Blue Cross Blue Shield Blue Care Network of Michigan

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Effective Date: 02/08/2024

Spravato® (esketamine)

HCPCS: J3490, S0013

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 (TRD)
      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 are 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 an oral antidepressant with which patient has not previously experienced non-response
   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: 60 days
      ii. TRD: 60 days initially then 6 months at a time thereafter

c. Renewal Criteria:
    i. Acute suicidal ideation: Not applicable as no further authorization will be provided
    ii. TRD: Documented improvement in symptoms of depression

***Note: Coverage and approval duration 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.

Background Information:

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

- TRD is a subset of MDD that is unresponsive to traditional and/or first-line therapeutic options. Though there is not a universal definition or staging model for TRD, a commonality among the many that have been proposed is an inadequate response to at least two trials of antidepressant pharmacotherapy.

- Antidepressants and psychotherapy are recommended first-line options to treat depression by The American Psychiatry Association guidelines for the treatment of depression (2010) and The American Psychological Association clinical practice guideline for the treatment of depression (2019). 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 comorbid conditions and psychosocial factors reviewed, and the treatment plan adjusted.

- For most patients, a selective serotonin reuptake inhibitor (SSRI) or serotonin norepinephrine reuptake inhibitor (SNRI) is an optimal treatment option, though other antidepressants like mirtazapine or bupropion can also be considered. 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.

- Treatment plan adjustments can 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 augmenting the antidepressant with psychotherapy or other pharmacologic agents.

- Pharmacologic augmentation of antidepressants can utilize other non-monoamine oxidase inhibitor (MAOI) antidepressants, generally from a different pharmacologic class, lithium, thyroid hormone, or a second-generation antipsychotic.

- Psychotherapy options with clinical evidence supporting their use include cognitive behavioral therapy (CBT), interpersonal psychotherapy, psychodynamic therapy, and problem-solving therapy. Effectiveness studies have demonstrated similar effects across psychotherapy. When combining treatment with psychotherapy and pharmacologic agents, the American Psychological Association recommends CBT or interpersonal psychotherapy with an SSRI or SNRI. 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.

- Spravato's approval for TRD was based on the Phase III SUSTAIN-1 and TRANSFORM-2 clinical trials that showed statistically significant superiority of Spravato over placebo in patients with TRD. TRANSFORM-2 measured the short-term (four week) efficacy of Spravato while SUSTAIN-1 evaluated long-term efficacy.

    - In TRANSFORM-2, 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 double-blind 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).

    - In the longer-term SUSTAIN-1 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%.

    - The oral antidepressants used in these trials were provided by the sponsor and represented the most commonly used standard of care antidepressants. The choice of which to administer was determined by the investigator based on patient-centric factors and availability in the participating study country.

- For the treatment of suicidal behaviors in patients with MDD, American Psychiatric Association guidelines (2010) 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.

- Two Phase III 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 comprehensive standard of care treatment, including an inpatient psychiatric hospitalization and a newly initiated or optimized oral antidepressant therapy. Antidepressant therapy consisted of either antidepressant monotherapy or an antidepressant plus augmentation therapy. Augmentation medications considered to be standard of care included typical and atypical antipsychotics, lithium, anticonvulsants, and any additional antidepressants used in conjunction with another 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.

- 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 MDD with acute suicidal ideation or behavior. Additionally, 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.

- Guidelines have not been updated to include the place in therapy of any ketamine products. There is no literature supporting the safety and efficacy of Spravato in combination with intravenous (IV) ketamine, which is often used off-label for psychiatric indications like TRD and MDD with suicidal ideation despite the lack of FDA approval.

References:

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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.
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14. American Psychological Association. (2019). Clinical practice guideline for the treatment of depression across three age cohorts. Retrieved from https://www.apa.org/depression-guideline on November 20, 2022.

<table>
<tr><th colspan="3">Policy History</th></tr>
<tr><th>#</th><th>Date</th><th>Change Description</th></tr>
<tr><td>1.8</td><td>Effective Date: 02/08/2024</td><td>Annual review of criteria was performed, no changes were made</td></tr>
<tr><td>1.7</td><td>Effective Date: 02/02/2023</td><td>Updated step criteria b.iii. to allow use of any oral antidepressant in conjunction with Spravato and changed the authorization period to 60 days</td></tr>
<tr><td>1.6</td><td>Effective Date: 10/06/2022</td><td>Annual review of criteria was performed, no changes were made.</td></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: 04/16/2020</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.*