STATE OF IOWA DEPARTMENT OF
Health AND Human
SERVICES

Spravato (esketamine nasal spray)
PAM–021

Iowa Medicaid Program:	Prior Authorization	**Effective Date:**	01/01/2021
Revision Number:	5	**Last Rev Date:**	04/19/2024
Reviewed By:	Medicaid Medical Director	**Next Rev Date:**	04/18/2025
Approved By:	Medicaid Clinical Advisory Committee	**Approved Date:**	04/16/2021

Overview

Medication:[1]	esketamine
Brand Name:	Spravato®
Pharmacologic Category:	N-methyl-D-aspartate (NMDA) receptor antagonist
FDA-Approved Indication(s):	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 • Limitations of use - The effectiveness of Spravato® in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of Spravato®. - Spravato® is not approved as an anesthetic agent. The safety and effectiveness of Spravato® as an anesthetic agent have not been established.
How Supplied:	Available in a stoppered glass vial within a nasal spray device. Each nasal spray device delivers two sprays containing a total of 28 mg of esketamine: • 56 mg dose kit: unit-dose carton containing two 28 mg nasal spray devices • 84 mg dose kit: unit-dose carton containing three 28 mg nasal spray devices
Dosage† and Administration:	• Spravato must be administered under the direct supervision of a healthcare provider. • A treatment session consists of nasal administration of Spravato and post-administration observation under supervision. • Monitor patients for changes in respiratory status for at least 2 hours (including pulse oximetry) at each treatment session. • Assess blood pressure prior to treatment. Do not administer Spravato if an increase in blood pressure or intracranial pressure poses a serious risk. After treatment, reassess blood pressure at 40 minutes and subsequently as clinically warranted. † See following tables for dosing recommendations for FDA-approved indications.
Benefit Category:	Medical

Treatment-Resistant Depression (TRD)			
Treatment Phase	Time Frame	Administration Frequency	Dosage
Induction	Weeks 1 to 4	Twice per week	Day 1 starting dose: 56 mg Subsequent doses: 56 mg or 84 mg
Maintenance	Weeks 5 to 8	Once weekly	56 mg or 84 mg
Maintenance	Week 9 & after	Every 2 weeks or once weekly*	56 mg or 84 mg

* Dosing frequency should be individualized to the least frequent dosing to maintain remission/response

Major Depressive Disorder (MDD) with Acute Suicidal Ideation or Behavior			
Treatment Phase	Time Frame	Administration Frequency	Dosage
Treatment	Weeks 1 to 4 ‡	Twice per week	Day 1 starting dose: 56 mg Subsequent doses: 56 mg or 84 mg

‡ After 4 weeks of treatment with Spravato®, evidence of therapeutic benefit should be evaluated to determine need for continued treatment. The use of Spravato® beyond 4 weeks has not been systematically evaluated in the treatment of depressive symptoms in patients with major depressive disorder (MDD) with acute suicidal ideation or behavior.

BOXED WARNING

Sedation: Patients are at risk for sedation after administration of Spravato®.

Dissociation: Patients are at risk for dissociative or perceptual changes after administration of Spravato®.

Respiratory Depression: Respiratory depression has been observed in postmarketing experience.

- Because of the risks of sedation, dissociation, and respiratory depression, patients must be monitored for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting.

Abuse and Misuse: Spravato® has the potential to be abused and misused. Consider the risks and benefits of prescribing Spravato® prior to use in patients at higher risk of abuse. Monitor patients for signs and symptoms of abuse and misuse.

- Because of the risks of serious adverse outcomes resulting from sedation, dissociation, respiratory depression, abuse and misuse, Spravato® is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the SPRAVATO REMS.

Suicidal Thoughts and Behaviors: Antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors. Spravato® is not approved for use in pediatric patients.

Descriptive Narrative

Major depressive disorder (MDD) is a psychiatric condition that clinically manifests through changes in mood and cognition as well as a loss of interest or pleasure lasting at least 2 weeks. Annual prevalence of a major depressive disorder among U.S. adults is 7.1%, among whom half receive medication treatment for their condition.

Failure to respond or achieve remission after 2 or more trials of medication treatment for MDD of adequate dose and duration is typically referred to as treatment-resistant depression (TRD), but a universally accepted definition of TRD is lacking. Estimates of the prevalence of TRD vary widely in the literature (12% - 55%) in part due to the lack of uniformity in the criteria used to define it.

A research article posted in the Journal of Clinical Psychiatry in 2021 assessed the national economic burden of TRD and of medication-treated MDD in the United States (encompassing health care costs, productivity costs, and unemployment costs. The total annual incremental burden incurred by adults with medication-treated MDD relative to those without MDD was $92.7 billion, including:

- $45.5 billion (49.1%) in health care costs;
- $28.8 billion (31.1%) in productivity costs; and
- $18.3 billion (19.8%) in unemployment costs.

Adults with TRD accounted for $43.8 billion (47.2%) of these incremental costs.[2]

DSM-5 Diagnostic Criteria for a Major Depressive Episode[3]

(DSM V: Diagnostic and Statistical Manual of Mental Disorders)

A. Five or more of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure (NOTE: Do not include symptoms that are clearly attributable to another medical condition).
   1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observations made by others (e.g., appears tearful) (NOTE: In children and adolescents, can be irritable mood).
   2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
   3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5 percent of body weight in a month) or decrease or increase in appetite nearly every day (NOTE: In children, consider failure to make expected weight gain).
   4. Insomnia or hypersomnia nearly every day.
   5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
   6. Fatigue or loss of energy nearly every day.
   7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
   8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by their subjective account or as observed by others).
   9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the direct physiological effects of a substance or to another medical condition.

Tools for Measuring Depression

Evaluation of depression and response to treatment is accomplished utilizing a standard rating scale to survey the type and severity of symptoms. There are several standardized rating scales available including the following:

- Beck Depression Inventory (BDI)
- Geriatric Depression Scale (GDS)
- Hamilton Depression Rating Scale (HAM-D)
- Inventory of Depressive Symptomatology-Systems Review (IDS-SR)
- Montgomery-Asberg Depression Rating Scale (MADRS)
- Personal Health Questionnaire Depression Scale (PHQ-9)
- Quick Inventory of Depressive Symptomatology (QIDS)

Guidelines

Clinical practice guidelines for the treatment of depression were last updated prior to FDA-approval of Spravato® in 2019.

Criteria

Prior authorization is required.

Use of ketamine as an intravenous (IV) infusion is not FDA-approved and is not a covered benefit.

Treatment Resistant Depression (TRD)

Spravato® is considered medically necessary when **ALL** of the following are met:

1. Member meets the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria for major depressive disorder (MDD) within the previous 4 weeks; **AND**
2. Member is 18 years of age or older; **AND**
3. Depression has been determined to be treatment-resistant (in the current depressive episode, member has not responded adequately to at least two different antidepressants of adequate dose and duration); **AND**
4. Member has not responded to an adequate trial of augmentation therapy or cognitive behavioral therapy during the current depressive episode. Augmentation therapy includes an antidepressant drug plus one of the following, but not limited to, a second-generation antipsychotic, lithium, triiodothyronine, or buspirone; **AND**
5. Member will continue to use oral antidepressant therapy in addition to Spravato®; **AND**
6. Member has **NOT** been diagnosed with any of the following:
    a. Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation; **AND/OR**
    b. Intracerebral hemorrhage; **AND**
7. Prescribed by, or in consultation with, a psychiatrist or a psychiatric or mental health nurse practitioner; **AND**
8. Treatment will be administered at a facility that is certified under the Spravato® Risk Evaluation and Mitigation Strategy (REMS) program; **AND**
9. Dose does not exceed 84 mg (3 nasal spray devices) twice weekly during the 4-week induction phase or 84 mg (3 nasal spray devices) per week during the maintenance phase.

Spravato® is considered medically necessary for continuation of therapy when **ALL** of the following are met:

1. Member has a diagnosis of major depressive disorder (MDD) and is currently receiving medication through the Iowa Medicaid benefit or has previously met initial approval criteria; **AND**
2. The Member has had at least a 50 percent reduction in symptoms of depression compared to baseline using a standard rating scale that reliably measures depressive symptoms; **AND**
3. Member will continue oral antidepressant therapy in conjunction with Spravato®; **AND**
4. Prescribed by, or in consultation with, a psychiatrist or a psychiatric or mental health nurse practitioner; **AND**
5. Treatment will be administered at a facility that is certified under the Spravato® Risk Evaluation and Mitigation Strategy (REMS) program; **AND**
6. Dose does not exceed 84 mg (3 nasal spray devices) per week.

Major Depressive Disorder (MDD) with Acute Suicidal Ideation or Behavior

Spravato® is considered medically necessary when **ALL** of the following are met:

1. Member meets the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria for major depressive disorder (MDD) within the previous 4 weeks; **AND**
2. Member is judged to be at risk for suicide by a clinician based on consideration of suicidal behavior, expressed suicidal ideation, or overall clinical assessment consistent with significant continuing risk of suicide; **AND**
3. Member is 18 years of age or older; **AND**
4. Prescribed in combination with initiation or optimization of oral antidepressant therapy; **AND**
5. Member has **NOT** been diagnosed with any of the following:
    a. Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation; **AND/OR**
    b. Intracerebral hemorrhage; **AND**
6. Prescribed by, or in consultation with, a psychiatrist or a psychiatric or mental health nurse practitioner; **AND**
7. Treatment will be administered at a facility that is certified under the Spravato® Risk Evaluation and Mitigation Strategy (REMS) program; **AND**
8. Dose does not exceed 84 mg (3 nasal spray devices) twice weekly for a total of 4 weeks.*

* The use of Spravato®, in conjunction with an oral antidepressant, beyond 4 weeks has not been systematically evaluated in the treatment of depressive symptoms in patients with major depressive disorder (MDD) with acute suicidal ideation or behavior.

Approval Duration and Quantity Limits

Diagnosis	Initial	Continuation
Treatment resistant depression (TRD)	3 months 8 kits† per first 28 days, then 4 kits per 28 days	6 months 4 kits per 28 days
Major depressive disorder (MDD) with acute suicidal ideation or behavior	4 weeks 8 kits† for 28-day course of therapy	Not applicable

†Spravato is available in two formulations:

- 56 mg kit (containing two nasal spray devices, each containing 28 mg of esketamine)
- 84 mg kit (containing three nasal spray devices, each containing 28 mg of esketamine)

Coding and Product Information

The following list(s) of codes and product information are provided for reference purposes only and may not be all inclusive. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment, nor does the exclusion of a code imply that its association to the HCPCS code is inappropriate.

HCPCS	Description
S0013	Esketamine, nasal spray, 1 mg
E&M	Use appropriate evaluation and management (E&M) codes when billing for healthcare provider services required for Spravato administration and post-administration observation

ICD-10	Description
F32.0	Major depressive disorder, single episode, mild
F32.1	Major depressive disorder, single episode, moderate
F32.2	Major depressive disorder, single episode, severe without psychotic features
F32.4	Major depressive disorder, single episode, in partial remission
F32.5	Major depressive disorder, single episode, in full remission
F32.9	Major depressive disorder, single episode, unspecified
F33.0	Major depressive disorder, recurrent, mild
F33.1	Major depressive disorder, recurrent, moderate
F33.2	Major depressive disorder, recurrent, severe without psychotic features
F33.40	Major depressive disorder, recurrent, in remission, unspecified
F33.41	Major depressive disorder, recurrent, in partial remission
F33.42	Major depressive disorder, recurrent, in full remission
F33.9	Major depressive disorder, recurrent, unspecified

NDC (strength)	Labeler	Dosage	Pkg Size	Pkg Qty	Units/Pkg
50458-0028-00 (28 mg device)*	Janssen Pharmaceuticals, Inc.	1 mg	1	1	28
50458-0028-02 (56 mg kit)	Janssen Pharmaceuticals, Inc.	1 mg	1	2	56
50458-0028-03 (84 mg kit)	Janssen Pharmaceuticals, Inc.	1 mg	1	3	84

* 28 mg device is only sold as part of a 56 mg or 84 mg kit. NDC provided for informational purposes only.

Compliance

1. Should conflict exist between this policy and applicable statute, the applicable statute shall supersede.
2. Federal and State law, as well as contract language, including definitions and specific contract provisions or exclusions, take precedence over medical policy and must be considered first in determining eligibility for coverage.

3. Medical technology is constantly evolving, and Iowa Medicaid reserves the right to review and update medical policy on an annual or as-needed basis.

Medical necessity guidelines have been developed for determining coverage for member benefits and are published to provide a better understanding of the basis upon which coverage decisions are made. Medical necessity guidelines are developed for selected physician-administered medications found to be safe and proven to be effective in a limited, defined population or clinical circumstances. They include concise clinical coverage criteria based on current literature review, consultation with practicing physicians in the service area who are medical experts in the particular field, FDA and other government agency policies, and standards adopted by national accreditation organizations. Criteria are revised and updated annually, or more frequently if new evidence becomes available that suggests needed revisions.

References

[1] Spravato prescribing information (10/2023). Janssen Pharmaceuticals, Inc.: Titusville, NJ. Available online at www.spravatohcp.com. Accessed January 8, 2024.

[2] Zhdanava M, Pilon D, et al. The Prevalence and National Burden of Treatment-Resistant Depression and Major Depressive Disorder in the United States. J Clin Psychiatry. 2021 Mar 16;82(2):20m13699. PMID: 33989464.

[3] American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders.* Fifth edition. Washington, D.C.: American Psychiatric Association; 2013.

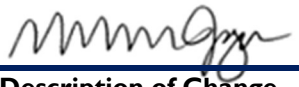
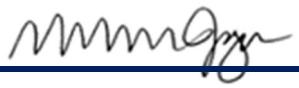
Development of utilization management criteria may also involve research into other state Medicaid programs, other payer policies, consultation with experts and review by the Medicaid Clinical Advisory Committee (CAC). These sources may not be referenced individually unless they are specifically published and are otherwise applicable to the criteria at issue.

Criteria Change History

Change Date	Changed By	Description of Change	Version
[mm/dd/yyyy]			
Signature			

Change Date	Changed By	Description of Change	Version
04/19/2024	CAC	Annual review. Added administration information to Overview table, including recommendation updated in 10/2023 prescribing information to monitor patient respiratory status during treatment. In Descriptive Narrative, added information from research article discussing the national economic burden of TRD and of medication-treated MDD in the U.S. Added NDC for individual 28 mg device. Updated references.	5
Signature William (Bill) Jagiello, DO			

Criteria Change History *(continued)*

Change Date	Changed By	Description of Change	Version
04/21/2023	CAC	Annual review. Incorporated "contraindications" and "experimental/ investigational" into the criteria language (instead of as separate sections). Updated references where applicable.	4
Signature			
William (Bill) Jagiello, DO			
Change Date	**Changed By**	**Description of Change**	**Version**
04/15/2022	CAC	Annual review. Rewrite.	3
Signature			
William (Bill) Jagiello, DO			
Change Date	**Changed By**	**Description of Change**	**Version**
02/14/2022	Medical Director	Clarifying language added to Coding section.	2
Signature			
William (Bill) Jagiello, DO			
Change Date	**Changed By**	**Description of Change**	**Version**
04/16/2021	CAC	Criteria implementation.	1
Signature			
William (Bill) Jagiello, DO			

CAC = Medicaid Clinical Advisory Committee