

Clinical Policy: Ketamine (Ketalar)

Reference Number: CP.PMN.296

Effective Date: 09.01.24

Last Review Date: 08.26

Line of Business: Commercial, HIM/ICHRA, Medicaid

[Coding Implications](#)[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

Description

Ketamine (Ketalar[®]) is a non-selective, non-competitive N-methyl D-aspartate (NMDA) receptor antagonist.

FDA Approved Indication(s)

Ketalar is indicated:

- As the 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
- As a supplement to other anesthetic agents

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation[®] that Ketalar and ketamine are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria**A. Requests for Ketamine (must meet all):**

1. Diagnosis of one of the following (a, b, or c):
 - a. An FDA approved indication;
 - b. A use supported by one of the following (i or ii, *see Appendix D*):
 - i. Micromedex DrugDex with strength of recommendation Class I or IIa;
 - ii. Evidence from at least two high-quality, published studies in reputable peer-reviewed journals or evidence-based clinical practice guidelines that provide all of the following (1 – 4):
 - 1) Adequate representation of the member's clinical characteristics, age, and diagnosis;
 - 2) Adequate representation of the prescribed drug regimen;
 - 3) Clinically meaningful outcomes as a result of the drug therapy in question;
 - 4) Appropriate experimental design and method to address research questions;
 - c. One of the following off-label indications (i or ii, *see Appendix E*):
 - i. Treatment-resistant depression (TRD);
 - ii. Major depressive disorder (MDD);

2. If request is for brand Ketalar, member must use generic ketamine, unless contraindicated or clinically significant adverse effects are experienced;
3. For TRD and MDD, all of the following (a-e):
 - a. Request is for intravenous (IV) ketamine;
 - b. Prescribed by or in consultation with a psychiatrist;
 - c. Age $\geq$ 18 years;
 - d. Member meets one of the following (i or ii):
 - i. Request is for the treatment of a member in a State with limitations on step therapy in certain mental health settings (*see Appendix E*);
 - ii. For all other requests, both of the following (1 and 2):[†]

[†]For Illinois HIM requests, the step therapy requirements below do not apply as of 1/1/2026 per IL HB 5395

 - 1) Failure of TWO antidepressants from the following, each tried for $\geq$ 4 weeks at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated: SSRI, SNRI, bupropion, mirtazapine, vilazodone;
 - 2) Failure of ONE of the following antidepressant augmentation therapies, each used for $\geq$ 4 weeks, unless clinically significant adverse effects are experienced or all are contraindicated: second-generation antipsychotic, lithium, thyroid hormone, buspirone;
 - e. Request meets one of the following (i, ii, or iii):
 - i. Dose does not exceed 0.5 mg/kg IV for up to 8 doses;
 - ii. Dose does not exceed 1 mg/kg IV as a single dose;
 - iii. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 3 months

B. Other diagnoses/indications (must meet 1 or 2):

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
 - a. For drugs on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace/ICHRA, and CP.PMN.255 for Medicaid; or
 - b. For drugs NOT on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace/ICHRA, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace/ICHRA, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I

1. Re-authorization is not permitted. Members must meet the initial approval criteria.

Approval duration: Not applicable

B. Other diagnoses/indications (must meet 1 or 2):

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
 - a. For drugs on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace/ICHRA, and CP.PMN.255 for Medicaid; or
 - b. For drugs NOT on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace/ICHRA, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace/ICHRA, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

- A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace/ICHRA, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

MDD: major depressive disorder
NMDA: non-competitive N-methyl D aspartate
SNRI: serotonin norepinephrine reuptake inhibitor

SSRI: selective serotonin reuptake inhibitor
TCA: tricyclic antidepressant
TRD: treatment-resistant depression

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
SSRI		
citalopram (Celexa®)	20 mg PO QD; may increase to 40 mg PO QD after one week	40 mg/day ($\leq$ 60 years) 20 mg/day ($>$ 60 years)

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
escitalopram (Lexapro [®])	10 mg PO QD; may increase to 20 mg PO QD after 1 week	20 mg/day
fluoxetine (Prozac [®] , Prozac Weekly [®])	Prozac: 20 mg PO QD; may increase by 10-20 mg after several weeks Prozac Weekly: 90 mg PO q week beginning 7 days after the last daily dose	Prozac: 80 mg/day Prozac Weekly: 90 mg/week
paroxetine (Paxil [®] , Paxil CR [®] , Pexeva [®])	Paxil, Pexeva: 20 mg PO QD; may increase by 10 mg every week as needed Paxil CR: 25 mg PO QD; may increase by 12.5 mg every week as needed	Paxil, Pexeva: 50 mg/day Paxil CR: 62.5 mg/day
sertraline (Zoloft [®])	50 mg PO QD; may increase every week as needed	200 mg/day
vilazodone (Viibryd [®])	20-40 mg PO QD	40 mg/day
Trintellix [®] (vortioxetine)	10-20 mg PO QD	20 mg/day
SNRIs		
duloxetine (Cymbalta [®])	20 mg PO BID or 30 mg PO BID or 60 mg PO QD	120 mg/day
venlafaxine (Effexor [®] , Effexor XR [®])	Effexor: 75 mg/day PO in 2-3 divided doses; may increase by 75 mg every 4 days as needed Effexor XR: 75 mg PO QD; may increase by 75 mg every 4 days as needed	Effexor: 225 mg/day (outpatient) or 375 mg/day (inpatient) Effexor XR: 225 mg/day
desvenlafaxine (Pristiq [®] , Khedezla [®])	50 mg PO QD	400 mg/day
Fetzima [®] (levomilnacipran)	20 mg PO QD for 2 days, then 40 mg PO QD; may increase by 40 mg every 2 days	120 mg/day
Second Generation Antipsychotics		
aripiprazole (Abilify [®])	2 to 15 mg PO QD	15 mg/day
Rexulti [®] (brexpiprazole)	0.5 to 3 mg PO QD	3 mg/day
Vraylar [®] (cariprazine)*	0.5 to 4.5 mg PO QD	4.5 mg/day
olanzapine (Zyprexa [®])*	5 to 20 mg PO QD	20 mg/day
quetiapine (Seroquel [®] , Seroquel XR [®])*	Seroquel: 25 to 400 mg PO QD Seroquel XR: 150 mg to 300 mg po QD	Seroquel: 400 mg/day Seroquel XR: 300 mg/day
risperidone (Risperdal [®])*	0.25 to 3 mg PO QD	3 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
ziprasidone (Geodon [®])*	20 to 80 mg PO BID	160 mg/day
Other Antidepressants		
bupropion (Aplenzin [®] , Budeprion SR [®] , Budeprion XL [®] , Forfivo XL [®] , Wellbutrin [®] , Wellbutrin SR [®] , Wellbutrin XL [®])	Varies	Immediate-release: 450 mg/day (300 mg/day if pediatric) Sustained-release: 400 mg/day Extended-release (HCl): 450 mg/day Extended-release (HBr): 522 mg/day
buspirone*	15 to 20 mg/day PO in 2 divided doses	60 mg/day
mirtazapine (Remeron [®])	15 to 45 mg PO QD	45 mg/day
lithium*	300 mg PO QD or BID; up to 600 to 1,200 mg PO daily in divided doses	1,200 mg/day
thyroid hormone*	25 to 50 mcg/day PO	62.5 mcg/day

Therapeutic alternatives are listed as Brand name[®] (generic) when the drug is available by brand name only and generic (Brand name[®]) when the drug is available by both brand and generic.

**Off-label*

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s):
 - In patients for whom a significant elevation of blood pressure would be a serious hazard
 - Hypersensitivity to ketamine or to any excipient
- Boxed warning(s): none reported

Appendix D: General Information

- Ketamine has been used in low doses for the treatment of severe and treatment-resistant depression associated with MDD. TRD is often defined as the failure of at least 2 trials of first-line antidepressants given in an adequate dosage for an adequate duration of therapy. In patients with refractory forms of depression, ketamine usually has been given in subanesthetic doses as an IV infusion.
 - Per the 2021 Canadian Network for Mood and Anxiety Treatments (CANMAT) Task Force Recommendations for the use of racemic ketamine in adults with MDD, IV ketamine is considered a third-line recommendation for adults with TRD. Treatment resistance should exceed minimum criteria for TRD, such as failed trials of 2 or more first-line antidepressants from different classes and 1 or more adjunctive agents (level 4). The typical protocol for IV ketamine is a dose of 0.5 mg/kg infused over 40 minutes, given as a single infusion, or as a course of repeated infusions administered 2 to 3 times per week for a total of 4 to 8 infusions.

- Per 2022 Department of Veterans Affairs and the Department of Defense clinical practice guideline for the management of MDD, for patients with MDD who have not responded to several adequate pharmacological trials, ketamine or esketamine are suggested as an option for augmentation.
- Appropriate experimental design methods:
 - Randomized, controlled trials are generally considered the gold standard; however:
 - In some clinical studies, it may be unnecessary or not feasible to use randomization, double-blind trials, placebos, or crossover.
 - Non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs.
 - Case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.
- Micromedex DrugDex Strength of Evidence, Strength of Recommendation, and Efficacy Definitions (Tables 1, 2, and 3):

Table 1. Strength of Recommendation		
Class I	Recommended	The given test or treatment has been proven to be useful, and should be performed or administered.
Class IIa	Recommended, In Most Cases	The given test, or treatment is generally considered to be useful, and is indicated in most cases
Class IIb	Recommended, In Some Cases	The given test, or treatment may be useful, and is indicated in some, but not most, cases.
Class III	Not Recommended	The given test, or treatment is not useful, and should be avoided.
Class Indeterminate	Evidence Inconclusive	Not applicable

Table 2. Strength of Evidence	
Category A	Category A evidence is based on data derived from: Meta-analyses of randomized controlled trials with homogeneity with regard to the directions and degrees of results between individual studies. Multiple, well-done randomized clinical trials involving large numbers of patients
Category B	Category B evidence is based on data derived from: Meta-analyses of randomized controlled trials with conflicting conclusions with regard to the directions and degrees of results between individual studies. Randomized controlled trials that involved small numbers of patients or had significant methodological flaws (e.g., bias, drop-out rate, flawed analysis, etc.). Nonrandomized studies (e.g., cohort studies, case-control studies, observational studies)
Category C	Category C evidence is based on data derived from: Expert opinion or consensus, case reports or case series
No Evidence	Not applicable

Table 3. Efficacy		
Class I	Effective	Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is effective
Class IIa	Evidence Favors Efficacy	Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion favors efficacy.
Class IIb	Evidence is Inconclusive	Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion argues against efficacy.
Class III	Ineffective	Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is ineffective.

Appendix E: States with Limitations against Redirections in Certain Mental Health

State	Step Therapy Prohibited?	Notes
TX	No	<i>*Applies to HIM requests only*</i> Failure of a ≥ 4-week trial of ONE of the following at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated: Major depressive disorder: SSRI, SNRI, other generic antidepressant (e.g., bupropion, TCA, mirtazapine) Treatment-resistant depression: antidepressant augmentation therapy (e.g., second-generation antipsychotic, lithium, thyroid hormone, buspirone)

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Induction of anesthesia	<i>Intravenous (IV) route:</i> 1 mg/kg to 4.5 mg/kg <i>Intramuscular (IM) route:</i> 6.5 mg/kg to 13 mg/kg as a single dose	Various
Maintenance of anesthesia	Various	Various
Supplement to other anesthetic agents	Various	Various
TRD†	0.5 mg/kg IV administered over 40 minutes; may repeat at a frequency of 1 to 3 times weekly; may increase dose to 0.75 to 1 mg/kg based on response and tolerability	1 mg/kg/dose
MDD†		

†Off-label use

VI. Product Availability

Multiple-dose vials (for injection): 10 mg/mL, 50 mg/mL, 100 mg/mL

VII. References

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Coding Implications

HCPCS Codes	Description
J3490	Unclassified drugs

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created.	05.07.24	08.24
3Q 2025 annual review: no significant changes; references reviewed and updated. Added step therapy bypass for IL HIM per IL HB 5395.	06.30.25	08.25
3Q 2026 annual review: no significant changes; for product availability, added 10 mg/mL multi-dose vial; added ICHRA line of business; references reviewed and updated.	04.20.26	08.26

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health

plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note:

For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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