

Clinical Policy: Esketamine (Spravato)

Reference Number: CP.PMN.199

Effective Date: 06.01.19

Last Review Date: 05.23

Line of Business: Commercial, HIM, Medicaid

[Coding Implications](#)

[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, in conjunction with an oral antidepressant, is indicated 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:

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

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 Centene Corporation[®] 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 TRD;
2. Prescribed by or in consultation with a psychiatrist;
3. Age ≥ 18 and < 65 years (*see Appendix E*);
4. Member has a documented baseline Patient Health Questionnaire (PHQ-9) score ≥ 15 , indicating moderately severe major depression, within the previous four weeks (*see Appendix D*);
5. Member meets one of the following (a or b):
 - a. Request is for the treatment of a member in a State with limitations on step therapy in certain mental health settings (*see Appendix F*);
 - b. For all other requests, both the following (i and ii):

- i. Failure of TWO antidepressants 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 ≥ 4 weeks, unless clinically significant adverse effects are experienced or all are contraindicated (e.g., selective serotonin reuptake inhibitor [SSRI], serotonin-norepinephrine reuptake inhibitor [SNRI], tricyclic antidepressant [TCA], bupropion, mirtazapine);
 - ii. Failure of TWO of the following antidepressant augmentation therapies, each used for ≥ 4 weeks, unless clinically significant adverse effects are experienced or all are contraindicated: second-generation antipsychotic, lithium, thyroid hormone, buspirone;
6. Currently stabilized on an oral antidepressant for at least two weeks (must not be one of the aforementioned agents previously failed) and (a):
 - a. Spravato will be used in combination with oral antidepressant;
7. Member meets one of the following (a or b):
 - a. No prior history of treatment with Spravato;
 - b. Documentation of a prior positive response to Spravato as documented by a history of $\geq 50\%$ reduction in PHQ-9 score;
8. Dose does not exceed 168 mg per week during four week induction phase.

Approval duration: 3 months (up to 23 nasal spray devices)

B. Major Depressive Disorder with Suicidal Ideation or Behavior (must meet all):

1. Diagnosis of MDD;
2. Prescribed by or in consultation with a psychiatrist;
3. Age ≥ 18 years;
4. Spravato is prescribed in combination with initiation or optimization of oral antidepressant therapy;
5. Member is recently (within the last 5 days) discharged from or currently in an acute or subacute inpatient care for suicidality;
6. Member meets one of the following (a or b):
 - a. No prior history of treatment with Spravato;
 - b. Documentation of a prior positive response to Spravato (*see Appendix E*);
7. Member meets one of the following (a, b, or c):
 - a. Montgomery-Åsberg Depression Rating Scale (MADRS) score is ≥ 20 (moderate depression) (*see Appendix D*);
 - b. Hamilton Rating Scale for Depression (HAM-D) score is ≥ 17 (moderate depression) (*see Appendix D*);
 - c. PHQ-9 score is ≥ 15 (moderately severe depression) (*see Appendix D*);
8. Dose does not exceed 84 mg (3 nasal spray devices) twice weekly.

Approval duration: 4 weeks (up to 23 nasal spray devices)

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

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):

- a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
 - b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

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

1. Member meets one of the following (a or b):
 - a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
 - b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B*);
2. Member is responding positively to therapy as evidenced by at least a 50% reduction in PHQ-9 score compared to baseline (*see Appendix D*);
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. Major Depressive Disorder with Suicidal Ideation or Behavior

1. Re-authorization is not permitted. Members must meet the initial approval criteria.

Approval duration: Not applicable

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

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
 - a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
 - b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for 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 – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration
HAM-D: Hamilton Rating Scale for Depression
MADRS: Montgomery-Åsberg Depression Rating Scale
MDD: major depressive disorder
NMDA: non-competitive N-methyl D aspartate

PHQ-9: Patient Health Questionnaire
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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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
TCA's		
amitriptyline (Elavil [®])	50 to 100 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
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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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
bupirone*	15 to 20 mg/day PO in 2 divided doses	60 mg/day
mirtazapine (Remeron [®])	15 to 45 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.
- 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.

Appendix D: PHQ-9, MADRS, and HAM-D Rating Scales

- The PHQ-9 is a 9-item multiple choice questionnaire used for diagnosis, screening, monitoring and measuring the severity of depression.

PHQ-9 Score	Depression Severity
5 – 9	Minimal symptoms
10 – 14	Minor depression Major depression, mild
15 – 19	Major depression, moderately severe
> 20	Major depression, severe

- The MADRS is a 10-item diagnostic questionnaire used to measure the severity of depressive episodes in patients with mood disorders.

MADRS Score	Depression Rating
0 – 6	Normal/symptom absent
7 – 19	Mild depression
20 – 34	Moderate depression
> 34	Severe depression

- The HAM-D17 scale is a 17-item depression assessment scale to assess severity of, and change in, depressive symptoms.

HAM-D Score	Depression Rating
0 – 7	Normal, absence or remission of depression
8 – 16	Mild depression
17 – 23	Moderate depression
> 24	Severe depression

Appendix E: General Information

- Positive responses to therapy include but are not limited to:
 - Previous demonstrated improvement in depressive symptoms
 - Rapid reduction in depressive symptoms and thus rapid reduction in suicidality, either during hospitalization, or during a previous episode of suicidality.
 - Improvement from baseline in PHQ-9, MADRS, or HAM-D17 score.

- The efficacy of Spravato for the treatment of TRD in geriatric patients was evaluated in a 4-week, randomized, double-blind study with patients receiving placebo or Spravato intranasally plus an oral antidepressant (TRANSFORM-3).
 - The trial included patients between the ages of 65 and 74 years old.
 - At the end of four weeks, Spravato plus antidepressant did not achieve statistically significant difference when compared to those receiving placebo plus antidepressant on the primary efficacy endpoint of change from baseline to Week 4 on the MADRS.
 - During the double-blind phase, TEAEs occurred in 70.8% (51/72) of patients receiving antidepressant plus Spravato and 60.0% (39/65) receiving antidepressant plus placebo. Overall, safety results were consistent with those reported in previous esketamine studies in younger adults, including those in patients ≥ 75 years old.

Appendix F: States with Limitations against Redirections in Certain Mental Health Settings

State	Step Therapy Prohibited?	Notes
TX	No	<i>*Applies to HIM requests only*</i> Failure of ONE of the following antidepressant augmentation therapies, used for ≥ 4 weeks, unless clinically significant adverse effects are experienced or all are contraindicated: second-generation antipsychotic, lithium, thyroid hormone, buspirone

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
TRD	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
Depressive symptoms with MDD with acute suicidal ideation or behavior	Administer in conjunction with an oral antidepressant. Administer 56 mg or 84 mg nasally twice weekly for 4 weeks.	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; July 2020. Available at: <http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/SPRAVATO-pi.pdf>. Accessed February 7, 2023.
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>.
3. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc. Updated periodically. Accessed February 7, 2023.
4. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* 2001;16(9):606–613.
5. Montgomery–Åsberg Depression Rating Scale. Available at: http://www.liquisearch.com/montgomery%E2%80%93%C3%85sberg_depression_rating_scale/interpretation. Accessed February 9, 2022.
6. Sharp, Rachel. The Hamilton rating scale for depression. *Occupational Medicine.* 2015; 65(4):340.
7. Ochs-Ross R, Daly EJ, Zhang Y et al. Efficacy and safety of esketamine nasal spray plus an oral antidepressant in elderly patients with treatment-resistant depression TRANSFORM-3. *Am J Geriatr Psychiatry.* 2020 Feb;28(2):121-141.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
G2082	Office or other outpatient visit for the evaluation and management of an established patient that requires the supervision of a physician or other qualified health care professional and provision of up to 56 mg of esketamine nasal self-administration, includes 2 hours post administration observation
G2083	Office or other outpatient visit for the evaluation and management of an established patient that requires the supervision of a physician or other qualified health care professional and provision of greater than 56 mg esketamine nasal self-administration, includes 2 hours post administration observation

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created.	03.12.19	05.19

Reviews, Revisions, and Approvals	Date	P&T Approval Date
No significant changes; finalized line of business to apply to HIM.	06.25.19	
2Q 2020 annual review: no significant changes; references reviewed and updated.	02.07.20	05.20
Added requirements for PHQ-9 score of at least 15 for initial approval with a decrease of at least 50% from baseline for continued approval.	04.28.20	08.20
Criteria added for new FDA-approved indication: MDD with acute suicidality; for TRD indication initial review: added a time frame to the PHQ-9 score of 4 weeks to ensure assessment is current, added criteria for either no previous use of Spravato or prior positive response to ensure appropriate use, added requirement for psychiatrist prescriber and added upper limit of 65 years of age; updated HCPCS codes for administration; updated Appendix D; references reviewed and updated.	10.20.20	11.20
Criteria for major depressive disorder with suicidal ideation or behavior revised to state: member is recently (within the last 5 days) discharged from “or currently in an” acute or subacute inpatient care for suicidality; references to HIM.PHAR.21 revised to HIM.PA.154.	11.18.20	02.21
2Q 2021 annual review: corrected upper age limit to less than 65 years; references reviewed and updated.	02.01.21	05.21
2Q 2022 annual review: no significant changes; references reviewed and updated.	02.09.22	05.22
Reduced trial duration of antidepressants for TRD from at least 8 weeks to 4 weeks	06.07.22	08.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.05.22	
2Q 2023 annual review: for TRD added clarification that Spravato be used in combination with oral antidepressant; references reviewed and updated.	02.07.23	05.23
For TRD, added redirection bypass for members in a State with limitations on step therapy in certain mental health settings along with Appendix F, which includes Texas with requirements for single drug redirection for HIM requests.	07.11.23	

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.

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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.

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