



MEDICAL COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 01/21/14
LAST REVIEW DATE: 01/30/18
LAST CRITERIA REVISION DATE:
ARCHIVE DATE:

INTRAVENOUS KETAMINE INFUSION FOR TREATMENT OF DEPRESSION

Non-Discrimination Statement and Multi-Language Interpreter Services information are 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 Medical Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Medical Coverage Guideline 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.

Medical Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Medical Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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INTRAVENOUS KETAMINE INFUSION FOR TREATMENT OF DEPRESSION (cont.)

Description:

Intravenous (IV) infusions of the anesthetic ketamine have been investigated for the treatment of depression including severe and drug resistant depression. IV infusions of ketamine are 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.

Criteria:

- Intravenous ketamine for the treatment of depression is considered ***experimental or investigational*** based upon:
 1. Lack of final approval from the Food and Drug Administration, and
 2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
 3. Insufficient evidence to support improvement of the net health outcome, and
 4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
 5. Insufficient evidence to support improvement outside the investigational setting.

Resources:

Literature reviewed 01/30/18. We do not include marketing materials, poster boards and non-published literature in our review.

1. Aan Het Rot M, Zarate CA, Jr., Charney DS, Mathew SJ. Ketamine for depression: where do we go from here? *Biol Psychiatry*. Oct 1 2012;72(7):537-547.
2. Arunogiri S, Keks NA, Hope J. Should ketamine be used for the clinical treatment of depression? *Australasian psychiatry : bulletin of Royal Australian and New Zealand College of Psychiatrists*. Aug 2016;24(4):381-384.
3. Cusin C, Ionescu DF, Pavone KJ, et al. Ketamine augmentation for outpatients with treatment-resistant depression: Preliminary evidence for two-step intravenous dose escalation. *The Australian and New Zealand journal of psychiatry*. Jan 2017;51(1):55-64.

INTRAVENOUS KETAMINE INFUSION FOR TREATMENT OF DEPRESSION (cont.)

Resources: (cont.)

4. Fassauer GM, Hofstetter R, Hasan M, et al. Ketamine metabolites with antidepressant effects: Fast, economical, and eco-friendly enantioselective separation based on supercritical-fluid chromatography (SFC) and single quadrupole MS detection. *Journal of pharmaceutical and biomedical analysis*. Nov 30 2017;146:410-419.
5. Hassamal S, Spivey M, Pandurangi AK. Augmentation Therapy With Serial Intravenous Ketamine Over 18 Months in a Patient With Treatment Resistant Depression. *Clinical neuropharmacology*. Sep-Oct 2015;38(5):212-216.
6. Howland RH. Ketamine for the treatment of depression. *J Psychosoc Nurs Ment Health Serv*. Jan 2013;51(1):11-14.
7. Ibrahim L, Diazgranados N, Franco-Chaves J, et al. Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs add-on riluzole: results from a 4-week, double-blind, placebo-controlled study. *Neuropsychopharmacology*. May 2012;37(6):1526-1533.
8. Ionescu DF, Swee MB, Pavone KJ, et al. Rapid and Sustained Reductions in Current Suicidal Ideation Following Repeated Doses of Intravenous Ketamine: Secondary Analysis of an Open-Label Study. *J Clin Psychiatry*. Jun 2016;77(6):e719-725.
9. Mathew SJ, Shah A, Lapidus K, et al. Ketamine for treatment-resistant unipolar depression: current evidence. *CNS Drugs*. Mar 1 2012;26(3):189-204.
10. McGirr A, Berlim MT, Bond DJ, Fleck MP, Yatham LN, Lam RW. A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes. *Psychol Med*. Mar 2015;45(4):693-704.
11. Murrough JW, Iosifescu DV, Chang LC, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. *Am J Psychiatry*. Oct 1 2013;170(10):1134-1142.
12. Parsaik AK, Singh B, Khosh-Chashm D, Mascarenhas SS. Efficacy of Ketamine in Bipolar Depression: Systematic Review and Meta-analysis. *Journal of psychiatric practice*. Nov 2015;21(6):427-435.
13. Price RB, Iosifescu DV, Murrough JW, et al. Effects of ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in treatment-resistant depression. *Depress Anxiety*. Apr 2014;31(4):335-343.
14. Price RBL, D V. Intravenous Ketamine for the Treatment of Mental Health Disorders. 2014.



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Resources: (cont.)

15. Rasmussen KG, Lineberry TW, Galardy CW, et al. Serial infusions of low-dose ketamine for major depression. *J Psychopharmacol*. May 2013;27(5):444-450.
16. Singh JB, Fedgchin M, Daly EJ, et al. A Double-Blind, Randomized, Placebo-Controlled, Dose-Frequency Study of Intravenous Ketamine in Patients With Treatment-Resistant Depression. *Am J Psychiatry*. Aug 01 2016;173(8):816-826.
17. Sos P, Klirova M, Novak T, Kohutova B, Horacek J, Palenicek T. Relationship of ketamine's antidepressant and psychotomimetic effects in unipolar depression. *Neuro Endocrinol Lett*. 2013;34(4):287-293.
18. Szymkowicz SM, Finnegan N, Dale RM. A 12-month naturalistic observation of three patients receiving repeat intravenous ketamine infusions for their treatment-resistant depression. *J Affect Disord*. May 2013;147(1-3):416-420.
19. UpToDate.com. Bipolar Disorder in Adults: Pharmacotherapy for Acute Depression. 11/09/2017, 07/13/2016, 11/18/2014, .
20. UpToDate.com. Unipolar Depression in Adults: Management of Highly Resistant (Refractory) Depression. 11/21/2017, 12/30/2015, 10/20/2015, 12/16/2014.
21. Vande Voort JL, Morgan RJ, Kung S, et al. Continuation phase intravenous ketamine in adults with treatment-resistant depression. *J Affect Disord*. Dec 2016;206:300-304.

FDA Product Approval Information for Ketalar® (ketamine hydrochloride injection):

- FDA-approved indication: The sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation, best suited for short procedures but it can be used, with additional doses, for longer procedures. The induction of anesthesia prior to the administration of other general anesthetic agents. To supplement low-potency agents, such as nitrous oxide.



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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>

Multi-Language Interpreter Services:

Spanish: Si usted, o alguien a quien usted está ayudando, tiene preguntas acerca de Blue Cross Blue Shield of Arizona, tiene derecho a obtener ayuda e información en su idioma sin costo alguno. Para hablar con un intérprete, llame al 602-864-4884.

Navajo: Díí kwe'é atah nilínigíí Blue Cross Blue Shield of Arizona haada yit'éego bina'idííkidgo éí doodago Háida bíjá anilyeedígíí t'áadoo le'é yína'idííkidgo beehaz'áanii hólo díí t'áa hazaadk'ehjí háká a'doowolgo bee haz'á doo baqah ilínigóó. Ata' halne'ígíí kojí' bich'í' hodíilnih 877-475-4799.

Chinese: 如果您，或是您正在協助的對象，有關於插入項目的名稱 Blue Cross Blue Shield of Arizona 方面的問題，您有權利免費以您的母語得到幫助和訊息。洽詢一位翻譯員，請撥電話 在此插入數字 877-475-4799。

Vietnamese: Nếu quý vị, hay người mà quý vị đang giúp đỡ, có câu hỏi về Blue Cross Blue Shield of Arizona quý vị sẽ có quyền được giúp và có thêm thông tin bằng ngôn ngữ của mình miễn phí. Để nói chuyện với một thông dịch viên, xin gọi 877-475-4799.

Arabic:

إن كان لديك أو لدى شخص تساعد أسئلة بخصوص Blue Cross Blue Shield of Arizona، فلديك الحق في الحصول على المساعدة والمعلومات الضرورية بلغتك من دون أية تكلفة. للتحدث مع مترجم اتصل بـ 877-475-4799.

