An Independent Licensee of the Blue Cross Blue Shield Association

EVIDENCE-BASED CRITERIA
SECTION: SPECIALTY MEDICAL DRUGS

NEXT ANNUAL REVIEW DATE: 1ST QTR 2025

ORIGINAL EFFECTIVE DATE: 02/15/22
LAST REVIEW DATE: 02/15/24
CURRENT EFFECTIVE DATE: 05/16/24
LAST CRITERIA REVISION DATE: 05/16/24
ARCHIVE DATE:

KETAMINE injection, for intravenous or intramuscular use

Non-Discrimination Statement is located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Evidence-Based Criteria must be read in its entirety to determine coverage eligibility, if any.

This Evidence-Based Criteria provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Evidence-Based Criteria are subject to change as new information becomes available.

For purposes of this Evidence-Based Criteria, the terms "experimental" and "investigational" are considered to be interchangeable.

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Criteria:

Refer to FDA website for current indications and dosage.

- **Criteria for approval:** Ketamine injection is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is or is in consultation with an anesthesiologist, nurse anesthetist, or surgeon

  2. Request is for **ONE** of the following indications:

     - Use as 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
     - Use as supplement to other anesthetic agents

  3. There are **NO** contraindications including:

     - Individuals for whom a significant elevation in blood pressure would be a serious hazard
     - Known hypersensitivity to ketamine or any excipient

- Ketamine injection for all other indications not previously listed is considered ***experimental or investigational*** and will not be covered when any one or more of the following criteria are met:

  1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
  3. Insufficient evidence to support improvement of the net health outcome; or
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives; or
  5. Insufficient evidence to support improvement outside the investigational setting.

  These indications include, *but are not limited to:*

  - Treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, or duration.
  - Treatment of chronic neuropathic pain, chronic daily headache, fibromyalgia, depression and obsessive-compulsive disorder

Description:

Ketamine injection is a general anesthetic indicated for the following:

KETAMINE injection, for intravenous or intramuscular use

- As the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation
- For the indication of anesthesia prior to the administration of other general anesthetic agents
- As a supplement to other anesthetic agents

For FDA approved indications, also known as labeled indications, the FDA has reviewed and approved the medication for the specified use(s) for final marketing based on adequate, well-controlled clinical trials, which have documented safety and effectiveness. The use of an FDA approved medication for conditions, indications or in circumstances other than those approved by the FDA is known as “off-label use” (also referred to as unapproved use or unlabeled use). Unapproved or unlabeled uses include a variety of situations ranging from completely unstudied uses to scientifically investigated uses where the manufacturer has not asked the FDA for formal approval.

Intravenous (IV) infusions of the anesthetic ketamine have been investigated for the treatment of psychiatric disorders, including depression, obsessive compulsive disorder (OCD), bipolar disorder, post-traumatic stress disorder (PTSD), and suicidal ideation. IV ketamine for depression is usually reserved for severe or drug resistant depression. IV infusions of ketamine are typically administered in an outpatient setting and may include multiple infusions. Treatment resistant depression typically refers to major depressive episodes that do not respond satisfactorily after two trials of antidepressant monotherapy; however, the definition has not been standardized. Treatment refractory depression typically refers to unipolar major depressive episodes that are highly resistant to treatment and do not respond satisfactorily to many sequential treatment regimens. However, the definition has not been standardized, and there is no clear demarcation between treatment refractory depression and treatment resistant depression. For these psychiatric disorders, ketamine has been some efficacy documented in published case reports, retrospective reviews or small open-labeled or controlled trials. These trials are deemed weak to moderate evidence and are limited by trial type, sample size, and short duration. Most of the trials concluded that additional randomized controlled trials are needed to establish long-term safety and efficacy of IV ketamine for psychiatric disorders. Esketamine is a nasal spray of one enantiomer of ketamine that is FDA approved for treatment treatment-resistant depression in adults, in conjunction with an oral antidepressant. Esketamine is not addressed in this Evidence-Based Criteria.

IV Ketamine has also have been investigated for the treatment of chronic pain including pain associated with neuropathic pain disorders such as phantom limb pain, post-herpetic neuralgia, complex regional pain syndromes, diabetic neuropathy, pain related to stroke or spinal cord injuries, chronic pain associated with fibromyalgia, and pain from migraines or chronic daily headaches. IV infusions of anesthetics are given in the inpatient or outpatient setting and may be part of a pain management program. Similar to psychiatric disorders, the evidence for ketamine to treat chronic pain is insufficient to determine long-term efficacy and safety and effects and benefits for health outcomes. Randomized control trials were small, short-term and had no active comparator.

The increase in off-label use of ketamine has led to several reports of hepatobiliary dysfunction prompting the FDA label change in 2020 to recommend liver function monitoring. Other severe adverse effects include arrhythmias, seizures, loss of consciousness, confusion, hallucinations, aggression or even death.

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History:	Date:	Activity:
Pharmacy and Therapeutics Committee	05/16/24	Revision to guidelines
Pharmacy and Therapeutics Committee	02/15/24	Review with revisions: resources
Pharmacy and Therapeutics Committee	02/16/23	Review with revisions
Medical Policy Panel	02/15/22	Approved guideline
Clinical Pharmacist	02/02/22	Development

Coding:

CPT: 96365, 96366, 96374 (for reference purposes only and may not be all inclusive)
HCPCS: J3490

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Resources:

Literature reviewed 02/15/24. We do not include marketing materials, poster boards and non-published literature in our review.

1. Abdi, S. Complex regional pain syndrome in adults: Treatment, prognosis, and prevention. In: UpToDate, Shefner JM, Fishman, Goddeau Jr, RP (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last update on January 19, 2023. Accessed on December 5, 2023.

2. Bahji A, Vazquez GH, Zarate CA, Jr. Comparative efficacy of racemic ketamine and esketamine for depression: A systematic review and meta-analysis. *J Affect Disord*. Jan 1 2021;278:542-555. doi:10.1016/j.jad.2020.09.071

3. Black, SA, Maxwell LG. General anesthesia in neonates and children: agents and techniques. In: UpToDate, Sun LS, Crowley M (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last update on May 19, 2022. Accessed on March 7, 2024.

4 Bravenec B. General anesthesia: intravenous induction agents. In: UpToDate, Joshi GP, Walls RM, Nussmeier NA (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last update on October 26, 2022. Accessed on March 7, 2024.

5. Cohen SP, Bhatia A, Buvanndran 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.

6. Dean RL, Marquardt T, Hurducas C, et al. Ketamine and other glutamate receptor modulators for depression in adults with bipolar disorder. *Cochrane Database Syst Rev*. Oct 8 2021;10:CD011611. doi:10.1002/14651858.CD011611.pub3

7. Ketamine hydrochloride prescribing information, revised by AuroMedics Pharma LLC 06/2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed December 5, 2023.

8. King A, Benedetto W, Plichta A. Induction of general anesthesia: overview. In: UpToDate, Joshi GP, Nussmeier NA (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last update on August 18, 2022. Accessed on March 7, 2024.

9. Pickering G, Pereira B, Morel V, et al. Ketamine and magnesium for refractory neuropathic pain: A randomized, double-blind, crossover trial. *Anesthesiology*. Jul 2020; 133(1): 154-164

10. Portenoy RK, Ahmed E, Keilson YK. Cancer pain management: Role of adjuvant analgesics (coanalgesics). In UpToDate, Abrahm J, Shah S (Eds), UpToDate, Waltham MA.: UpToDate

Inc. Available athttp://uptodate.com. Topic last update on December 16, 2022. Accessed on December 5, 2023.

11. Sigtermans MJ, van Hilten JJ, Bauer MCR, et al. Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. *Pain*. 2009;145:304-311

12. Tauben D, Stacey BR. Pharmacologic management of chronic non-cancer pain in adults. In: UpToDate, Fishman S, Crowley M (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last update on July 27, 2023. Accessed on December 5, 2023.

13. Thase M, Connolly KR. Ketamine and esketamine for treating unipolar depression in adults: Administration, efficacy, and adverse effects. In: UpToDate, Roy-Byrne PP, Solomon D (Eds) UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last update on August 24, 2023. Accessed on December 5, 2023.

14. Veraart JKE, Smith-Apeldoorn SY, Spaans HP, Kamphuis J, Schoevers RA. Is ketamine an appropriate alternative to ECT for patients with treatment resistant depression? A systematic review. *J Affect Disord*. Feb 15 2021;281:82-89. doi:10.1016/j.jad.2020.11.123

15. Zhou Y, Wang C, Lan X, et al. The effectiveness of repeated intravenous ketamine on subjective and objective psychosocial function in patients with treatment-resistant depression and suicidal ideation. *J Affect Disord*. 2022;304:78-84.

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Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ's Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ's Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html