Blue Cross Blue Shield Blue Care Network of Michigan

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Effective Date: 10/07/2021

Spravato™ (esketamine)

FDA approval: March 5, 2019
HCPCS: J3490, S0013
Benefit: Medical

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. Diagnosis of depressive symptoms in adults with Major Depressive Disorder with acute suicidal ideation
      i. Must receive standard of care treatment for acute suicidal ideation, including a comprehensive treatment plan that involves cognitive behavioral therapy or interpersonal psychotherapy and optimization or initiation of oral antidepressant therapy.
      OR
   b. Diagnosis of treatment resistant depression
      i. Trial and failure of at least two different oral antidepressants AND two augmentation therapies for at least 6 weeks. Each oral antidepressant and augmentation therapy must be used in combination with each other (augmentation therapies include but not limited to lithium, buspirone, and olanzapine).
      ii. Pharmacotherapy must be in combination with cognitive behavioral therapy or interpersonal psychotherapy weekly for at least 8 weeks of treatment to yield at least moderate improvement (20% diminution in symptoms). If no improvement, the clinician should review and reappraise the treatment plan.
      iii. Must be used in combination with one of the following oral antidepressants – duloxetine, sertraline, escitalopram, venlafaxine AND must not have experienced prior non-response to listed therapies.
   c. Prescribed by or in consultation with a psychiatrist
   d. Must not be used in combination with intravenous ketamine
   e. FDA approved age
   f. Trial and failure, contraindication, or intolerance to the preferred drugs as listed in BCBSM/BCN's utilization management medical drug list.

B. Quantity Limitations, Authorization Period and Renewal Criteria
   a. Quantity Limits: Align with FDA recommended dosing.
   b. Authorization Period:

i. Acute suicidal ideation: 1 month, no further authorization will be provided.
ii. TRD: 1 month initially then 6 months at a time thereafter
    1. Renewal Criteria: documented improvement in symptoms of depression

***Note: Coverage may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Therapeutic considerations:

A. **FDA approved indication/Diagnosis**

**Please refer to most recent prescribing information.*

B. **Background Information**

a. Spravato is a N-methyl-D-aspartate (NMDA) receptor antagonist which is indicated for the treatment of (1) treatment-resistant depression (TRD) in adults when used in conjunction with an oral antidepressant and (2) depressive symptoms in patients with Major Depressive Disorder (MDD) with acute suicidal ideation.

b. The approval for TRD was based on two of five Phase III clinical trials showing a statistically significant superiority of Spravato over placebo, one that measured the short-term (four week) efficacy of the drug and another that measured long-term efficacy.

    i. Patients were randomized to Spravato (flexible dose; 56 mg or 84 mg) or placebo nasal spray in combination with an oral antidepressant (either duloxetine, escitalopram, sertraline, or extended-release venlafaxine) in 3 phases: a screening/prospective observational phase (4-7 weeks), a DB induction phase (4 weeks), and a follow-up phase (24 weeks). The Spravato active group showed a greater improvement from baseline to day 28 in mean Montgomery-Asberg Depression Rating Scale (MADRS) compared to the placebo group (primary endpoint P=0.020).

    ii. In the longer-term trial, patients were randomized to a 5 phase study consisting of a screening/prospective observational phase (4-7 weeks) and open-label induction phase (4 weeks) for direct-entry patients only, an optimization phase (12 weeks; open-label for direct-entry patients and double-blind for transfer-entry patients), a maintenance phase (variable duration; double-blind for all patients), and a follow-up phase (2 weeks) with a primary efficacy endpoint of time to relapse among stable remitters during the maintenance phase. Spravato active group significantly delayed relapse compared to placebo (P=0.003) along with the risk of relapse decreased by 51%.

c. The American Psychiatry Association treatment guidelines recommend antidepressants as first line therapy. For most patients, a selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor (SNRI), mirtazapine, or bupropion are optimal treatment options. Initial selection of an antidepressant medication is largely based on the anticipated side effects, safety or tolerability of side effects for the individual patient, pharmacological properties of the medication, and additional factors such as medication response in prior episodes, cost, and patient preference.

d. If at least a moderate improvement in symptoms is not observed within 4–8 weeks of treatment initiation, the diagnosis should be reappraised, side effects assessed, complicating co-occurring conditions and psychosocial factors reviewed, and the treatment plan adjusted.

e. Treatment plan adjustments include optimizing current medication dose if the side effect burden is tolerable and the upper limit of a medication dose has not been reached. Additional opportunities include switching to another antidepressant from the same class or a different class or using augmented therapy such as antipsychotics or lithium.

f. Guidelines confirm a 20% higher response rate when combining pharmacotherapy and various forms of time-limited psychotherapies with the larger impact seen among patients with more severe symptoms and among those with more chronic depressive disorders.

g. Treatment guidelines do not recommend other forms of ketamine for the use in treatment resistant depression. Intravenous ketamine use is not FDA approved for this indication and is considered an off-label use.

h. Two phase 3 clinical trials, ASPIRE I and ASPIRE II, evaluated Spravato's use in patients with moderate to severe MDD and acute suicidal ideation. Patients were given Spravato 84 mg twice weekly for 4 weeks or placebo. All patients received standard of care treatment, including an inpatient psychiatric hospitalization and a newly initiated or optimized oral antidepressant. Spravato plus the standard-of-care treatment reduced MADRS by 15.9 and 16.0 points, in ASPIRE I and II respectively, compared to placebo. The secondary endpoint of reduction in suicidal ideation severity was not met.

i. The effectiveness of Spravato in preventing suicide 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.

j. For the treatment of suicidal behaviors in patients with MDD, American Psychiatric Association guidelines recommend selecting an antidepressant agent with a low risk of toxicity in overdose, such as an SSRI or SNRI. In highly anxious or agitated patients, trazadone, low dose second-generation antipsychotics, gabapentin, and divalproex may be used. Benzodiazepines should be used only in the short term if the benefits outweigh the risks. Patients with acute suicidal ideation should be treated in the setting that is least restrictive, yet most likely to be safe and effective. Guidelines have not been updated to include the place in therapy of any ketamine products.for direct-entry patients only, an optimization phase (12 weeks; open-label for direct-entry patients and double-blind for transfer-entry patients), a maintenance phase (variable duration; double-blind for all patients), and a follow-up phase (2 weeks) with a primary efficacy endpoint of time to relapse among stable remitters during the maintenance phase. Spravato active group significantly delayed relapse compared to placebo (P=0.003) along with the risk of relapse decreased by 51%.

C. **Efficacy**

**Please refer to most recent prescribing information.*

D. **Medication Safety Considerations**

**Please refer to most recent prescribing information.*

E. **Dosing and administration**

**Please refer to most recent prescribing information.*

F. **How supplied**

**Please refer to most recent prescribing information.*

References:

1. Spravato [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; February 2020.
2. American Psychiatric Association. Arlington (VA): Practice Guidelines for the Treatment of Patients with Major Depressive Disorder. November 2010. Available from: http://www.psychiatryonline.com/pracGuide/PracticePDFs/PG_Depression3rdEd.pdf. Accessed on March 7, 2019.
3. Wisniewski SR, Fava M, Trivedi MH, et al. Acceptability of second-step treatments to depressed outpatients: a STAR*D report. Am J Psychiatry 2007; 164:753–760.
4. Johnson and Johnson Press Release. Janssen announces U.S. FDA approval of spravato (esketamine) CIII nasal spray for adults with treatment-resistant depression (TRD) who have cycled through multiple treatments without relief. March 5, 2019. Available at: https://www.janssen.com/janssen-announces-us-fda-approval-spravato-esketamine-ciii-nasal-spray-adults-treatment-resistant. Accessed on March 7, 2019.
5. Clinicaltrials.gov. A study of intranasal esketamine plus an oral antidepressant for relapse prevention in adult participants with treatment-resistant depression (SUSTAIN-1). (NCT02493868) Available at: https://clinicaltrials.gov/ct2/show/NCT02493868. Accessed on March 7, 2019.
6. Clinicaltrials.gov. A study to evaluate the efficacy, safety, and tolerability of intranasal esketamine plus an oral antidepressant in elderly participants with treatment-resistant depression (TRANSFORM-3). (NCT02422186) Available at: https://clinicaltrials.gov/ct2/show/NCT02422186. Accessed on March 7, 2019.
7. IPD Analytics RxBrief: Spravato Nasal Spray Approved for Adults with Major Depressive Disorder with Acute Suicidal Ideation. September 2020..
8. American Psychiatric Association. Arlington (VA): Practice Guidelines for the Assessment and Treatment of Patients With Suicidal Behaviors. November 2010. Available from: https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/suicide.pdf. Accessed on September 15, 2020.

<table>
<tr><th colspan="3">Policy/UM Medical Management System Update History</th></tr>
<tr><th>#</th><th>Date</th><th>Change Description</th></tr>
<tr><td>1.5</td><td>Effective Date:
10/07/2021</td><td>Annual review of criteria was performed, no changes were made.</td></tr>
<tr><td>1.4</td><td>Effective Date:
10/08/2020</td><td>Policy created for Spravato.

Moved previously approved criteria from the full drug review document, which will be retired, to this policy.

Various criteria were updated including criteria for a new indication</td></tr>
<tr><td>1.3</td><td>Effective Date:
4/16/2020</td><td>Annual Review</td></tr>
<tr><td>1.2</td><td>Effective Date:
02/03/2020</td><td>UM medical management system update for MAPPO and BCNA

<table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><tr><td>BCBS</td><td>Yes</td></tr><tr><td>BCN</td><td>Yes</td></tr><tr><td>MAPPO</td><td>Yes</td></tr><tr><td>BCNA</td><td>Yes</td></tr></table></td></tr>
<tr><td>1.1</td><td>Effective Date:
06/01/2019</td><td>UM medical management system update for BCBS and BCN

<table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><tr><td>BCBS</td><td>Yes</td></tr><tr><td>BCN</td><td>Yes</td></tr><tr><td>MAPPO</td><td>No</td></tr><tr><td>BCNA</td><td>No</td></tr></table></td></tr>
<tr><td>1.0</td><td>Effective Date:
05/09/2019</td><td>New Policy</td></tr>
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** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm.*