

Medical Policy

Intravenous Ketamine for Treatment-Resistant Depression

Policy Number: 031

	Commercial and Qualified Health Plans	MassHealth
Authorization required	X	
Authorization not required		
Not covered		X

Overview

The purpose of this document is to describe the guidelines Mass General Brigham Health Plan utilizes to determine medical appropriateness for intravenous ketamine for treatment-resistant major depressive disorders or severe suicidal ideation. Administration of IV Ketamine for Primary PTSD with severe depressive symptoms will be considered on an individual case basis. The treating specialist must request prior authorization for the procedure.

Administration of IV ketamine is considered investigational in all other situations.

Ketamine is an antagonist of the N-methyl-D-aspartate receptor and a dissociative anesthetic. There are two main types of ketamine used to treat treatment-resistant major depression. Racemic ketamine, which is most often given as an infusion into the bloodstream. This is sometimes called intravenous, or IV- ketamine. It is a mixture of two mirror-image molecules: “R” and “S” ketamine. While it was approved decades ago as an anesthetic by the FDA, it is used off-label to treat depression.

The administration of intravenous ketamine must occur in a hospital setting or provider’s office and must be monitored by a psychiatrist or other specialist with expertise in IV ketamine administration. In addition, the prescriber must be a specialist in the area of the member’s diagnosis (e.g. psychiatrist) or has consulted with a specialist in the area of the member’s diagnosis.

For Mass General Brigham Health Plan’s Esketamine nasal spray coverage criteria, please refer to the [Spravato](#) pharmacy policy.

Coverage Guidelines

Initial Treatment (Initial authorization for 28 days)

Intravenous ketamine may be considered medically necessary for members 18 years of age or older with treatment resistant major depressive disorders or severe suicidal ideation (for which a rapid treatment onset is necessary) when the request meets **ALL** the medical necessity criteria indicated below:

1. The member meets the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria for unipolar major depressive disorder **(See Table A)**.
2. The member is to receive intravenous ketamine together with an oral antidepressant and/or mood stabilizer.
3. The member’s current depressive episode is severe based on **any** of the following within the past 30 days:
 - a. Hamilton Rating Scale for Depression (HAM-D) score ≥ 17 **(See Table B); OR**
 - b. Montgomery-Asberg Depression Rating Scale (MADRS) ≥ 28 **(See Table C); OR**
 - c. Quick Inventory of Depressive Symptomatology-Self Report 16 item **(See Table D); OR**

- d. Patient Health Questionnaire-9 (PHQ-9) score 15 or greater (**See Table E**).
4. The member has tried and had an inadequate therapeutic response to a combination of four antidepressants including augmentation, when appropriate, or psychotherapy from different classes in the current episode. The antidepressants must be from at least two or more different antidepressant classes (i.e. Tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, mirtazapine, or bupropion). An augmenting agent can include medications such as lithium, atypical antipsychotic, or thyroid hormone T3.
5. A satisfactory medication trial is defined by the following:
 - a. The length of the trial was at least 6 weeks at generally accepted doses or of sufficient duration as defined by the treating physician at the generally accepted doses; **AND**
 - b. The member was $\geq 80\%$ adherent to the medication throughout the trial.
6. A psychiatrist has evaluated the patient and determined and documented in the patient's medical record that the patient qualifies as a candidate for IV ketamine.

Coverage Guidelines

Reauthorization Guidelines

Intravenous ketamine to treat treatment resistant depressive disorders may be reauthorized for one year when the request meets **ALL** the medical necessity criteria indicated below:

1. The member is to receive intravenous ketamine together with an oral antidepressant or mood stabilizer.
2. The member experienced improvement in depression symptoms as evaluated with a proper depression rating scale (e.g. Clinical Global Impression Scale (CGI), Quick Inventory of Depressive Symptomatology-Self Report 16 item, Patient Health Questionnaire-9, HAM-D, MADRS); **AND/ OR** the member has significantly improved from a functional point of view.
3. The member does not have current substance use disorder or is in remission (complete abstinence for one month) or is in maintenance treatment for substance use disorder.

Dosing

The recommended adult dosage of intravenous ketamine during the induction and maintenance phases are as follows:

1. Induction phase (weeks 1-4): Administered 2-3 times per week with a starting dose of 0.5mg/kg per 40 minutes IV and adjusted based on tolerability and clinical response. Evidence of therapeutic benefit should be evaluated at the end of the induction phase to determine need for continued treatment and dosage requirement.
2. Maintenance or discontinuation of treatment is followed by a period of adjusting the frequency of treatment based on empirically determined duration of responses for each patient.

Exclusions

1. The member is pregnant or breastfeeding or at risk of becoming pregnant.
2. Current or past history of primary psychotic disorder (e.g. schizophrenia). Presence of psychotic features in the context of severe depression will be considered on an individual case by case basis.
3. The member has dementia.
4. The member is hypersensitive to esketamine, ketamine, or any of the excipients.
5. The member has a current active substance use disorder and is unwilling to receive treatment for it.
6. The member underwent a previous intravenous ketamine treatment at adequate doses, and it did not reduce symptoms or improve function.
7. The member has a current episode (within 7 days) of delirium.
8. The member has aneurysmal vascular disease such as:
 - a. Thoracic and abdominal aorta; **OR**
 - b. Intracranial and peripheral arterial vessels; **OR**



c. Arteriovenous malformation; **AND**

The member not been cleared by a cardiovascular or neurovascular specialist.

9. The member has had a recent (<6 months) intracerebral hemorrhage. If there is history of an intracerebral hemorrhage longer than 6 months ago, neurology or neurovascular clearance must be obtained.
10. The member has current uncontrolled hypertension (systolic blood pressure >160 mm HG or diastolic blood pressure > 90 mm Hg), cardiac arrhythmia, or unstable/ symptomatic cardiovascular disease— Requires clearance by Cardiology.
11. Members with cerebrospinal fluid (CSF) obstructive states (e.g. severe head injury, central congenital or mass lesions)—Requires clearance by Neurology.
12. Intraocular pressure pathology (e.g. uncontrolled glaucoma, acute globe injury)—Requires clearance by Ophthalmology.
13. The member has a diagnosis of uncontrolled hyperthyroidism (possibility of severe tachycardia or hypertension)—Requires medical clearance.
14. The member has a diagnosis of Porphyria (possibility of triggering an acute porphyria reaction)
15. The member has an active pulmonary infection or severe pulmonary disease (increased risk for apnea, low oxygen level).
16. The member is not under the ongoing care of psychiatrist/APRN/PCP or is **not willing to sign a release of information** in order to communicate with their primary team and with patient’s family.
17. Current or previous abuse of ketamine.

Codes

Authorized CPT/HCPCS Codes	Code Description
J3490	Unclassified drugs (Must be coupled with the appropriate National Drug Code [NDC] number)
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour

Effective

October 2022: Annual Update. Coverage guidelines clarified to remove language requiring patient be considered for electroconvulsive therapy. References updated.

April 1, 2021: Effective Date

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TABLE A.

Diagnostic Criteria for Unipolar Major Depressive Episode

Criteria	
Five or more symptoms for 2 weeks (one of which must be either depressed mood or anhedonia)	<ol style="list-style-type: none">1. Depressed mood most of the day nearly every day.2. Diminished interest or loss of pleasure in almost all activities (anhedonia)3. Significant weight change or appetite disturbance4. Sleep disturbance (insomnia or hypersomnia)5. Fatigue or loss of energy6. Diminished ability to think or concentrate; indecisiveness7. Feelings of excessive guilt or worthlessness8. Psychomotor agitation or retardation9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide
Symptoms cause clinically significant distress or functional impairment	
The symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition	
The episode is not better explained by a psychotic illness	
There has never been a manic or hypomanic episode	



TABLE B.

Hamilton Rating Scale for Depression (HAM-D)

Criteria	
This clinician-rated scale is commonly used as a tool for the assessment of a patient's depression severity, before, during, and after treatment. The total score ranges from 0 to 52.	
0–7	Normal
8–16	Mild Depression
17–23	Moderate Depression
≥ 24	Severe Depression

TABLE C.

Montgomery-Asberg Depression Rating Scale (MADRS)

Criteria	
MADRS is a ten-item diagnostic questionnaire used by psychiatrists to evaluate the efficacy of antidepressant treatment by assessing the severity of depressive symptoms. The total score ranges from 0 to 60. The following cut-offs are used to classify the depression severity:	
0–6	No Depression (No symptoms)
7–19	Mild Depression
20–34	Moderate Depression
35–60	Severe Depression



TABLE D.

Quick Inventory of Depression Symptomatology Scale (QIDS)

Criteria	
This scale is a self-report measure of depression. Questions correlate with the nine DSM-IV symptom criterion domains, Including: Sleep disturbance, Sad mood, Decrease/increase in appetite/weight, Concentration, Self-criticism, Suicidal ideation, Interest, Energy/fatigue, Psychomotor agitation/retardation.	
1-5	No Depression
6-10	Mild depression
11-15	Moderate Depression
16-20	Severe Depression
21-27	Very Severe Depression

TABLE E.

Patient Health Questionnaire-9 (PHQ-9)

Criteria	
The PHQ-9 is the depression module, which scores each of the nine DSM-IV criteria as "0" (not at all) to "3" (nearly every day). Major depression is diagnosed if 5 or more of the 9 depressive symptom criteria have been present at least more than half the days in the past 2 weeks, and 1 of the symptoms is depressed mood or anhedonia.	
1-4	Minimal Depression
5-9	Mild depression
10-14	Moderate Depression
15-19	Moderately Severe Depression
20-27	Severe Depression

