esketamine (Spravato™)

Policy # 00681
Original Effective Date: 07/18/2019
Current Effective Date: 08/10/2020

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider esketamine (Spravato™)‡ for the treatment of treatment-resistant depression to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for esketamine (Spravato) will be considered when the following criteria are met:

- Patient is greater than or equal to 18 years of age; AND
- Spravato will be used in conjunction with an oral antidepressant; AND
- Patient has a diagnosis of treatment-resistant depression confirmed by trial and failure of more than one antidepressant from at least 2 different classes for at least 8 weeks each. (see policy background information for alternative antidepressants with classes).

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers esketamine (Spravato) when the patient selection criteria are not met to be **investigational.***

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Background/Overview

Spravato is a nasal spray formulation of esketamine, a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist. It is indicated in conjunction with an oral antidepressant for the treatment of treatment-resistant depression in adults. The mechanism by which it exerts its antidepressant effect is unknown, but it is known that esketamine causes an increased glutamate release which ultimately leads to increased release of various neurotrophic factors. Esketamine is the S-enantiomer of racemic ketamine, a drug that has been available for decades as an anesthetic agent. It has also been reported as a drug of abuse due to its dissociative and hallucinogenic effects. Spravato is a schedule III controlled substance and carries a boxed warning for sedation, dissociation, abuse and misuse, and suicidal thoughts and behaviors. The recommended dose of Spravato is 56 mg intranasally on Day 1, followed by 56 mg or 84 mg twice weekly for Weeks 1 to 4. For Weeks 5 to 8, Spravato should be administered once weekly at a dose of 56 mg or 84 mg. On Week 9 and thereafter, the dosing frequency should be individualized to the least frequent dosing to maintain remission/response (either once every 2 weeks or once weekly) at a dose of 56 mg or 84 mg. Because Spravato is only available in a device containing 28 mg of esketamine, the 56 mg dose requires two devices and the 84 mg dose requires 3 devices. Spravato must be administered under the direct supervision of a healthcare provider and the patient must be observed for at least 2 hours following administration. Patients should not engage in potentially hazardous activities, such as driving a motor vehicle or operating machinery, until the next day after a restful sleep. Due to the risks of serious adverse outcomes, Spravato is only available through a restricted distribution system via a Risk Evaluation and Mitigation Strategy (REMS).

Major depressive disorder is a serious, life-threatening condition with high rates of morbidity and a chronic disease course. It is considered the leading cause of disability worldwide and is also associated with increased mortality rates. About 30% to 40% of patients with major depressive disorder fail to respond to first-line treatments including oral antidepressant medications of all classes (see Table 1 for antidepressant classes with representative generic drugs). For regulatory purposes, the FDA considers patients to have treatment-resistant depression if they have major depressive disorder and they have not responded to treatment despite trials of at least two antidepressants given at adequate doses for an adequate duration in the current episode of depression. Treatment-resistant depression differs from an adjunctive treatment indication which applies to patients who have a partial, but insufficient, response to their current oral antidepressant and may benefit from add-on treatment. This patient population is typically less severely ill than the

treatment-resistant depression population, and these patients are frequently on their first antidepressant. Also, adjunctive treatment trials have lower depression scale cutoff scores for study entry than treatment-resistant depression trials.

Antidepressant Classes

Class	Representative generic drugs
Selective Serotonin Reuptake Inhibitors (SSRIs)	sertraline, fluoxetine, citalopram, escitalopram, paroxetine
Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)	venlafaxine, desvenlafaxine, duloxetine
Norepinephrine and Dopamine Reuptake Inhibitor	bupropion
Serotonin and α_2 adrenergic antagonist	mirtazapine
Mixed Serotonergic Effects	nefazodone, trazodone, vilazodone
Monoamine oxidase inhibitors	phenelzine, selegiline, tranylcypromine
Tricyclic antidepressants (TCA)	amitriptyline, nortriptyline, desipramine, imipramine, doxepin

Prior to the approval of Spravato, only one medication was FDA-approved for treatment-resistant depression, Symbyax®‡, which is a fixed-dose combination of olanzapine and fluoxetine. Intravenous ketamine, a schedule III controlled substance, is FDA-approved as an anesthetic agent and is not indicated for use in treatment-resistant depression. However, it has been studied for use in major depressive disorder and several other psychiatric indications and has been administered off-label for these uses. In addition, ketamine has been reported as a drug of abuse, due to its dissociative and hallucinogenic effects. Other off-label pharmacological interventions for treatment-resistant depression include augmentation with additional antidepressants, antipsychotics, lithium, thyroid hormone, buspirone, and other medications.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Spravato was approved in March 2019 for the treatment of adults with treatment-resistant depression in conjunction with an oral antidepressant.

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Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Spravato was approved based on two clinical trials, a short-term trial (TRANSFORM-2) and a long-term trial (SUSTAIN-1).

TRANSFORM-2 was a 4-week, randomized, placebo-controlled, double-blind, multicenter study in adult patients 18-<65 years old with treatment-resistant depression (n=223). Included patients met Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria for major depressive disorder and in the current episode had not responded adequately to at least two different antidepressants of adequate dose and duration. After discontinuing prior antidepressant treatments, patients were randomized to receive twice weekly doses of intranasal Spravato or intranasal placebo. All patients also received open-label concomitant treatment with a newly initiated daily oral antidepressant (duloxetine, escitalopram, sertraline or extended-release venlafaxine as determined by the investigator based on patient's prior treatment history). Spravato could be titrated up to 84 mg starting with the second dose based on investigator discretion. The primary efficacy measure was change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score at the end of the 4-week double-blind induction phase. The MADRS is a ten-item, clinician-rated scale used to assess severity of depressive symptoms. Scores on the MADRS range from 0 to 60 with higher scores indicating more severe depression. Spravato plus a newly initiated oral antidepressant demonstrated statistical superiority on the primary efficacy measure compared to placebo nasal spray plus a newly initiated oral antidepressant. The Spravato group had a least squares mean change from baseline in MADRS score of -19.8 vs a change of -15.8 in the placebo group. This corresponded to a least squares mean difference of -4.0 between the Spravato group and the placebo group (95% CI: -7.3, -0.6).

SUSTAIN-1 was a long-term randomized, double-blind, parallel-group, multicenter study in adults 18-<65 years old who were known remitters and responders to Spravato (n=705). Stable remission

was defined as MADRS total score ≤12 for at least 3 of the last 4 weeks. Stable response was defined as MADRS total score reduction ≥50% for the last 2 weeks of optimization and not in remission. After at least 16 initial weeks of treatment with Spravato and an oral antidepressant, stable remitters and stable responders were randomized separately to continue intranasal treatment with Spravato or switch to placebo nasal spray, in both cases with continuation of their oral antidepressant. The primary study endpoint was time to relapse in the stable remitter group. Relapse was defined as a MADRS total score of ≥22 for 2 consecutive weeks or hospitalization for worsening depression or any other clinically relevant event indicative of relapse. Patients in stable remission who continued treatment with Spravato experienced a statistically significantly longer time to relapse of depressive symptoms than did patients on placebo with an estimated hazard ratio of 0.49 (95% CI: 0.29, 0.84). Time to relapse was also significantly delayed in the stable responder population. These patients experienced a statistically significantly longer time to relapse than patients on placebo with a hazard ratio of 0.3 (95% CI: 0.16, 0.55).

References

1. Spravato [package insert]. Janssen Pharmaceuticals Inc. Lakewood, NJ. Updated May 2019.
2. Spravato Drug Evaluation. Express Scripts. Updated March 2019.
3. Teter CJ, Kando JC, Wells BG. Major Depressive Disorder. In: Dipiro JT, Talbert RL, Yee GC, et al, (Eds). Pharmacotherapy—A Pathophysiologic Approach. 9th ed. New York, NY: McGraw-Hill. 2014:1047-1066.

Policy History

Original Effective Date: 07/18/2019
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07/03/2019	Medical Policy Committee review
07/18/2019	Medical Policy Implementation Committee approval. New policy.
05/18/2020	Coding update
07/02/2020	Medical Policy Committee review
07/08/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/11/2020	Coding update

Next Scheduled Review Date: 07/2021

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Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	G2082, G2083, J3490 Adding code eff 1/1/2021: S0013
ICD-10 Diagnosis	F32.0-F32.9, F33.0-F33.9

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into

standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.