Ketalar® (Ketamine) and Spravato® (Esketamine)

Policy Number: 2026D0069Q
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➲ Instructions for Use

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Community Plan Policy

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Application

UnitedHealthcare Commercial

This Medical Policy applies to UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit plans.

Coverage Rationale

➲ See Benefit Considerations

This policy refers to the following ketamine products:

- Ketalar (ketamine)
- Spravato (esketamine)

Spravato (Esketamine) Nasal Spray

Spravato is proven for the treatment of treatment-resistant depression (TRD) when all of the following criteria are met:

- **Initial Therapy**
  - Diagnosis of major depressive disorder (treatment-resistant); **and**
  - Patient has not experienced a clinically meaningful improvement after treatment with at least two different antidepressants; **and**
  - Provider and/or the provider's healthcare setting is certified in the Spravato REMS program; **and**
  - Spravato dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
  - Initial authorization will be for no longer than 12 months
- **Continuation of Therapy**
  - Documentation of positive clinical response to Spravato therapy; **and**
  - Provider and/or the provider's healthcare setting is certified in the Spravato REMS program; **and**
  - Spravato dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
  - Reauthorization will be for no longer than 12 months

Spravato is medically necessary for the treatment of treatment-resistant depression (TRD) when all of the following criteria are met:

- **Initial Therapy**
  - Diagnosis of major depressive disorder (treatment-resistant), according to the current DSM (i.e., DSM-5-TR), by a mental health professional; **and**
  - Submission of medical records (e.g., chart notes, laboratory values) documenting baseline scoring (prior to starting Spravato) on at least **one** of the following clinical assessments has been completed:
    - Beck Depression Inventory (BDI)
    - Hamilton Rating Scale for Depression (HAMD)
    - Montgomery-Asberg Depression Rating Scale (MADRS)
    - 9-item Patient Health Questionnaire (PHQ-9)
    - Quick Inventory of Depressive Symptomatology (QIDS)

    and
  - History of failure of a trial of at least two different antidepressants or treatment regimens for a duration of at least 8 weeks each (document medication, date, and duration of trial):
    - An antidepressant or treatment regimen would include any of the following classes or combinations:
      - Selective serotonin reuptake inhibitors (e.g., citalopram, fluoxetine, paroxetine, sertraline)
      - Serotonin norepinephrine reuptake inhibitors (e.g., duloxetine, venlafaxine, etc.)
      - Bupropion
      - Tricyclic antidepressants (e.g., amitriptyline, clomipramine, nortriptyline, etc.)
      - Mirtazapine
      - Monoamine oxidase inhibitors (e.g., selegiline, tranylcypromine, etc.)
      - Serotonin modulators (e.g., nefazodone, trazodone, etc.)
      - Augmentation with antipsychotics, lithium, or thyroid hormone

    and
  - Provider and/or the provider's healthcare setting is certified in the Spravato REMS program; **and**
  - Prescribed by or in consultation with a psychiatrist; **and**
  - Spravato dosing is in accordance with the United States Food and Drug Administration (FDA) approved labeling; **and**
  - Initial authorization will be for no longer than 12 months
- **Continuation of Therapy**
  - Documentation of remission or a positive clinical response to Spravato therapy; **and**
  - Submission of medical records (e.g., chart notes, laboratory values) documenting baseline and recent (within the last month) scoring on at least **one** of the following assessments demonstrating remission or clinical response (e.g., score reduction from baseline) as defined by the:
    - BDI
    - HAMD
    - MADRS
    - PHQ-9
    - QIDS

    and
  - Provider and/or the provider's healthcare setting is certified in the Spravato REMS program; **and**
  - Prescribed by or in consultation with a psychiatrist; **and**
  - Spravato dosing is in accordance with the United States FDA approved labeling; **and**
  - Reauthorization will be for no longer than 12 months

Spravato is proven for the treatment of depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior when all of the following criteria are met:

- **Initial Therapy**
  - Diagnosis of major depressive disorder; **and**
  - Patient is experiencing an acute suicidal ideation or behavior; **and**
  - Provider and/or the provider's healthcare setting is certified in the Spravato REMS program; **and**
  - Spravato dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
  - Initial authorization will be for no longer than 12 months

Spravato is medically necessary for the treatment of depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior when all of the following criteria are met:

- **Initial Therapy**
  - Diagnosis of major depressive disorder according to the current DSM (i.e., DSM-5-TR), by a mental health professional; **and**

- Patient is experiencing an acute suicidal ideation or behavior; **and**
- Patient is to receive Spravato therapy in conjunction with a newly initiated or optimized oral antidepressant; **and**
- Provider and/or the provider's healthcare setting is certified in the Spravato REMS program; **and**
- Spravato dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
- Initial authorization will be for no longer than 12 months

Spravato is unproven and not medically necessary for the following:

- Anesthetic agent
- Chronic pain (including but not limited to nonmalignant pain, fibromyalgia, neuropathic pain, Complex Regional Pain Syndrome, Reflex Sympathetic Dystrophy)
- Migraine headaches

Ketalar (Ketamine) Injection

Ketamine injection is considered medically necessary and may be covered for the following:

- Anesthesia for diagnostic and surgical procedures that do not require skeletal muscle relaxation
- The induction of anesthesia prior to administration of other anesthesia agents
- As supplemental anesthesia for low-potency agents, such as nitrous oxide

Ketamine injection is investigational, and therefore not proven or medically necessary for the following:

- Psychiatric disorders (including but not limited to depression, bipolar disorder, and posttraumatic stress disorder)
- Chronic pain (including but not limited to nonmalignant pain, fibromyalgia, neuropathic pain, complex regional pain syndrome, reflex sympathetic dystrophy)
- Migraine headaches

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J0013	Esketamine, nasal spray, 1 mg
J3490	Unclassified drugs

Diagnosis Code	Description
F33.0	Major depressive disorder, recurrent, mild
F33.1	Major depressive disorder, recurrent, moderate
F33.2	Major depressive disorder, recurrent severe without psychotic features
F33.3	Major depressive disorder, recurrent, severe with psychotic symptoms
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

Background

Major depressive disorder (MDD) is a serious and life-threatening condition with high rates of individual and society-level morbidity, and a chronic disease course. Over 16 million people in the United States and over 300 million people worldwide have depression. Patients with MDD may be unable to work, maintain relationships, attend to self-care, and in the most severe cases may become hospitalized or attempt or commit suicide. MDD is considered the leading cause of disability worldwide and also is associated with increased mortality rates (at a median rate of 10 years of life lost). About 30 to 40% of patients with MDD fail to respond to first-line treatments including oral antidepressant medications of all

classes [selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), etc.] and/or psychotherapy. In addition, the onset of treatment response for these modalities, even when effective, often takes at least four weeks, leading to greater suffering, expense, and risk.

Patients who have failed at least two trials of antidepressant treatment generally comprise the population with treatment-resistant depression (TRD); however, the definition of TRD has not been standardized. Relative to other patients with MDD, patients with TRD can incur even more severe morbidity, with higher rates of hospitalization, suicidal ideation and behavior, and medical complications. Standard of care measures for TRD include switching to a different antidepressant (of either the same or a different class), adding an adjunctive treatment to an ongoing antidepressant (typically a drug with a different mechanism of action), adding or switching psychotherapy, or referral for a procedure such as electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS).

Spravato (esketamine) is the S-enantiomer of racemic ketamine, and is a non-selective, non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor. The mechanism by which esketamine exerts its antidepressant effect is unknown.[14]

Ketamine is a rapid-acting general anesthetic producing an 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. The mechanism of action is primarily due to antagonism of NMDA receptors in the central nervous system.[1]

Ketamine for the treatment of psychiatric disorders and pain has been gaining popularity. Studies available currently are of poor design, lacking adequate sample size and duration. Because of this, additional studies are needed to determine the safety and efficacy for the use of ketamine for these indications. Ketamine is not FDA approved for the treatment of any psychiatric disorder and there is no evidence to suggest that it is safer, more effective, or works faster than medications that are FDA approved for the treatment of certain psychiatric disorders. Known safety concerns associated with the use of ketamine products include abuse and misuse, psychiatric events, increases in blood pressure, respiratory depression (slowed breathing), and lower urinary tract and bladder symptoms.

Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy.

Clinical Evidence

Chronic Pain

Schwartzman et al conducted a randomized double-blind placebo-controlled trial to evaluate the effectiveness of intravenous ketamine in the treatment of complex regional pain syndrome (CRPS). Patients were evaluated for 2 weeks or longer before treatment and for 3 months after. All subjects received normal saline with or without ketamine intravenously for 4 hours (25 mL/ hour) daily for 10 days. The results showed that intravenous ketamine administered in an outpatient setting resulted in statistically significant ($p < 0.05$) reductions in many pain parameters. It also showed that subjects in the placebo group did not experience treatment effect in any parameter. The authors conclude that the results of this study warrant a larger randomized placebo-controlled trial using higher doses of ketamine and a longer follow-up period.

Noppers et al performed a randomized double blind, active placebo-controlled trial to evaluate the analgesic efficacy of ketamine on fibromyalgia pain. Twenty-four fibromyalgia patients were randomized to receive either ketamine or the active placebo, midazolam by intravenous infusion. Visual Analogue Pain Scores (VAS) and ketamine plasma samples were collected after the infusion. In addition, an 8-week follow-up collected pain scores derived from the fibromyalgia impact questionnaire (FIQ) were collected weekly. Fifteen minutes after infusion completion, the number of patients showing a reduction in pain scores > 50% was 8 vs. 3 ($p < 0.05$), at t = 180 min 6 vs. 2 (ns), at the end of week-1, 2 vs. 0 (ns), and at end of week 8, 2 vs. 2 in the ketamine and midazolam groups, respectively. For VAS and FIQ scores no significant differences in treatment effects were observed in the 2.5 hours following infusion or during the 8-week follow-up. Adverse events were mild to moderate in both study groups. The authors conclude that a short-term infusion of ketamine is insufficient to induce long-term analgesic effects in fibromyalgia patients.

Psychiatric Disorders

Esketamine

Esketamine is indicated for the treatment of treatment-resistant depression (TRD) in adults as monotherapy or in conjunction with an oral antidepressant. Esketamine is also indicated for depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior. Spravato is not approved as an anesthetic agent. The safety and effectiveness of Spravato as an anesthetic agent have not been established.

The safety and efficacy of esketamine was examined in four phase 3 international randomized controlled trials comparing intranasal esketamine and intranasal placebo. Three studies were of similar short-term parallel group design, and one was a randomized withdrawal maintenance-of-effect design. The majority of subjects in all the studies were women in their 40s and 50s, white, with higher body mass index (BMI > 24). Depending on the study, around 33 to 40% of enrolled subjects had failed three or more antidepressant (AD) treatments by the start of screening, and 12 to 17% had failed at least four. Each treatment was added to one of four newly initiated oral antidepressants (duloxetine, venlafaxine XR, escitalopram, or sertraline), each dosed daily beginning at the start of the treatment phase. For the first 4 weeks of treatment, the nasal spray was administered twice weekly. For the maintenance-of-effect study and for long-term open-label safety studies, the nasal spray was administered weekly for the next 4 weeks post-induction phase, then either weekly or every other week for ongoing maintenance.

The primary outcome measure used for the studies was the Montgomery-Asberg Depression Rating Scale (MADRS). To decrease the introduction of bias, all MADRS score evaluations were performed by independent, remote (via telephone), blinded raters. Scales were administered on study visit days prior to intranasal esketamine (or placebo) dosing and with a few exceptions (shorter-term secondary endpoints) were meant to assess symptoms over the previous 7 days. Baseline mean MADRS total scores for 3 of the studies ranged from 37 to 38 and for the geriatric study, the mean was 35. These baseline mean scores indicate greater illness severity for the treatment population in the esketamine phase 3 studies than is typical for MDD development programs.

The key inclusion criteria involved the definition of TRD for the patients included: Patients were required to meet DSM-5 diagnostic criteria for recurrent MDD or single-episode MDD (duration ≥ 2years) without psychotic features, which was verified by the structured Mini International Neuropsychiatric Interview. Patients must have been experiencing moderate to severe depressive symptomatology based on specified scores of the Inventory of Depressive Symptomatology-Clinician rated, 30-itemand MADRS at Weeks 1, 2, and 4 of the screening/observational phase. In all controlled phase 3 studies, treatment resistance was defined in accordance with the regulatory definition, i.e., a lack of clinically meaningful improvement (defined for phase 3 studies as ≤ 25%) in the current episode of depression after treatment with at least 2 different AD agents prescribed in adequate dosages for an adequate duration (defined for phase 3 studies as at least 6 weeks).

In two studies (one parallel-group study and the randomized withdrawal study), esketamine was statistically superior to placebo on the study's primary efficacy endpoint; in the other two short-term parallel group studies, esketamine was not. In the study, TRANSFORM-2, patients in the esketamine treatment group experienced statistically significantly greater improvement in depressive symptoms, as measured by the change from baseline to endpoint in the MADRS, than patients in the placebo group. On the MADRS, the mean difference between esketamine and placebo was statistically significant at most time points throughout the 28 days of double-blind treatment (except Day 15). In the SUSTAIN-1, trial, direct entry patients or from TRANSFORM-1 or TRANSFORM-2, were enrolled. All subjects who experienced ≥ 50% reduction from baseline in MADRS total score by the end of acute 4-week treatment were eligible to enter the optimization phase, where they received at least 12 weeks of open-label esketamine treatment with oral antidepressant ongoing. There was a statistically significant difference in time to relapse of depression favoring those patients randomized to continue esketamine versus those who were switched to placebo (with oral antidepressant ongoing in both arms) in the stable remitters group. The secondary endpoint of time to relapse in the stable responders group was also statistically significant.

In a phase 3, randomized, double-blind, active controlled, multicenter study, Popova et al compared the efficacy and safety of switching patients with treatment-resistant depression from an ineffective antidepressant to a flexible dosed esketamine nasal spray, plus a newly initiated antidepressant or to a newly initiated antidepressant plus placebo nasal spray. The study consisted of three phases: (1) a 4-week screening and prospective observation phase during which treatment response to the current ongoing oral antidepressants was assessed; (2) a 4-week treatment phase during which participants received a new oral antidepressant combined with either esketamine nasal spray or placebo nasal spray; and (3) a post-treatment follow-up phase of up to 24 weeks. At study entry, participants had documented (retrospectively) nonresponse (≤ 25% improvement) to one to five antidepressants. Four hundred thirty-five patients were screened and

223 underwent treatment (114 in the esketamine plus antidepressant group and 109 in the antidepressant plus placebo group). Only 197 completed the 28-day double-blind treatment phase. The primary efficacy endpoint was the change in MADRS score from baseline (day 1) to endpoint (day 28). Change in MADRS score with esketamine plus antidepressant was significantly greater than with antidepressant plus placebo at day 28 (difference of least square means = -4.0, SE = 1.69, 95% CI = -7.31, -0.64); likewise, clinically meaningful improvement was observed in the esketamine plus antidepressant arm at earlier time points. The five most common adverse events (dissociation, nausea, vertigo, dysgeusia, and dizziness) all were observed more frequently in the esketamine plus antidepressant arm than in the antidepressant plus placebo arm; 7% and 0.9% of patients in the respective treatment groups discontinued study drug because of an adverse event. Adverse events in the esketamine plus antidepressant arm generally appeared shortly after dosing and resolved by 1.5 hours after dosing. Despite the high response to the oral antidepressant plus placebo comparator, results the study results showed a clinically relevant, favorable improvement in depressive symptoms with esketamine (either 56 mg or 84 mg) nasal spray plus a newly initiated antidepressant. The authors concluded that esketamine nasal spray is safe and effective for patients with treatment-resistant depression.

Esketamine was evaluated in two identical Phase 3 short-term (4-week) randomized, double-blind, multicenter, placebo-controlled studies, ASPIRE I and ASPIRE II, in adults with moderate-to-severe MDD (MADRS total score > 28) who had active suicidal ideation and intent. In these studies, patients received treatment with esketamine 84 mg or placebo nasal spray twice weekly for 4 weeks. All patients received comprehensive standard of care treatment, including an initial inpatient psychiatric hospitalization and a newly initiated or optimized oral antidepressant (AD monotherapy or AD plus augmentation therapy) as determined by the investigator. After completion of the 4-week treatment period with esketamine/ placebo, study follow-up continued through Day 90. The primary efficacy measure was the change from baseline in the MADRS total score at 24 hours after first dose (Day 2). In ASPIRE I and II, esketamine plus standard of care demonstrated statistical superiority on the primary efficacy measure compared to placebo nasal spray plus standard of care. 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 (Day 2). 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 ASPIRE I and II, esketamine plus standard of care did not demonstrate superiority compared to placebo nasal spray plus standard of care in improving CGI-SS-r. In both ASPIRE I and II, 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.

A meta-analysis of randomized double-blind controlled-placebo trials (RCTs) evaluated the effectiveness, tolerability, and safety of intranasal esketamine in treating major depressive disorder (MDD). Four RCTs with 7 active arms covering 708 patients with MDD on intranasal esketamine (n = 419) and placebo (n = 289) were included. Compared with placebo, adjunctive intranasal esketamine was associated with significantly greater study-defined response (RR = 1.39, 95%CI: 1.18 to 1.64, p < 0.0001) and remission (RR = 1.42, 95%CI: 1.17 to 1.72, p = 0.0004) at endpoint assessment. Intranasal esketamine had greater study-defined response starting at 2 hours (RR = 2.77, 95%CI: 1.62 to 4.76, p = 0.0002), peaking at 24 hours (RR = 5.42, 95%CI: 1.38 to 21.20, p = 0.02), and at least lasting for 28 days (RR = 1.36, 95%CI: 1.16 to 1.58, p = 0.0001). Similarly, intranasal esketamine had significantly greater study-defined remission starting at 2 hours (RR = 7.71, 95%CI: 2.16 to 27.55, p = 0.002), peaking at 24 hours (RR = 6.87, 95%CI: 1.55 to 30.35, p = 0.01), and lasting for 28 days (RR = 1.38, 95%CI: 1.11 to 1.72, p = 0.004). Intranasal esketamine had a significantly higher rate of discontinuation due to intolerability (RR = 3.50, 95%CI: 1.38 to 8.86, p = 0.008). Discontinuation due to any reasons and inefficacy were similar between the two groups.

The approval of Spravato for an expanded indication as monotherapy for the treatment of treatment-resistant depression (TRD) was based on a randomized, double-blind, placebo-controlled study in 378 adult patients with TRD. After discontinuing prior antidepressant treatments if applicable, patients were randomized to receive twice weekly doses of intranasal Spravato 56 mg or 84 mg or intranasal placebo for four weeks. The primary endpoint was change from baseline in the MADRS total score at day 28. The least-squares mean change from baseline in MADRS total score at day 28 was -11.4 with Spravato 56 mg, -13.0 with Spravato 84 mg, and -6.3 with placebo. Spravato 56 mg and 84 mg monotherapy demonstrated a statistically significant improvement in the primary endpoint.

Ketamine

McCloud et al assessed the effects of ketamine and other glutamate receptor modulators in alleviating the acute symptoms of depression in people with bipolar disorder. The authors included randomized controlled trials comparing ketamine with other active psychotropic drugs or saline placebo in adults with bipolar depression in their review. Regarding ketamine, the authors concluded that there is limited evidence in favor of a single intravenous dose of ketamine over placebo with regard to response rate in the first 24 hours after treatment. In addition, ketamine did not show any better efficacy regarding remission in bipolar depression. While ketamine may have the potential to have a rapid

and transient antidepressant effect, the efficacy of a single intravenous dose is limited.
Coyle et al completed a systematic review of the literature and analyzed data from 21 studies where ketamine was used as an antidepressant. The authors concluded that effectiveness was significantly greater for repeat than single infusion at 4 hours, 24 hours, and 7 days. For single infusion studies, effect sizes were large and significant at 4 hours, 24 hours, and 7 days. Effectiveness for open-label and participant-blind infusions were not significantly different at any time point. The authors concluded that single ketamine infusions elicit a significant antidepressant effect from 4 hours to 7 days. There were a small number of studies at 12-14 days post infusion that failed to reach significance. Results suggest a discrepancy in peak response time depending upon primary diagnosis: 24 hours for MDD and 7 days for bipolar disorder. The authors concluded that further placebo-controlled studies are needed to evaluate the effect of ketamine over time.

Lee et al conducted a meta-analysis to assess the efficacy of ketamine compared to placebo for the reduction of depressive symptoms in patients who meet criteria for a major depressive episode. The authors reviewed two electronic databases for randomized, placebo-controlled trials of ketamine treatment for patients with major depressive disorder or bipolar depression while using a standardized rating scale. The authors included 5 studies in the quantitative meta-analysis. The overall effect size at day 1 was large and statistically significant with an overall standardized mean difference of 1.01 (95% confidence interval 0.69–1.34) ($p < 0.001$), with the effects sustained at 7 days after drug administration. The authors concluded that the effect of ketamine on depressive symptoms at days 1 and 7 post administration supports a potential, new, and effective pharmacotherapy with rapid onset, efficacy, and good tolerability.

Wan et al pooled data from 205 intravenous ketamine infusions in 97 participants with DSM-4-defined major depressive disorder from 3 clinical trials. They evaluated the safety and tolerability through attrition, adverse events (AEs), hemodynamic changes, and assessments of psychosis and dissociation. The overall antidepressant response rate, defined as a ≥ 50% improvement in MADRS score, was 67%, or 65 of 97 patients. Four of 205 or 1.95% infusions were discontinued due to AEs. The overall attrition rate was 3.1% or 3 of 97 patients. The most frequent AEs within four hours of the infusion were drowsiness, dizziness, poor coordination, blurred vision, and feeling strange or unreal. Protocol-defined hemodynamic changes occurred in ~1/3 of patients. In addition, ketamine resulted in small, but significant increases in psychotomimetic and dissociative symptoms (all $p < 0.05$). There were no cases of persistent psychotomimetic effects, adverse medical effects, or increased substance use in a subgroup of patients with available long-term follow-up information. The authors concluded that in this group of patients with TRD, ketamine was safe and well tolerated and further research investigating the safety of ketamine in severe and refractory depression is warranted.

Migraine Headache

Lauritsen et al (2016) evaluated the use of intravenous ketamine in patients with refractory migraine treated in the hospital setting. The authors completed a retrospective chart review, which identified six patients with refractory migraine admitted from 2010 through 2014 for treatment with intravenous ketamine. A standard protocol was used to administer ketamine starting with a dose of 0.1 mg/kg/hour. and increased by 0.1 mg/kg/hour. every 3 to 4 h as tolerated until a target pain score of 3/10 was achieved and maintained for 8 hours or more. Visual Analogue Scale (VAS) scores at time of hospital admission were obtained as well as average baseline VAS scores prior to ketamine infusion. The age range of study patients was 29-54 years with a median age of 36.5. Additionally, 83% were women. Pre-treatment pain scores ranged from 9 to 10. All patients achieved a target pain level of 3 or less for 8 hours; the average ketamine infusion rate at target was 0.34 mg/kg/hour (range 0.12-0.42 mg/kg/hr.). One patient reported a transient out-of-body hallucination following an increase in infusion rate, which resolved after decreasing the rate. There were no other significant side effects. The authors concluded that IV ketamine was safely administered in the hospital setting to patients with refractory chronic migraine. Treatment was associated with short term improvement in pain severity in 6 of 6 patients with refractory chronic migraine. Prospective placebo-controlled trials are needed to assess short term and long-term efficacy of IV ketamine in refractory chronic migraine.

Pomeroy et al investigated the use of intravenous, subanesthetic ketamine for chronic migraine (CM) or new daily persistent headache (NDPH) in a retrospective review. Upon admission, the mean headache pain rating, using a 0-10 pain scale was an average of 7.1 and decreased to 3.8 at discharge ($p < 0.0001$). Seventy-two percent (55/77) of patients experienced at least a 2-point improvement in headache pain at discharge. There were some acute responders that maintained this improvement in headache pain at their follow-up office visit, but sustained response did not achieve statistical significance (15/77, 27.3%). The mean duration of infusion was 4.8 days. Overall, patients tolerated ketamine. The authors concluded that subanesthetic ketamine infusions may be beneficial in individuals with CM or NDPH who have failed other treatments. Controlled trials are needed to confirm this.

Etchison et al evaluated the efficacy and safety of low-dose intravenous (IV) ketamine for treatment of acute migraine in the emergency department (ED) in a randomized, double-blind, placebo-controlled trial. 34 subjects were randomized to receive 0.2 mg/kg of IV ketamine or an equivalent volume of normal saline by IV push. Numeric Rating Scale (NRS-11) pain scores (0 = ”no pain” and 10 = ”worst pain imaginable”), categorical pain intensity scores from 0 to 3 (0 = “no

headache" and 3 = "severe headache"), functional disability scores from 0 to 3 (0 = "no disruption of daily activities" and 3 = "performance of daily activities is severely impaired"), side effects using the Side Effects Rating Scale for Dissociative Anesthetics (SERSDA) model, and adverse events were assessed at baseline and 30 minutes post-treatment. The primary outcome was between-group difference in NRS-11 score reduction at 30 minutes, and required a 2-point difference in NRS-11 scale for statistical significance. The authors found no statistically significant difference or clinically significant difference in NRS-11 score reduction between the groups after 30 minutes [median NRS-11 score reduction = 1 (interquartile range {IQR} 0 to 2.25) for ketamine group and 2 (IQR 0 to 3.75) for placebo group]. SERSDA scores in the ketamine group were significantly greater for generalized discomfort at 30 minutes (p = 0.008) and fatigue at 60 minutes (p = 0.0216). Authors concluded that ketamine was overall well tolerated; however, 0.2 mg/kg IV ketamine was not efficacious in treating migraine and future studies should be investigated for more effective dosing and routes of administration.

Technology Assessments

Psychiatric Disorders

Hayes compiled a Medical Technology Directory on ketamine for treatment-resistant unipolar depression or posttraumatic stress disorder (PTSD) dated November 21, 2017. Regarding treatment-resistant depression (TRD) in adults, Hayes assigned a rating of C, potential but unproven benefit. This rating reflects preliminary positive evidence from a number of studies, and the potential for bias in these results due to shortcomings in study design. For PTSD, Hayes assigned a rating of D2, insufficient published evidence to assess the safety and/or impact on health outcomes or patient management. This rating reflects the small amount of evidence available for this use.

For ketamine used as an adjunct to electroconvulsive therapy to increase antidepressant effects of this treatment in patients with TRD, Hayes assigned a rating of C. This rating reflects a large body of low quality, inconsistent evidence.

Hayes compiled a Medical Technology Directory on ketamine for treatment-resistant bipolar depression (BPD), dated November 19. 2017. Hayes assigned a rating of D2. This rating reflects insufficient evidence regarding the efficacy and safety of ketamine as an add-on to medical treatment for treatment-resistant BPD. This rating also reflects a very-low quality body of evidence limited by a small number of studies, lack of long term follow up, and comparative studies.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Spravato is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist indicated for the treatment of:

- Treatment-resistant depression (TRD) in adults, as monotherapy or in conjunction with an oral antidepressant.
- Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior in conjunction with an oral antidepressant.

Spravato is not approved as an anesthetic agent. The safety and effectiveness of Spravato as an anesthetic agent have not been established.

Spravato 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 Spravato is:
  - Only dispensed in healthcare settings and administered to patients who are enrolled in the program.
  - Administered by patients under the direct observation of a healthcare provider and those patients are monitored by a healthcare provider for at least 2 hours after administration of Spravato.
  - Only dispensed and administered in healthcare settings.
- Pharmacies must be certified in the REMS and must only dispense Spravato to healthcare settings that are certified in the program.

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

Ketamine is indicated as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Ketamine is indicated for the induction of anesthesia prior to the administration of other general anesthetic agents. Ketamine is indicated to supplement low-potency anesthetic agents, such as nitrous oxide.[1]

References

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Policy History/Revision Information

Date	Summary of Changes

05/01/2026	**Template Update**
	• Transferred content to shared policy template that applies to both UnitedHealthcare Commercial and Individual Exchange benefit plans
	• Added *Application* section to indicate this policy applies to:
	  ○ UnitedHealthcare Commercial benefit plans
	  ○ Individual Exchange benefit plans
	Supporting Information
	• Updated *References* section to reflect the most current information
	• Archived previous policy versions 2026D0069P and IEXD0069.10

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.