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Subject: Zuranolone (Zurzuvae) Oral Capsules

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DESCRIPTION:

Zuranolone (Zurzuvae) is the second neuroactive steroid GABA-A (gamma-aminobutyric acid-A) receptor positive modulator approved by the Food and Drug Administration (FDA) in August 2023 for the treatment of postpartum depression (PPD) in adults. The first agent in the class was brexanolone (Zulresso), which was approved by the FDA in March 2019. Zuranolone and brexanolone are analogs of allopregnanolone, an endogenous steroid hormone metabolite that increases during pregnancy and then declines abruptly after birth. In some women, this decline is thought to trigger depression and anxiety. Zuranolone is the first oral drug therapy, as brexanolone is an intravenous infusion administered over 2.5 days in a hospital setting. Other agents used for PPD include oral antidepressants, which have been used off-label with varying degrees of success.

There are several terms that encompass mood disorders that occur during pregnancy and soon after delivery. These mood disorders can be broadly categorized as: (1) postpartum blues (“the baby blues”), (2) perinatal depression (encompassing prenatal and postpartum depression), and (3) postpartum psychosis. Many women have the baby blues in the days following childbirth (approximately 50% to 80% of all mothers). For most women, the baby blues are temporary and ranges from a few days to up to 2 weeks after childbirth. Symptoms are not usually severe and there are effective ways to handle them. The symptoms of perinatal depression last longer than the baby blues and are more severe. A very small number of women (1 or 2 in 1,000) suffer a rare and severe form of depression called postpartum psychosis that is considered a medical emergency. An estimated 9 to 12% of women experience some degree of PPD and it is one of the most common complications of pregnancy and the postpartum period. It is well established that perinatal depression can result in adverse short- and long-term effects on both the mother and child. Risk factors for PPD include personal or family history of anxiety or depression, sociological factors (e.g., low income, social conflict, physical or psychological abuse, recent stressful life events, single marital status), and factors that negatively impact newborn care (e.g., lack of social support, premature or low-birth-weight infant, breastfeeding problems, infant temperament). It is

thought that fewer than half of PPD cases are diagnosed in clinical practice, and there has been a more intense focus on screening and prevention. The American Academy of Pediatricians (AAP) recommend integrating PPD screening and surveillance at the 1-, 2-, 4-, and 6-month well-child visits. The American College of Gynecologists (ACOG) recommend all obstetrician–gynecologists and other obstetric care providers complete a full assessment of mood and emotional well-being, including screening for postpartum depression and anxiety with a validated instrument, during the comprehensive postpartum visit for each patient (which ACOG states should occur no later than 12 weeks after birth).

Clinical diagnosis of PPD is based on Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) criteria for Major Depressive Disorder (MDD) with peripartum onset. Criteria include five or more depressive symptoms present for ≥ 2 weeks, for most of nearly every day and cause clinically significant distress or impairment in social, occupational, or other important areas of function. The duration of the peripartum or postpartum period varies among references. The DSM-5 defines MDD with peripartum onset as an episode of major depression with onset during pregnancy or within four weeks of delivery. The ACOG define perinatal depression to include major and minor depressive episodes that occur during pregnancy or in the first 12 months after delivery. Treatment of PPD depends on the severity of depressive symptoms and includes psychotherapy and/or antidepressant medication. Selective serotonin reuptake inhibitors (SSRIs) are typically the drugs of choice. Sertraline is often recommended as first-line therapy because it passes minimally through breast milk. In patients with more severe symptoms, additional drug therapy (e.g., benzodiazepines, adjunctive antipsychotic agents) may be needed to treat severe anxiety or depression with psychotic features. For patients with suicidal intent or psychosis, hospitalization may be required. Electroconvulsive therapy (ECT) may be appropriate in some situations due to its more immediate effect.

The efficacy and safety of zuranolone (Zurzuvae) for the treatment of PPD in adults was evaluated in two randomized, placebo-controlled, double-blind, multicenter studies [Study 1 (Skylark) and Study 2 (Robin)] in women with PPD who met the criteria for a major depressive episode (DSM-5) with onset of symptoms in the third trimester or within 4 weeks of delivery. In these studies, concomitant use of existing oral antidepressants was allowed for patients taking a stable dose of oral antidepressant for at least 30 days before baseline. These studies included patients with 17-item Hamilton depression rating scale (HAMD-17) scores greater than or equal to 26 at baseline. In Study 1, patients received 50 mg of zuranolone (N=98) or placebo (N=97) once daily in the evening with fat-containing food for 14 days, with the option to reduce the dosage based on tolerability to 40 mg once daily for those receiving zuranolone. In Study 2, patients received a zuranolone capsule (formulation similar to 40 mg of commercial zuranolone) (N=76) or placebo (N=74) once daily in the evening with food for 14 days. The baseline demographics of the patients were similar between the treatment and placebo groups in both studies. In Study 1, patients had a mean age of 30 years (range: 19-44 years); were 70% Caucasian, 22% African American, 1% Asian, and 7% were other races; and 38% were of Hispanic or Latino ethnicity. Baseline use of stable oral antidepressants was reported in 15% of patients. In Study 2, patients had a mean age of 28 years (range: 18-44 years); were 56% Caucasian, 41% African American, 1% Asian, and 2% were other races; and 23% were of Hispanic or Latino ethnicity. Baseline use of stable oral antidepressants was reported in 19% of patients. In both studies, patients were followed for a minimum of 4 weeks after the treatment course with a primary endpoint of change from baseline in depressive symptoms as measured by the HAMD-17 total score at Day 15. The results are included in Table 1, which demonstrated a statistical difference in the change in HAMD-17 scores from baseline.

Table 1: Change from Baseline in the HAMD-17 Total Score at Day 15

Study	Treatment Group	N	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo subtracted Difference (95% CI)
1 (Skylark)	Zuranolone 50 mg	98	28.6 (2.49)	-15.6 (0.82)	-4.0 (-6.3, -1.7)
	Placebo	97	28.8 (2.34)	-11.6 (0.82)	
2 (Robin)	Zuranolone 40 mg equivalent	76	28.4 (2.09)	-17.8 (1.04)	-4.2 (-6.9, -1.5)
	Placebo	74	28.8 (2.32)	-13.6 (1.07)	

SD=standard deviation; LS=least squares; SE=standard error; CI=confidence interval

The most common adverse reactions associated with zuranolone (Zurzuvae) therapy were somnolence, dizziness, diarrhea, fatigue, nasopharyngitis, and urinary tract infection. The manufacturer provides guidance on dosage reduction for certain adverse reactions such as CNS depressant effects.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of zuranolone (Zurzuvae) **meets the definition of medical necessity** when **ALL** of the following are met ("1" to "7"):

1. Member is 18 years of age or older
2. Member has a confirmed diagnosis of moderate or severe postpartum depression, defined as having a major depressive episode that began no earlier than the third trimester and no later

than the first 4 weeks following delivery – the date (or approximate time frame) of the onset of the major depressive episode must be provided

3. Treatment will be initiated no later than 1 year following the member's delivery date – the member's child's date of birth must be provided
4. Member has **NOT** previously received zuranolone or brexanolone following their most recent childbirth
5. The medication will not be prescribed concomitantly with a CYP3A inducer (e.g., rifampin, carbamazepine, St. John's Wort)
6. Prescribed by, or in consultation with, a psychiatrist
7. The dose does not exceed 50 mg once daily for 14 days

Approval duration: 30 days (to allow for a single treatment course)

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Zuranolone (Zurzuvae) is a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator indicated for the treatment of postpartum depression (PPD) in adults, and it can be used alone or as an adjunct to oral antidepressant therapy.
- The recommended dosage is 50 mg orally once daily in the evening with fat-containing food for 14 days.
- Zuranolone (Zurzuvae) has abuse potential with associated risks of misuse, abuse, and substance use disorder including addiction, and it is associated with the potential for physical dependence. It is classified as a schedule IV controlled substance.

Dose Adjustments

- If CNS depressant effects occur, the zuranolone (Zurzuvae) dosage may be reduced to 40 mg once daily.
- No dosage adjustment for zuranolone (Zurzuvae) is needed for mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. However, for severe hepatic impairment (Child-Pugh C) the dosage should be reduced to 30 mg orally once daily.
- No dosage adjustment for zuranolone (Zurzuvae) is needed for mild renal impairment (eGFR 60 to 89 mL/min/1.73 m^2). However, for moderate or severe renal impairment (eGFR < 60 mL/min/1.73 m^2) the dosage should be reduced to 30 mg orally once daily.
- Concomitant administration of zuranolone (Zurzuvae) with CYP3A4 inducers should be avoided, as it reduces zuranolone concentrations. No dosage modification is recommended when zuranolone (Zurzuvae) is concomitantly used with a moderate CYP3A4 inhibitor. However, if zuranolone (Zurzuvae) is administered with a strong CYP3A4 inhibitor, the dosage should be reduced to 30 mg orally once daily.

Drug Availability

- Zuranolone (Zurzuvae) capsules
  - 20 mg (NDC 64406-029-01 for bottle of 14)
  - 25 mg (NDC 64406-030-01 for bottle of 14; NDC 64406-030-02 for blister pack of 28)
  - 30 mg (NDC 64406-031-01 for bottle of 14)

PRECAUTIONS:

Boxed Warning

- Zuranolone (Zurzuvae) causes driving impairment 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 zuranolone (Zurzuvae) administration for the duration of the 14-day treatment course. Inform patients that they may not be able to assess their own driving competence, or the degree of driving impairment caused by zuranolone (Zurzuvae)

Contraindications

- None

Precautions/Warnings

- **CNS Depressant Effects:** Zuranolone (Zurzuvae) can cause CNS depressant effects such as somnolence and confusion and may increase a patient's risk of falls. Other CNS depressants such as alcohol, benzodiazepines, opioids, tricyclic antidepressants, or drugs that increase zuranolone concentration, may increase impairment of psychomotor performance or CNS depressant effects such as somnolence, cognitive impairment, and the risk of respiratory depression. If patients develop CNS depression, consider dosage reduction or discontinuation of zuranolone (Zurzuvae).
- **Suicidal Thoughts and Behavior:** Consider changing the therapeutic regimen, including discontinuing zuranolone (Zurzuvae), in patients whose PPD worsens, or who experience emergent suicidal thoughts and behaviors.
- **Embryo-fetal Toxicity:** Based on findings from animal studies, zuranolone (Zurzuvae) may cause fetal harm when administered during pregnancy. In rat studies following exposure during gestation or throughout gestation and lactation, adverse effects on development (fetal malformations, embryofetal and offspring mortality, growth deficits) were observed. In addition, neuronal death was observed in rats exposed to zuranolone during a period of brain development that in humans begins during the third trimester of pregnancy and continues during the first few years after birth. Inform patients of the potential risk to an infant exposed to zuranolone (Zurzuvae) in utero and advise females of reproductive potential to use effective contraception during treatment with zuranolone (Zurzuvae) and for one week after the final dose.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, not otherwise specified

ICD-10 Diagnosis Codes That Support Medical Necessity

F53.0	Postpartum depression

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

1. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2024. URL www.clinicalpharmacilogy-ip.com Accessed 1/31/24.
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3. Micromedex Healthcare Series [Internet Database]. Greenwood Village, CO: Thomson Healthcare. Updated periodically. Accessed 1/31/24.
4. Deligiannidis KM, Meltzer-Brody S, Maximos B, et al. Zuranolone for the Treatment of Postpartum Depression. Am J Psychiatry. 2023;180(9):668-675. doi: 10.1176/appi.ajp.20220785.
5. Deligiannidis KM, Meltzer-Brody S, Gunduz-Bruce H, et al. Effect of Zuranolone vs Placebo in Postpartum Depression: A Randomized Clinical Trial [published correction appears in JAMA

Psychiatry. 2022 Jul 1;79(7):740] [published correction appears in JAMA Psychiatry. 2023 Feb 1;80(2):191]. JAMA Psychiatry. 2021;78(9):951-959. doi:10.1001/jamapsychiatry.2021.1559.

6. Zurzuvae (zuranolone) oral capsules [package insert]. Biogen, Inc., Cambridge (MA): November 2023.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 02/14/24.

GUIDELINE UPDATE INFORMATION:

04/1/24	New Medical Coverage Guideline – Zuranolone (Zurzuvae) oral capsules for the treatment of moderate to severe postpartum depression in adults.