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Drug Class Update with New Drug Evaluation: Antidepressants

Date of Review: December 2023

Date of Last Review: February 2023
Dates of Literature Search: 12/01/2022 - 09/15/2023
Brand Name (Manufacturer): Zurzuvae (Biogen Inc)
Dossier Received: no

Generic Name: zuranolone

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The purpose of this class update is to evaluate new evidence for the use of antidepressants and review the evidence for zuranolone, a newly approved drug for postpartum depression (PPD).

Plain Language Summary:
- This review looks at new research for medicines used to treat depression, called antidepressants. Certain antidepressants are also used for other conditions, such as helping people to stop smoking and to reduce pain. There is also a new drug recently approved by the Food and Drug Administration (FDA) for depression that occurs in the post-partum period (4 weeks or less after having a baby) called zuranolone.
- The antidepressant called bupropion was shown to be more helpful at helping people quit smoking compared to a sugar pill (placebo) or no treatment.
- The antidepressant called duloxetine has shown benefit in reducing pain intensity when compared to placebo.
- The National Institute for Health and Care Excellence (NICE) looked at the studies for the antidepressant esketamine in people that have depression that has not resolved with treatment with at least 2 other antidepressants, but they could not find enough information to routinely recommend esketamine for these people.
- The American College of Physicians (ACP) recommends antidepressants to be tried as a first treatment option in people with depression. Behavioral counseling is also recommended as initial therapy.
- The Food and Drug Administration approved the antidepressant zuranolone for treating people with post-partum depression. Zuranolone helped improve symptoms of depression more than placebo in people who had recently given birth that had a diagnosis of severe depression.
- Based on this information, no changes to the antidepressant preferred drug list for the Oregon Health Plan fee-for-service program is recommended. Members may not use zuranolone for more than 14 days as recommended by the FDA.

Research Questions:
1. Is there new comparative evidence related to efficacy of antidepressants for important outcomes (e.g., symptom reduction and remission)?

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2. Is there new comparative evidence for harms for antidepressants?
3. Are there specific populations based on demographic characteristics, such as age, race, ethnicity, pregnancy status, or people with certain comorbidities, for which certain antidepressants are better tolerated or more effective than other antidepressants in improving symptoms and remission of depression?
4. What is the comparative evidence for efficacy and harms for zuranolone?

Conclusions:

- Two new systematic reviews with meta-analyses, 2 new clinical guidelines and one new drug approval were identified for this review.
- A Cochrane review evaluated antidepressants for long-term smoking cessation and found high quality evidence that bupropion had higher smoking cessation rates compared to placebo or no treatment (relative risk [RR] 1.60; 95% confidence interval [CI], 1.49 to 1.72).[1] Serious adverse events were not found to differ between groups. Evidence for other antidepressants for efficacy in smoking cessation was insufficient.
- A Cochrane review evaluated the use of antidepressants for managing chronic pain in adult patients.[2] Duloxetine 60 mg daily was found to provide substantial pain relief (50% or more reduction in pain intensity from baseline) compared to placebo, which was clinically and statistically significant (RR 1.91; 95% CI, 1.69 to 2.17). The review found insufficient evidence to assess safety outcomes, such as adverse events and withdrawals.
- Guidance from NICE on the use of esketamine in treatment-resistant depression found a reduction in the Montgomery-Asberg Depression Rating Scale (MADRS) score for patients treated with esketamine versus placebo (-19.8 vs. -15.8, respectively).[3] The difference seen with esketamine was clinically significant but the NICE was uncertain of the evidence. Current guidance does not support esketamine for individuals with treatment-resistant depression.
- The American College of Physicians (ACP) strongly recommend treatment with a second-generation antidepressant (e.g., selective serotonin reuptake inhibitors [SSRI] or serotonin-norepinephrine reuptake inhibitor [SNRI]) in adults in the acute phase of major depressive disorder based on moderate quality evidence.[4]
- In August 2023, zuranolone received FDA- approval for treatment of postpartum depression (PPD). Efficacy from two phase 3 trials demonstrated a reduction in the 17-point Hamilton Depression Rating Scale (HAMD-17) by 4.0 and 4.2 points more than placebo in patients that had severe PPD, which was statistically and clinically significant.[5,6] The most common adverse events associated with zuranolone were somnolence, dizziness, diarrhea, fatigue, nasopharyngitis, and urinary tract infections.
- There is insufficient evidence to determine the most effective therapies for treatment-resistant depression in any identified populations based on age, race ethnicity, or people with certain co-morbidities.

Recommendations:

- No changes to the Oregon Health Plan fee-for-service preferred drug list (PDL) are recommended.
- Implement safety edit for zuranolone to ensure product use is limited to populations with established safety and efficacy.
- After evaluation of costs in the executive session, no PDL changes were recommended.

Summary of Prior Reviews and Current Policy

- Antidepressants are designated preferred or part of the voluntary PDL.
- There is insufficient evidence of clinically significant differences in efficacy and safety between specific antidepressants or classes of antidepressants. Previous recommendations are to base antidepressant treatment selection on patient characteristics, adverse effects and cost.
- At the February 2023 meeting, no PDL changes were recommended based on review of recently published evidence. The PA criteria for tricyclic antidepressants, esketamine and brexanolone were updated.

Background:
Antidepressant medications are categorized based on mechanism of action and chemical structure. They are classified as first-generation (tricyclic antidepressants [TCAs] and monoamine oxidase inhibitors [MAOIs]) and second-generation antidepressants (SSRIs, serotonin and norepinephrine reuptake inhibitors [SNRIs], and newer antidepressants). They are used for a wide variety of psychiatric conditions including depression, post-traumatic stress disorder (PTSD), bipolar disorder, obsessive compulsive disorder, anxiety disorders and bulimia.[7] Specific antidepressants have Food and Drug Administration (FDA) labeled indications for other conditions including fibromyalgia (not a funded diagnosis by the Health Evidence Review Commission), diabetic peripheral neuropathy, PPD, premenstrual dysphoric disorder, and smoking cessation.[7] This review highlights antidepressant therapies with new evidence for the treatment of PPD, smoking cessation and chronic pain.

Postpartum depression is a common medical condition in females, with an incidence of 13.2% in new female parents.[1] Postpartum depression is defined as depressive symptoms that occur within 4 weeks after giving birth. Untreated PPD can result in maternal suicide as wells as negative effects to infant and child development.[1] The pathophysiology of PPD is thought to be due to neuroactive steroids and gamma-aminobutyric acid (GABA) changes.[2] Currently there are 2 approved therapies for PPD, oral zuranolone and brexanolone (given as a continuous intravenous [IV] infusion over 60 hours). Antidepressant medications are also used as adjunctive therapy for smoking cessation, in which bupropion has the most evidence for improving quit rates.[3] There is evidence for the use of antidepressants to assist in the management of chronic pain. Chronic pain is defined as pain lasting 3 or more months with estimated incidence rates of one in 5 adults worldwide.[1] Depression is found to be more common in individuals with chronic pain. Guidance from NICE in 2022 recommends the use of duloxetine, amitriptyline, fluoxetine, paroxetine, citalopram and sertraline for the management of chronic pain.[4]

The choice of antidepressant is typically dependent on patient preference and adverse effect profile, as current evidence demonstrates little difference in efficacy between agents. Second-generation antidepressants are recommended as first-line agents due to improved tolerability, decreased risk of adverse events, and less risk for overdose, compared to first-generation antidepressants. For the treatment of moderate to severe depression in adults, guidelines from both NICE and the American Psychiatric Association (APA) recommend combination antidepressant and psychotherapy.[4,8] SSRIs are recommended by NICE as a first-line option, though individual drug choice can vary depending on adverse effects. APA guidelines support SSRIs, SNRIs, mirtazapine, or bupropion as reasonable first-line treatment options.

It is not uncommon for first-line treatments to fail to manage depressive symptoms. It is estimated that for major depressive disorder, about two-thirds of patients have an inadequate response to initial therapy and about one-third of patients have treatment-resistant depression.[3] 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 at adequate doses.[9] There is little evidence to guide next steps in therapy after an initial treatment failure.[3] Common treatment options used in clinical practice include trial of a different first-line antidepressant, use of an antidepressant from a different class, and augmentation of current therapy with a second agent. All antidepressants for major depressive disorder (MDD) have an FDA black box warning for suicide risk in young adults and can be associated a discontinuation syndrome when agents are abruptly stopped. Other notable adverse events include risk for serotonin syndrome, which increases when used in combination with other serotonergic medications, and anticholinergic adverse events.

Goals of treatment for antidepressants typically include symptom and function improvement, remission, and relapse prevention. A wide variety of rating scales are used to evaluate symptom improvement, quality of life, and function in patients treated with antidepressants. Scales vary depending on the condition. There is some evidence that measurement-based care (MBC), via depression rating scale improves outcomes. However, the recommendation from the Veterans Administration (VA)/ Department of Defense (DoD) for use of these scales was weak due to lack of high-quality supporting evidence.[7] Some of the most

commonly used rating-scales and thresholds include the MADRS and HAM-D. The MADRS is a 10-item scale which assesses depression symptoms (range 0 to 60) with higher scores indicating more severe depression.[11] The HAM-D is a clinician-rated, 17-item scale to assess symptoms (range 0 to 52) with scores of 10-13 indicating mild depression, 14-17 indicating mild to moderate depression and 17 and greater indicating moderate to severe depression.[11] The FDA has stated that this tool is valuable in the study of depressive symptoms but may be associated with a higher representation of evaluation of somatic symptoms (e.g., insomnia and somatic anxiety) compared to other tools. Remission is defined as the person being free from depressive symptoms for several months after two or more depressive episodes and typically a 50% improvement in symptom score from baseline is used to evaluate response to therapy.[11] A 2-point improvement on the MADRS may be associated with a minimum clinically important improvement and HAM-D scores of 3 to 7 points may be clinically significant.[11]

In Oregon, mental health drug classes, including antidepressants, are carved out from the coordinated care organizations (CCOs) and paid for by fee-for-service. Non-preferred products do not automatically require prior authorization, but safety criteria are in place for esketamine, brexanolone, and TCAs in children. In the second quarter of 2023 there were over 373,000 antidepressant medication claims for Oregon Health Plan (OHP) members.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search terms used for this review are available in **Appendix 2**. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), NICE, Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Cochrane – Antidepressants for Smoking Cessation

In a 2023 Cochrane review, the use of antidepressants for assisting long-term smoking cessation was studied. Comparisons between antidepressants, placebo and other active treatments were evaluated.[1] A literature search up till April 2022 identified 124 studies, enrolling 48,832 participants. A majority of participants were adults with four studies enrolling adolescents, ages 12-21 years old. Studies had at least 6 months of follow up. Thirty-four studies were found to be at high-risk of bias.

In trials evaluating bupropion compared to placebo, or no pharmacological treatment, high-quality evidence showed bupropion was associated with higher smoking cessation rates (RR 1.60; 95% CI, 1.49 to 1.72).[1] Serious adverse events were similar between groups (RR 1.16; 95% CI, 0.90 to 1.48) (moderate quality evidence).[1] There was no clear evidence that there was a difference in smoking cessation rates between bupropion 150 mg daily and 300 mg daily. Individuals taking bupropion were more likely to drop out of trials early compared to placebo or no pharmacological treatment (RR 1.44; CI, 1.27 to 1.65) (high quality evidence).[1] Fifteen RCTs comparing combination therapy of bupropion and nicotine replacement therapy (NRT) compared to NRT alone demonstrated similar smoking cessation rates (RR 1.17; 95% CI, 0.95 to 1.44) based on low quality evidence. Similar rates of severe adverse events and dropouts between the treatment groups were found based on low quality evidence.[1] Bupropion monotherapy may be less effective than varenicline alone (RR of 0.73; 95% CI, 0.67 to

0.80; moderate strength of evidence). Combinations of bupropion and varenicline demonstrated no statistical or clinical difference in smoking cessation rates compared to varenicline alone (RR of 1.21; 95% CI, 0.95 to 1.55; moderate quality of evidence).[1] Comparisons of bupropion to combination NRT (e.g., nicotine patches plus one other form of nicotine) demonstrated lower smoking cessation rates with combination NRT (RR 0.74; 95% CI, 0.55 to 0.98). No differences were found in severe adverse events and withdrawals due to treatment between the two treatment groups (low quality evidence).

There is low quality evidence that bupropion use may result in higher smoking cessation rates compared to nortriptyline; however, the results were not statistically significant and results were imprecise (RR 1.30; 95% CI, 0.93 to 1.82; 3 trials).[1] Data from 6 trials demonstrated that nortriptyline use was associated with higher smoking cessation rates compared to placebo (RR 2.03; 95% CI, 1.48 to 2.78). There was insufficient evidence to assess harms of nortriptyline. Evidence from 4 studies did not demonstrate evidence that SSRIs were effective for smoking cessation (RR 0.93; 95% CI, 0.71 to 1.22); however, there was a low number of studies available for analysis. Monoamine oxidase inhibitors were studied in 6 trials and found that they may to be more effective for smoking cessation than control, but results were not statistically significant due to imprecision (RR 1.29; 95% CI, 0.93 1.79).[1] Studies with venlafaxine and St. John's wort had insufficient evidence to support conclusions. There was insufficient evidence to effectively assess harms in studies with SSRIs, MAOIs, and St. John's wort. The link between depression and quit rates was not explored in most studies. Harms were difficult to estimate due to low event rates that caused them to be underpowered to determine a difference.

Cochrane – Antidepressants for Pain Management in Adults with Chronic Pain

A 2023 systematic review and network meta-analysis evaluated the use of antidepressants for managing chronic pain in adult patients.[2] There was a paucity of high-quality evidence from other other sources, so the conclusions from the network meta-analysis are included in this summary. There were 176 studies including 28,664 participants included in the review.[2] Literature was searched till January of 2022. Placebo and active treatments comparisons were studied. Antidepressants included in the review were: amitriptyline, bupropion, citalopram, clomipramine, desipramine, desvenlafaxine, doxepin, duloxetine, escitalopram, fluoxetine, imipramine, milnacipran, mirtazapine and nortriptyline. Pain conditions studied were: fibromyalgia (59 studies); neuropathic pain (49 studies); musculoskeletal pain (40 studies).[2] Pain due to headaches were excluded. The primary outcome was a 50% decrease in pain intensity, pain relief, mood and adverse events. Pain relief was measured by 0-10 visual analog scale (VAS), 0-100 VAS and the Brief Pain Inventory scale. The duration of the included RCTs was an average of 10 weeks.

Duloxetine was found to be most effective for pain based on moderate to high quality evidence. There is moderate quality evidence that duloxetine 60 mg daily provided a small to moderate effect for substantial pain relief (50% or more reduction in pain intensity from baseline) compared to placebo (RR 1.91; 95% CI, 1.69 to 2.17).[2] Investigators calculated the findings as a number needed to benefit (NNTB) of 7.1 for this outcome.[1] A reduction in continuous pain intensity was reduced more in those treated with duloxetine compared to placebo (standard mean difference [SMD] -0.31; 95% CI, -0.39 to -0.24).[2] Compared to placebo, duloxetine demonstrated a small improvement in mood based on moderate evidence (SMD -0.16; 95% CI, -0.22 to -0.1). Duloxetine 60 mg daily was found to be as effective as higher doses (duloxetine 120 mg daily).

Milnacipran 100 mg daily was found to be moderately effective for chronic pain (e.g., fibromyalgia) relief. There was a small reduction in pain intensity demonstrated with milnacipran compared to placebo (SMD -0.22; 95% CI, -0.39 to -0.06) (moderate quality of evidence).[2] There was low quality evidence that milnacipran provide substantial pain relief with a NNTB of 11, based on evidence from 2 studies. No additional benefit was demonstrated with doses higher than 100 mg.

All other antidepressants had insufficient evidence to draw conclusions on benefit for chronic pain. There was very low quality evidence available on adverse events for all therapies, therefore additional evidence is needed to determine strong conclusions.

After review, 6 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[10–13]

New Guidelines:
High Quality Guidelines:

NICE – Esketamine Nasal Spray for Treatment-resistant Depression
A December 2022 Technology Appraisal Guidance from NICE evaluated the evidence for the use of esketamine.[3] The appraisal was primarily based on the 2 phase trials (TRANSFORM-2 and SUSTAIN-1). Additional supportive evidence was from 4 trials: TRANSFORM-1, TRAMSFORM-3, SUSTAIN-2 and SUSTAIN-3. Trials included patients 18 to 64 years of age with moderate to severe depression comparing esketamine plus an oral antidepressant to placebo plus an oral antidepressant.[3] The primary outcome was the change in MADRS score based on symptom response, which was a reduction in score of 50% or more from baseline. Remission rates were also a primary endpoint, defined as a MADRS score of 12 or less with minimal or no symptoms. The mean reduction in MADRS score from baseline in patients who had not responded to 2 antidepressants was 19.8 for esketamine and 15.8 for placebo (with concomitant oral antidepressant).[3] NICE felt that the evidence was limited by an unknown placebo response in the trials, short trial duration, subgroups could more clearly defined and small trial populations. Overall, NICE found that the evidence suggests that esketamine is more effective than placebo but the evidence is uncertain. The committee concluded that esketamine is not recommended for those with treatment-resistant depression.[3]

ACP – Nonpharmacological and Pharmacologic Treatments of Adults in Acute Phase of Major Depressive Disorder
In a 2023 guideline from the ACP provided guidance for the treatment of adults in the acute phase of major depressive disorder (MDD).[4] Major depressive disorder is characterized by at least 5 symptoms and is associated with more severe and an increased number of symptoms.[4] Acute phase encompasses treatment till remission, defined as resolution of symptoms. Recommendations were for pharmacological and non-pharmacological therapies used for treatment in the ambulatory care setting. Evidence for recommendations came from a systematic review and network meta-analysis performed in 2023. Methodology for the guideline followed ACP guideline process which includes assessment and grading of the literature using GRADE methodology. Recommendations for pharmacotherapy will be presented.

Recommendations from the ACP are for adults with MDD for initial and second-line treatments in the acute phase.[4]

- Monotherapy with cognitive behavioral therapy (CBT) or second-generation antidepressant therapy is recommended first-line in the acute phase of moderate to severe MDD (strong recommendations; moderate quality evidence).
- Combination of CBT and second-generation antidepressants as initial treatment of moderate to severe MDD is conditional recommendation based on low quality of evidence.
- In adults with mild MDD CBT is recommended as initial therapy (conditional recommendation based on low quality evidence).
- In patients that do not respond to initial treatment should be: 1) switching to or augmenting with CBT 2) switching to a different second-generation antidepressant or augmenting with a second antidepressant (conditional recommendation based on low quality of evidence). It is recommended that treatment selection be based on patient characteristics and potential treatment benefits and harms.

New Formulations or Indications:
None identified.

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts.

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Levomilnacipran[14]	FETZIMA	August 2023	Warnings and Precautions	Pediatric patients 7 years to less than 18 years of age treated with levomilnacipran was associated with an increased risk of new-onset hypertension (systolic and/or diastolic). The safety and efficacy of levomilnacipran has not been established in pediatric patients for the treatment of major depressive disorder.

Randomized Controlled Trials:
Citations were manually reviewed for relevant randomized controlled trials from the initial Medline literature search. After further review, all citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION:

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Zuranolone is a neuroactive steroid GABA A receptor positive modulator FDA-approved for the treatment of PPD in August of 2023.[15] The dose of zuranolone is 50 mg once daily in the evening for 14 days, taken with fat-containing food to increase absorption. Zuranolone can be used as monotherapy or as an adjunct to oral antidepressant treatment. Two phase 3 trials provided evidence for efficacy in those with PPD.[5,6] Results from the phase 3 trials will be presented as well as 2 additional studies in patients with MDD (not currently approved for this indication) (**Table 4**).

The phase 3 trials enrolled patients with severe PPD, characterized by severe depression (HAMD-17 scores of 26 points or more). Most of the participants were White and had a mean age of 28 to 31 years. Approximately 15% to 20% of patients were taking a concomitant antidepressant.[16] Participants had to cease lactating or temporarily stop providing breast milk to their infant before starting therapy and 7 days after the last dose. The primary endpoint in both studies was change from baseline of 17-point HAM-D score at day 15. Secondary outcomes included change in HAM-D at day 45 and change from baseline in MADRS score at day 15.[5,6]

Zuranolone 30 mg daily was evaluated in one PPD study and 50 mg daily in the second PPD study, both compared to placebo.[5] In both studies zuranolone and placebo were given for 14 days with the primary endpoint assessment at day15. There was a clinically and statistically significant reduction in HAM-D scores at day 15 in both studies compared to placebo (least square mean [LSM] of -4.0 to -4.2 points). Results out to day 45 demonstrated a 2.9 to 4.1 point decrease in HAM-D scores compared to placebo.[16] Changes in MADRS scores ranged from -4.6 to -5.1, which were clinically and statistically significant. Improvements in anxiety and CGI-I were also improved through day 45 in the those patients who received 50 mg zuranolone compared to placebo.[6] Changes in CGI-I at day 15 were reduced -2.2 points for zuranolone compared to -1.6 points for placebo (LSM -0.6; 95% CI, -0.9 to -0.2; p=0.005).[5]

Limitations to the evidence for PPD include lack of data for repeated course of zuranolone in patients who experience relapse of depressive symptoms. Long-term efficacy beyond 45 days is unknown. There is insufficient safety data for the use of zuranolone in individuals who breastfeed. External validity was limited in all studies due to lack of details on study sites and location.

Clinical Safety:

Common adverse reactions for those patients taking zuranolone are: somnolence, dizziness, diarrhea, fatigue, nasopharyngitis, and urinary tract infections **(Table 2**).[15] The discontinuation rates due to AE were low in both trials, ranging from 1%-4.1% for zuranolone and 0%-2% for placebo.[1,9] Severe adverse events occurred in 3%-4% of patients in the treatment group compared to 1%-4% in the placebo group. There is a FDA boxed warning for driving impairment due to central nervous system depressant effects. Patients should wait at least 12 hours after administration before driving. There is no evidence of sexual dysfunction with the use of zuranolone when studied in patients with MDD.[17] There is a risk of misuse, abuse, and substance use disorder, including addiction, with the use of zuranolone. The FDA has recommended that the DEA assign a schedule IV designation to zuranolone as there is some evidence that it may cause physical dependence; however final status is pending.[16] Patients with mild, moderate or severe substance use disorders within the previous 12 months were excluded from one trial and those with a history of alcohol or drug abuse were exclusionary criteria for the second trial. Nonclinical data shows a risk for major congenital malformations and neuronal apoptosis with fetal exposure so contraception is recommended for females of reproductive potential. There is insufficient data on long-term safety outcomes.

Table 2. Adverse Events of Zuranolone (2% or more of treated patients)[15]

Adverse Reaction	Placebo	Zuranolone
Somnolence	6%	36%
Dizziness	9%	13%
Diarrhea	2%	6%
Fatigue	2%	5%
Urinary tract infection	4%	5%

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Remission of depression
2) Reduction of depressive symptoms (e.g., HAM-D or MADRS score changes)
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Change from baseline in HAM-D scores

Table 3. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	The mechanism of action is not fully understood but thought to be due to the positive allosteric modulation of $GABA_A$ receptors
Oral Bioavailability	Not described
Distribution and Protein Binding	Distribution is greater than 500 L Protein binding is greater than 99.5%
Elimination	45% urine and 41% feces
Half-Life	19.7 to 24.6 hours
Metabolism	CYP3A4 predominately

Table 4. 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. Deligiannidis, et al[6] DB, PC, PG, Phase 3, RCT	1. Zuranolone 50 mg/day 2. Placebo Study treatment: 14 days Follow-up: 45 days	Demographics: Mean Age: 31 years Mean Body mass index: 30.25 Mean HAM-D (17-point): 28.7 White: 69% Black: 21.5% Key Inclusion Criteria: - 18 to 45 years - HAM-D score of 26 points or more - Major depressive episode with onset during the third trimester of pregnancy or 4 weeks or less postpartum and were 12 months or less postpartum Key Exclusion Criteria: - Breastfeeding during study period - Bipolar disorder - Psychotic disorder - Attempted suicide - Risk of suicide in the current episode of PPD	ITT: 1. 98 2. 97 PP: 1. 86 2. 87 Attrition: 1. 12 (12%) 2. 10 (10%)	Primary Endpoint: Change from baseline in HAM-D score at day 15: 1. -15.6 points 2. -11.6 points LSM -4.0 points (95% CI, -6.3 to -1.7) P = 0.001 Secondary Endpoints: Change from baseline in HAM-D score at day 45: 1. -14.8 points 2. -12.5 points LSM -2.9 points (95% CI, -4.5 to 0) P=0.050 Change in MADRS score at day 15: 1. -19.7 points 2. -14.6 points LSM -5.1 points (95% CI, -8.4 to -1.7) P = 0.003	NA for all	Severe AE: 1. 3 (3.1%) 2. 1 (1.0%) AE leading to discontinuation: 1. 4 (4.1%) 2. 2 (2.0%) Somnolence: 1. 26 (26.5%) 2. 5 (5.1%) Dizziness: 1. 13 (13.1%) 2. 10 (10.2%) Sedation: 1. 11 (11.2%) 2. 1 (1.0%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Unclear) Patients, clinicians, and study personnel were blinded to treatment allocation. Randomization process was not described. Performance Bias: (Unclear) Patients, clinicians, and study personnel blinded to treatment allocation. There was no information on if placebo was matching to active treatment. Detection Bias: (Unclear) Outcome assessment was not described. Attrition Bias: (High) Results were analyzed on ITT population, but attrition levels were above 10% in the treatment group. Assessment of missing data was not described. Reporting Bias: (Low) Study was performed as described and endpoints assessed as described. Other Bias: (Unclear) manufacturer funded. **Applicability**: Patient: Results are most applicable to patients with severe depression and without other mental health disorders. Intervention: Zuranolone dose is appropriate and is one of the dosing regimens recommended by the manufacturer. Comparator: Placebo comparison appropriate because efficacy had not been established yet and there is no gold standard treatment for PPD. Outcomes: Outcomes: The HAMD and MADRS are standard measurement tools in the treatment of depression. Setting: Not described.

2. Deligiannidis, et al[5] DB, PC, Phase 3, RCT	1. Zuranolone 30 mg/day 2. Placebo Study treatment: 14 days Follow-up: 45 days	Demographics: Mean Age: 28.35 years Mean Body mass index: 31 Mean HAM-D (17-point): 28.6 Baseline antidepressant use: 19.5% White: 42% Black: 31% Key Inclusion Criteria: - 18 to 45 years - 6 months or fewer post-partum - HAMD-17 score of 26 points or more - Major depressive episode with onset during the third trimester of pregnancy or 4 weeks or less postpartum - Stable psychotropic use for more than 30 days, if taking psychotropics Key Exclusion Criteria: - Breastfeeding during study period - Seizures - Psychotic disorder - Attempted suicide - Active alcoholism or drug addiction	ITT: 1. 77 2. 76 PP: 1. 76 2. 74 Attrition: 1. 1 (1%) 2. 2 (3%)	Primary Endpoint: Change from baseline in HAMD-17 total score at day 15: 1. -17.8 points 2. -13.6 points LSM -4.2 points (95% CI, -6.9 to -1.5) P = 0.003 Secondary Endpoints: Change from baseline in HAM-D score at day 45: 1. -15.6 points 2. -11.6 points LSM -4.1 points (95% CI, -6.7 to -1.4) p-value = 0.003 Change in MADRS score at day 15: 1. -17.8 points 2. -13.6 points LSM -4.6 points (95% CI, -8.3 to -0.8) P = 0.02	NA for all	Severe AE: 1. 3 (4%) 2. 3 (4%) AE leading to discontinuation: 1. 1 (1%) 2. 0 (0%) Somnolence: 1. 12 (15%) 2. 8 (11%) Dizziness: 1. 6 (8%) 2. 4 (6%) Sedation: 1. 4 (5%) 2. 0	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomization 1:1 with randomization codes generated by an independent statistical vendor by an interactive response technology implementation. Baseline characteristics were well balanced. Performance Bias: (Low) Subjects, clinicians, and study team blinded to treatment allocation. Matched placebo capsules to maintain blinding. Detection Bias: (Unclear) No details provided on how outcomes were analyzed. Attrition Bias: (Low) Results were analyzed via ITT analysis and attrition rates were low. Reporting Bias: Study was performed as described and endpoints assessed as described. Other Bias: (Unclear) Funded by manufacturer. **Applicability**: Patient: Results are most applicable to patients who have severe depression and not on antidepressant therapy upon initiation. Intervention: Zuranolone dose was lower than previous studies but well tolerated. Comparator: Placebo comparison appropriate because efficacy had not been established yet and there is no gold standard treatment for PPD. Outcomes: The HAMD and MADRS are standard measurement tools in the treatment of depression. Setting: Thirty-three outpatient centers.

Abbreviations: AE = adverse event; ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; ITT = intention to treat; HAMD = Hamilton Depression Rating Scale; LSM = least square mean; MADRS = Montgomery-Asberg Depression Rating Scale: MD = mean difference; MDD = major depressive disorder; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PC = placebo controlled; PG = parallel group; PP = per protocol; PPD = postpartum depression; RCT = randomized controlled trial.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
amitriptyline HCl	AMITRIPTYLINE HCL	TABLET	Y
amitriptyline HCl	ELAVIL	TABLET	Y
bupropion HCl	BUPROPION XL	TAB ER 24H	Y
bupropion HCl	WELLBUTRIN XL	TAB ER 24H	Y
bupropion HCl	BUPROPION HCL SR	TAB SR 12H	Y
bupropion HCl	WELLBUTRIN SR	TAB SR 12H	Y
bupropion HCl	BUPROPION HCL	TABLET	Y
citalopram hydrobromide	CITALOPRAM HBR	SOLUTION	Y
citalopram hydrobromide	CELEXA	TABLET	Y
citalopram hydrobromide	CITALOPRAM HBR	TABLET	Y
desipramine HCl	DESIPRAMINE HCL	TABLET	Y
desipramine HCl	NORPRAMIN	TABLET	Y
desvenlafaxine succinate	DESVENLAFAXINE SUCCINATE ER	TAB ER 24H	Y
desvenlafaxine succinate	PRISTIQ	TAB ER 24H	Y
doxepin HCl	DOXEPIN HCL	CAPSULE	Y
doxepin HCl	DOXEPIN HCL	ORAL CONC	Y
duloxetine HCl	CYMBALTA	CAPSULE DR	Y
duloxetine HCl	DULOXETINE HCL	CAPSULE DR	Y
escitalopram oxalate	ESCITALOPRAM OXALATE	TABLET	Y
escitalopram oxalate	LEXAPRO	TABLET	Y
fluoxetine HCl	FLUOXETINE HCL	CAPSULE	Y
fluoxetine HCl	PROZAC	CAPSULE	Y
fluoxetine HCl	FLUOXETINE HCL	SOLUTION	Y

fluoxetine HCl	FLUOXETINE HCL	TABLET	Y
fluvoxamine maleate	FLUVOXAMINE MALEATE	TABLET	Y
imipramine HCl	IMIPRAMINE HCL	TABLET	Y
mirtazapine	MIRTAZAPINE	TAB RAPDIS	Y
mirtazapine	REMERON	TAB RAPDIS	Y
mirtazapine	MIRTAZAPINE	TABLET	Y
mirtazapine	REMERON	TABLET	Y
nefazodone HCl	NEFAZODONE HCL	TABLET	Y
nortriptyline HCl	NORTRIPTYLINE HCL	CAPSULE	Y
nortriptyline HCl	PAMELOR	CAPSULE	Y
nortriptyline HCl	NORTRIPTYLINE HCL	SOLUTION	Y
paroxetine HCl	PAROXETINE HCL	TABLET	Y
paroxetine HCl	PAXIL	TABLET	Y
sertraline HCl	SERTRALINE HCL	ORAL CONC	Y
sertraline HCl	ZOLOFT	ORAL CONC	Y
sertraline HCl	SERTRALINE HCL	TABLET	Y
sertraline HCl	ZOLOFT	TABLET	Y
venlafaxine HCl	EFFEXOR XR	CAP ER 24H	Y
venlafaxine HCl	VENLAFAXINE HCL ER	CAP ER 24H	Y
venlafaxine HCl	VENLAFAXINE HCL	TABLET	Y
amoxapine	AMOXAPINE	TABLET	V
bupropion HBr	APLENZIN	TAB ER 24H	V
bupropion HCl	BUPROPION XL	TAB ER 24H	V
bupropion HCl	FORFIVO XL	TAB ER 24H	V
citalopram hydrobromide	CITALOPRAM HBR	CAPSULE	V
clomipramine HCl	ANAFRANIL	CAPSULE	V
clomipramine HCl	CLOMIPRAMINE HCL	CAPSULE	V
desvenlafaxine	DESVENLAFAXINE ER	TAB ER 24H	V
dextromethorphan HBr/bupropion	AUVELITY	TAB IR ER	V
duloxetine HCl	DRIZALMA SPRINKLE	CAP DR SPR	V
escitalopram oxalate	ESCITALOPRAM OXALATE	SOLUTION	V
esketamine HCl	SPRAVATO	SPRAY	V
fluoxetine HCl	FLUOXETINE DR	CAPSULE DR	V
fluvoxamine maleate	FLUVOXAMINE MALEATE ER	CAP ER 24H	V
imipramine pamoate	IMIPRAMINE PAMOATE	CAPSULE	V
isocarboxazid	MARPLAN	TABLET	V
levomilnacipran HCl	FETZIMA	CAP SA 24H	V
levomilnacipran HCl	FETZIMA	CAP24HDSPK	V
paroxetine HCl	PAROXETINE HCL	ORAL SUSP	V
paroxetine HCl	PAXIL	ORAL SUSP	V

paroxetine HCl	PAROXETINE CR	TAB ER 24H	V
paroxetine HCl	PAROXETINE ER	TAB ER 24H	V
paroxetine HCl	PAXIL CR	TAB ER 24H	V
paroxetine mesylate	PEXEVA	TABLET	V
phenelzine sulfate	NARDIL	TABLET	V
phenelzine sulfate	PHENELZINE SULFATE	TABLET	V
protriptyline HCl	PROTRIPTYLINE HCL	TABLET	V
selegiline	EMSAM	PATCH TD24	V
sertraline HCl	SERTRALINE HCL	CAPSULE	V
tranylcypromine sulfate	TRANYLCYPROMINE SULFATE	TABLET	V
trimipramine maleate	TRIMIPRAMINE MALEATE	CAPSULE	V
venlafaxine besylate	VENLAFAXINE BESYLATE ER	TAB ER 24	V
venlafaxine HCl	VENLAFAXINE HCL ER	TAB ER 24	V
vilazodone HCl	VIIBRYD	TAB DS PK	V
vilazodone HCl	VIIBRYD	TABLET	V
vilazodone HCl	VILAZODONE HCL	TABLET	V
vortioxetine hydrobromide	TRINTELLIX	TABLET	V
brexanolone	ZULRESSO	VIAL	
escitalopram oxalate	ESCITALOPRAM OXALATE	TABLET	
olanzapine/fluoxetine HCl	OLANZAPINE-FLUOXETINE HCL	CAPSULE	
olanzapine/fluoxetine HCl	SYMBYAX	CAPSULE	
trazodone HCl	TRAZODONE HCL	TABLET	

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to September 07, 2023

Search terms

#	Searches	Results
1	amitriptyline.mp. or Amitriptyline/	9920
2	bupropion.mp. or Bupropion/	5621
3	citalopram.mp. or Citalopram/	7733
4	desipramine.mp. or Desipramine/	7977
5	desvenlafaxine.mp. or Desvenlafaxine Succinate/	545
6	doxepin.mp. or Doxepin/	1534
7	duloxetine.mp. or Duloxetine Hydrochloride/	3289
8	escitalopram.mp. or Escitalopram/	3270
9	fluoxetine.mp. or Fluoxetine/	15686

10	fluvoxamine.mp. or Fluvoxamine/	3321
11	imipramine.mp. or Imipramine/	13543
12	mirtazapine.mp. or Mirtazapine/	2726
13	nefazodone.mp.	802
14	nortriptyline.mp. or Nortriptyline/	3272
15	paroxetine.mp. or Paroxetine/	6844
16	sertraline.mp. or Sertraline/	6035
17	venlafaxine.mp. or Venlafaxine Hydrochloride/	5014
18	amoxapine.mp. or Amoxapine/	487
19	clomipramine.mp. or Clomipramine/	4129
20	Dextromethorphan/ or dextromethorphan.mp.	3190
21	isocarboxazid.mp. or Isocarboxazid/	416
22	levomilnacipran.mp. or Levomilnacipran/	101
23	phenelzine.mp. or Phenelzine/	1688
24	protriptyline.mp. or Protriptyline/	415
25	selegiline.mp. or Selegiline/	3011
26	tranylcypromine.mp. or Tranylcypromine/	2311
27	trimipramine.mp. or Trimipramine/	548
28	vilazodone.mp. or Vilazodone Hydrochloride/	267
29	vortioxetine.mp. or Vortioxetine/	672
30	brexanolone.mp.	135
31	trazodone.mp. or Trazodone/	2349
32	esketamine.mp.	799

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZURZUVAE safely and effectively. See full prescribing information for ZURZUVAE.

ZURZUVAE™ (zuranolone) capsules, for oral use, [controlled substance schedule pending]
Initial U.S. Approval: [pending controlled substance scheduling]

WARNING: IMPAIRED ABILITY TO DRIVE OR ENGAGE IN OTHER POTENTIALLY HAZARDOUS ACTIVITIES

See full prescribing information for complete boxed warning.

ZURZUVAE causes driving impairment due to central nervous system (CNS) depressant effects. Advise patients not to drive or engage in other potentially hazardous activities until at least 12 hours after administration. Patients may not be able to assess their own driving competence or the degree of impairment caused by ZURZUVAE *(5.1, 5.2)*.

INDICATIONS AND USAGE

ZURZUVAE is a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator indicated for the treatment of postpartum depression (PPD) in adults. (1)

DOSAGE AND ADMINISTRATION

- Administer with fat-containing food. (2.1)
- Recommended dosage is 50 mg orally once daily in the evening for 14 days. (2.1)
- Dosage may be reduced to 40 mg once daily if CNS depressant effects occur. (2.1)
- ZURZUVAE can be used alone or as an adjunct to oral antidepressant therapy. (2.1)
- *Severe Hepatic Impairment:* Recommended dosage is 30 mg orally once daily in the evening for 14 days. (2.3, 8.6)
- *Moderate or Severe Renal Impairment:* Recommended dosage is 30 mg orally once daily in the evening for 14 days. (2.4, 8.7)

DOSAGE FORMS AND STRENGTHS

Capsules: 20 mg, 25 mg, and 30 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- *CNS Depressant Effects:* ZURZUVAE can cause CNS depressant effects such as somnolence and confusion. If patients develop CNS depression, consider dosage reduction or discontinuation of ZURZUVAE. (5.2)
- *Suicidal Thoughts and Behavior:* Consider changing the therapeutic regimen, including discontinuing ZURZUVAE, in patients whose PPD worsens, or who experience emergent suicidal thoughts and behaviors. (5.3)
- *Embryo-fetal Toxicity:* May cause fetal harm. Advise a pregnant woman of the potential risk to an infant exposed to ZURZUVAE in utero. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during ZURZUVAE treatment and for one week after the final dose. (5.4, 8.1, 8.2, 8.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥5% and greater than placebo) were somnolence, dizziness, diarrhea, fatigue, nasopharyngitis, and urinary tract infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sage Therapeutics, Inc. at 1-844-987-9882 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- *CNS Depressants:* Concomitant use may increase impairment of psychomotor performance or CNS depressant effects. If use with another CNS depressant is unavoidable, consider dosage reduction.(7)
- *Strong CYP3A4 Inhibitors:* Concomitant use may increase the risk of ZURZUVAE-associated adverse reactions. Reduce the ZURZUVAE dosage to 30 mg orally once daily in the evening for 14 days when used concomitantly with a strong CYP3A4 inhibitor. (2.2, 7)
- *CYP3A4 Inducers:* Concomitant use may decrease the efficacy of ZURZUVAE. Avoid concomitant use. (2.2, 7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Appendix 4. Key Inclusion Criteria

Population	Patients with MDD and PPD
Intervention	Antidepressant treatment
Comparator	Placebo or active treatment comparison
Outcomes	Reduction in depressive symptoms and remission of symptoms
Setting	Outpatient

Zuranolone (Zurzuvae)

Goal(s):

- To ensure appropriate use of zuranolone in patients with post-partum depression.

Length of Authorization:

- One time use only.

Requires PA:

- Zuranolone requires a prior authorization approval due to safety concerns.

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 and age (e.g., ≥18 years)?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Does the patient have moderate to severe post-partum depression? Note: Zuranolone is not indicated for major depressive disorder but can be covered for depression meeting the clinical diagnosis of post-partum depression (e,g., moderate to severe depression with peripartum onset).	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Has the patient been previously treated with zuranolone for severe post-partum depression related to their most recent pregnancy?	**Yes:** Pass to RPh. Deny; medical appropriateness. Multiple courses of zuranolone have not been studied.	**No:** Approve for a single 14-day treatment.

P&T/DUR Review: 12/23 (KS)
Implementation: 1/1/24

Brexanolone (Zulresso)

Goal(s):
- To ensure appropriate use of brexanolone in patients with post-partum depression.

Length of Authorization:
- One time use only.

Requires PA:
- Brexanolone requires a prior authorization approval due to safety concerns (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.	
• Is this an FDA approved indication and age (e.g., ≥15 years)?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
• Is the patient with moderate to severe post-partum depression?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
• Has the patient been previously treated with brexanolone for severe post-partum depression related to their most recent pregnancy?	**Yes:** Pass to RPh. Deny; medical appropriateness. Multiple doses of brexanolone have not been studied.	**No:** Go to #5

Approval Criteria		
• Has the patient had an adequate trial (6-8 weeks) of an oral antidepressant?	**Yes:** Approve for a single, continuous, intravenous infusion over 60 hours (titrated per prescribing recommendations)	**No:** Pass to RPh. Deny; recommend trial of oral antidepressant

P&T/DUR Review: 12/23 (KS) 2/23 (KS), 2/21(SS) 7/19 (KS)
Implementation: 4/1/23; 8/19/19

Tricyclic Antidepressants

Goal(s):
- Ensure safe and appropriate use of tricyclic antidepressants in children less than 12 years of age
- Discourage off-label use not supported by compendia

Length of Authorization:
- Up to 12 months

Requires PA:
- Tricyclic antidepressants in children younger than the FDA-approved minimum age (new starts)
- Auto-PA approvals for:
  - Patients with a claim for an SSRI or TCA in the last 6 months
  - Prescriptions identified as being written by a mental health provider

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/

Table 1. FDA-Approved Indications of Tricyclic Antidepressants

Drug	FDA-Approved Indications	Maximum Dose	Minimum FDA-Approved Age
amitriptyline HCl	Depression	50 mg	12
amoxapine	Depression	400 mg	18
clomipramine HCl	Obsessive-compulsive disorder	200 mg	10
desipramine HCl	Depression	300 mg	10

		(150 mg for 10-19 years of age)	
doxepin HCl	Depression Anxiety	150 mg	12
imipramine HCl	Depression Nocturnal enuresis	75 mg	6
imipramine pamoate	Depression	200 mg	18
maprotiline HCl	Depression Bipolar depression Dysthymia Mixed anxiety and depressive disorder	225 mg	18
nortriptyline HCl	Depression	50 mg	12
protriptyline HCl	Depression	60 mg	12
trimipramine maleate	Depression	100 mg	12

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Does the dose exceed the maximum FDA-approved dose (**Table 1**)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #3
3. Is the request for an FDA-approved indication and age (**Table 1**)?	**Yes:** Approve for up to 6 months	**No:** Go to #4
4. Is the request for prophylactic treatment of headache or migraine and is the therapy prescribed in combination with cognitive behavioral therapy?	**Yes**: Approve for up to 6 months	**No:** Go to #5
5. Is the drug prescribed by or in consultation with an appropriate specialist for the condition (e.g., mental health specialist, neurologist, etc.)?	**Yes**: Approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness.

Esketamine (Spravato)

Goal(s):

- To ensure safe and appropriate use of esketamine in patients with treatment resistant depression.

Length of Authorization:

- Up to 6 months

Requires PA:

- Esketamine requires a prior authorization approval due to safety concerns (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. Does the patient have treatment resistant depression (failure of two separate antidepressant trials which were each given for at least 6 weeks at therapeutic doses)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness. Recommend an adequate trial (minimum of 6-8 weeks) of 2 or more antidepressants.

Approval Criteria		
6. Is the patient currently on an FDA approved dose of an oral antidepressant?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness. Esketamine is indicated for use with an oral antidepressant.
7. 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 requested doses (either 56 mg and/or 84 mg for titration) not to exceed 23 units total.

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 #4
2. Is the request for administration of esketamine once weekly or every 2 weeks?	**Yes:** Go to #3	**No**: Pass to RPh. Deny; medical appropriateness.
3. Has the patient been adherent to oral antidepressant therapy?	**Yes:** Approve for up to 6 months (maximum of 12 per 28 days)	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
4. 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 23 nasal spray devices (each device contains 28 mg of esketamine)

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