POLICY STATEMENT:
Based upon our review and assessment of the peer-reviewed literature, the use of ketamine (administered via oral, parenteral, sublingual or intranasal methods) for the treatment of psychiatric disorders, including but not limited to treatment resistant depression, has not been medically proven effective and is considered investigational.

Refer to Corporate Medical Policy # 7.03.03 regarding Ketamine Infusion Therapy for the Treatment of Chronic Pain Syndromes.

POLICY GUIDELINES:
The Federal Employee Health Benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.

DESCRIPTION:
Major depressive disorder (MDD) is a severe, recurrent and disabling mental illness that is highly prevalent worldwide and often associated with a negative impact on the quality of life and productivity. The efficacy of current pharmacological agents for depression is disappointing. In addition to the low response rate, the long delay of traditional antidepressants in the onset of therapeutic action (up to 12 weeks) increases the burden of illness, morbidity, and the risk of suicidal behavior. Researchers have explored antidepressant options that sidestep the lag period for improvements in symptoms. There has been a growing investigation into the pathophysiology of mood disorders and more extensive research into other neurotransmitter signaling cascades such as the glutamatergic systems that may offer a realistic, rapid-acting target for drug development in mood disorders. More recently, ketamine, a noncompetitive, high-infinity antagonist of the NMDA type glutamate receptor used for the induction and maintenance of anesthesia, has been investigated for treatment-resistant depression (TRD). It is also being investigated in the treatment of other psychiatric conditions that include bipolar depression, post-traumatic stress disorder, obsessive compulsive disorder, and autism spectrum disorders.

Ketamine is manufactured in liquid form or as a crystallized powder for reconstitution into a liquid. It is usually administered parentally (intravenous, subcutaneous or intramuscular) but can be administered orally (liquid or pill form), sublingually, or intra-nasally (spray or powder). Ketamine has been safely used for the induction and maintenance of general anesthesia and procedural sedation for many years. The mechanism of action through which ketamine exerts its antidepressant effects is not fully understood. It has the potential to cause marked changes acutely in cognitive function and psychological wellbeing, both through the dense population of NMDA receptors located in the cerebral cortex and hippocampus and via its effects on the transmission of modulatory, ascending monoamines such as dopamine and serotonin in the striatum and cortex.

RATIONALE:
Ketamine hydrochloride injection is FDA-indicated 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, and to supplement low-potency agents, such as nitrous oxide. Ketamine for the treatment of psychiatric disorders is an off-label use.
The majority of literature investigates the use of ketamine in depression. While preliminary studies demonstrate promising short-term outcomes in patients suffering from treatment-resistant depression, there is insufficient long-term data to support its integration into the clinical treatment armamentarium at this time. Not only do investigators need to decipher the neurobiological mechanisms underlying the putative antidepressant actions of ketamine, more studies demonstrating its safety and efficacy are necessary on critical issues such as dose optimization, delivery drug routes and methods to prevent relapse following the resolution of depressive symptoms. There are several known potential risks associated with repeat ketamine administration that include physiological and psychological effects, substance abuse potential, urinary cystitis and hepatotoxicity.

The first study to examine the anti-depressant effects of ketamine was a repeated measures design of 9 patients (Berman et al, 2000). Only 7 patients completed the study, and of those 7, four experienced positive benefits of a diluted ketamine infusion. This was a short-term, “proof of concept” study that was designed to just test whether ketamine had the anti-depressant effects reported in other studies, but not carefully analyzed. This study demonstrated pretty strongly that ketamine did have such effects. Additional studies since then have demonstrated the positive short-term effects of ketamine in TRD and other related affective disorders. For example, Murrough and colleagues (2013) conducted a clinical study in patients with TRD. Subjects were randomized in a 2:1 ratio to receive either 0.5 mg/kg ketamine or 0.045 mg/kg midazolam. Treatments were infused over 40 minutes. Of 73 patients, 47 received ketamine and 25 received midazolam. Reduction in MADRS at 24 hours post-infusion was the primary outcome. Baseline MADRS scores were 32.6±6.1 and 31.1±5.6 for ketamine and midazolam groups, respectively. The ketamine group demonstrated lower MADRS scores than the midazolam group (7.95 mean reduction). Mean MADRS scores 24 hours post infusion were 14.77 and 22.72 for ketamine and midazolam groups, respectively. Response, defined as ≥50% decrease in MADRS scores, was a secondary outcome. In the ketamine group, 64% met response and 28% met response in the midazolam group (p≤0.001). The most common side effects associated with ketamine were dizziness, blurred vision, headache, nausea or vomiting, dry mouth, poor coordination, poor concentration, and restlessness. Dissociative symptoms occurred in 17% of ketamine subjects but resolved by two hours post-infusion. No severe psychotic symptoms were reported.

Numerous concerns about most of the research trials done to-date have been noted. It is difficult to perform a truly blinded intervention with ketamine due to its psychological effects. Blier et al. (2012) point out that using a saline injection as a placebo sham treatment isn’t really adequate, as patients detect ketamine’s “mild psychotomimetic effects.” They also point out holes in the research: “the level of physiologic monitoring that should be implemented, its potential neurotoxicity, and its dependence potential.” Ketamine can produce dependence on the drug and there are studies that have actually looked at ketamine-dependent people. These studies have demonstrated that such dependence results in abnormalities of white matter in bilateral frontal and left temporoparietal regions of the brain (Liao, et al. 2010, 2011). Further investigations into the consequences of long-term ketamine use are necessary.

CODES: Number Description
Eligibility for reimbursement is based upon the benefits set forth in the member’s subscriber contract.
CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.

Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).

CPT: 96365 Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour

96366 each additional hour (list separately in addition to code for primary procedure)
**SUBJECT:** KETAMINE FOR THE TREATMENT OF PSYCHIATRIC DISORDERS  
**POLICY NUMBER:** 3.01.13  
**CATEGORY:** Technology Assessment  
**EFFECTIVE DATE:** 02/19/15  
**REVISED:** 02/18/16, 02/16/17  
**PAGE:** 3 OF 5

96374  Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug

**HCPCS:** No specific codes, however, J3490, unclassified drug, may be billed for ketamine

**ICD9:** Investigational for all diagnosis codes

**ICD10:** Investigational for all diagnosis codes

**REFERENCES:**


Murrough JW. Et al. Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial. Psychol Med 2015 Dec;45(16):3571-80.


* key article

**KEY WORDS:**

Ketamine, N-methyl-D-aspartate antagonist, Treatment resistant depression.

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**CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS**

Based upon our review, the use of ketamine in the treatment of psychiatric disorders is not addressed in National or regional CMS coverage determinations or policies.