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Prior Authorization Update: Esketamine Monotherapy

Plain Language Summary:

- Esketamine is a medicine that people take to improve symptoms of depression (such as sadness, low mood, loss of interest) when at least 2 other medicines have not improved these symptoms. It is a spray that is inhaled in the nose and must be given during a clinic visit. After taking esketamine, providers monitor for side effects of the medicine for at least 2 hours in the clinic.
- Esketamine has mostly been studied in combination with other antidepressant medicines. However, a recent study showed that esketamine improved depression symptoms when it is prescribed to people who were not taking other antidepressant medicines.
- The Oregon Health Authority currently requires providers to document that someone has tried at least 2 other antidepressants and are currently taking another antidepressant before they will pay for esketamine.
- We recommend that the Oregon Health Authority be allowed to pay for esketamine for people who are not currently taking other antidepressants but continue to require documentation that that people have previously tried at least 2 other antidepressants.

Conclusions:

- Esketamine recently received approval from the Food and Drug Administration (FDA) for monotherapy in people with treatment-resistant depression. The randomized controlled trial (RCT) used for FDA approval enrolled people with moderate to severe depression symptoms (with an average Montgomery-Åsberg Depression Rating Scale [MADRS] of 37 at baseline).[1] The RCT is currently unpublished and risk of bias cannot be fully assessed.
- Depression symptoms (evaluated by MADRS) improved an average of -11.4 and -13.0 points from baseline for esketamine 56 mg and 84 mg compared to -6.3 points with placebo (least square mean difference [LSMD] -5.1; 95 % CI -7.9 to -2.3 and LSMD -6.8; 95% CI -9.5 to -4.1).[1] The MADRS score is a 10 item scale with a total score from 0 to 60 points with larger scores indicating more severe depression. In clinical trials, scores of less than 10 or 12 have been used to indicate remission, improvement of more than 50% from baseline indicate response to treatment, and improvements as small as 2 points may be clinically relevant.[2,3]

Recommendations:

- Update PA criteria to permit monotherapy with esketamine in people with treatment-resistant depression.

Background

There is no consistent definition in the literature for treatment-resistant depression; however, it is often described as failure to 2 or more antidepressants given for an adequate dose and duration.[4] It is not uncommon for first-line treatments to fail to manage depressive symptoms. It is estimated that for major depressive disorder, about one-thirds of patients have an inadequate response to initial therapy and one-third of patients have inadequate response to 2 therapies.[4] There is little evidence to guide next steps in therapy after an initial treatment failure.[4] Common treatment options used in clinical practice include a

trial of a different first-line antidepressant from the same class, use of an antidepressant from a different class, and augmentation of current therapy with a second agent. The Oregon Mental Health Clinical Advisory Group evaluated evidence of medications for treatment-resistant depression in December 2021. The following therapies are listed as evidence-supported options to augment antidepressant therapy for people with treatment-resistant depression:[5]

- Antidepressants: bupropion, mirtazapine
- Antipsychotics such as aripiprazole, brexpiprazole, quetiapine, olanzapine, risperidone, ziprasidone, and cariprazine.
- Esketamine
- Lithium
- Modafinil

This review evaluates new evidence for esketamine when used as monotherapy for treatment-resistant depression. Evidence related to the efficacy and safety of medications for treatment-resistant depression have previously been reviewed by the P&T committee. Evidence of benefit for esketamine is mixed depending on the population and outcome studied. Initial approval was based on 4 placebo-controlled phase 3 RCTs in adults with moderate to severe major depressive disorder (MDD) who had failed to have benefit with at least 2 alternative antidepressants for the current depressive episode. Two studies demonstrated improvement in depressive symptoms compared to placebo when esketamine was added to an oral antidepressant.[6,7] Two studies did not meet their primary endpoint for improvement of depression symtpoms,[7,8] and esketamine did not improve depression symptoms compared to placebo in a RCT of older adults (≥ 65 years of age) with MDD.[8] Data was supported by an open-label, non-comparative study evaluating esketamine use for up to 1 year.[9] In 2 additional RCTs, esketamine improved depression symptoms but not symptoms of suicide in hospitalized patients with MDD at high risk for suicide.[10,11] One RCT directly compared esketamine to quetiapine in adults with treatment-resistant depression (on background therapy with selective serotonin reuptake inhibitors [SSRIs] or serotonin norepinephrine reuptake inhibitors [SNRIs]).[12] Esketamine improved remission rates compared to quetiapine extended release (ER) at 8 weeks with an absolute risk reduction (ARR) of 9.5% and number needed to treat (NNT) of 11.[12]

New Indication:

In January 2025, esketamine received FDA-approval as monotherapy for treatment-resistant depression based on results of one placebo-controlled RCT (NCT04599855).[1,13] Efficacy and safety data from this trial are summarized in **Tables 1 and 2**. After 28 days, esketamine improved depression symptoms (evaluated with the MADRS) compared to placebo. The MADRS score is a 10 item scale with a total score from 0 to 60 points with larger scores indicating more severe depression. In clinical trials, scores of less than 10 or 12 indicate remission, improvement of more than 50% from baseline indicate response to treatment, and worsening of scores to 22 or more define relapse.[2] However, the scale is also non-linear, and improvements of 2 points have been documented as clinically relevant.[3] People enrolled in the study had an average baseline MADRS score of 37 indicating moderate to severe depression symptoms. The average improvement from baseline was -11.4 points and -13.0 points for esketamine 56 mg and 84 mg compared to -6.3 points with placebo (LSMD -5.1; 95 % CI -7.9 to -2.3 and LSMD -6.8; 95% CI -9.5 to -4.1).[1] As this trial is currently unpublished, the risk of bias and applicability cannot be fully assessed. About 20% of randomized patients were not included in final analysis and details about included patients and how missing data was handled are not currently available. The most common adverse events associated with esketamine were dissociation, nausea/vomiting, dizziness, headache, and anxiety. These events may have contributed to unblinding of treatment groups and increased risk for performance or detection bias.

Table 1. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1.NCT04599855[1,13] DB, PC, MC, RCT	1. Esketamine intranasal twice weekly 56 mg 2. Esketamine intranasal twice weekly 84 mg 3. Placebo 1:1:2 Duration: 4 weeks Participants could enroll in an open label, extension period up to 16 weeks	Demographics: - Median age 46 years - 61% female - Non-Hispanic: 89.9% - Race 87% White 7% Black - Average MADRS: 37 Key Inclusion Criteria: - Adults ≥ 18 years of age - MDD without psychotic features - Symptom duration ≥ 2 years - Treatment-resistant depression (i.e., ≤25% improvement to ≥2 antidepressants of adequate dose and duration in the current depressive episode) - Inventory of Depressive Symptomology-Clinician score ≥ 34 (30 items) - Medically stable (e.g, no abnormal vital signs, labs, electrocardiogram, physical or medical history of clinical significance) - Stable dose of thyroid hormone or normal TSH/free T4) Key Exclusion Criteria: - Prior nonresponse to ≥ 7 treatments of electroconvulsive therapy in the current depressive episode - Vagal nerve stimulation or deep brain stimulation in the current depressive episode - History of seizures	ITT: 1. 106 2. 121 3. 250 PP: 1. 86 2. 95 3. 197 Attrition: 1. 5 2. 14 3. 12 Open label enrollment 1. 99 2. 106 3. 237	Primary Endpoint: Change from baseline in MADRS at 28 days (PP) 1. LSM -11.4 (SE 1.2) 2. LSM -13.0 (SE 1.2) 3. LSM -6.3 (SE 0.8) 1 vs. 3: -5.1 (95% CI -7.9 to -2.3) 2 vs. 3: -6.8 (95% CI -9.5 to -4.1) Secondary Endpoint: Change from baseline in MADRS at 2 days 1. LSM -13.9 (SD 10.15) 2. LSM -13.0 (SD 9.68) 3. LSM -9.7 (SD 10.27) 1 vs. 3: -3.8 (95% CI -6.29 to -1.22) 2 vs. 3: -3.4 (95% CI -5.89 to -1.00)	NA	Discontinuation due to AE 1. 1 (1%) 2. 5 (4%) 3. 2 (1%) Serious AE: 1. 1 (1%) 2. 2 (1%) 3. 3 (1%) Non-serious AE: 1. 69 (66%) 2. 80 (66%) 3. 73 (29%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: No details available. Study is unpublished and risk of bias cannot be fully assessed. Performance Bias: Matched placebo. Potential for unblinding due to adverse events. The most common adverse events included nausea, dizziness, headache, and disassociation. Detection Bias: Matched placebo. Potential for unblinding due to adverse events. Attrition Bias: Unclear how missing data was handled. Primary analysis was not based on the ITT population. Reporting Bias: Study is unpublished and risk of bias cannot be fully assessed. Other Bias: Study is unpublished and risk of bias cannot be fully assessed. **Applicability**: Patient: Included patients had treatment-resistant MDD for the current depressive episode based on ≤ 25% improvement after 2 alternative antidepressants. Average baseline MADRS score is indicative of moderate-severe depression. Intervention: Dosing of esketamine was consistent with FDA-labeled induction dose for treatment-resistant depression. During the open-label continuation study period, the dose was reduced to one does every week or every other week. Comparator: Placebo Outcomes: MADRS is an established outcome assessment used in clinical trials of depression. Setting: 54 locations in the United States

Abbreviations: AE = adverse events; CI = confidence interval; DB = double blind; FDA = Food and Drug Administration; ITT = intention to treat; LSM = least square mean; MADRS = Montgomery-Åsberg Depression Rating Scale; MC = multicenter; MDD = major depressive disorder; NA = not applicable; PC = placebo controlled; PP = per protocol; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; TSH = thyroid stimulating hormone

Table 2. Common adverse events occurring in >5% of people with treatment-resistant depression and at a greater rate with esketamine monotherapy compared to placebo

	Esketamine (56 and 84 mg) (n=226)	Placebo (n=250)
Dissociation*	28%	4%
Nausea	25%	8%
Dizziness	22%	7%
Headache	19%	9%
Anxiety	10%	4%
Vomiting	7%	<1%
Feeling drunk	7%	<1%
Lethargy	7%	5%
Sedation	6%	2%

*includes dissociation, depersonalization/derealization disorder, derealization, diplopia, photophobia, vision blurred, feeling hot, paresthesia, and tinnitus

Esketamine labeling includes a box warning for sedation, dissociation, respiratory depression, abuse and misuse, and suicidal thoughts and behaviors.[1] The Risk Evaluation and Mitigation Strategies (REMS) program is intended to monitor and manage risk for these adverse events. Other warnings and precautions include risk cognitive impairment, increased blood pressure, impaired ability to drive or operate machinery, ulcerative or interstitial cystitis, and embryo-fetal toxicity.[1]

References:

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10. Fu D-J, Ionescu DF, Li X, et al. Esketamine Nasal Spray for Rapid Reduction of Major Depressive Disorder Symptoms in Patients Who Have Active Suicidal Ideation With Intent: Double-Blind, Randomized Study (ASPIRE I). *The Journal of clinical psychiatry.* 2020;81(3).
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12. Reif A, Bitter I, Buyze J, et al. Esketamine Nasal Spray versus Quetiapine for Treatment-Resistant Depression. *N Engl J Med.* 2023;389(14):1298-1309.
13. ClinicalTrials.gov. U.S. National Library of Medicine. http://clinicaltrials.gov/study/NCT04599855. Accessed April 17, 2025.

Esketamine (Spravato)

Goal(s):
- To ensure safe and appropriate use of esketamine in patients with treatment-resistant depression or suicidal ideation.

Length of Authorization:
- Up to 6 months

Requires PA:
- Esketamine (pharmacy and physician administered claims).

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request for maintenance dosing of esketamine (for determining response to therapy) OR for continuation after initiation during a recent hospitalization?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the patient 65 years or older?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #5
5. Is the member currently engaged in or been referred for psychotherapy?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
6. Is there prescriber attestation or documentation of treatment-resistant depression based on all the following criteria: a. Diagnosis of unipolar major depressive disorder b. Patient has tried at least 2 different antidepressants in which: i. There has been inadequate response after at least 6 weeks of treatment at an average minimum therapeutic dose or greater; or ii. The patient has not been able to continue treatment for at least 6 weeks due to intolerable side effects. Minimum therapeutic doses can be found here: https://www.oregon.gov/oha/HPA/DSI-Pharmacy/MHCAGDocs/Switching-Between-Anti-Depressant-Medications.pdf	**Yes:** Go to #9	**No:** Go to #7
7. Is the request for treatment of major depressive disorder in the setting of acute suicidal ideation or behavior?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness. Recommend an adequate trial (minimum of 6-8 weeks) of 2 or more antidepressants.
8. Is there a documented plan to optimize oral antidepressant treatment in one of the following ways: a. Titrating the dose of the current antidepressant to a therapeutic level b. Switching to a different antidepressant OR c. Adding oral augmentation therapy (e.g., a second antidepressant, an atypical antipsychotic, or mood stabilizer)?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
9. Does the patient have documentation of any of the following: • Current Aneurysmal vascular disease or arterial venous malformation OR • History of Intracerebral hemorrhage OR • Current Pregnancy OR • Current Uncontrolled hypertension (e.g., >140/90 mmHg)	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve up to 28 days for induction (either 56 mg and/or 84 mg for titration) not to exceed 24 units total to be covered within the approved time window. The approved time window typically spans 60 days to accommodate scheduling visits.

Renewal Criteria		
1. Is there documentation that the patient demonstrated an adequate response during the 4-week induction phase (an improvement in depressive symptoms)?	**Yes:** Go to #2	**No**: Go to #3
2. Is the request for administration of esketamine once weekly or every 2 weeks?	**Yes:** Approve for up to 6 months (maximum of 12 per 28 days)	**No**: Pass to RPh. Deny; medical appropriateness.
3. Has the patient been on therapy for at least 4 weeks?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve for completion of induction phase (total 28 days of treatment with a maximum of 24 nasal spray devices (each device contains 28 mg of esketamine)

P&T/DUR Review: 6/25(SS);6/24(KS);2/24; 12/23 (KS); 2/23, 10/21; 2/21; 7/19
Implementation:8/1/25; 7/1/24; 1/1/22; 3/1/21; 8/19/19