**Zuranolone (Zurzuvae®)**
FDA approved August 2023, Biogen Inc. & Sage Therapeutics Inc.
(Controlled Substance Schedule: Pending FDA review)

**Indication**: Zuranolone is indicated for the treatment of postpartum depression (PPD) in adults.

**Mechanism of Action**: Zuranolone, a neuroactive steroid is an allosteric positive modulator of GABA-A receptors. GABA may play a key role in modulating vulnerability to PPD, however, the mechanism by which zuranolone exerts its antidepressant effect is not fully understood.

| | Brexanolone | Zuranolone |
|---|---|---|
| **Dosage** | • Continuous IV infusion over 60 hours | • 50 mg PO QPM for 14 days. Reduce to 40 mg QPM if CNS depressant effects occur |
| **Administration** | • A healthcare provider must be available to monitor clt during infusion | • Administer with fat-containing food |
| **Renal impairment** | • No dosage adjustments required.<br>• Avoid use in clts with eGFR < 15 mL/min/1.73 $m^2$ due to potential accumulation | • 30 mg QPM in moderate or severe impairment |
| **Hepatic impairment** | • No dosage adjustment needed | • 30 mg QPM in severe impairment |
| **How Supplied** | • 100 mg/20 mL single-dose vial | • 20 mg, 25 mg, & 30 mg capsules |
| **Pregnancy Considerations** | • Use in pregnancy may cause fetal harm (based on animal studies of other drugs that enhance GABAergic inhibition) | • May harm fetus, animal studies show risk. Advise pregnant women / females who may become pregnant. Use contraception during treatment & one-week post-final dose |
| **Lactation** | • Brexanolone is transferred to breastmilk, however infant exposure is expected to be low (low oral bioavailability) | • Zuranolone found in low levels in breastmilk; unknown effects on breastfed infant & milk production |

## Drug Drug Interactions

| Concomitant Medication | Brexanolone | Zuranolone |
|---|---|---|
| CNS depressants | Additive effects, may increase r/o sedation | May worsen psychomotor impairment / CNS depressant effects |
| Antidepressants | Higher incidence of sedation-related events | |
| Strong CYP3A4 Inhibitors | | Increased r/o AEs. If unavoidable, reduce dose to 30 mg daily |
| CYP3A4 Inducers | | May decrease zuranolone efficacy. Avoid concomitant use |

## Adverse Effects

| | Brexanolone | Zuranolone |
|---|---|---|
| Most frequently reported AEs (≥5% & greater than placebo) | Sedation/somnolence, dry mouth, loss of consciousness, flushing/hot flush, dizziness, presyncope & vertigo | Somnolence, dizziness, diarrhea, fatigue, nasopharyngitis, & UTI |

## Warnings & Precautions

| | Brexanolone | Zuranolone |
|---|---|---|
| **BB warnings** | • Excessive sedation & sudden loss of consciousness<br>• Available through REMS | • Impaired ability to drive or engage in potentially hazardous activities due to CNS effects. Avoid driving or risky activities for 12 hours post-dose. Self-assessment of impairment may be unreliable |
| **Other warnings** | • Suicidal thoughts & behavior | • CNS Depressant Effects such as somnolence & confusion • Suicidal thoughts & behavior • Embryo-fetal toxicity |

**Pharmacokinetics**

| | Brexanolone | Zuranolone |
|---|---|---|
| **Metabolism** | extensively metabolized by non-CYP pathways via keto-reduction, glucuronidation, & sulfation | extensively metabolized mainly by CYP3A4 |
| **Half-life** | 9 hours | ~ 19.7 to 24.6 hours |
| **Steady state** | - | 3 to 5 days |
| **Excretion** | 47% feces, 42% urine | 41% feces, 45% urine |
| **Tmax** | - | 5 to 6 hours |
| **Effect of food** | N/A | • low-fat meal (400 to 500 calories, 25% fat) increases Cmax 3.5-fold • high-fat meal (800 to 1,000 calories, 50% fat) increases Cmax 4.3-fold • Tmax unaffected |

**Clinical Trials**

- Studies involved: Study 1, Study 2, ROBIN study (double-blind, randomized, placebo-controlled)
- Participants: Women with PPD, symptoms starting in the 3rd trimester or within 4 weeks of delivery
- Treatment Duration: 14 days, with at least 4-week follow-up
- Concomitant Medication: Allowed if on stable oral antidepressant dose for at least 30 days before baseline.
- Primary Endpoint: Change in the Hamilton Rating Scale for Depression (HAMD-17) scores at Day 15
    - Study 1 (SKYLARK)
    - Participants: 200 women with severe PPD (baseline HAMD-17 score of ≥26; ~22% Black or African American & 38% Hispanic or Latina)
      Treatment: Zuranolone 50 mg
      Mean Change: -15.6 (zuranolone) vs. -11.6 (placebo). Placebo-subtracted difference: -4.0
    - Study 2
      Treatment: Zuranolone ~40 mg
      Mean change: -17.8 (zuranolone) vs. -13.6 (placebo). Placebo-subtracted difference: -4.2
    - ROBIN study
      Women aged 18-45 with severe PPD received 30 mg zuranolone or placebo for 14 days, with follow-up until day 45
        - Zuranolone significantly improved both depression & anxiety symptoms at days 3, 15, and 45 compared to placebo ($P < .05$)
        - Zuranolone was associated with sustained improvements in both depression & anxiety symptoms, as observed on days 15 & 45. Also showed potential benefits in reducing insomnia & enhancing overall functional health

- Key Findings
    - Statistically significant improvement in symptoms compared to placebo after 14 days of treatment. The treatment effect was maintained 4-weeks after the final dose of zuranolone
    - SKYLARK: Significant reduction in depressive symptoms noticed as early as day 3 & sustained through Day 45
    - ROBIN: Significant improvement in both depression & anxiety symptoms.
    - Safety Profile
        - Generally well-tolerated. Common side effects in patients treated with zuranolone 50 mg: Somnolence, dizziness, diarrhea, fatigue, & UTI
    - Clinical implications, limitations and considerations
        - Effective in improving PPD & anxiety symptoms. May be particularly useful for women with concurrent anxiety and/or insomnia

        - Antidepressant effects significant and sustained
        - HAMD-17, a standard but subjective measure in antidepressant trials
        - Only women with onset of major depressive episode in the 3rd trimester or within 4 weeks postpartum were included
        - Many patients were on oral antidepressants, which could affect results
        - Results may not be generalizable due to strict inclusion/exclusion criteria
        - Brief study duration limits sensitivity for calculating delayed AEs, and small sample size for calculating uncommon AEs & subpopulation effects
        - Unknown effect past 45 days or need for maintenance therapy for full remission

**Role in Therapy**

- The first FDA-approved once-daily oral treatment for PPD
    - offers relatively short 14-day treatment course
    - while traditional antidepressants are effective for PPD, zuranolone offers faster symptom relief, showing effects much earlier than the typical 2-4 weeks
    - durability of antidepressant effects remains uncertain, but trials report relief lasting up to 45 days
- Appears to offer novel approach by targeting not just depressive symptoms but also comorbid conditions like anxiety & insomnia
    - synthetic version of allopregnanolone, a neurosteroid linked to mood regulation. PPD may be tied to sensitivity to hormonal fluctuations, including a drop in allopregnanolone levels. May stabilize mood by replenishing depleted neurosteroid
    - novel mechanism of action as a GABA-A receptor agonist
- Safety Profile
    - Generally well-tolerated in clinical trials. Most common AEs include headache, dizziness, & sedation
    - Breastfeeding
        - Not tested on breastfeeding women. Pumping milk in advance could be an option. Some SSRIs are known to be breastfeeding-safe
        - Lack of data could be a deterrent, as clinical trial participants were asked to avoid breastfeeding
    - Warnings include possible suicidal thoughts & behavior, sleepiness & confusion, potential for fetal harm (use effective contraception), and a black box warning that patients should not drive or engage in potentially hazardous activities for at least 12 hours after taking the medication
    - Potential for abuse; scheduling as a controlled substance by DEA anticipated within 90 days (Brexanolone has Schedule IV designation)
- Duration and Relapse
    - Unclear if the benefits extend beyond 30 days post-treatment. Traditional antidepressants often require 6-12 months of continued treatment to prevent relapse
- FDA issued a Complete Response Letter for Zuranolone's NDA for treating MDD
    - insufficient evidence to support effectiveness in treating MDD (additional studies required), also concern re suicidal ideations & behaviors
    - Uncertain future for zuranolone in MDD benefits Axsome Therapeutics' Auvelity, the first approved oral, fast-acting antidepressant
- Other treatment options for PPD
    - Mild to moderate PPD: Individual/group psychotherapy, psychosocial support
        - Mild to moderate unipolar major depression

- Antidepressants (eg, SSRI, SNRI & mirtazapine) are considered a reasonable alternative if psychotherapy is not an option or if the clt has previously responded to antidepressants
- Pharmacotherapy & psychotherapy combination treatment is useful for some clients

- Moderate to severe PPD: Psychotherapy in combination with medication
  - Off-label medication options include SSRIs, SNRIs, ER/SR bupropion, and nortriptyline
  - Undetectable levels of sertraline, paroxetine, and nortriptyline in nursing infants
- Severe PPD: Hospitalization, treatment with adjunctive medications, and ECT
  - For treatment-resistant pts, UpToDate suggests brexanolone or ECT
  - Breastfeeding patients
    - SSRIs are generally considered safe for breastfeeding moms, as drug levels in infants are often undetectable & toxicity is rare
    - A review of 34 studies on SSRI use in breastfeeding found that paroxetine & sertraline generally resulted in undetectable levels in infants, while fluoxetine was more likely to accumulate. Infants with elevated serum levels were most common in those exposed to fluoxetine and citalopram, however, the data do not suggest switching SSRIs for pts already responding well to these meds.
    - Paroxetine & sertraline use for breastfeeding women starting antidepressants is in line with guidance from the U.S. National Library of Medicine's LactMed database
    - Fluvoxamine has fewer studies in nursing infants compared to other SSRIs but data suggest it may be safe for breastfeeding.
  - SNRIs - Venlafaxine and desvenlafaxine appear safe based on observational studies and the absence of adverse events in infants. However, they may expose infants more than some other antidepressants. Duloxetine may be compatible with breastfeeding, but the safety evidence is limited
  - Mirtazapine may be compatible with breastfeeding, although fewer studies are available compared to SSRIs and SNRIs
  - Bupropion's compatibility with breastfeeding is unclear due to limited studies & potential seizure risk
  - TCAs – nortriptyline is preferable for lactating women starting treatment with a TCA due to its safety record
- Antidepressant monotherapy is usually preferred over an antidepressant plus benzo for pts with anxiety or insomnia
  - Brexanolone (BRX) has shown efficacy for anxiety & insomnia compared to placebo
- Non-breastfeeding patients seeking quick relief - Brexanolone or standard treatments for severe depression, if brexanolone is not an option
- Brexanolone’s comparative efficacy with other antidepressants
  - In a 2022 study, O. Vasiliu found that SSRIs are the most evidence-based pharmacological treatments for PPD. Sertraline led in clinical trial support, followed by escitalopram/citalopram and fluoxetine. Additional supported antidepressants include venlafaxine, desvenlafaxine, nortriptyline, and bupropion. A maintenance treatment of 6-12 months is considered optimal for women at low risk of recurrence following remission. The study concluded that SSRIs are the most supported by evidence, and BRX is a promising new drug

- Findings from a meta-analysis show that only estradiol and brexanolone were significantly more effective than a placebo in treating PPD. According to the Surface Under the Cumulative Ranking Curve, estradiol was the most effective, followed by paroxetine and zuranolone. However, brexanolone was associated with higher dropout rates, indicating it may not be as well-tolerated compared to other studied antidepressants.
- A study funded by Sage Therapeutics evaluated the cost-effectiveness of brexanolone versus SSRIs and concluded that BRX is a cost-effective option for treating PPD. Despite higher initial costs, the study found BRX to be cost-effective over an 11-year period when considering quality-adjusted life years.
- Future Research
    - Need to determine long-term effects, including the necessity for booster doses or maintenance therapy
    - Effects on domain-specific outcomes like anhedonia, circadian rhythm, and arousal systems
    - Potential application in other conditions such as bipolar depression
    - Longer term data needed to assess the risk of relapse

**Comparison of Brexanolone and Zuranolone**

- both brexanolone & zuranolone are neuroactive steroids with novel antidepressant mechanisms as positive allosteric modulators of GABA-A receptors
- Brexanolone approved in 2019, shows rapid response achieving remission within 24-48 hours, making it appealing for severe PPD cases. It, however, requires 60-hour hospital stay for IV infusion, has risks like loss of consciousness, & costs ~$34,000
    - Low utilization due to long IV infusion, REMS requirements, and continuous monitoring due to sedation risks
- Zuranolone is an oral improvement over brexanolone, featuring ~22 hour half-life versus brexanolone's 9 hours
    - Offers rapid relief & does not require 60-hour IV infusion, making it potentially more convenient & accessible
    - Taking a pill for 2 weeks is easier and doesn't require leaving the baby for several days
    - Viewed as a potentially significant alternative, especially if more affordable than the IV option. However, women with a history of responding well to other meds may prefer sticking to those
    - OB-GYN or midwife could prescribe this treatment without the need for a psychiatric consultation?

**Potential Candidates**

- Zuranolone may be particularly beneficial for women with severe symptoms, suicidal ideation, or limited access to long-term psychiatric care, although more research is needed.
- Candidates deterred by the need for hospitalization or long-term therapy. Relatively faster onset & short two-week treatment may make it more appealing.
- candidates experiencing severe or ongoing, treatment-resistant PPD or suicidal ideation
- Zuranolone could serve as an adjunct or bridge med for some patients (~15-20% of clts continued other long-term antidepressants)

**Clinical Practice Guidelines**

- Organization: ACOG [13]
- Title: Treatment and Management of Mental Health Conditions During Pregnancy and Postpartum
- Date published: June 2023
- Critique Summary: Recommendations are based on evidence and/or expert opinion through a rigorous literature search and critique. The guidelines provide practical recommendations to guide physicians regarding the available treatment options for perinatal mental health treatment. Guidelines emphasize that treatment options must be individualized for patient-centered care.

| Review Element | | Issues that Affect Reliability of Guideline |
|---|---|---|
| **Funding Source** | • ACOG has neither solicited nor accepted any commercial involvement in the development of the content of these guidelines.<br>• All ACOG Committee members and authors disclosed their relationship and potential conflicts of interest with external entities, where the authors could financially benefit from the products mentioned in the guidelines. | None |
| **Patient Population Considered** | Patient population clearly described. Guidelines are meant for pregnant or postpartum individuals with mental health conditions with onset that may have predated the perinatal period or may have occurred for the first time in pregnancy or the first year postpartum or may have been exacerbated in that time. | None |
| **Systematic Methods Used to Search for Evidence** | Literature search was clearly described. Databases that were searched: Cochrane Library, Cochrane Collaboration Registry of Controlled Trials, EMBASE, PubMed, and MEDLINE. Parameters for the search included human-only studies published in English. Medications and pregnancy searches were limited to 2018-present; subpopulations and health equity searches were limited to 2000-present. An updated literature search was completed in December of 2022, and a final supplementary literature search was performed in February 2023. | None |
| **Criteria for Selecting Evidence and** | Recommendations are classified by strength and evidence quality. Ungraded Good Practice Points are included to provide guidance | None |

| | | |
|---|---|---|
| **Formulating Recommendations** | when a formal recommendation could not be made because of inadequate or nonexistent evidence.<br><br>**<u>Strength of Recommendation</u>**:<br><br>**STRONG**<br><br>• ACOG recommends: Benefits clearly outweigh harms and burdens. Most patients should receive the intervention<br>• ACOG recommends against: Harms and burdens clearly outweigh the benefits. Most patients should not receive the intervention.<br>**CONDITIONAL**<br><br>• ACOG suggests: The balance of benefits and risks will vary depending on patient characteristics and their values and preferences. Individualized, shared decision making is recommended to help patients decide on the best course of action for them.<br>**<u>Quality of Evidence</u>**<br><br>**HIGH**<br><br>• Randomized controlled trials, systematic reviews, and meta-analyses without serious methodologic flaws or limitations (e.g., inconsistency, imprecision, confounding variables).<br>• Very strong evidence from observational studies without serious methodologic flaws or limitations. There is high confidence in the accuracy of the findings and further research is unlikely to change this.<br>**MODERATE**<br><br>• Randomized controlled trials with some limitations. Strong evidence from observational studies without serious methodologic flaws or limitation.<br>**LOW**<br><br>• Randomized controlled trials with serious flaws. Some evidence from observational studies.<br>**VERY LOW**<br><br>• Unsystematic clinical observation. Very indirect evidence from observational studies. | |
| **Overview of Recommendations** | • ACOG recommends that psychotherapy be considered a first-line treatment for mild-to-moderate perinatal depression. **(STRONG RECOMMENDATION, MODERATE-QUALITY EVIDENCE)**<br><br>• ACOG recommends that selective serotonin reuptake inhibitors be used as first-line pharmacotherapy for perinatal depression. Serotonin-norepinephrine reuptake inhibitors are reasonable alternatives. Pharmacotherapy should be individualized based | Minor: Guidelines have not been updated to include Zurzuvae. |

| | | |
|---|---|---|
| | on prior response to therapy (if applicable). If there is no pharmacotherapy history, sertraline or escitalopram are reasonable first-line medications.<br>**(STRONG RECOMMENDATION, LOW-QUALITY EVIDENCE)**<br>• ACOG recommends consideration of brexanolone administration in the postpartum period for moderate-to-severe perinatal depression with onset in the third trimester or within 4 weeks postpartum. The decision to use brexanolone should balance the benefits (e.g., rapid onset of action) with the risks and challenges (e.g., limited access, high cost, lack of data supporting safety with breastfeeding, requirement for inpatient monitoring during the infusion, lack of efficacy data beyond 30 days).<br>**(STRONG RECOMMENDATION, MODERATE-QUALITY EVIDENCE)** | |

**Expert Opinion**

Comments from Lovella Diaz:

- If I were to prescribe it, it will be with an antidepressant medication like Zoloft as recommended by UCLA health. I would prescribe it only postpartum (not even the 3rd trimester of pregnancy) for 14 days. My understanding is that the benefits can begin as early as 3 days. The median response rate is 9 days. Notable peak effect a little over a week, lasting benefit of 45 days. However, through my experience, postpartum depression last on average for about a year.
- I envision prescribing the new drug along with SSRI. By the time Zurzuvae wears off the SSRI would kick in. It's a promising pill in combination with other treatment modalities. I would let pt know that currently there are no studies on its effect on breastmilk.
- I foresee many of my patient buy into this if the benefit effect is seen as early as 3 days. The compliance of taking medication would increase. If patients are reluctant due to no data on breastfeeding, I can tell them to pump breastmilk for 14 days and resume breastfeeding after 14 days. If it is too much of a hassle, or not important to them, they have the option to stop breastfeeding and take the medicine.
- I would not prescribe this medication if I suspect any form of bipolar d/o, or substance use mood d/o.
- I would start this medication first week after they deliver.
- Referral from SMMH uses only Edinburg Postnatal Depression Scale (EPDS) scores:
- Mild depression (7–13), Moderate depression (14–19), Severe depression (19–30). Mothers scoring above 12 or 13 are likely to suffer from depression and should seek medical attention.
- Question 10 on the EPDS tool addresses suicidal ideation. If a patient scores higher than zero, referrals and immediate assessment needs to be implemented. EPDS is a screening tool and should never override clinical judgment.

**Cost Comparison**

| Drug and Manufacturer | Dosage Forms & Strengths | Dosing Regimen | Cost per Treatment Cycle |
|---|---|---|---|
| Zurzuvae (zuranolone)<br><br>*[Biogen Inc.]* | • Oral capsules: 20 mg, 25 mg, and 30 mg | • 50 mg (2 x 25 mg capsules) orally once daily in the evening for 14 days.<br>• If patients experience CNS depressant effects within the 14 days period, consider reducing the dosage to 40 mg once daily in the evening within the 14 day period.<br>• Administer with fat-containing food (e.g., 400 to 1,000 calories, 25% to 50% fat).<br>• The safety and effectiveness of Zurzuvae use beyond 14 days in a single treatment course have not been established. | $15,900 for<br><br>2x25mg or 2x20mg |
| Zulresso (brexanolone)<br><br>*[Sage Therapeutics, Inc.]* | • Single-dose vial: 100 mg/20 mL (5 mg/mL) | Intravenous (IV) infusion over a total of 60 hours (2.5 days) as follows:<br><br>• 0 to 4 hours: Initiate at 30 mcg/kg/hour<br>• 4 to 24 hours: Increase dosage to 60 mcg/kg/hour<br>• 24 to 52 hours: Increase dosage to 90 mcg/kg/hour (a reduction to 60 mcg/kg/hour may be considered for patients who do not tolerate 90 mcg/kg/hour)<br>• 52 to 56 hours: Decrease dosage to 60 mcg/kg/hour<br>• 56 to 60 hours; Decrease dosage to 30 mcg/kg/hour | $44,700.00 |

[a] Estimated cost based on AWP for brands per Medispan as of 01/15/2023 for one cycle of medication consisting of 14 days of Zurzuvae and 60 hours of Zulresso, as detailed in the prescribing information.

**Formulary Recommendation**

*For reference: Zulresso (Brexanolone) Prior Authorization*

- *Exclusion Criteria: Use in patients who are pregnant or have active psychosis, history of schizophrenia, bipolar disorder, or schizoaffective disorder.*
- *Required Medical Information: Documentation of ALL the following:*
  1) *diagnosis of severe postpartum depression confirmed by a rating scale such as Montgomery-Asberg depression rating scale (MADRS) with a score of greater than 34 or the Hamilton Rating Scale for Depression (HAM-D) with a score of greater than 25 or PHQ-9 with a score of greater than 20 performed by a psychiatrist,*
  2) *trial and failure (i.e., inadequate response) of or intolerance to antidepressant therapies*
  3) *therapeutic failure with ECT or not a candidate for ECT, and*
  4) *patient meets DSM-V diagnosis of PPD within 6 months postpartum at screening with a major depressive episode with onset no earlier than the third trimester and no later than 4 weeks after delivery.*
- *Age Restrictions: 18 years of age or older.*
- *Prescriber Restrictions: Prescribed by, or in consultation with, a psychiatrist, obstetrician, or gynecologist.*
- *Coverage Duration: 30 days*
- *Other Criteria: Must be administered in a facility that is enrolled in the Zulresso REMS program.*

**Zurzuvae (Zuranolone) is a CMS protected class, need to add to CA formulary with PA criteria**

**BHRS & HealthWorx: nonformulary**

**PA criteria**

- Exclusion Criteria: Use in patients who are pregnant or have active psychosis, history of schizophrenia, bipolar disorder, or schizoaffective disorder.
- Required Medical Information: Documentation of ALL the following:
  1. diagnosis of severe postpartum depression confirmed by a rating scale such as Montgomery-Asberg depression rating scale (MADRS) with a score of greater than 34 or the Hamilton Rating Scale for Depression (HAM-D) with a score of greater than 25 or PHQ-9 with a score of greater than 20, or Edinburg Postnatal Depression Scale (EPDS) of 19 or greater
  2. trial and failure (i.e., inadequate response) of or intolerance to antidepressant therapies
  3. patient meets DSM-V diagnosis of PPD within 6 months postpartum at screening with a major depressive episode with onset no earlier than the third trimester and no later than 4 weeks after delivery.
- Age Restrictions: 18 years of age or older.
- Prescriber Restrictions: Prescribed by, or in consultation with, a psychiatrist, obstetrician, or gynecologist.
- Quantity Limit:
  - 28 capsules of 20 mg per 365 days
  - 28 capsules of 25 mg per 365 days
  - 14 capsules of 30 mg per 365 days

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