zuranolone (Zurzuvae™)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO285

Description

Zuranolone (Zurzuvae) is an orally administered neuroactive steroid $GABA_A$ receptor positive allosteric modulator.

Length of Authorization

I. Initial: One time fill
- Renewal: No renewal

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
zuranolone (Zurzuvae)	Postpartum depression	20mg capsule	28 capsules/14 days
		25mg capsule	
		30mg capsule	14 capsules/14 days

Initial Evaluation

I. **Zuranolone (Zurzuvae)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. A diagnosis of **Postpartum Depression** when the following are met:
      1. Member has moderate to severe depressive symptoms as demonstrated by an objective measurement scale score consistent with severe designation (e.g., HAMD-17, MADRS, PHQ-9, etc.); **AND**
      2. Member experienced onset of depressive symptoms during the third trimester of pregnancy OR within the first four weeks after delivery; **AND**
      3. Request is within 12 months of delivery; **AND**
      4. Member has discontinued breastfeeding; **OR**
         i. Member has agreed to temporarily hold breastfeeding for course of therapy and one week following; **AND**
      5. Treatment with at least one SSRI (e.g., citalopram [Celexa], escitalopram [Lexapro], fluoxetine [Prozac], sertraline [Zoloft], etc.) OR SNRI (e.g., duloxetine [Cymbalta], desvenlafaxine succinate [Pristiq], venlafaxine [Effexor], etc.) has been ineffective, contraindicated, or not tolerated.

II. Zuranolone (Zurzuvae) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Major Depressive Disorder (MDD)

III. Zuranolone (Zurzuvae) is considered investigational when used for all other conditions, including but not limited to:
   A. Use in the pediatric population
   B. Depressive episodes in bipolar II disorder
   C. Episodic treatment of MDD and/or PPD
   D. Treatment resistant depression
   E. Other psychiatric disorders

Renewal Evaluation

I. Zuranolone (Zurzuvae) is not eligible for renewal.

Supporting Evidence

I. The safety and efficacy of zuranolone (Zurzuvae) was evaluated in a total of five phase 3 randomized, double-blind, placebo-controlled trials that made up two clinical programs. The LANDSCAPE clinical program (MOUNTAIN, WATERFALL, CORAL) focused on major depressive disorder (MDD), while the NEST clinical program (ROBIN, SKYLARK) focused on postpartum depression (PPD). As of February 2025, the FDA has only approved zuranolone (Zurzuvae) for treatment of PPD.

II. Zuranolone (Zurzuvae) was studied in adult patients aged 18 and older and has not been evaluated for safety and/or efficacy in pediatric patients.

III. **PPD**

- The SKYLARK trial was a randomized, double-blind, placebo-controlled trial that evaluated the safety and efficacy of a single 14-day course of zuranolone 50mg compared to placebo in adult women with severe postpartum depression, as evidenced by a baseline HAMD-17 score of at least 26, who had onset of depressive symptoms during the third trimester or first four weeks after delivery. All patients were required to be within 12 months postpartum. The primary efficacy endpoint was change from baseline in HAMD-17 score at day 15, which was met (LS means, -15.6 (0.80) vs. -11.6 (0.89), p=0.007).
- Patients who were actively breastfeeding were excluded from participation in the clinical trials. To be included, patients were required to have either completely ceased breastfeeding or agreed not to provide breastmilk to their infant(s) from just prior to receiving the study drug on day one of the trial period until seven days after the last dose of the study drug. Data from a Phase 1, single-center, open-label study conducted in healthy, lactating adult females that was designed to evaluate the

pharmacokinetics and safety of zuranolone (Zurzuvae) demonstrated that the estimated relative infant dose (RID), calculated as the infant dose divided by the maternal dose, was 0.357% on day 5 and the estimated daily infant dose was 0.00124 mg/kg/day. The estimated mean RID was consistent with a low fraction of unbound zuranolone (Zurzuvae) in plasma (≤0.52%). Maternal milk production decreased by 8.3% (41.2 [140.11] mL) in volume collected at day five compared to baseline. Investigators noted that the interpretation of the effect of zuranolone (Zurzuvae) on milk production is limited due to variability inter-patient milk production at baseline, lack of placebo control, and the small sample size (N=15).

IV. The majority of TEAEs observed throughout the clinical program were considered mild or moderate in severity, with serious adverse events (SEAs) occurring in <2% of zuranolone (Zurzuvae) treated patients. Across the clinical program, there was no observed increase in incidence of suicidal ideation. The most common TEAEs (>5%) include headache, somnolence, dizziness, nausea, sedation, fatigue, and diarrhea.

V. For treatment of PPD, the American Academy of Family Physicians (AAFP) and National Institute for Health (NIH) recommend psychotherapy alone for mild-to-moderate PPD and pharmacologic treatment with select SSRIs and SNRIs for moderate-to-severe PPD. The antidepressants recommended for PPD include citalopram, escitalopram, fluoxetine, paroxetine, sertraline, desvenlafaxine, duloxetine, venlafaxine, and bupropion. While these antidepressants generally provide some symptom improvement within the first week of use, full therapeutic effects may not be realized until 4-6 weeks after initiation. Given that zuranolone (Zurzuvae) demonstrated symptom improvement as early as 2-days after first dose and clinically meaningful improvement by day 15 in clinical trials, an exception may be considered in cases of severe PPD where faster onset of action is clinically warranted.

- Brexanolone (Zulresso) is an IV-administered neuroactive steroid GABAA receptor positive allosteric modulator that FDA-approved in the setting of PPD. This 60-hour continuous infusion is currently recommended by UpToDate for patients with severe PPD who prioritize fast onset of action and should be followed by a guideline-recommended SSRI or SNRI as maintenance therapy. As of July 2023, guidelines have not been updated to include brexanolone (Zulresso) or zuranolone (Zurzuvae), so there is minimal insight as to the appropriate use of zuranolone (Zurzuvae) following prior treatment with brexanolone (Zulresso) in the current or previous episode of PPD.

Investigational or Not Medically Necessary Uses

I. Zuranolone (Zurzuvae) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Major Depressive Disorder

i. The safety and efficacy of zuranolone (Zurzuvae) in the setting of adult patients with severe MDD was evaluated in the LANDSCAPE clinical program, which is made up of three clinical trials: the MOUNTAIN, WATERFALL, and CORAL clinical trials. The MOUNTAIN and WATERFALL clinical trials evaluated zuranolone (Zuzuvae) as either monotherapy or adjunct to antidepressant therapy, as long as they were established on therapy on a stable antidepressant dose for at least 60 days prior to baseline. The CORAL clinical trial evaluated zuranolone (Zurzuvae) when co-initiated with standard of care antidepressant therapy. The primary endpoint in all trials was the change from baseline (CFB) in the baseline Hamilton Depression Rating Scale (HAMD-17) at day 15, with the exception of the CORAL trail which evaluated this endpoint at day 3. The primary endpoint was statistically significant in favor of zuranolone (Zurzuvae) in the WATERFALL (least square mean [LSM] change, -14.1 [SE=0.5] vs. -12.3 [SE=0.5], p=0.01) and CORAL (LSM change, -8.9 vs. -7.0, p=0.004) clinical trials, but not the MOUNTAIN clinical trial.

ii. Although the results of the LANDSCAPE clinical program demonstrated statistically significant change from baseline in HAMD-17 scores, this did not correlate to a clinically meaningful change compared to placebo, defined as a difference of 4 or more points on the HAMD-17 scale. Due to a lack of clinically meaningful impact on depressive symptoms compared to placebo, the value of zuranolone (Zurzuvae) as compared to standard of care antidepressant therapy remains undefined at this time.

iii. On August 4, 2023, the FDA released a complete response letter (CRL) for the new drug application (NDA) for zuranolone (Zurzuvae) for the MDD indication. The CRL stated that the application did not provide substantial evidence of effectiveness to support approval of zuranolone (Zurzuvae) for the treatment of MDD, and that an additional study or studies will be needed. Given variable primary endpoint results and lack of clinically meaningful impact on depressive symptoms compared to placebo throughout the clinical program, treatment of MDD with zuranolone (Zurzuvae) is not medically necessary.

B. Use in the pediatric population

C. Depressive episodes in bipolar II disorder

D. Episodic treatment of MDD and/or PPD

i. As of August 2023, zuranolone (Zurzuvae) has only been approved as a single treatment course for treatment of PPD. Zuranolone (Zurzuvae) is also being evaluated in an ongoing, open-label, phase 3, observational trial evaluating the safety and tolerability of an initial course of zuranolone (Zurzuvae) 30mg or 50mg and the need for repeat courses in adults with MDD for up to 1 year. At the primary cutoff point in November 2021, zuranolone (Zurzuvae) appeared to generally well tolerated, with reported treatment emergent adverse events

(TEAEs) consistent with existing clinical trial data. Most patients in the zuranolone (Zurzuvae) 50mg cohort received one or two total treatment courses during the study period, up to one year (79.5% [116/146]), with median time to first repeat treatment course of 249 days. There are no studies currently underway to evaluate episodic treatment in PPD.

E. Treatment resistant depression
F. Other psychiatric disorders

References

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Related Policies

Policy Name	Disease state
esketamine (Spravato™) Policy	Treatment resistant depression (TRD) and Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior

Policy Implementation/Update:

Action and Summary of Changes	Date
Annual Review; Added criterion to allow coverage in moderate to severe depression, use within 12 months postpartum, and renewal evaluation	02/2025
Policy created	08/2023