Medical Drug Clinical Criteria

Subject:	Ketamine injection (Ketalar)		
Document #:	CC-0215	**Publish Date:**	09/18/2023
Status:	Reviewed	**Last Review Date:**	08/18/2023

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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 indications

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.

HCPCS

J3490	Unclassified Drugs when specified as [Ketalar]

ICD-10 Diagnosis

ALL Diagnoses

Document History

Reviewed: 08/18/2023
Document History:

- 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

References

1. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: July 6, 2023.
2. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
3. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; Updated periodically.
4. Alviar MJM, Hale T, Lim-Dungca M. Pharmacologic interventions for treating phantom limb pain. Cochrane Database of Systematic Reviews 2016, Issue 10. Art. No.: CD006380. DOI: 10.1002/14651858.CD006380.pub3.
5. Barr J, Fraser GL, Puntillo K, et al. Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit. Crit Care Med. 2013;41(1):263-306.
6. Bell RF, Eccleston C, Kalso EA. Ketamine as an adjuvant to opioids for cancer pain. Cochrane Database Syst Rev. 2017 Jun 28;6:CD003351. doi: 10.1002/14651858.CD003351.pub3.
7. Brinck EC, Tiippana E, Heesen M, Bell RF, Straube S, Moore RA, Kontinen V. Perioperative intravenous ketamine for acute postoperative pain in adults. Cochrane Database Syst Rev. 2018 Dec 20;12:CD012033. doi: 10.1002/14651858.CD012033.pub4.
8. Brophy GM, Bell R, Claassen J, et al; Neurocritical Care Society Status Epilepticus Guideline Writing Committee. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care. 2012;17(1):3-23.
9. Caddy C, Amit BH, McCloud TL, et al. Ketamine and other glutamate receptor modulators for depression in adults. Cochrane Database Syst Rev. 2015 Sep 23;(9):CD011612. doi: 10.1002/14651858.CD011612.pub2.
10. Chaparro LE, Smith SA, Moore RA, Wiffen PJ, Gilron I. Pharmacotherapy for the prevention of chronic pain after surgery in adults. Cochrane Database of Systematic Reviews 2013, Issue 7. Art. No.: CD008307. DOI: 10.1002/14651858.CD008307.pub2.
11. 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 Jul;43(5):521-546. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6023575/pdf/aap-43-521.pdf.
12. Costi D, Cyna AM, Ahmed S, et al. Effects of sevoflurane versus other general anaesthesia on emergence agitation in children. Cochrane Database of Systematic Reviews 2014, Issue 9. Art. No.: CD007084. DOI: 10.1002/14651858.CD007084.pub2.
13. Devlin JW, Skrobik Y, Gélinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med. 2018;46(9):e825-e873.
14. Frey TM, Florin TA, Caruso M, Zhang N, Zhang Y, Mittiga MR. Effect of Intranasal Ketamine vs Fentanyl on Pain Reduction for Extremity Injuries in Children: The PRIME Randomized Clinical Trial. *JAMA Pediatr.* 2018 Dec 28. doi: 10.1001/jamapediatrics.2018.4582. [Epub ahead of print]

15. Graudins A, Meek R, Egerton-Warburton D, et al: The PICHFORK (Pain in Children Fentanyl or Ketamine) Trial: A Randomized Controlled Trial Comparing Intranasal Ketamine and Fentanyl for the Relief of Moderate to Severe Pain in Children With Limb Injuries. *Ann Emerg Med*. 2015; 65(3):248-254.
16. Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. Ann Emerg Med. 2011;57(5):449-461.
17. Jat KR, Chawla D. Ketamine for management of acute exacerbations of asthma in children. Cochrane Database Syst Rev. 2012 Nov 14;11:CD009293. doi: 10.1002/14651858.CD009293.pub2.
18. McCloud TL, Caddy C, Jochim J, et al. Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults. Cochrane Database Syst Rev. 2015 Sep 29;(9):CD011611. doi: 10.1002/14651858.CD011611.pub2.
19. McIntyre RS, Rosenblat JD, Nemeroff CB, et.al. Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: An international expert opinion on the available evidence and implementation. *Am J Psychiatry*. 2021; 178:383-399.
20. Messina AG, Wang M, Ward MJ, Wilker CC, Smith BB, Vezina DP, Pace NL. Anaesthetic interventions for prevention of awareness during surgery. Cochrane Database of Systematic Reviews 2016, Issue 10. Art. No.: CD007272. DOI: 10.1002/14651858.CD007272.pub2
21. O'Connell NE, Wand BM, McAuley J, Marston L, Moseley GL. Interventions for treating pain and disability in adults with complex regional pain syndrome- an overview of systematic reviews. Cochrane Database of Systematic Reviews 2013, Issue 4. Art. No.: CD009416. DOI: 10.1002/14651858.CD009416.pub2.
22. Reynolds SL, Bryant KK, Studnek JR, Hogg M, Dunn C, Templin MA, Moore CG, Young JR, Walker KR, Runyon MS. Randomized Controlled Feasibility Trial of Intranasal Ketamine Compared to Intranasal Fentanyl for Analgesia in Children with Suspected Extremity Fractures. Acad Emerg Med. 2017;24:1430-1440. Available at https://onlinelibrary.wiley.com/doi/epdf/10.1111/acem.13313.
23. 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; 74:399-405. Available at https://vailmed.com/PDF/Consenus%20Statement%20on%20the%20Use%20of%20Ketamine%20in%20the%20Treatment%20of%20Mood%20Disorders%20JAMA%20Psychiatry.pdf. Accessed on July 6, 2023.
24. 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 Jul;43(5):456-466. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6023582/pdf/aap-43-456.pdf.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.