Mass General Brigham
Health Plan

# Medical Policy
# Intravenous Ketamine for Treatment-Resistant Depression

**Policy Number:** 031

| | Commercial and Qualified Health Plans | MassHealth | Medicare Advantage |
|---|---|---|---|
| Authorization required | X | X | X |
| Authorization not required | | | |
| Not covered | | | |

**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.

For Mass General Brigham Health Plan's Esketamine nasal spray coverage criteria, please refer to the Spravato pharmacy policy for commercial/exchange members, or to the Antidepressants pharmacy policy for MGB ACO members.

**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. 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 ≥ 80% adherent to the medication throughout the trial.
5. 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.
6. 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.

**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 misuse of ketamine.

**MassHealth Variation**
Mass General Brigham Health Plan uses the MassHealth Drug List for coverage determinations for members of the MGB ACO. Criteria for Ketalar (IV ketamine) are found in Table 17: Antidepressants.

**Medicare Variation**
Mass General Brigham Health Plan uses guidance from the Centers for Medicare and Medicaid Services (CMS) for coverage determinations for its Medicare Advantage plan members. National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), Local Coverage Articles (LCAs), and documentation included in the Medicare manuals are the basis for coverage determinations. When there is no guidance from CMS for the requested service, Mass General Brigham Health Plan's medical policies are used for coverage determinations. **At the time of Mass General Brigham's most recent policy review, there were no NCDs or LCDs for intravenous ketamine for treatment-resistant major depressive disorder.**

**Codes**

**The following codes are included below for informational purposes only. Inclusion of a code does not constitute or imply coverage or reimbursement.**

**This list of codes applies to commercial and MassHealth plans only.**

| 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 |

**Summary of Evidence**
Limited available treatment options for treatment-resistant depression (generally defined as depressive symptoms refractory to at least 2 antidepressants; see Thase and Connolly [2022]) include adjunctive therapy with a second-generation antipsychotic; add-on pharmacotherapy with lithium, thyroid hormone, or other antidepressants; psychotherapy; transcutaneous magnetic stimulation; and electroconvulsive therapy (ECT).

Individuals with severe, treatment-resistant depression demonstrate impairment in functioning, may report suicidal ideation or demonstrated suicidal behavior, and often require hospitalization. There is now fair-quality evidence demonstrating the safety and efficacy of IV ketamine in inducing remission of severe, treatment-resistant depression, at least in the short term.

The most compelling evidence favoring IV ketamine for severe, treatment-refractory depression comes from the RCT by Anand et al. (2023), who found that ketamine was noninferior to ECT for treatment-resistant nonpsychotic depression. Both groups in this high-quality study showed moderate remission rates (55 vs. 41%) and six-month relapse rates (35 vs. 56%).

Single-arm studies by Cusin et al. (2017) and Ionescu et al. (2016), and also placebo-controlled or midazolam-controlled trials by Fava et al. (2020), Grunebaum et al. (2018), Murrough et al. (2015), Shiroma et al. (2020), Singh et al. (2016) demonstrated efficacy of IV ketamine for treatment-resistant depression. These findings were confirmed by a retrospective chart review by Oliver et al. (2022). Philips et al. (2020) used a double-blinded crossover study design with midazolam to demonstrate that IV ketamine improved symptoms of suicidality in individuals with both treatment-resistant depression and suicidal ideation; additionally, following relapse of symptoms, open-label ketamine produced a sustained response.

A Cochrane review by Dean et al. (2021) concluded that ketamine may result in remission in unipolar major depression at 24 hours, and may reduce depression rating scales at 24 hours, but the evidence was of very low certainty. A consensus statement by McIntyre et al. (2021) highlighted the unknown long-term efficacy and safety profile of ketamine for treatment-resistant depression. A consensus statement from the American Psychiatric Association by Sanacora et al. (2017) highlighted the need for safety precautions in a controlled environment and the paucity of longer-term efficacy data.

Based on the evidence summarized above, Mass General Brigham Health Plan considers IV ketamine to be medically necessary for selected individuals with treatment-resistant major depression or severe suicidal ideation. Given the need for safety precautions and the paucity of evidence on long-term efficacy, the treatment requires careful patient selection and close monitoring.

**Effective**
March 2025: Ad hoc update. Summary of evidence added. References updated.
October 2024: Annual update. Clarified Medicare Variation language.
September 2024: Ad hoc update. MassHealth Variation added.
March 4, 2024: Ad hoc update. Table changed to reflect coverage for MassHealth members.
October 2023: Annual update. Medicare Advantage added to table. Minor editorial refinements to overview section; moved language to coverage guidelines; intent unchanged. Medicare Variation language added. References updated.
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) | 1. Depressed mood most of the day nearly every day.<br>2. Diminished interest or loss of pleasure in almost all activities (anhedonia)<br>3. Significant weight change or appetite disturbance<br>4. Sleep disturbance (insomnia or hypersomnia)<br>5. Fatigue or loss of energy<br>6. Diminished ability to think or concentrate; indecisiveness<br>7. Feelings of excessive guilt or worthlessness<br>8. Psychomotor agitation or retardation<br>9. 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 |