com/news/articles/2020-08-03/johnson-johnson-spray-approved-for-treating-suicidal-people. Accessed September 28, 2020.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/2020	03/06/2020
Policy was reviewed: 1. Clinical policy title was updated. 2. Dosage information and background updated. 3. Line of business updated. 4. Initial approval criteria for approval updated. 5. Continued therapy approval criteria II.A.1 was rephrased to “Member is currently receiving medication that has been authorized by RxAdvance..” 6. Appendix B reviewed with updated drugs. 7. Appendices A & D updated with general information 8. References were reviewed and updated.	09/28/2020	12/07/2020