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Subject: Esketamine (Spravato®) Nasal Spray

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DESCRIPTION:

Esketamine (Spravato) nasal spray was first approved by the Food and Drug Administration (FDA) in March 2019, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (TRD) in adults. In July 2020, the FDA approved an additional indication of, in conjunction with an oral antidepressant, the treatment of depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior. Prior to FDA approval, esketamine nasal spray was granted Breakthrough Therapy Designation for TRD in November 2013, and for MDD with imminent risk for suicide in August 2016. Esketamine is the active isomer of ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist. There is lack of a consensus definition for TRD, but it is often defined as those who have failed at least two standard antidepressant treatments. However, many patients with TRD have failed numerous antidepressant treatments, and may also have had a trial of augmentation therapy. Failure of treatment can be either lack of an initial response or not achieving remission following an initial response. Response is generally defined as a 50% decrease in score on a standarized depression scale, and remission is maintaining below a certain score on a standarized depression scale where the patient experiences few, if any, symptoms of depression. Prior to the approval of esketamine nasal spray, the only other medication approved by the FDA specifically for TRD is the combination capsule of olanzapine and fluoxetine (brand name Symbyax). Of note, esketamine nasal spray is the first NMDA antagonist to receive FDA approval for major depression. Esketamine nasal spray is also the first and only treatment approved for the management of acute suicidal ideation or behavior.

The most current guidelines from the American Psychiatric Association (APA) for the treatment of major depressive disorder (MDD) (October 2010) do not address the use of esketamine (or ketamine) but do address incomplete or lack of treatment response to initial therapy. About 30 to 40% of patients with MDD fail to respond to first-line treatments. The first step is to assess that the antidepressant medication has been used for an adequate dose and duration. Generally, at least 4 to 6 weeks is necessary before concluding that a patient is not responsive or only partially responsive to a particular

medication. After this, there are several therapeutic options including: optimizing the initial treatment, changing to a different treatment, and combining treatments. Changing to a different antidepressant is a common strategy. However, it should be noted that the likelihood of remission is lower with subsequent antidepressants (second-step treatment remission rates of about 25%, and subsequent therapies with remission rates of 13 to 14%). The guidelines state that antidepressant medications can be “augmented” with another non-monoamine oxidase inhibitor (MAOI) antidepressant (often called combination antidepressant therapy) or with other, non-antidepressant agents (augmentation therapy), which may be particularly helpful for patients who have had a partial response to antidepressant monotherapy. Options include adding a second non-MAOI antidepressant medication from a different pharmacological class, taking care to avoid drug-drug interactions, or adding an adjunctive, non-antidepressant medications, such as lithium, thyroid hormone, an anticonvulsant, a psychostimulant, or a second-generation (atypical) antipsychotic. The guidelines address that some options have limited evidence while others have more robust data. Of the non-antidepressant augmentation agents only lithium, thyroid hormone, and the second-generation antipsychotics are recommended in the guidelines with at least moderate clinical confidence. Of note, the most current data shows that adjunctive treatment with atypical antipsychotic medications has the most consistent evidence for efficacy in TRD.

The safety and efficacy of esketamine nasal spray leading to FDA-approval for TRD was primarily based on one short-term study and one long-term study. The short-term study (TRANSFORM-2, Study 1, NCT02418585) was a randomized, placebo-controlled, double-blind, multicenter, 4-week, Phase 3 trial in adult patients 18 to <65 years old with TRD. Patients had to meet the DSM-5 criteria for MDD and, in the current depressive episode, had not responded adequately to at least two different antidepressants of adequate dose and duration. Patients had to also have an Inventory of Depressive Symptomatology-Clinician rated (IDS-C30) total score of 34 or greater at the time of screening and a Montgomery-Asberg Depression Rating Scale (MADRS) total score of 28 or greater prior to treatment. Patients were excluded if they previously demonstrated nonresponse of depressive symptoms to esketamine or ketamine, current or prior diagnosis of certain other psychiatric disorders (e.g., bipolar, psychosis, etc.), history of moderate or severe substance or alcohol use disorder, or suicidal or homicidal ideation in the prior 6 months. After discontinuing prior antidepressant treatments, patients were randomized to receive twice weekly doses of intranasal esketamine (flexible dose; 56 mg or 84 mg) or intranasal placebo. All patients also received open-label concomitant treatment with a newly initiated daily oral antidepressant (AD) (duloxetine, escitalopram, sertraline, or extended-release venlafaxine as determined by the investigator based on patient's prior treatment history). Esketamine nasal spray could be titrated up to 84 mg starting with the second dose based on investigator discretion. The demographic and baseline disease characteristics were similar for the esketamine nasal spray and placebo nasal spray groups. Patients had a median age of 47 years (range 19 to 64 years) and were 62% female, 93% white, and 5% black. The newly initiated oral AD was an SSRI in 32% of patients and an SNRI in 68% of patients. The primary efficacy measure was change from baseline in the MADRS total score at the end of the 4-week induction phase. The esketamine nasal spray plus antidepressant arm demonstrated statistical superiority in the primary efficacy measure vs. the placebo plus antidepressant arm. Esketamine nasal spray resulted in a decrease in score of 19.8 (from a baseline value of 37), vs. a decrease of 15.8 for placebo (from a baseline value of 37.3) [a difference of -4 (95% CI -7.3: -0.6), p=0.01]. Most of the esketamine nasal spray treatment difference vs. placebo was observed at 24 hours. Between 24 hours and Day 28, both the esketamine nasal spray and placebo groups continued to improve; the difference between the

groups generally remained but did not appear to increase over time through Day 28. At Day 28, 67% of the patients randomized to esketamine nasal spray were receiving 84 mg twice weekly.

The long-term study (SUSTAIN-1, Study 2, NCT02493868) was a randomized, double-blind, parallel group, multicenter maintenance-of-effect study in adults 18 to <65 years of age who were known remitters and responders to esketamine nasal spray. Patients in this study were responders in one of two short-term controlled trials (Study 1 and another 4-week study) or in an open-label direct-enrollment study in which they received flexibly dosed esketamine nasal spray (56 mg or 84 mg twice weekly) plus daily oral AD in an initial 4-week phase. Stable remission was defined as a MADRS total score ≤12 for at least 3 of the last 4 weeks. Stable response was defined as a MADRS total score reduction ≥50% for at least 3 of the last 4 weeks and not in remission. After at least 16 initial weeks of treatment with esketamine nasal spray and an oral AD, stable remitters and stable responders were randomized separately to continue intranasal treatment with esketamine nasal spray or switch to placebo nasal spray, in both cases with continuation of their oral AD. The primary study endpoint was time to relapse in the stable remitter group. Relapse was defined as a MADRS total score ≥22 for 2 consecutive weeks or hospitalization for worsening depression or any other clinically relevant event indicative of relapse. The demographic and baseline disease characteristics of the two groups were similar. Patients had a median age of 48 years (range 19 to 64 years) and were 66% female, 90% white, and 4% black. Patients in stable remission who continued treatment with esketamine nasal spray plus oral AD experienced a statistically significantly longer time to relapse of depressive symptoms than did patients on placebo nasal spray plus oral AD. The time to relapse was as follows: esketamine nasal spray plus oral AD – 25th percentile (153 days) and median (not estimable) vs. placebo nasal spray plus oral AD – 25th percentile (33 days) and median (273 days). The estimated hazard ratio of esketamine nasal spray plus oral AD relative to placebo nasal spray plus oral AD based on weighted estimates was 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 of depressive symptoms than patients on placebo nasal spray plus oral AD. The time to relapse was as follows: esketamine nasal spray plus oral AD – 25th percentile (217 days) and median (635 days) vs. placebo nasal spray plus oral AD – 25th percentile (24 days) and median (88 days). The estimated hazard ratio (95% CI) of esketamine nasal spray plus oral AD relative to placebo nasal spray plus oral AD based on Cox proportional hazards model was 0.30 (95% CI: 0.16, 0.55). The majority of stable remitters (69%) received every-other-week dosing for the majority of time during the maintenance phase; 23% of stable remitters received weekly dosing. Among stable responders, 34% received every-other-week dosing and 55% received weekly dosing the majority of time during the maintenance phase. Of the patients randomized to esketamine nasal spray, 39% received the 56 mg dose and 61% received the 84 mg dose.

The safety and efficacy of esketamine nasal spray leading to FDA-approval for MDD with acute suicidal ideation or behavior was based on two identical Phase 3, short-term (4-week) randomized, double-blind, multicenter, placebo-controlled trials, Study 3 (n=223, NCT03039192) and Study 4 (n=226, NCT03097133), in adults with moderate-to-severe MDD (MADRS total score >28) who had active suicidal ideation and intent. In both studies, patients received either esketamine nasal spray 84 mg or placebo nasal spray twice weekly for 4 weeks. After the first dose, a one-time dose reduction to 56 mg was allowed for patients unable to tolerate the 84 mg dose. All patients received comprehensive standard of care treatment, including an initial inpatient psychiatric hospitalization and a newly initiated or optimized oral AD (AD monotherapy or AD plus augmentation therapy) as determined by the

investigator. After completion of the 4-week treatment period, study follow-up continued through Day 90. The median patient age was 40 years (range 18 to 64 years), 61% were female; 73% Caucasian and 6% Black; and 63% of patients had at least one prior suicide attempt. Prior to entering the study, 92% of the patients were receiving antidepressant therapy. During the study, as part of standard of care treatment, 40% of patients received AD monotherapy, 54% of patients received AD plus augmentation therapy, and 6% received both AD monotherapy/AD plus augmentation therapy. The primary endpoint was the change from baseline in the MADRS total score at 24 hours after first dose. In both studies, esketamine nasal spray demonstrated a statistically superior reduction in the MADRS total score at 24 hours vs. placebo [Study 3: -15.9 vs. -12, least-square (LS) mean difference of -3.8; and Study 4: -16 vs. -12.2, LS mean difference of -3.9]. The secondary efficacy measure was the change in Clinical Global Impression of Suicidal Severity-Revised (CGI-SS-r) score at 24 hours after first dose. The CGI-SS-r is a one-item, clinician-rated assessment used to rate the current severity of a patient's suicidal ideation and behavior. Scores on the CGI-SS-r range from 0 to 6, with higher scores indicating more severe suicidal ideation and behavior. In both studies, esketamine nasal spray did not demonstrate superiority compared to placebo in improving CGI-SS-r. In both studies, esketamine's treatment difference compared to placebo was observed starting at 4 hours. Between 4 hours and Day 25, both the esketamine and placebo groups continued to improve; the difference between the groups generally remained but did not appear to increase over time through Day 25.

POSITION STATEMENT:

Initiation of esketamine (Spravato) nasal spray **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "7"):

1. **EITHER** of the following ("a" or "b"):
    a. Member has a confirmed diagnosis of moderate-to-severe, treatment-resistant depression associated with Major Depressive Disorder (MDD) as evidenced by **BOTH** of the following ("i" and ii"):
        i. Clinical assessment using **ANY** of the following standardized depression rating scales with a score corresponding to moderate-to-severe depression despite antidepressant treatment of the member's current depressive episode – the rating scale used and the member's baseline score (within the past 30 days and prior to initiation of esketamine nasal spray) while receiving antidepressant treatment must be provided
            - 9-item Patient Health Questionnaire (PHQ-9) total score of 15 or greater
            - 10-item Montgomery-Asberg Depression Rating Scale (MADRS) total score of 28 or greater
            - 16-item Quick Inventory of Depressive Symptomatology Clinician Rating (QIDS-C16) total score of 16 or greater
            - 17-item Hamilton Rating Scale for Depression (HAMD17) total score of 22 or greater
        ii. The member has had inadequate responses, during their current depressive episode, to at least **THREE** different antidepressant medications of adequate dose and duration (i.e., at least 6 weeks) from at least **TWO** different drug classes, **AND** at least one antidepressant medication has been used in combination with a non-antidepressant augmentation agent

(see categories and medications below) - the member's antidepressant treatment history (mediations used with corresponding dosages and durations) during their current depressive episode meeting these requirements must be provided

- Selective serotonin reuptake inhibitors (SSRI) - citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, or sertraline
- Serotonin-norepinephrine reuptake inhibitors (SNRI) - desvenlafaxine, duloxetine, levomilnacipran (Fetzima), milnacipran (Savella), or venlafaxine
- Tricyclic antidepressants (TCA) - amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, or trimipramine
- Heterocyclic antidepressants (HCA) – amoxapine, maprotiline, mirtazapine, or trazadone
- Monoamine oxidase inhibitors (MAOIs) – isocarboxazid (Marplan), phenelzine, selegiline (EMSAM), or tranylcypromine
- Miscellaneous antidepressants – bupropion, nefazodone, vilazodone (Viibryd), or vortioxetine (Trintellix)
- Non-antidepressant augmentation agents – a second-generation antipsychotic [aripiprazole, brexpiprazole (Rexulti), olanzapine, quetiapine, risperidone, or ziprasidone], buspirone (Buspar), liothyronine, or lithium

b. Member has a confirmed diagnosis of major depressive disorder (MDD) with acute suicidal ideation or behavior, and meets **EITHER** of the following ("i" or "ii"):

   i. Member required either an emergency department (ED) visit with observation or an inpatient psychiatric hospitalization, **AND** the member will or has received their first dose of esketamine nasal spray during the ED observation or hospitalization

   ii. **ALL** of the following:

   - The provider attests that, in the absence of the requested drug, within the next 24 to 48 hours the member will require an ED visit or an inpatient psychiatric hospitalization
   - After release from the first esketamine nasal spray treatment with observation, the member has the ability to abide by a safety plan and maintain their own safety independent of external support/help (e.g., safe home environment)
   - A comprehensive treatment plan, including frequent contact, regular re-assessment of risk, a well-articulated safety plan, and follow-up esketamine nasal spray treatments, has been developed

2. Esketamine nasal spray is prescribed by, or in consultation with, a psychiatrist
3. Member is 18 years of age or older
4. Esketamine nasal spray will be used in combination with an antidepressant medication
5. Member does not have **ANY** of the following ("a" to "d"):

   a. Known or suspected aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels) or arteriovenous malformation

   b. History of intracerebral hemorrhage

c. Severe hepatic impairment (Child-Pugh Class C)

d. Pregnant or actively trying to become pregnant

6. Esketamine nasal spray will be administered under the direct observation of a healthcare provider at a healthcare facility certified in the SPRAVATO REMS program

7. Dosage of esketamine nasal spray does not exceed 84 mg twice per week for the first 4 weeks (i.e., eight 56 mg or 84 mg Dose Kits per 28 days). For the following 8 weeks (when used for treatment-resistant depression) the dosage does not exceed 84 mg once per week (i.e., total of four 56 mg or 84 mg Dose Kits per 28 days).

Approval duration:

- For MDD with acute suicidal ideation or behavior - 4 weeks
- For treatment-resistant depression – 12 weeks

Continuation of esketamine (Spravato) nasal spray **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "8"):

1. An authorization or reauthorization for esketamine nasal spray has been previously approved by Florida Blue or another health plan in the past 12 months for the treatment of treatment-resistant depression [see initiation criteria for MDD with acute suicidal ideation or behavior], **OR** the member has previously met **ALL** criteria for treatment-resistant depression

2. Member has had a beneficial response to treatment as indicated by the following depending on the duration of use ("a" or "b"):

   a. Less than 6 months of treatment - member had a clinically meaningful response to esketamine nasal spray defined as a reduction in the HAMD17, MADRS, PHQ-9, and/or QIDS-C16 total score of greater than 50% - the member's baseline HAMD17, MADRS, PHQ-9, and/or QIDS-C16 score **AND** at least **TWO** follow-up scores at different assessment dates with greater than 50% improvement must be provided

   b. 6 or more months of treatment – **BOTH** of the following ("i" and "ii)"

      i. Member continues to maintain a positive clinical response and has not had a relapse of depression symptoms

      ii. The dosing frequency has been individualized to the least frequent dosing to maintain remission/response

3. Esketamine nasal spray is being prescribed by, or in consultation with, a psychiatrist

4. Member is 18 years of age or older

5. Esketamine nasal spray is being used in combination with an antidepressant medication

6. Member does not have **ANY** of the following ("a" to "d"):

   a. Known or suspected aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels) or arteriovenous malformation

   b. History of intracerebral hemorrhage

   c. Severe hepatic impairment (Child-Pugh class C)

d. Pregnant or actively trying to become pregnant

7. Esketamine nasal spray is being administered under the direct observation of a healthcare provider at a healthcare setting certified in the SPRAVATO REMS program
8. Dosage of esketamine nasal spray does not exceed 84 mg once per week (i.e., total of four 56 mg or 84 mg Dose Kits per 28 days)

Approval duration: 6 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Spravato is indicated, in conjunction with an oral antidepressant, for the treatment of: (1) treatment-resistant depression (TRD) in adults, and (2) 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, and use does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose. Spravato is not approved as an anesthetic agent. The safety and effectiveness of Spravato as an anesthetic agent have not been established.
- 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 for at least 2 hours until the patient is safe to leave. Blood pressure should be monitored before and after treatment. Refer to the package labeling for more detail monitoring recommendations.
- The recommended dosages for the treatment of TRD in adults are provided below. Dosage adjustments should be made based on efficacy and tolerability. Evidence of therapeutic benefit should be evaluated at the end of the induction phase to determine need for continued treatment.
    - Induction Phase (Weeks 1 to 4):
        - Day 1 starting dose - 56 mg
        - Subsequent doses - 56 mg or 84 mg twice per week
    - Maintenance Phase
        - Weeks 5 to 8: 56 mg or 84 mg once per week
        - Week 9 and after: 56 mg or 84 mg every 2 weeks or once weekly*

          *Dosing frequency should be individualized to the least frequent dosing to maintain remission/response
- The recommended dosage for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior is 84 mg twice per week for 4 weeks. Dosage may be reduced to 56 mg twice per week based on tolerability. After 4 weeks of treatment with Spravato, evidence of therapeutic benefit should be evaluated to determine need for continued treatment. Use, 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.

- The nasal spray device delivers a total of 28 mg of esketamine. To prevent loss of medication, do not prime the device before use. Use 2 devices (for a 56 mg dose) or 3 devices (for an 84 mg dose), with a 5-minute rest between use of each device.

Dose Adjustments

- Renal impairment - specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed
- Hepatic impairment - no dosage adjustments are required in mild to moderate hepatic impairment (Child-Pugh class A and B). However, mean esketamine AUC and t1/2 values were higher in patients with moderate hepatic impairment compared to those with normal hepatic function, and these patients may need to be monitored for adverse reactions for a longer period of time. Use is not recommended in severe hepatic impairment (Child-Pugh class C) because the drug has not been studied in this population.

Drug Availability

- Available as an aqueous solution of esketamine hydrochloride 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 (supplied as 32.3 mg of esketamine hydrochloride). Available in the following presentations:
    - 56 mg Dose Kit: Unit-dose carton containing two 28 mg nasal spray devices (56 mg total dose)
    - 84 mg Dose Kit: Unit-dose carton containing three 28 mg nasal spray devices (84 mg total dose)

  Within each kit, each 28 mg device is individually packaged in a sealed blister
- Store at 20° to 25°C (68° to 77°F); excursions permitted from 15° to 30°C (59° to 86°F)

PRECAUTIONS:

Boxed Warning

WARNING: Sedation; Dissociation; Abuse and Misuse, and Suicidal Thoughts and Behaviors

- 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
    - Because of the risks of sedation and dissociation, 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, and 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 in pediatric patients

Contraindications

- Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels) or arteriovenous malformation
- History of intracerebral hemorrhage
- Hypersensitivity to esketamine, ketamine, or any of the excipients

Precautions/Warnings

- **Sedation** - In clinical trials, 48% to 61% of esketamine-treated patients developed sedation based on the Modified Observer's Alertness/Sedation scale, and 0.3% to 0.4% of patients experienced loss of consciousness. Because of the possibility of delayed or prolonged sedation, patients must be monitored by a healthcare provider 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. Closely monitor for sedation with concomitant use of esketamine with CNS depressants
- **Dissociation** - The most common psychological effects of esketamine were dissociative or perceptual changes (including distortion of time, space and illusions), derealization and depersonalization (61% to 84% of esketamine -treated patients developed dissociative or perceptual changes based on the Clinician Administered Dissociative Symptoms Scale). Given its potential to induce dissociative effects, carefully assess patients with psychosis before administering esketamine; treatment should be initiated only if the benefit outweighs the risk. Because of the risks of dissociation, patients must be monitored by a healthcare provider 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** – Esketamine is a Schedule III controlled substance (CIII) and may be subject to abuse and diversion. Assess each patient's risk for abuse or misuse prior to prescribing and monitor all patients for the development of these behaviors or conditions, including drug-seeking behavior, while on therapy. Individuals with a history of drug abuse or dependence are at greater risk; therefore, use careful consideration prior to treatment of individuals with a history of substance use disorder and monitor for signs of abuse or dependence.
- **SPRAVATO Risk Evaluation and Mitigation Strategy (REMS) –** Esketamine nasal spray is available only through a restricted program under a REMS called the SPRAVATO REMS because of the risks of serious adverse outcomes from sedation, dissociation, and abuse and misuse. Important requirements of the SPRAVATO REMS include the following:
    - Healthcare settings must be certified in the program and ensure that esketamine nasal spray is:
        - Only dispensed and administered in healthcare settings
        - Patients treated in outpatient settings (e.g., medical offices and clinics) must be enrolled in the program

        - Administered by patients under the direct observation of a healthcare provider and that those patients are monitored by a healthcare provider for at least 2 hours after administration of esketamine nasal spray.
    - Pharmacies must be certified in the REMS and must only dispense esketamine nasal spray to healthcare settings that are certified in the program

      Further information, including a list of certified pharmacies is available at www.SPRAVATOrems.com or 1-855-382-6022

- **Suicidal Thoughts and Behaviors in Adolescents and Young Adults -** In pooled analyses of placebo-controlled trials of chronically administered antidepressant drugs (SSRIs and other antidepressant classes), the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. Monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy and at times of dosage changes.
- **Increases in Blood Pressure** - Esketamine nasal spray causes increases in systolic and/or diastolic blood pressure (BP) at all recommended doses. Increases in BP peak approximately 40 minutes after esketamine nasal spray administration and last approximately 4 hours. Approximately 8% to 19% of esketamine -treated patients and 1% to 4% of placebo-treated patients experienced an increase of greater than or equal to 40 mmHg in systolic BP and/or 25 mmHg in diastolic BP in the first 1.5 hours after administration at least once during the first 4 weeks of treatment. Patients with cardiovascular and cerebrovascular conditions and risk factors may be at an increased risk of associated adverse effects.
- **Cognitive Impairment** - Esketamine nasal spray may impair attention, judgment, thinking, reaction speed and motor skills.
- **Impaired Ability to Drive and Operate Machinery** - Do not drive or operate machinery until the next day after a restful sleep.
- **Ulcerative or Interstitial Cystitis** - Has been reported in individuals with long-term off-label use or misuse/abuse of ketamine. In clinical studies with esketamine nasal spray, there was a higher rate of lower urinary tract symptoms (pollakiuria, dysuria, micturition urgency, nocturia, and cystitis) vs. placebo-treated patients. No cases of esketamine-related interstitial cystitis were observed in any of the studies, which included treatment for up to a year. Monitor for urinary tract and bladder symptoms during the course of treatment, and refer to an appropriate healthcare provider as clinically warranted
- **Embryo-fetal Toxicity** - Esketamine is not recommended during pregnancy. There are insufficient data on esketamine use in pregnant women to draw conclusions about any drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Based on published findings from pregnant animals treated with ketamine, the racemic mixture of arketamine and esketamine, esketamine nasal spray may cause fetal harm when administered to pregnant women Consider pregnancy planning and prevention in females of reproductive potential.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

G2082	Office or other outpatient visit for the evaluation and management of an established patient that requires the supervision of a physician or other qualified health care professional and provision of up to 56 mg of esketamine nasal self-administration, includes 2 hours post-administration observation
G2083	Office or other outpatient visit for the evaluation and management of an established patient that requires the supervision of a physician or other qualified health care professional and provision of greater than 56 mg esketamine nasal self-administration, includes 2 hours post-administration observation
J3490	Unclassified drugs
S0013	Esketamine, nasal spray, 1 mg [for non-Medicare plans ONLY]

ICD-10 Diagnosis Codes That Support Medical Necessity

F33.0 – F33.9	Major depressive disorder, recurrent
R45.851	Suicidal ideations

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: BCBSF has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of guideline creation.

DEFINITIONS:

Hamilton Rating Scale for Depression (HAM-D) - a clinician-rated scale designed to measure depression severity and detect changes due to antidepressant treatment. The two common versions have either 17 or 21 question; however, only the first 17 items are scored on the 21-question version. Eight questions are scored from 0 to 4 and nine are scored from 0 to 2. The scores are summed for a total possible score of 0 to 50. Higher scores represent more severe condition.

Montgomery-Asberg Depression Scale (MADRS) - a clinician-rated scale designed to measure depression severity and detect changes due to antidepressant treatment. Scale consists of 10 items (apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, interest level, pessimistic thoughts, and suicidal thoughts), each of which is scored from 0 (item is not present or is normal) to 6 (severe or continuous presence of symptoms), summed for a total possible score of 0 to 60. Higher scores represent more severe condition.

Patient Health Questionnaire (PHQ-9) - a self-rated scale designed to measure depression severity and detect changes due to antidepressant treatment. The PHQ-9 incorporates a total of 9 question based on the nine DSM-V criteria listed under criterion A for Major Depressive Disorder. Each symptom is scored from 0 (not at all) to 3 (nearly every day) and summed to a total score of 0 to 27. Higher scores represent more severe condition.

Quick Inventory of Depressive Symptomatology Clinician Rating (QIDS-C16) – a clinician-rated scale designed to measure depression severity and detect changes due to antidepressant treatment. There is also a self-rated version (QIDS-SR16). The 16 question "quick" version is derived from the longer 30-item Inventory of Depressive Symptomatology (IDS). Each question is scored from 0 to 3 and then, based on a calculation, a total score of 0 to 27 is derived. Higher scores represent more severe condition.

RELATED GUIDELINES:

None

OTHER:

Montgomery-Asberg Depression Scale (MADRS)

- Electronic vision - https://www.mdcalc.com/montgomery-asberg-depression-rating-scale-madrs

Hamilton Rating Scale for Depression (HAM-D)

- Electronic vision – https://www.mdcalc.com/hamilton-depression-rating-scale-ham-d

Patient Health Questionnaire (PHQ-9)

- Electronic vision – https://www.mdcalc.com/phq-9-patient-health-questionnaire-9

Quick Inventory of Depressive Symptomatology Clinician Rating (QIDS-C16)

- Electronic vision – https://www.mdcalc.com/quick-inventory-depressive-symptomatology-qids

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 03/09/22.

GUIDELINE UPDATE INFORMATION:

06/15/19	New Medical Coverage Guideline.
04/15/20	Review and revision to guideline consisting of updating the description, position statement, definitions, other section, and references.
09/15/20	Revision to guideline consisting of updating the description, position statement, dosage/administration, precautions, billing/coding, and references based on the new FDA-approved indication of treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior.
01/01/21	Revision: Added HCPCS code S0013.
04/15/21	Review and revision to guideline consisting of updating the position statement and references.
04/15/22	Review and revision to guideline consisting of updating the references.
08/15/22	Revision: Added HCPCS codes G2082 and G2083.
11/15/22	Revision to guideline consisting of updating the position statement to include buspirone (Buspar) as a qualifying non-antidepressant augmentation agent.