BlueCross BlueShield of Vermont

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Ketamine
Corporate Medical Policy

File Name: Ketamine
File Code: 5.01.VT204
Origination: 12/2020
Last Review: 09/2026
Next Review: 08/2027
Effective Date: 01/01/2027

Description/Summary

Ketamine, a CIII controlled substance, produces a cataleptic-like state in which the individual is dissociated from the surrounding environment by direct action on the cortex and limbic system. Ketamine is a noncompetitive NMDA (N-methyl-D-aspartate) receptor antagonist that blocks glutamate receptors. Glutamate is an excitatory neurotransmitter that helps regulate information processing and overall communications between brain and various regions of the body.

Note: This policy does not address the use of the enantiomer of ketamine, esketamine, which is approved by the Food and Drug Administration (FDA) and available as a trade agent sold by a manufacturer for intranasal office administration only. For medical necessity criteria regarding esketamine administration, refer to Blue Cross VT Pharmacy policy.

Policy Guidelines

Ketamine is FDA approved as a general anesthetic. This policy is intended to guide the off-label use of ketamine HCl infusion in adults with a treatment-resistant depressive episode associated with major depressive disorder (MDD). It is thought that ketamine triggers reactions in the brain that enable a degree of neuronal plasticity, possibly due to glutamate surge. However, other neurotransmitters, including the opioid system, may be involved based on results of certain studies, heightening concerns about abuse potential. Per Blue Cross VT Policy, Ketamine for treatment-resistant Major Depressive Disorder may only be administered via intravenous formulation, following all state and federal procedural regulations for outpatient intravenous administration, including being administered under direct supervision by a qualified licensed medical professional according to relevant state and federal regulations.

When a service may be considered medically necessary

1. Individual is at least 18 years of age and has a current major depressive episode associated with unipolar major depressive disorder and meets one of the following:
    a. The depressive episode is severe, as documented by a standardized rating scale that reliably measures depressive symptoms (i.e., HAM-D-17 score ≥24 or MADRS score ≥28; **OR**
    b. The depressive episode is accompanied by acute suicidal ideation or behavior; **AND**
2. Individual has demonstrated inadequate response to (<25% improvement in depression symptoms or scores), clinically significant intolerance of, or contraindication) to at least four different U.S. Food and Drug Administration approved antidepressants, from at least two different pharmacological classes (i.e., selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), bupropion, mirtazapine, etc.), not including dissociative medications, and each used at therapeutic dosages for at least 6 weeks; in addition, individual has had at least 2 trials of adjunctive pharmacotherapy (adding adjunct medication to a therapeutic antidepressant, i.e., aripiprazole or buspirone augmentation, etc.); **AND**
3. Failure of a trial of a psychotherapy known to be effective in the treatment of major depressive disorder of an adequate frequency and duration, without significant improvement in depressive symptoms, as documented by standardized rating scales that reliably measure depressive symptoms; **AND**
4. Individual has no history of psychosis; **AND**
5. Individual's history of controlled substance prescriptions has been checked using the state prescription drug monitoring program (PDMP), according to the prescriber; **AND**
6. Individual does not currently meet criteria for a substance use disorder, unless in remission; **AND**
7. Individual is not pregnant or breastfeeding; **AND**
8. Ketamine is intravenously infused; **AND**
9. Resuscitative equipment should be available during use, as IV administration or overdose may cause respiratory depression or apnea and other complications; **AND**
10. Individual is monitored for respiratory depression, apnea, or other complications during the infusion, and for an appropriate time after the infusion; **AND**
11. Ketamine is being prescribed by a psychiatrist or psychiatric advanced practice registered nurse; **AND**
12. Ketamine is not being prescribed for a pain syndrome; **AND**
13. Ketamine infusion will be administered through the individual's medical benefit

When a service may be considered investigational

- Subcutaneous infusion, sublingual, oral, nasal, rectal, transdermal administration, or any preparation of ketamine for administration other than by intravenous route is considered **investigational**.

- Administration of ketamine for chronic pain of any kind is considered **investigational.**

- Ketamine Assisted Therapy (KAP), a form of psychedelic-assisted therapy, is

considered **investigational**.

Legislative Guidelines

This policy complies with Vermont Act 128 V.S.A. § 4089e. Added 1997, effective April 27, 1998.

Reference Resources

1. Anand A, Mathew SJ, Sanacora G, et al. Ketamine versus ECT for nonpsychotic treatment-resistant major depression. N Engl J Med. 2023;389(10):958-966. PMID: 37224232. doi:10.1056/NEJMoa2302399.
2. Cavenaghi VB, da Costa LP, Lacerda ALT, et al. Subcutaneous ketamine in depression: a systematic review. Front Psychiatry. 2021;12:513068. Published May 28, 2021. doi:10.3389/fpsyt.2021.513068.
3. Hovda N, Gerrish W, Frizzell W, Shackelford R. A systematic review of the incidence of medical serious adverse events in sub-anesthetic ketamine treatment of psychiatric disorders. J Affect Disord. 2024;345:262-271. PMID: 37875227. doi:10.1016/j.jad.2023.10.120.
4. Joneborg I, Lee Y, Di Vincenzo JD, et al. Active mechanisms of ketamine-assisted psychotherapy: a systematic review. J Affect Disord. 2022;315:105-112. PMID: 35905796. doi:10.1016/j.jad.2022.07.028.
5. Ketalar (ketamine hydrochloride) injection [prescribing information]. Par Health USA, LLC. DailyMed. Accessed August 16, 2026. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=14e8f864-8b8a-4e7e-8439-e510d3107063.
6. Mathai DS, Cluck M, Aslam AM, et al. Interdisciplinary, Delphi-driven consensus guidelines on the use of intravenous ketamine infusions for depressive disorders from the American Society of Ketamine Physicians, Psychotherapists, and Practitioners (ASKP3). J Affect Disord. 2026;411:121970. PMID: 42144140. doi:10.1016/j.jad.2026.121970.
7. Nikolin S, Rodgers A, Schwaab A, et al. Ketamine for the treatment of major depression: a systematic review and meta-analysis. EClinicalMedicine. 2023;62:102127. PMID: 37593223. doi:10.1016/j.eclinm.2023.102127.
8. Smith-Apeldoorn SY, Veraart JKE, Spijker J, Kamphuis J, Schoevers RA. Maintenance ketamine treatment for depression: a systematic review of efficacy, safety, and tolerability. Lancet Psychiatry. 2022;9(11):907-921. PMID: 36244360. doi:10.1016/S2215-0366(22)00317-0.
9. Spravato (esketamine) nasal spray [prescribing information]. Janssen Pharmaceuticals, Inc. Revised January 2025. DailyMed. Accessed August 16, 2026. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d81a6a79-a74a-44b7-822c-0dfa3036eaed.

Document Precedence

Blue Cross and Blue Shield of Vermont (Blue Cross VT) Medical Policies are developed to provide clinical guidance and are based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. The applicable group/individual contract and member certificate language, or employer's benefit plan if an ASO group, determines benefits that are in effect at the time of service. Since medical practices and knowledge are constantly evolving, Blue Cross VT reserves the right to review and revise its medical policies periodically. To the extent that there may be any conflict between medical policy and contract/employer benefit plan language, the member's contract/employer benefit plan language takes precedence.

Audit Information

Blue Cross VT reserves the right to conduct audits on any provider and/or facility to ensure compliance with the guidelines stated in the medical policy. If an audit identifies instances of non-compliance with this medical policy, Blue Cross VT reserves the right to recoup all non-compliant payments.

Administrative and Contractual Guidance

Benefit Determination Guidance

Prior approval may be required and benefits are subject to all terms, limitations and conditions of the subscriber contract.

NEHP/ABNE members may have different benefits for services listed in this policy. To confirm benefits, please contact the customer service department at the member's health plan.

Federal Employee Program (FEP): Members may have different benefits that apply. For further information please contact FEP customer service or refer to the FEP Service Benefit Plan Brochure. It is important to verify the member's benefits prior to providing the service to determine if benefits are available or if there is a specific exclusion in the member's benefit.

Coverage varies according to the member's group or individual contract. Not all groups are required to follow the Vermont legislative mandates. Member Contract language takes precedence over medical policy when there is a conflict.

If the member receives benefits through an Administrative Services (ASO) only group, benefits may vary or not apply. To verify benefit information, please refer to the member's employer benefit plan documents or contact the customer service department. Language in the employer benefit plan documents takes precedence over medical policy when there is a conflict.

Policy Implementation/Update information

12/2020	New policy supersedes all prior policies concerning this benefit
01/2022	Policy Reviewed. Input received from specialty provider. References updated. Clarifying statements in policy guidelines and medical necessity criteria. Coding table removed effective 4/1/2022.
01/2023	Policy reviewed; references updated no changes to policy statement.
05 2023	Policy reviewed. Added clarifying language re investigational status of ketamine-assisted psychotherapy services and included new reference.
08/2024	Policy reviewed. Added clarifying language regarding standardized rating scales. Removed medical necessity criteria bullet regarding ketamine use as a general anesthetic for children under 12 as this policy does not guide such clinical use. Minor grammatical and formatting changes made for clarity and consistency. No changes to policy intent.
07/2025	Policy reviewed. No changes to policy statement or intent.
09/2026	Policy reviewed. Added clarifying language around indications and updated threshold scores for MDD severity. Updated references.

Eligible providers

Qualified healthcare professionals practicing within the scope of their license(s).

Approved by Blue Cross VT Medical Directors

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