

Medical Drug Clinical Criteria

Subject: Ketamine injection (Ketalar)

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Overview

This document addresses the use of Ketalar (ketamine HCl) injection. Ketamine is a nonbarbiturate general anesthetic agent. The mechanism of action is due to the antagonism of the N-methyl-D-aspartate (NMDA) receptors in the central nervous system.

Ketamine injection is FDA approved for the following indications:

- 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, with additional doses, for longer procedures.
- For the induction of anesthesia prior to the administration of other general anesthetic agents.
- To supplement low-potency agents, such as nitrous oxide.

Because of the risk of blood pressure elevation, ketamine injection is contraindicated in those in whom a significant blood pressure elevation would be hazardous. In addition, psychological manifestations can occur that vary between pleasant dream-like states to vivid imagery, hallucinations, and emergence delirium. No residual psychological effects are known to have resulted from use of ketamine injection.

Ketamine injection has been used off-label in a variety of indications including treatment resistant depression, chronic pain, and complex regional pain syndrome (CRPS). Ketamine was given designated orphan drug status for CRPS on 2/1/19 (<https://www.accessdata.fda.gov/scripts/opdlisting/oopd/listResult.cfm>) but has not received FDA approval for the treatment of CRPS. The studies for use of ketamine injection for these indications are often small and uncontrolled. American Hospital Formulary System (AHFS) Drug Information (DI) compendia provides an off-label use of Ketamine for chronic pain; however, due to limited controlled studies for such, AHFS DI suggests that additional studies are needed to determine long-term benefits and risks, optimum dosages, and durability of response.

Expert opinion released in 2021 indicates that ketamine (along with esketamine) presents a novel treatment for treatment-resistant depression (TRD). With regard to ketamine, the opinion does indicate that “a legitimate criticism, as it relates to interpreting the effect sizes reported with single or repeat-dose ketamine in TRD, is the possibility that non-specific effects such as functional unblinding (e.g., by patients experiencing dissociation or euphoric responses) and expectancy may inadvertently inflate the efficacy of ketamine” and that there “remains a lack of sufficient evidence to guide dose optimization with intravenous ketamine” (McIntyre 2021). Multiple Cochrane reviews have included ketamine as a treatment for pain, depression and CRPS with the conclusions that while there is some evidence of efficacy for the treatment of these conditions, larger and more rigorous controlled trials are needed (Alviar 2016, Bell 2017, Brinck 2018, Chaparro 2013, O’Connell 2013, Caddy 2015, McCloud 2015, Costi 2014). AHFS DI compendia provides an off-label use of Ketamine for treatment-resistant depression with an accompanying statement that use has been limited to controlled settings, and that clinical trial enrollment should be considered instead in order to fully evaluate the efficacy and safety of such use. AHFS’ recommendation was taken from a special communication published in the Journal of the American Medical Association (JAMA) Psychiatry on the use of ketamine in the treatment of mood disorders (Sanacora 2017).

Clinical Criteria

When a drug is being reviewed for coverage under a member’s medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Ketalar (ketamine injection)

Requests for Ketalar (ketamine injection) may be approved if the following criteria are met:

- I. Individual is using as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation; **OR**
- II. Individual is using for induction of anesthesia prior to the administration of other general anesthetic agents; **OR**
- III. Individual is using to supplement low-potency agents, such as nitrous oxide; **OR**
- IV. Use in pediatric acute pain when administered intranasally (DrugDex B, IIa).

Ketalar (ketamine injection) may not be approved when the above criteria are not met and for all other indication, including, but not limited to the following:

- I. Major depressive disorder
- II. Depressive episodes
- III. Phobic disorders
- IV. Anxiety disorders
- V. Post-traumatic stress disorder
- VI. Chronic pain
- VII. Homicidal and suicidal ideations.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT

96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96366	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)]
96367	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); additional sequential infusion of a new drug/substance, up to 1 hour (List separately in addition to code for primary procedure)
96368	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); concurrent infusion (List separately in addition to code for primary procedure)
96374	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug
96375	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); each additional sequential intravenous push of a new substance/drug (List separately in addition to code for primary procedure)
96376	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); each additional sequential intravenous push of the same substance/drug provided in a facility (List separately in addition to code for primary procedure)

HCPCS

J3490	Unclassified Drugs [when specified as ketamine HCl injection (Ketalar)]
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ICD-10 Diagnosis

ALL Diagnoses

When services may not be approved when the drug is specified as (ketamine HCl injection) Ketalar:

For the procedure codes listed above when criteria are not met or for situations designated in the Clinical Indications section as may not be approved including but not limited to the following ICD-10-DM codes

ICD-10 Diagnosis

F32.0-F32.A	Depressive episode
F33.0-F33.9	Major depressive disorder, recurrent
F40.00-F40.10	Phobic and anxiety disorders
F41.0-F41.9	Other anxiety disorders
F43.10-F43.12	Post-traumatic stress disorder (PTSD)
G89.21-G89.29	Chronic pain, not elsewhere classified
G89.4	Chronic pain syndrome

Document History

Reviewed: 08/15/2025

Document History:

- 08/15/2025 – Annual Review: No changes. Coding Reviewed: No changes.
- 03/10/2025 – Select Review: Add examples of non-approvable indications to criteria. Coding Reviewed: Added CPT codes 96365-96368, 96374-96376. Added services that may not be approved when drug is specified as ketamine HCl (Ketalar) - ICD-10-CM codes F32.0-F32.A, F33.0-F33.9, F40.00-F40.10, F41.0-F41.9, F43.10-F43.12, G89.21-G89.29, G89.4, R45.850-R45.851.08/16/2024 – Annual Review: No changes. Coding Reviewed: No changes.
- 08/18/2023 – Annual Review: No changes.
- 09/12/2022 – Annual Review: No changes. Coding Reviewed: No changes.
- 09/13/2021 – Select Review: Add new clinical criteria document for Ketalar (ketamine injection). Coding Reviewed: Added HCPCS J3490, ICD-10 All Diagnosis

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