Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCCNS067.0825	**CENTRAL NERVOUS SYSTEM DRUGS** **ZURZUVAE ®** (zuranolone capsules)
Effective Date: 10/1/2025	**Review/Revised Date**: 06/24, 06/25 (MTW)
Original Effective Date: 04/24	**P&T Committee Meeting Date**: 02/24, 08/24, 08/25
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

REQUIRED MEDICAL INFORMATION:
Authorization requires all the following criteria to be met:
1. Diagnosis of moderate to severe major depressive disorder with documentation or provider attestation that depressive symptoms began between the third trimester of pregnancy to the first four weeks following delivery
2. Patient is within the first twelve months postpartum
3. Submission of validated screening tool results (for example, Hamilton Depression Rating Scale [HAM-D], Patient Health Questionnaire-9 [PHQ-9], Montgomery-Asberg Depression Rating Scale [MADRS]) confirming diagnosis
4. Member has not received prior treatment with Zurzuvae® for the current pregnancy
5. Patient has tried and failed a formulary generic selective serotonin reuptake inhibitor (SSRI) or serotonin and norepinephrine reuptake inhibitor (SNRI) for the current episode of postpartum depression (after 4-6 weeks at an adequate dose) or has an intolerance/contraindication to all selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs). This may be waived in cases of severe postpartum depression.

EXCLUSION CRITERIA:
- Past medical history of seizures
- Past medical history of bipolar disorder, schizophrenia, or schizoaffective disorder

- Current pregnancy

AGE RESTRICTIONS:
May be approved for patients aged 18 years and older

PRESCRIBER RESTRICTIONS: N/A

COVERAGE DURATION:
Initial authorization will be approved for one month (one 14-day fill) per pregnancy. Reauthorization will not be allowed, only one treatment course allowed per pregnancy.

QUANTITY LIMIT:
- 20 mg and 25 mg capsules: 28 capsules per 180 days
- 30 mg capsules: 14 capsules per 180 days

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Zuranolone (Zurzuvae®) is a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator. The mechanism of action is not fully understood but thought to be related to its positive allosteric modulation of GABA-A receptors.

The recommended dosage is 50 mg orally once daily in the evening for 14 days, with fat-containing food (400 to 1,000 calories, 25-50% fat). It can be used alone or as an adjunct to oral antidepressant therapy.

FDA APPROVED INDICATIONS:
The treatment of postpartum depression in adults.

POSITION STATEMENT:

The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) defines postpartum depression (PPD) as major depressive disorder 'with peripartum onset', with the episode beginning during gestation or within four weeks post childbirth. In practice, most experts define the postpartum period as the first year after delivery, however symptoms most often begin within the first few months (~six weeks) of childbirth.

Treatment of postpartum depression depends on the severity of the patient's symptoms. Guidelines recommend psychotherapy or antidepressants as first-line treatment options for patients with mild-to-moderate PPD. Cognitive behavioral therapy and interpersonal psychotherapy should be considered as an adjuvant to antidepressants in moderate-to-severe PPD and in cases where women are reluctant to take antidepressants. Additional drug therapy may be needed for patients with severe symptoms (including benzodiazepines or adjunctive antipsychotic agents for patients with severe anxiety or depression with psychotic features). Patients with suicidal intent or psychosis may need to be hospitalized. Due to its more immediate effect, electroconvulsive therapy may be appropriate in some situations.

According to the American College of Obstetricians and Gynecologists (ACOG) guidelines for the Treatment and Management of Mental Health Conditions During Pregnancy and Postpartum, SSRIs are considered first-line medications for the treatment of perinatal depression and anxiety disorders. SNRIs may be used as an alternative to SSRIs. For patients that have been successfully treated with an antidepressant in the past, that medication should be the therapy of choice. If a patient does not have a prior history of antidepressant use or prior therapies were unsuccessful, sertraline is usually preferred due to extensive data regarding the safety in this population. Escitalopram is a reasonable alternative based on data regarding efficacy and acceptability in the general population. Fluoxetine has a long half-life and active metabolites, which have been associated with an increased risk of neonatal adaptation syndrome and accumulation in breastfed infants, however, this data should not deter the use of fluoxetine if a patient has a history of successful treatment with it outside of pregnancy. Once an effective dose of antidepressant is reached, therapy is often continued for six to 12 months to prevent relapse of symptoms.

For patients with moderate to several PPD with onset in the third trimester or ≤4 weeks postpartum, the ACOG guideline recommends consideration of Zulresso® (brexanolone). The only other FDA-approved treatment for postpartum depression, it is administered by continuous IV infusion over 60 hours and can only be given by healthcare providers in certain healthcare facilities. Due to the need for continuous

IV infusion, inpatient administration, restricted REMs program, and adverse effects, this therapy is usually reserved for the most severe cases of postpartum depression.

After the FDA approval of zuranolone in 2023, ACOG came out with a practice advisory recommending the consideration of zuranolone in the postpartum period (within 12 months postpartum) for depression that has onset in the third trimester or ≤4 weeks postpartum. The decision to use zuranolone should assess the benefits (for example, significantly improved and rapidly resolved symptoms) with the risks and challenges (for example, potential suicidal thoughts or behavior, sedation that precludes performing some activities of daily living like driving, and lack of efficacy data beyond 45 days).

Depression Rating Scales: Examples of evidence-based rating scales include:

- Beck's Depression Inventory (BDI)
  - 1 to 10 - Not depressed
  - 11 to 16 - Mild mood disturbance
  - 17 to 20 - Borderline clinical depression
  - 21 to 30 - Moderate depression
  - 31 to 40 – Severe depression
  - Over 40 -Extreme depression
- Hamilton Depression Rating Scale (HAM-D or HDRS or HRSD)
  - 0 to 7: Not depressed
  - 8 to 13: Mild (subthreshold)
  - 14 to 18: Moderate (mild)
  - 19 to 22: Severe (moderate)
  - >23: Very severe (severe)
- Montgomery-Asberg Depression Rating Scale (MADRS)
  - 0 to 6: Not depressed
  - 7 to 19: Mild Depression
  - 20 to 34: Moderate Depression
  - 35 to 60: Severe Depression
- Patient Health Questionnaire-9 (PHQ-9)
  - 0 to 4: Not depressed
  - 5 to 9: Mild
  - 10 to 14: Moderate
  - 15 to 19: Moderately Severe
  - 20 to 27: Severe

The efficacy of zuranolone was demonstrated in two phase 3, randomized, double-blind, placebo-controlled clinical trials, SKYLARK (N=195) and ROBIN (N=153). In both trials individuals were women 18-45 years old, with a baseline HAM-D score of ≥26, with major depressive episode onset during the third trimester or ≤4 weeks

postpartum. In the Skylark trial, individuals must have been within 12 months postpartum and in the Robin trial, they must have been within 6 months postpartum. Participants were randomized to receive zuranolone or placebo for 14 days, with follow-up to day 45. Patients on a stable dosage of antidepressants for ≥30 days prior to first study treatment dose were allowed to continue. All patients stopped lactating or agreed not to provide breast milk to their infant from first study drug dose through seven days following last study drug dose. Individuals were excluded if they had a history of bipolar disorder, schizophrenia, schizoaffective disorder, active psychosis, history of nonfebrile seizures, or a history of attempted suicide. At baseline, 15.3% of individuals in the Skylark trial were using antidepressants, and 21% in the zuranolone group and 18% in the placebo group in the Robin trial. Most common adverse effects were somnolence, dizziness, diarrhea, fatigue, nasopharyngitis, and urinary tract infection. Limitations of these trials include unknown long-term safety/efficacy, high placebo effect, small size, high attrition in the Skylark trial (12% zuranolone, 10% placebo), and unknown safety/efficacy with repeat administration.

- Efficacy (Skylark):
    - Change from baseline in HAM-D total score at day 15 (primary endpoint): Zuranolone: -15.6 points; Placebo: -11.6 points; LSM difference: -4.0 points (95% CI, -6.3 to -1.7; p = 0.001)
    - Mean change from baseline in HAM-D score at Day 3: Zuranolone: -9.5 points; Placebo: -6.1 points; LSM difference: -3.4 points (95% CI, -5.4 to -1.4; p = 0.001)
    - Mean change from baseline in HAM-D score at Days 45: Zuranolone: -17.9 points; Placebo: -14.4 points; LSM difference: -3.5 points (95% CI, -6.0 to -1.0; p = 0.007)
    - HAM-D response (reduction of ≥50% from baseline in HAM-D) at day 15: 57.0% (N=53) zuranolone vs. 38.9% (N=35) placebo; odds ratio=2.02, 95% CI=1.11, 3.67; p=0.02
    - HAM-D remission (HAM-D score ≤7) at day 15: 26.9% (N=25) zuranolone vs. 16.7% (N=15) placebo; odds ratio=1.78, 95% CI=0.88, 3.62; p=0.11
- Efficacy (Robin):
    - Change from baseline in HAM-D total score at day 15 (primary endpoint): Zuranolone: -17.8 points; Placebo: -13.6 points; LSM difference: -4.2 points (95% CI, -6.9 to -1.4; p = 0.003)
    - Mean change from baseline in HAM-D score at Day 3: Zuranolone: -12.5 points; Placebo: -9.8 points; LSM difference: -2.7 points (95% CI, -5.1 to -0.3; p = 0.03)
    - Mean change from baseline in HAM-D score at Days 45: Zuranolone: -15.6 points; Placebo: -11.6 points; LSM difference: -4.1 points (95% CI, -6.7 to -1.4; p = 0.003)

- HAM-D response (reduction of ≥50% from baseline in HAM-D) at day 15: 72% (53 of 74) zuranolone vs 48% (35 of 73) placebo; OR, 2.6; 95% CI, 1.3-5.2; P = .005
- HAM-D remission (HAM-D score ≤7) at day 15: 45% (33 of 74) zuranolone vs 23% (17 of 73) placebo; OR, 2.5; 95% CI, 1.2-5.2; P = .01

Zuranolone contains a boxed warning regarding the impaired ability to drive or engage in other potentially hazardous activities due to central nervous system (CNS) depressant effects. Patients should be advised not to drive or engage in other potentially hazardous activities until at least 12 hours after administration.

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