Position Statement on the Utilization of Intranasal Spray of Spravato (esketamine) for Treatment of Treatment-Resistant Depression

Effective Date: 05/07/2020
Date of Approval by Committee: 05/07/2020
Date Updated in Database: 05/07/2020

Rationale: To provide a guideline for providers requesting Spravato for treatment of Treatment-Resistant Depression (TRD).

Purpose: Behavioral health considers Evidence and Expert Consensus based literature findings in reviewing treatment of individuals with Treatment-Resistant Depression (TRD).

In 2019, the FDA has approved the use of Spravato TM in conjunction with an antidepressant as a novel treatment for TRD. The Prior Authorization (PA) criteria for Spravato treatment is described in the Centene Clinical Policy for health plans affiliated with Centene and it is consistent with policies developed by other health plan pharmacies. This is an outline of behavioral health's Spravato treatment requests process. There are 2 distinct treatment phases defining the initial acute stabilization and then the continuing treatment when the initial treatment results in a clinically meaningful outcome: ***Initial Approval*** describes treatment consisting of 4 weeks followed by ***Continued Therapy*** approval for up to 6 months treatment.

Background: Spravato TM (esketamine) is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist. Spravato, in conjunction with an antidepressant is approved by the FDA for the treatment of TRD in adults (>18 to). During the Induction Phase of treatment, Spravato is administered by the treating physician twice a week with a starting dose of 56mg, followed by subsequent doses of 56 or 84mg for the first four weeks or treatment. In the Maintenance Phase, during weeks 5-8, Spravato is administered once weekly at 56 or 84mg, and starting with week 9 and after it could be administered once weekly or every other week at 56 or 84mg, depending on "the least frequent dosing that maintains response/ remission. Special precautions should be taken in patients with hepatic impairments. The treating physician must fully observe all the FDA established REM requirements. The typical side effects expected may include a transient change in cognition (dissociation) an increase in the blood pressure, nausea and vomiting. That is why the patient must be monitored (line of sight) and the blood pressure must be assessed prior to each administration and reassessed within 40 minutes (esketamine plasma Tmax) after and then periodically over a period of up to 2 hours after administration. For patients showing a higher blood pressure prior to administration, proper consideration must be given to potential risks of short term pressure increases versus the treatment benefit. Also, patients should be advised to avoid food for at least 2 hours and to avoid drinking liquids for at least 30 minutes prior to administration.

There are limited available treatments effective for TRD. Other treatment modalities include electroconvulsive therapy (ECT) and Transcranial Magnetic Stimulation (TMS. The side effects and adverse events with the other modalities may include possible cognitive impairment, complications of anesthesia, seizures, and or headaches.

Mechanism of action: It is postulated that esketamine acts as an antagonist of the NMDA, receptors producing a transient increase in glutamate release and leading to stimulation of postsynaptic alpha-amino-

3hydroxy=5methyl-4-isoxazole propionic acid (AMPA) receptors and subsequently increasing neurotrophic signaling that restores synaptic function in the brain regions modulating mood.

Preauthorization Criteria (please refer to each plan's Policy for a complete description):

Providers must submit documentation (such as office chart notes, and other clinical information) supporting that the identified patient 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:

1. Diagnosis of treatment-resistant depression;
2. Age > 18 years;
3. Member has a documented baseline Patient Health Questionnaire – 9 (PHQ-9) score of at least 15, indicating moderately severe major depression
4. 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;
5. 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, buspirone;
6. Currently on an oral antidepressant for at least two weeks (must not be one of the aforementioned agents that previously failed);
7. Dose does not exceed 168 mg (6 nasal spray devices) per week. Approval duration: up to 23 nasal spray devices.

II. Continued Therapy

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member is responding positively to therapy as evidenced by at least a 50% reduction in PHQ-9 score compared to baseline (*Appendix A*);
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.
5. Approval duration: 6 months

MHN PROCEDURES for INITIAL Approval for Spravato Treatment Requests:

Contracting Providers

1. This will initially be handled as a benefit quote
2. Providers will be directed to contact the member's Health Plan Pharmacy for (PA) of the medication
3. Administration of the intranasal Spravato and supervision of the patient following treatment are paid as pass-through as long as there is a Pharmacy authorization on file.

Non Contracting Providers

A. If no Prior Authorization was obtained from Pharmacy:

1. This will be handled as benefit quotes
2. Providers will be directed to first contact the member's Health Plan Pharmacy for Prior Authorization (PA) before seeking a Single Care Agreement (SCA)
3. Pharmacy will inform behavioral health if benefit approval request is approved
4. Providers will call back behavioral health to request an SCA once the PA was approved.
5. Behavioral health clinician will advise that SCAs are approved IF no in-network providers are available to provide this treatment.
6. If providers accept this redirection, behavioral health clinicians will note this service as a benefit quote.

B. If PA was not yet obtained by provider from the Pharmacy but provider is persisting in requesting an SCA for Spravato treatment:

1. The case will be sent for secondary review with a behavioral health Medical Director
2. Behavioral Health Medical Director will review for medical necessity for treatment-resistant depression according to company policy and clinical expertise. Also, a minimum score of 15 on the baseline PHQ-9 depression severity scale will be required. A score of moderately severe to severe depression on a different standardized depression severity scale may be accepted.
3. MD will educate the provider that SCA would be approved when there are no other contracting providers able to provide the same treatment ***and contingent*** on PA approval from the Pharmacy. Provider must call behavioral health back after PA was approved.
4. Behavioral health MD will educate provider that if approved that PHQ-9 scores of depression severity or other standardized depression severity scales such as MADRS, Beck, or Hamilton Depression will be used to monitor and track response to treatment.
5. If the provider has not obtained prior authorization for the medication by the 5th business day, the CM will inform the reviewing behavioral health MD. A clinical denial of this SCA request.

C. If PA was obtained from Pharmacy for initial treatment

1. Clinician will confirm PA approval information with pharmacy
2. Clinician will search for any alternative contracting providers available to administer the medication and if none are found will bring the SCA request in reference to Spravato treatment to clinical rounds
3. Behavioral health MD will review Pharmacy PA and baseline severity score PHQ-9 (>15) or other standardized depression severity scale obtained from Pharmacy or MD.
4. SCA will be approved for 4 weeks of treatment as authorized by Pharmacy to complete the *initially approved* acute course of treatment.
5. Behavioral health will advise provider that an updated depression severity score will be required at the end of the *initial* treatment phase to determine response to the acute phase of treatment.

D. PROCEDURES for Continued Therapy Spravato Treatment After Initial Treatment of 4 weeks

1. After the initial 4 weeks of treatment, if the depression severity score shows a at least a 50% reduction from the baseline scores behavioral health will inform the provider that continued SCA approval is contingent upon pharmacy's PA for continued therapy.

2. If the score shows less than a 50% reduction from baseline scores in symptoms severity:
    1. Behavioral health will offer an MD: MD review to discuss the rationale for continuing Spravato when the response to the acute phase is not supporting continuation of treatment.
    2. Behavioral health MD may advise that treatment gains consistent with our Position Statement are not documented (e.g. 50% or more improvement in PHQ-9 score or Depression scale)
    3. Behavioral health MD may issue a medical necessity denial and advise an alternate treatment recommendation to meet the members' needs; such as IOP, PHP, ECT, TMS or other approved available treatment

E. If In-network behavioral health provider(s) is/are available to administer Spravato for member

1. The case will be sent to behavioral health MD for secondary review/consult with provider. Behavioral health MD will advise provider that in-network provider(s) is/are available to administer this course of treatment approved by Pharmacy and will issue an SCA denial.

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Appendix A: *PHQ-9 Rating Scale*

PHQ-9 is a standardized 9-item multiple choice self-assessment 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