

# Medical Policy Bulletin

## Title:

Intravenous Ketamine (Ketalar®) and Intranasal Esketamine (Spravato®)

## Policy #:

MA08.137e

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

---

## Policy

Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.

The Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition.

### MEDICALLY NECESSARY

#### KETAMINE (KETALAR)

Ketamine (Ketalar®), administered as an intravenous infusion, is considered medically necessary and, therefore, covered for individuals aged 16 and older for any of the following indications:

- As the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation
- For the induction of anesthesia prior to the administration of other general anesthetic agents
- As a supplement to other anesthetic agents
- As an adjuvant to opioids for management of cancer pain resistant to other analgesics in consultation with a pain or palliative care specialist

#### ESKETAMINE (SPRAVATO)

##### Initial Therapy for Esketamine (Spravato®)

Esketamine (Spravato), administered as a nasal spray, is considered medically necessary and, therefore, covered for individuals aged 18 and older with major depressive disorder (MDD) when used in conjunction with a newly initiated oral antidepressant (AD) when all of the following are met:

- The individual meets all of the following:
  - *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition text revision (DSM-5TR) criteria for MDD with either a single episode lasting greater than or equal to 2 years, or a recurrent major depressive disorder, without psychotic features

- Severe depression as determined by a validated rating scale (e.g., Beck Depression Inventory-II [BDI-II], Montgomery-Asberg Depression Rating Scale [MADRS], Patient Health Questionnaire-9 [PHQ-9], Hamilton Rating Scale for Depression [HAM-D])
- Inadequate response (defined as <25 percent improvement in the total score on the utilized depression scale) to at least two different US Food and Drug Administration (FDA)-approved drugs indicated for depression (e.g., duloxetine, escitalopram, sertraline, venlafaxine extended release) from at least two different classes (e.g., selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], tricyclic ADs [TCAs], FDA-approved augmentation agents) prescribed in adequate dosages for an adequate duration (defined as at least 6 weeks) with adherence at least greater than or equal to 80 percent
- The individual has one of the following:
  - Treatment-resistant depression (TRD)\*
  - Depressive symptoms in individuals with MDD with acute suicidal ideation or behavior\* who continue to receive comprehensive standard of care treatment (e.g., inpatient psychiatric hospitalization, cognitive behavioral therapy, augmentation therapy [the addition of a second drug to an existing AD with the aim of achieving an improved clinical response]) and without any of the following:
    - Moderate to severe substance or alcohol use disorder within 6 months prior to screening
    - Current or prior diagnosis of psychotic disorder
    - Positive urine test result(s) for phencyclidine, cocaine, or unprescribed amphetamines
- Individual is not receiving concurrent transcranial magnetic stimulation
- Esketamine (Spravato) is prescribed by, or in consultation with, a licensed behavioral health professional provider (e.g., psychiatrist, psychiatric nurse practitioner)
- Esketamine (Spravato) is administered under the direct supervision of a licensed healthcare professional provider and each treatment session includes both of the following:
  - Nasal administration of esketamine (Spravato)
  - Post-administration observation under supervision including the monitoring of vital signs for at least 2 hours until the individual is determined to be stable to leave the healthcare setting

\*The individual prescribed esketamine (Spravato) for TRD or MDD with acute suicidal ideation or behavior must be evaluated by the prescribing licensed behavioral health professional provider after 4 weeks of therapy to determine the need for continued treatment. The use of esketamine (Spravato) beyond 4 weeks has not been systematically evaluated in the treatment of depressive symptoms in individuals with MDD with acute suicidal ideation or behavior.

### **Reauthorization/Continuation Therapy for Esketamine (Spravato)**

Esketamine (Spravato) is considered medically necessary and, therefore, covered for reauthorization/continuation of therapy for TRD, along with an oral AD, after 16 weeks if one of the following is met:

- Total scores on the utilized depression scale are improved by at least 50 percent from baseline for at least 3 of the last 4 weeks
- Total scores on the utilized depression scale are indicative of remission

### **LIMITATIONS OF USE FOR ESKETAMINE (SPRAVATO)**

The effectiveness of esketamine (Spravato) in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use of esketamine (Spravato) does not preclude the need for hospitalization if clinically warranted, even if the individual experiences improvement after an initial dose of esketamine (Spravato).

### **EXPERIMENTAL/INVESTIGATIONAL**

All other uses for intranasal esketamine (Spravato) are considered experimental/investigational and, therefore, not covered unless the indication is supported as an accepted off-label use, as defined in the Company medical policy on Off-label Coverage for Prescription Drugs and Biologics. Esketamine (Spravato) is not approved as an anesthetic agent. The safety and effectiveness of esketamine (Spravato) as an anesthetic agent have not been established. The use of esketamine (Spravato) as an anesthetic agent is considered experimental/investigational and, therefore, not covered.

All other uses for IV ketamine (Ketalar) are considered experimental/investigational and, therefore, not covered unless the indication is supported as an accepted off-label use, as defined in the Company medical policy on Off-label Coverage for Prescription Drugs and Biologics (08.00.15). Ketamine (Ketalar) is not approved for the treatment

of depression. The use of ketamine (Ketalar) for the treatment of depression is considered experimental/investigational and, therefore, not covered.

## **REQUIRED DOCUMENTATION**

The individual's medical record must reflect the medical necessity for the care provided. These medical records may include, but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the drug.

---

## **Guidelines**

There is no Medicare coverage determination addressing this service; therefore, the Company policy is applicable.

## **BLACK BOX WARNINGS**

Refer to the specific manufacturer's prescribing information for any applicable Black Box warnings.

## **RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

Esketamine (Spravato) was approved by the US Food and Drug Administration (FDA) with a risk evaluation and mitigation strategy (REMS). The goal was to ensure that the benefits of the drug outweigh the risks of sedation, dissociation, and abuse and misuse through a restricted distribution program.

## **BENEFIT APPLICATION**

Subject to the terms and conditions of the applicable Evidence of Coverage, ketamine (Ketalar) and esketamine (Spravato) are covered under the medical benefits of the Company's Medicare Advantage products when the medical necessity criteria listed in this medical policy are met.

## **BECK DEPRESSION INVENTORY-II (BDI-II)**

Beck et al. (1961) developed an inventory for measuring depression in 1961. He revised the inventory to the latest version in 1996 (Beck et al., 1996). The inventory consists of 21 self-reported multiple-choice questions that measure the presence and severity of depression manifestations. Individuals rate the items based on their experiences in the past 2 weeks. Each manifestation is rated on a scale from 0 to 3 with higher numbers indicating increased severity. Total scores of 0 to 13 are considered to be minimal, 14 to 19 mild, 20 to 28 moderate, and 29 to 63 are considered to be severe.

## **HAMILTON RATING SCALE FOR DEPRESSION (HAM-D)**

Hamilton (1960) developed a scale to measure depression in 1960. He later published additional information on the use of the scale in 1967 (Hamilton, 1967). The scale consists of 17 items that are rated in order to determine the severity level of the individual's depression. The total scores can range from 0 to 52. Total scores of 0 to 7 are considered to be no depression, 8 to 16 mild depression, 17 to 23 moderate depression, and 24 or greater are considered to be severe depression.

## **MONTGOMERY-ASBERG DEPRESSION RATING SCALE (MADRS)**

Montgomery and Asberg (1979) developed a rating scale to assist providers in evaluating the severity of an individual's depression. Each item is rated on a scale of 0 to 6. The maximum score would be 60. A score of 10 or less indicates remission.

The rating is based on a clinical interview. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

The scale may be used for any time interval between ratings, whether weekly or otherwise, and this must be recorded.

1. Apparent sadness
2. Reported sadness
3. Inner tension
4. Reduced sleep
5. Reduced appetite
6. Concentration difficulties
7. Lassitude
8. Inability to feel
9. Pessimistic thoughts
10. Suicidal thoughts

Total scores of 0 to 6 are considered to be no depression, 7 to 19 mild depression, 20 to 34 moderate depression, 35 or greater are considered to be severe depression.

### **PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)**

Kroenke et al. (2001) developed a brief self-administered questionnaire to measure for common mental disorders. It consists of nine questions that are rated on a scale of 0 to 3 with higher numbers indicating increased severity. Total scores of 5 to 9 are considered to be mild, 10 to 14 moderate, 15 to 19 moderately severe, and 20 to 27 are considered to be severe.

### **DRUG INFORMATION**

In accordance with FDA prescribing information, esketamine (Spravato) is administered intranasally under the supervision of a professional provider. Evidence of therapeutic benefit should be evaluated at the end of the induction phase to determine need for continued treatment.

### **DOSING AND FREQUENCY REQUIREMENTS**

The Company reserves the right to modify the Dosing and Frequency Requirements listed in this policy to ensure consistency with the most recently published recommendations for the use of esketamine (Spravato). Changes to these guidelines are based on a consensus of information obtained from resources such as, but not limited to: the FDA, Company-recognized authoritative pharmacology compendia, or published peer-reviewed clinical research. The professional provider must supply supporting documentation (i.e., published peer-reviewed literature) in order to request coverage for an amount of esketamine (Spravato) outside of the Dosing and Frequency Requirements listed in this policy. For a list of Company-recognized pharmacology compendia, view our policy on off-label coverage for prescription drugs and biologics.

Accurate member information is necessary for the Company to approve the requested dose and frequency of this drug. If the member's dose, frequency, or regimen changes (based on factors such as changes in member weight or incomplete therapeutic response), the provider must submit those changes to the Company for a new approval based on those changes as part of the utilization management activities. The Company reserves the right to conduct post-payment review and audit procedures for any claims submitted for esketamine (Spravato).

### **TREATMENT-RESISTANT DEPRESSION (TRD)**

Recommended dosage for esketamine (Spravato) for treatment-resistant depression (TRD) in conjunction with an oral antidepressant (AD):

<b>Induction Phase</b>	<b>Weeks 1 to 4</b>	Day 1 starting dose: 56 mg
	Administer twice per week	Subsequent doses: 56 mg or 84 mg

<b>Maintenance Phase</b>	<b>Weeks 5 to 8</b>	
	Administer once weekly	56 mg or 84 mg
	<b>Week 9 and after</b>	
	Administer every 2 weeks or once weekly*	56 mg or 84 mg

\*Dosing frequency should be individualized to the least frequent dosing to maintain remission/response.

### **MAJOR DEPRESSIVE DISORDER (MDD) WITH ACUTE SUICIDAL IDEATION OR BEHAVIOR**

Recommended dosage for esketamine (Spravato) for MDD with acute suicidal ideation or behavior, in conjunction with an oral AD, is 84 mg twice weekly for 4 weeks. Dosage may be reduced to 56 mg twice weekly based on tolerability. After 4 weeks of treatment with esketamine (Spravato), evidence of therapeutic benefit should be evaluated to determine the need for continued treatment. The use of esketamine (Spravato), in conjunction with an oral AD, beyond 4 weeks has not been systematically evaluated in the treatment of individuals with MDD with acute suicidal ideation or behavior.

### **US FOOD AND DRUG ADMINISTRATION (FDA) STATUS**

Ketamine (Ketalar), administered as an intravenous infusion, was approved by the FDA on March 7, 2012, as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. It is best suited for short procedures but can be used for longer procedures with additional doses, for the induction of anesthesia prior to the administration of other general anesthetic agents, and to supplement low-potency agents such as nitrous oxide.

Esketamine (Spravato), administered intranasally, was approved by the FDA on March 5, 2019, to be used in conjunction with an oral AD for the treatment of TRD in adults. On July 31, 2020, esketamine (Spravato) was approved by the FDA to be used in conjunction with an oral AD for the treatment of depressive symptoms in individuals with MDD with acute suicidal ideation or behavior.

#### **PEDIATRIC USE**

The safety and effectiveness of ketamine (Ketalar) have not been established in individuals below the age of 16 years.

The safety and effectiveness of esketamine (Spravato) have not been established in individuals below the age of 18 years.

### **BILLING GUIDELINES**

Esketamine (Spravato), obtained through specialty pharmacy distribution, should not be reported separately by the professional provider. In this circumstance, professional providers should use unlisted evaluation and management service code, 99499, which must be reported with the description "Esketamine Observation" on the claim to report post-administration observation.

Inclusion of a code in this policy does not imply reimbursement. Eligibility, benefits, limitations, exclusions, provider contracts, and Company policies apply.

---

## **Description**

### **KETAMINE (KETALAR)**

Ketamine (Ketalar) is a nonselective, noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor and acts by blocking excitatory glutamate receptors in the central nervous system. This produces sedation, amnesia, and

analgesia. Ketamine (Ketalar) is a rapidly acting general anesthetic producing a dissociative anesthetic state characterized by profound analgesia, normal pharyngeal-laryngeal reflexes, normal or slightly enhanced skeletal muscle tone, cardiovascular and respiratory stimulation, and occasionally a transient and minimal respiratory depression. Intravenous (IV) ketamine (Ketalar) should be administered only by or under the supervision of individuals who are experienced with its use and potential complications.

Ketamine (Ketalar) is a known drug of abuse and is subject to control under the Federal Controlled Substances Act of 1970 as a schedule III drug. Although brief exposure to IV ketamine (Ketalar) in a hospital setting is not likely to cause addiction, the possibility of addiction exists, and individuals should be individually assessed for their risk. Ketamine (Ketalar) should be prescribed and administered with caution because of the risk of abuse. Tolerance and dependence may develop following prolonged administration of the drug.

#### PEER-REVIEWED LITERATURE

The first published human study involving ketamine (Ketalar) (Domino et al., 1965) was a phase I, open-label trial in which varying doses of ketamine (Ketalar) were administered by IV to 20 individuals. Ten of the individuals also received a repeat dosing after awakening from the first dosing of ketamine (Ketalar). Vital signs, level of consciousness, and laboratory studies were monitored before and after receiving ketamine (Ketalar). Since the time of this study, there have been over 100 separate studies involving thousands of individuals in thousands of operative and diagnostic procedures.

#### OTHER CONDITIONS OR INDICATIONS

##### **Acute/Chronic Pain**

Many studies have been undertaken to evaluate the use of IV ketamine (Ketalar) for acute and/or chronic pain (in which the individual's pain has lasted longer than 3 months). The conditions associated with the pain include, but are not limited to, migraines/headaches, neuropathic pain, perioperative pain, and fibromyalgia. The use of IV ketamine (Ketalar) for the treatment of acute and/or chronic pain is considered experimental/investigational.

Migraines cause over one million emergency department visits annually. There are many categories of pharmacological agents that can be used in the treatment of acute or chronic migraines. Some of these agents are opioids, corticosteroids, antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), and migraine-specific drugs, including triptans and ergotamine compounds. In an assessment of parenteral pharmacotherapies for use with acute migraines, the American Headache Society (Orr et al., 2016) concluded that no recommendation could be made regarding the role of ketamine (Ketalar) in the emergency department as there was insufficient evidence.

Neuropathic pain can be defined as pain that is initiated or caused by a focus in the nervous system, or by a dysfunction in the nervous system. Treatments for neuropathic pain can be targeted towards providing analgesia or the underlying cause of the pain. Because there may be more than one mechanism at work causing the pain, attempting to treat the pain can be complex. In a review of the current evidence on targeted pharmacotherapy for neuropathic pain (Granot et al., 2007) identified eight studies that evaluated the use of parenteral ketamine (Ketalar) for various types of neuropathic pain (spinal cord injury (SCI), complex regional pain syndrome (CRPS), nerve injury). All of the studies were done on too small a number of individuals to allow the results to be generalizable. The authors concluded that there was not enough clinical evidence to recommend any of the agents evaluated in the study with much certainty.

In a *Cochrane Database Systematic Review* article, Chaparro et al. (2013) identified 14 randomized controlled trials (RCTs) involving the use of ketamine (Ketalar) for the prevention of chronic pain after surgery. Thirteen of the 14 studies included too small a number of tested individuals to allow the results to be generalizable. The final study enrolled 352 individuals into the study, but only 25.9 percent of participants responded at 3 months and 10.2 percent at 6 months to chronic pain questionnaires, leading to attrition bias. In an updated *Cochrane Database Systematic Review* article, Carley et al. (2021) identified 13 new RCTs. No treatment effect of ketamine (Ketalar) over placebo was identified on the prevalence of any pain regardless of outcome timing (3 months, 6 months, or 12 months), duration of drug administration (one time dose,  $\leq 24$  hours,  $> 24$  hours), or type of surgical procedure in any of the 27 studies identified. Other systematic reviews and meta-analyses are mentioned in this review that reached the same conclusion.

Fibromyalgia is significant for chronic generalized musculoskeletal pain for which an inflammatory source or structural lesion cannot be identified. The pain in fibromyalgia has been associated with central sensitization. There may be more than one process that initiates the central sensitization, and one of these includes an NMDA receptor activation that ketamine (Ketalar) could block. In a study to evaluate the long-term effects from an infusion of ketamine (Ketalar) on fibromyalgia pain (Noppers et al., 2011), it was found that ketamine (Ketalar) produced a reduction of pain exceeding 50 percent in 15 minutes significantly more than midazolam did in the same time frame. At 180 minutes,

1 week, and 8 weeks, however, there was no significant difference between the two groups in reduction of pain. In a review of pharmacotherapy options for individuals with fibromyalgia (Clauw, 2008), ketamine (Ketalar) is not mentioned as an option for therapy.

Although many studies have been undertaken to evaluate the use of ketamine (Ketalar) for various acute and/or chronic pain syndrome, the long-term benefits have not been clearly demonstrated. The intense treatment protocols used in many studies would make the implementation of them difficult in practice. Optimal dosing and/or dosing regimens have not been established. Most of the studies enrolled too few individuals for the results to be generalizable. Many studies were not placebo controlled, blinding was inadequate, or the placebo was saline as opposed to another active drug. Multiple studies documented adverse events with some leading to individuals dropping out of the studies. Schwenk et al. (2018) acknowledge that the use of ketamine (Ketalar) outside of the operative or intensive care unit setting is limited by the potential for adverse cardiovascular and psychomimetic effects. Safe dose ranges for use have not been established. High-quality studies comparing varying dose ranges of ketamine (Ketalar) for individuals with acute pain conditions or comorbid conditions have not been accomplished. The overall net health benefit of IV ketamine (Ketalar) for use in acute/chronic pain syndromes is considered experimental/investigational.

### **Psychiatric Disorders**

Less than half of individuals who present for treatment of their initial episode of major depression will obtain remission. With each successive treatment, there is often less chance of an individual obtaining remission. There is no standardized definition of treatment-resistant depression (TRD). The term often refers to a major depressive episode that has not responded satisfactorily to two trials of antidepressant therapies. There is also no standardized definition for describing the results to antidepressant therapy. Often no response is defined as less than 25 percent improvement from baseline on a depression rating scale. There are many therapies that can be used to treat TRD. These therapies can include augmentation of an antidepressant with either another antidepressant and/or other drug (e.g., lithium), cognitive behavioral therapy (CBT), repetitive transcranial magnetic stimulation, vagus nerve stimulation, or interpersonal psychotherapy. Each of these therapies has possible benefits and side effects. There are some individuals who will not attain a lasting remission from the currently available treatments.

In a *Cochrane Database Systematic Review* article, Caddy et al. (2015), searched the literature for RCTs involving the use of IV ketamine (Ketalar) for depression. Nine trials were identified, four of which specified that the participants had TRD. It was found that there was limited evidence that ketamine (Ketalar) was more efficacious than placebo, but the quality of evidence was limited by the risk of bias in the studies and too few individuals being enrolled in the studies for the results to be generalizable. There was low-quality evidence that ketamine (Ketalar) influences the individuals' depression after 24 hours, but limited evidence of an effect at 1 week, and even less evidence of an effect at 2 weeks. Limited data were found on documentation of suicidality, cognition, drop-out rates, or changes in quality of life, which would be important to know.

Obsessive-compulsive disorder (OCD) is a spectrum of disorders that can include obsessive thoughts, compulsive behaviors, and anxiety. Disorders that can be included in this group include eating disorders and substance use/abuse disorders. There is some literature published on studies evaluating the use of ketamine (Ketalar) in individuals with OCD. Many of the trials are proof-of-concept/pilot studies, single case studies, or include groups of individuals too small for the results to be generalized. Martinotti et al. (2021) reviewed the literature for studies involving the use of ketamine (Ketalar) and esketamine (Spravato) in multiple psychiatric disorders. In the studies evaluating the use of IV ketamine (Ketalar), if evaluated at all, the published trials document little effect of ketamine (Ketalar) on OCD beyond 1 week following the infusion(s). Long-term outcomes were not documented. One study also documented the onset of worsening anxiety and suicidal thinking. The overall net health benefit of IV ketamine (Ketalar) in psychiatric disorders is considered experimental/investigational.

### **Professional Guidelines**

The American Headache Society published an article on the parenteral pharmacotherapy management of adults with acute migraine in the emergency department (Orr et al., 2016). Their conclusion was that no recommendation could be made regarding the role of IV ketamine (Ketalar). It was believed that the evidence for efficacy was insufficient.

The American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists published a joint set of consensus guidelines on the use of IV ketamine (Ketalar) for chronic pain (Cohen et al., 2018). They found the level of evidence for the use of IV ketamine (Ketalar) for SCI to be grade C with a low certainty. For the use of IV ketamine (Ketalar) for CRPS, they found the level of evidence to be grade B with low to moderate certainty for improvement in pain up to 12 weeks. For the use of IV ketamine (Ketalar) for other pain conditions (e.g., neuropathic pain, fibromyalgia, headache) they found the level of

evidence to be grade D with low certainty.

The American Psychiatric Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments published a consensus statement on the use of ketamine (Ketalar) in the treatment of mood disorders (Sanacora et al., 2017). They believed that ketamine (Ketalar) could be beneficial to some individuals with mood disorders, but it was important to consider that the published literature contained only studies with relatively small numbers of participants. There are many documented physical and psychotomimetic side effects that could prove dangerous to an individual receiving the drug. They believed that the literature did not demonstrate the safety and durability of ketamine (Ketalar) over time.

## **ESKETAMINE (SPRAVATO)**

Esketamine (Spravato), the S-enantiomer of racemic ketamine, is a nonselective, noncompetitive antagonist of NMDA. The mechanism by which esketamine (Spravato) exerts its antidepressant effect is unknown. Esketamine (Spravato) is a schedule III substance and may be subject to abuse and diversion. Esketamine (Spravato) should be prescribed and administered with caution because of the risk of abuse. Tolerance would be expected with prolonged use of esketamine (Spravato).

### **PEER-REVIEWED LITERATURE**

#### **Treatment-Resistant Depression (TRD): Short-Term Study**

The safety and efficacy of esketamine (Spravato) was evaluated in a randomized, placebo-controlled, double-blind, multicenter, short-term (4-week), phase III study (Popova et al., 2019) in adult individuals 18 to 64 years old with TRD. Individuals in the study met *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition text revision (DSM-5TR) criteria for major depressive disorder (MDD) and in the current depressive episode, had not responded adequately to at least two different antidepressants of adequate dose and duration. Key exclusion criteria included substance use disorder, suicidal ideation or behavior, homicidal ideation or intent, MDD with psychotic features, borderline personality disorder, bipolar or related disorders, antisocial personality disorder, obsessive-compulsive disorder, narcissistic personality disorder, psychotic disorder, histrionic personality disorder, autism, and intellectual disability. After discontinuing prior antidepressant treatments, individuals in the study were randomly assigned to receive twice weekly doses of intranasal esketamine (Spravato) (flexible dose; 56 mg or 84 mg) or intranasal placebo. All individuals 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 the individual's prior treatment history). Esketamine (Spravato) could be titrated up to 84 mg starting with the second dose based on investigator discretion. In the study, 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 10-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. Esketamine (Spravato) plus a newly initiated oral AD demonstrated statistical superiority on the primary efficacy measure compared to placebo nasal spray plus a newly initiated oral AD. Clinically meaningful improvement was also observed earlier with the esketamine (Spravato) arm as compared to the placebo arm.

#### **Treatment-Resistant Depression (TRD): Long-term Study**

The time to relapse of depression was evaluated in a long-term, randomized, double-blind, parallel-group, multicenter maintenance-of-effect phase III study (Daly et al., 2019) in adults 18 to 64 years of age who were known remitters and responders to esketamine (Spravato). Individuals in this study were responders in one of two short-term controlled trials (the Popova et al. 2019 study and another 4-week study) or directly enrolled in the study in which they received flexibly dosed esketamine (Spravato) (56 mg or 84 mg twice weekly) plus daily oral AD in an initial 4-week phase. Key exclusion criteria included substance use disorder, suicidal ideation or behavior, homicidal ideation or intent, MDD with psychotic features, borderline personality disorder, bipolar or related disorders, antisocial personality disorder, OCD, narcissistic personality disorder, psychotic disorder, histrionic personality disorder, autism, and intellectual disability. Stable remission was defined as a MADRS total score less than or equal to 12 for at least 3 of the last 4 weeks. Stable response was defined as a MADRS total score reduction from baseline of greater than or equal to 50 percent in the last 2 weeks but not in remission. A randomized withdrawal design was used to evaluate the time to relapse.

After an induction phase, individuals in the study entered a 12-week optimization phase during which the dosage of the study drug remained stable, but the frequency of dosing was reduced to once weekly for 4 weeks, then individualized to weekly or every 2 weeks based on the severity of the individuals' depressive symptoms. The oral antidepressant was continued throughout the study. Relapse was defined as a MADRS total score greater than or equal to 22 for two consecutive assessments separated by 5 to 15 days, or hospitalization for worsening depression

or any other clinically relevant event indicative of relapse.

Of the individuals in stable remission, 26.7 percent of individuals in the esketamine (Spravato) group and 45.3 percent of individuals in the placebo group experienced a relapse event during the optimization phase. Individuals who continued treatment with esketamine (Spravato) plus oral AD experienced a statistically significantly longer time to relapse of depressive symptoms than did individuals on placebo nasal spray plus an oral AD. Time to relapse was also significantly delayed in the stable responder population. These individuals experienced a statistically significantly longer time to relapse of depressive symptoms than individuals on placebo nasal spray plus oral AD as well.

#### Major Depressive Disorder (MDD): Short-Term Studies

ASPIRE I (Fu et al., 2020) and ASPIRE II (Ionescu et al., 2021) were identical phase III, short-term (4 week), randomized, double-blind, multicenter, placebo-controlled studies to evaluate the use of esketamine (Spravato) versus placebo in reducing MDD symptoms, including suicidal ideations. Individuals who met the DSM-5TR criteria for MDD without psychosis, age 18 to 64 years old, with moderate-to-severe MDD (MADRS score >28) with active suicidal ideation and intent received either esketamine (Spravato) or placebo twice weekly for 4 weeks. Key exclusion criteria included substance use disorder, MDD with psychotic features, bipolar disorder, OCD, borderline personality disorder, and antisocial personality disorder. All individuals received comprehensive standard of care treatment including an inpatient psychiatric hospitalization and a newly initiated or optimized oral AD. The initial dosage of esketamine (Spravato) was 84 mg but could be reduced to 56 mg if the individual could not tolerate the higher dosage. The primary endpoint of the study was improvement in MADRS scores 24 hours after the treatment. There was a statistically significant improvement in the esketamine (Spravato) MADRS scores (-16.4 in ASPIRE I; -15.7 in ASPIRE II) versus the placebo group MADRS scores (-12.8 in ASPIRE I; -12.4 in ASPIRE II). The onset of improvement was earlier with esketamine (Spravato), at 4 hours, versus with placebo as well. Both groups had rapid reduction in the severity of their suicidality, but the difference between the groups was not statistically significant and was believed to be likely due to both groups receiving inpatient hospital care.

#### Professional Guidelines

The American Psychiatric Association last issued clinical practice guidelines for depression in 2010. Because esketamine (Spravato) was approved by the US Food and Drug Administration in 2019, the drug was not included in the most recent guidelines. There is therefore no published guideline from the American Psychiatric Association that contains recommendations on the use of esketamine (Spravato) for use in TRD.

The Institute for Clinical and Economic Review published a summary on the effectiveness and value of intranasal esketamine (Spravato) for the management of TRD (Agboola et al., 2020). They found that esketamine (Spravato) demonstrated superiority when combined with an antidepressant as compared to an antidepressant alone. Concerns about the safety of the long-term use of esketamine (Spravato) remain, however.

#### OFF-LABEL INDICATIONS

There may be additional indications contained in the Policy section of this document due to evaluation of criteria highlighted in the Company's off-label policy, and/or review of clinical guidelines issued by leading professional organizations and government entities.

---

## References

### References

Agboola F, Atlas SJ, Touchette DR, et al. The effectiveness and value of esketamine for the management of treatment-resistant depression. *J Manag Care Spec Pharm*. 2020;26(1):16-20.

American Hospital Formulary Service (AHFS). Esketamine (Spravato®). AHFS Drug Information 2024. [UpToDate Lexidrug Web site]. 03/11/2024. Available at: <https://online.lexi.com/lco/action/home> [via subscription only]. Accessed April 19, 2024.

American Hospital Formulary Service (AHFS). Ketamine (Ketalar®). AHFS Drug Information 2024. [UpToDate Lexidrug Web site]. 04/03/2024. Available at: <https://online.lexi.com/lco/action/home> [via subscription only]. Accessed April 19, 2024.

American Psychological Association (APA). Montgomery and Asberg (MADRS) depression rating scale. [APA Web site]. 06/2019. Available at: <https://www.apa.org/depression-guideline/montgomery-asberg-scale.pdf>. Accessed April 19, 2024.

Beck AT, Steer RA, Brown GK. *Beck Depression Inventory: Second Edition*. San Antonio, TX: The Psychology Corporation; 1996.

Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961;4:561-571.

Bell RF, Eccleston C, Kalso EA. Ketamine as an adjuvant to opioids for cancer pain. *Cochrane Database Syst Rev*. 2017;Jun 28(6):CD003351.

Best SRD, Pavel DG, Hastrup N. Combination therapy with transcranial magnetic stimulation and ketamine for treatment-resistant depression: a long-term retrospective review of clinical use. *Heliyon*. 2019;5(8):e02187.

Bredlau AL, Thakur R, Korones DN, Dworkin RH. Ketamine for pain in adults and children with cancer: a systematic review and synthesis of the literature. *Pain Med*. 2013;14:1505-1517.

Caddy C, Amit BH, McCloud TL, et al. Ketamine and other glutamate receptor modulators for depression in adults (Review). *Cochrane Database Syst Rev*. 2015;Sep 23(9):CD011612.

Carley ME, Chaparro LE, Choiniere M, et al. Pharmacotherapy for the prevention of chronic pain after surgery in adults: an updated systemic review and meta-analysis. *Anesthesiology*. 2021;135(2):304-325.

Chaparro LE, Smith SA, Moore RA, et al. Pharmacotherapy for the prevention of chronic pain after surgery in adults (Review). *Cochrane Database Syst Rev*. 2013;Jul 24(7):CD008307.

Clauw DJ. Pharmacotherapy for patients with fibromyalgia. *J Clin Psychiatry*. 2008;69(suppl 2): 25-29.

Cohen SP, Bhatia A, Buvanendran A, et al. Consensus guidelines on the use of intravenous ketamine infusions for chronic pain from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Reg Anesth Pain Med*. 2018;43:521-546.

Daly EJ, Trivedi MH, Janik A, et al. Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression. *JAMA Psychiatry*. 2019;76(9):893-903.

Domino EF, Chodoff P, Corssen G. Pharmacologic effects of CI-581, a new dissociative anesthetic, in man. *Clin Pharmacol Ther*. 1965;6(3):279-291.

Elsevier's Clinical Pharmacology Compendium. Esketamine (Spravato®). [Clinical Key Web site]. 01/11/2024. Available at: <https://www.clinicalkey.com/#!/> [via subscription only]. Accessed April 19, 2024.

Elsevier's Clinical Pharmacology Compendium. Ketamine (Ketalar®). [Clinical Key Web site]. 01/31/2024. Available at: <https://www.clinicalkey.com/#!/> [via subscription only]. Accessed April 19, 2024.

Esketamine (Spravato®) [prescribing information]. Lakewood, NJ: Janssen Pharmaceuticals, Inc.; 10/2023. Available at: <https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/SPRAVATO-pi.pdf>. Accessed April 19, 2024.

Fu DJ, Ionescu DF, Li X, et al. Esketamine nasal spray for rapid reduction of major depressive disorder symptoms in patients who have active suicidal ideation with intent: double-blind, randomized study (ASPIRE I). *J Clin Psychiatry*. 2020;81(3):19M13191.

Granot R, Day RO, Cohen ML, et al. Targeted pharmacotherapy of evoked phenomena in neuropathic pain: a review of the current evidence. *Pain Medicine*. 2007;8(1):48-64.

Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56-62.

Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol*. 1967;6(4):278-296.

Ionescu DF, Fu DJ, Qiu X, et al. Esketamine nasal spray for rapid reduction of depressive symptoms in patients with major depressive disorder who have active suicidal ideation with intent: results of a phase 3, double-blind, randomized study (ASPIRE II). *Int J Neuropsychopharmacol*. 2021;24(1):22-31.

Ketamine (Ketalar®) [prescribing information]. Chestnut Ridge, NY: Par Pharmaceutical. 03/2022. Available at: [https://www.parpharm.com/products/sterile/ketalar/#:~:text=Ketalar®](https://www.parpharm.com/products/sterile/ketalar/#:~:text=Ketalar%20) | Par Pharmaceutical. Accessed April 19, 2024.

Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606-613.

Martinotti G, Chiappini S, Pettoruso M, et al. Therapeutic potentials of ketamine and esketamine in obsessive-compulsive disorder (OCD), substance use disorders (SUD) and eating disorders (ED): a review of the current literature. *Brain Sci*. 2021;11(7):856.

Merative Micromedex® DRUGDEX® (electronic version). Esketamine (Spravato®). [Micromedex Web site]. 02/28/2024. Available at: <https://www.micromedexsolutions.com/micromedex2/librarian> [via subscription only]. Accessed April 19, 2024.

Merative Micromedex® DRUGDEX® (electronic version). Ketamine (Ketalar®). [Micromedex Web site]. 04/08/2024. Available at: <https://www.micromedexsolutions.com/micromedex2/librarian> [via subscription only]. Accessed April 19, 2024.

Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Brit J Psychiat*. 1979;134:382-389.

National Comprehensive Cancer Network (NCCN). *NCCN Clinical Practice Guidelines in Oncology® - Adult cancer pain*. V2.2024. [NCCN Website]. 03/11/2024. Available at: [https://www.nccn.org/professionals/physician\\_gls/pdf/pain.pdf](https://www.nccn.org/professionals/physician_gls/pdf/pain.pdf) [via free subscription only]. Accessed April 19, 2024.

National Institutes of Health. The patient health questionnaire (PHQ-9) – overview. [National Institutes of Health website]. 1999. Available at: [https://coepes.nih.gov/sites/default/files/2020-12/PHQ-9 depression scale.pdf](https://coepes.nih.gov/sites/default/files/2020-12/PHQ-9%20depression%20scale.pdf). Accessed April 19, 2024.

National Institute of Neurological Disorders and Stroke (NINDS) Common Data Elements. Beck Depression Inventory II (BDI-II). [NINDS website]. 01/2024. Available at: [https://www.commondataelements.ninds.nih.gov/report-viewer/25193/Beck Depression Inventory II \(BDI-II\)](https://www.commondataelements.ninds.nih.gov/report-viewer/25193/Beck%20Depression%20Inventory%20II%20(BDI-II)). Accessed April 19, 2024.

Noppers I, Niesters M, Swartjes M, et al. Absence of long-term analgesic effect from a short-term S-ketamine infusion on fibromyalgia pain: a randomized, prospective, double blind, active placebo-controlled trial. *Eur J Pain*. 2011;15(9):942-949.

Orr SL, Friedman BW, Christie S, et al. Management of adults with acute migraine in the emergency department: the American Headache Society evidence assessment of parenteral pharmacotherapies. *Headache*. 2016;56:911-940.

Popova V, Daly EJ, Trivedi M, et al. Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized double-blind active-controlled study. *Am J Psychiatry*. 2019;176(6):428-438.

Rush AJ. Unipolar major depression in adults: choosing initial treatment. [Up to Date web site]. 03/21/2024. Available at: [https://www.uptodate.com/contents/unipolar-major-depression-in-adults-choosing-initial-treatment?search=Unipolar major depression in adults: choosing initial treatment&source=search\\_result&selectedTitle=1~150&usage\\_type=default&display\\_rank=1](https://www.uptodate.com/contents/unipolar-major-depression-in-adults-choosing-initial-treatment?search=Unipolar%20major%20depression%20in%20adults%3A%20choosing%20initial%20treatment&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1) [via subscription only]. Accessed April 19, 2024.

Sanacora G, Frye MA, McDonald W, et al. A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry*. 2017;74(4):399-405.

Schwenk ES, Viscusi ER, Buvanendran A, et al. Consensus guidelines on the use of intravenous ketamine infusions for acute pain management from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Reg Anesth Pain Med*. 2018;43(5):456-

466.

Thase M, Connolly KR. Unipolar treatment-resistant depression in adults: epidemiology, risk factors, assessment, and prognosis. [Up to Date Web site]. 01/11/2023. Available at: [https://www.uptodate.com/contents/unipolar-treatment-resistant-depression-in-adults-epidemiology-risk-factors-assessment-and-prognosis?search=Unipolar treatment resistant depression in adults: epidemiology, risk factors, assessment, and prognosis&source=search\\_result&selectedTitle=1~150&usage\\_type=default&display\\_rank=1](https://www.uptodate.com/contents/unipolar-treatment-resistant-depression-in-adults-epidemiology-risk-factors-assessment-and-prognosis?search=Unipolar+treatment+resistant+depression+in+adults:epidemiology,risk+factors,assessment,and+prognosis&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1) [via subscription only]. Accessed April 19, 2024.

UpToDate® Lexidrug™. Esketamine (Spravato®). [UpToDate Lexidrug Web site]. 02/29/2024. Available at: <https://online.lexi.com/lco/action/home> [via subscription only]. Accessed April 19, 2024.

UpToDate® Lexidrug™. Ketamine (Ketalar®). [UpToDate Lexidrug Web site]. 04/05/2024. Available at: <https://online.lexi.com/lco/action/home> [via subscription only]. Accessed April 19, 2024.

US Food and Drug Administration (FDA). Center for Drug Evaluation and Research. Esketamine (Spravato®) Prescribing Information. [FDA Web site]. 10/18/2023. Available at: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>. Accessed April 19, 2024.

US Food and Drug Administration (FDA). Center for Drug Evaluation and Research. Ketamine (Ketalar®) Prescribing Information. [FDA Web site]. 06/03/2022. Available at: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>. Accessed April 19, 2024.

---

## Coding

**Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.**

**The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.**

**In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.**

**The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.**

### CPT Procedure Code Number(s)

**THE FOLLOWING CODE IS USED TO REPRESENT A MINIMUM OF 2 HOURS OF POST ADMINISTRATION OBSERVATION OF INTRANASAL ESKETAMINE (Spravato®)**  
99499

---

### ICD - 10 Procedure Code Number(s)

N/A

---

### ICD - 10 Diagnosis Code Number(s)

**INTRANASAL ESKETAMINE (SPRAVATO®) IS CONSIDERED MEDICALLY NECESSARY FOR THE FOLLOWING INDICATIONS:**

- |        |  |
|--------|--|
| F32.0  | Major depressive disorder, single episode, mild                              |
| F32.1  | Major depressive disorder, single episode, moderate                          |
| F32.2  | Major depressive disorder, single episode, severe without psychotic features |
| F32.4  | Major depressive disorder, single episode, in partial remission              |
| F32.5  | Major depressive disorder, single episode, in full remission                 |
| F32.89 | Other specified depressive episodes  |

- F33.0 Major depressive disorder, recurrent, mild
- F33.1 Major depressive disorder, recurrent, moderate
- F33.2 Major depressive disorder, recurrent severe without psychotic features
- F33.40 Major depressive disorder, recurrent, in remission, unspecified
- F33.41 Major depressive disorder, recurrent, in partial remission
- F33.42 Major depressive disorder, recurrent, in full remission
- F33.8 Other recurrent depressive disorders
- F33.9 Major depressive disorder, recurrent, unspecified

### HCPCS Level II Code Number(s)

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

J0013 Esketamine, nasal spray, 1 mg

### THE FOLLOWING CODE(S) ARE USED TO REPRESENT Intravenous Ketamine (Ketalar®):

C9399 Unclassified drugs or biologicals

J3490 Unclassified drugs

### Policy History

Policy History

#### Revisions From MA08.137e:

03/20/2026	<p>This version of the policy will become effective 03/20/2026.</p> <p>The following code has been added to this policy:</p> <ul style="list-style-type: none"> <li>• J0013 Esketamine, nasal spray, 1 mg</li> </ul> <p>The following code has been deleted from the policy:</p> <ul style="list-style-type: none"> <li>• S0013 Esketamine, nasal spray, 1 mg</li> </ul>
------------	--

#### Revisions From MA08.137d:

12/29/2025	<p>This version of the policy will become effective 12/29/2025.</p> <p>The following policy criteria have been added to this policy:</p> <ul style="list-style-type: none"> <li>• Esketamine (Spravato), administered as a nasal spray, used as a monotherapy for individuals aged 18 and older with major depressive disorder (MDD) who have had an inadequate response to at least two oral antidepressants</li> </ul>
------------	--

	<ul style="list-style-type: none"> <li>• Psychiatric indications, including but not limited to, depression and bipolar disorder and is considered experimental/investigational and, therefore, not covered.</li> <li>• The use of ketamine (e.g. Ketalar) for the treatment of acute/chronic pain including but not limited to Complex Regional Pain Syndrome [CRPS]) is considered experimental/investigational</li> <li>• The concurrent use of ketamine and esketamine is considered experimental/investigational and, therefore, not covered</li> </ul>
--	---

**Revisions From MA08.137c:**

12/15/2025	This policy has been reissued in accordance with the Company's annual review process.
09/16/2024	<p>This version of the policy will become effective 09/16/2024.</p> <p>The following policy criteria have been <b>added</b> to this policy:</p> <ul style="list-style-type: none"> <li>• Requirement that the antidepressants used in the treatment of major depressive disorder that esketamine (Spravato) is being considered for be approved by the US Food and Drug Administration (FDA) for the indication of depression</li> <li>• Use of concurrent transcranial magnetic stimulation as a contraindication for the use of esketamine (Spravato)</li> </ul>

**Revisions From MA08.137b:**

01/02/2024	<p>This version of the policy will become effective 01/02/2024.</p> <p>The following policy criteria have been <b>revised</b> in this policy:</p> <ul style="list-style-type: none"> <li>• Additional depression scales (Beck Depression Inventory - II, Patient Health Questionnaire - 9, Hamilton Rating Scale for Depression) were added</li> <li>• The requirement that the depressive episode that was unresponsive to treatment with at least two different antidepressants be current</li> <li>• Reauthorization/continuation criteria for esketamine (Spravato)</li> </ul>
------------	--

**Revisions From MA08.137a:**

01/01/2024	<b>Effective 01/01/2024 this policy applies to New Jersey Medicare Advantage (MA) lines of business.</b>
01/01/2023	<p>This version of the policy will become effective 01/01/2023.</p> <p>The intent of this policy remains unchanged, but the policy has been updated to change the version of the Diagnostic and Statistical Manual of Mental Disorders to fifth edition text revision (DSM-5TR).</p>

**Revisions From MA08.137:**

04/04/2022	The following new policy has been developed to communicate the Company's coverage criteria for Intravenous Ketamine (Ketalar®) and Intranasal Esketamine (Spravato®). The policy will become effective 04/04/2022.
------------	--

Version Effective Date:

03/20/2026

Version Issued Date:

03/20/2026

Version Reissued Date:  
N/A