Zuranolone (ZURZUVAE)
National Drug Monograph
March 2024

VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Zuranolone is a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator.

Indication(s) Under Review in This Document

- Zuranolone is a schedule IV medication indicated for the treatment of postpartum depression (PPD) in adults.

Dosage Form(s) Under Review

- Capsules: 20mg, 25mg, and 30 mg

Clinical Evidence Summary

Efficacy Considerations

- The efficacy of zuranolone (SAGE-217), supporting its FDA approval, was evaluated from industry-sponsored studies, including two randomized, placebo-controlled, double-blind, multicenter studies (Study 1, NCT04442503, Deligiannidis et al 2023 and Study 2, NCT02978326, Deligiannidis et a 2021l) in women with PPD who met Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for a major depressive episode.
- Participants were women aged 18-45 years, 6 months or fewer postpartum, with PPD (major depressive episode beginning in the third trimester or within 4 weeks of delivery), and a baseline 17-item Hamilton Rating Scale for Depression (HAM-D 17) score $\geq$ 26 (severe depression).
- Concomitant use of existing oral antidepressants was allowed for patients on a stable dose for at least 30 days before baseline (15% Study1; 19% in Study 2).
- Subjects received zuranolone (50mg Study 1; ~40mg Study 2) once daily in the evening with fat-containing food for 14 days. A low-fat meal (400-500 calories, 25% fat) increases Cmax 3.5-fold and AUC approximately 1.8-fold. A high-fat meal (800-1000 calories, 50% fat) increases Cmax 4.3-fold and AUC approximately 2-fold, compared to the fasted conditions.

- The primary endpoint for Studies 1 and 2 was the change from baseline in depressive symptoms as measured by the HAM-D 17 total score at day 15.
- Patients who received zuranolone experienced greater improvement in depression scores compared to patients in the placebo group (Table 2).

Table 1. Baseline Characteristics of Study Participants [1]

Characteristic	**Study 1**	**Study 2**
Age, years, mean (range)	30 (19-44)	28 (18-44)
Race/ethnicity, %		
White	70	56
Black	22	41
Asian	1	1
Hispanic	38	23
Other	7	2
Concomitant AD medication (%)	15	19

Table 2. Primary Endpoint – Change from baseline to Day 15 in the HAM-D 17 total score[1,4]

Study 1	**Zuranolone 50 mg (N=98)**	**Placebo (N=97)**
Baseline HAM-D, Mean (SD)	28.6 (2.49)	28.8 (2.34)
LS Mean change from Baseline (SE)	-15.6 (0.82)	-11.6 (0.82)
Adjusted mean difference vs placebo (95% CI)	**-4.0 (-6.3, -1.7)**	-
p-value vs. placebo	<0.05	-
Study 2	**Zuranolone ~40mg (n-76)**	**Placebo (N-74)**
Baseline HAM-D, Mean (SD)	28.4 (2.09)	28.8 (2.32)
LS Mean change from Baseline (SE)	-17.8 (1.04)	-13.6 (1.07)
Adjusted mean difference vs placebo (95% CI)	**-4.2 (-6.9, -1.5)**	-
p-value vs. placebo	=0.003	
Minimal clinically meaningful change in HAM-D 17	**4-6 points**	

HAM-D 17: Hamilton Depression Rating Scale; CI: confidence interval; LS: least squares; SD: standard deviation; SE: standard error

Safety Considerations

Boxed warning for impaired ability to drive or engage in other potentially hazardous activities.

- 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 zuranolone 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.

Zuranolone can cause CNS depressant effects, patients may be a higher risk of falls, impacting their ability to care for an infant or other children. Other CNS depressants (e.g., alcohol, benzodiazepines, opioids, tricyclic antidepressants), may increase impairment of psychomotor performance or CNS depressant effects such as somnolence, cognitive impairment, and the risk of respiratory depression.

Table 3. Adverse Reactions with ≥2% of participants (Study 1)[1]

	Zuranolone N=98 (%)	Placebo N=98 (%)
Somnolence	36	6
Dizziness	13	9
Diarrhea	6	2
Fatigue	5	2
UTI	5	4
Memory impairment	3	0
Abdominal pain	3	0
Tremor	2	0
Hypoesthesia	2	0
Muscle twitching	2	0
Myalgia	2	0
Anxiety	2	1

Table 4. Adverse Reactions in >2% of participants (Study 2)[1]

	Zuranolone N=78 (%)	Placebo N=73 (%)
Somnolence	19	11
Nasopharyngitis	9	3
Dizziness	8	6
Fatigue	5	1
Diarrhea	5	3
Dry mouth	4	0
Sinus congestion	3	0
Toothache	3	0

Other warnings / precautions / drug interactions [1]

- Across PPD clinical studies at all doses studied (Studies 1 and 2), serious adverse reactions included confusional state (1%).
- May cause fetal harm when administer to a pregnant woman. Advise pregnant woman of the potential risk to an infant exposed to zuranolone in utero.
- Data from a clinical lactation study in 14 women indicate that zuranolone is present in low levels in human milk. There are no data on the effects of zuranolone on a breastfed infant and limited data on the effects on milk production
- Advise females of reproductive potential to use effective contraception during treatment with zuranolone and for one week after the final dose.
- Avoid concomitant use with CYP3A4 inducers.
- Zuranolone has dose-dependent abuse potential comparable to alprazolam.

Other Therapeutic Options

Table 5.

Drug	Formulary status	Clinical Guidance/ Indication	Other Considerations
Zuranolone	NF	PPD	Oral, 14 days
Brexanolone	NF	PPD	Injection, 60 hour in duration

Projected Place in Therapy

- PPD is a perinatal major depressive episode with an onset during pregnancy or within 4 weeks of delivery.[6] It can have serious effects on maternal-infant bond and later infant development.
- The prevalence of PPD in the United States is estimated at 12-13% of births.[7,8]
- Zuranolone is the second drug approved for PPD, but the first oral agent.
- Use is limited to a 14-day treatment course.
- Evidence from Studies 1 and 2 suggest that individuals with severe PPD may benefit from zuranolone. Zuranolone was only compared to placebo, not treatment as usual, making determination of step/place in therapy difficult. Further, the durability of its effect is unclear; current evidence suggests that usual care (oral antidepressant and/or evidence-based psychotherapy) will likely be needed for the maintenance management of PPD. The use of zuranolone must be weighed against other effective treatment options (e.g., interpersonal psychotherapy, cognitive-behavioral therapy, antidepressant medications) and the safety considerations for zuranolone.

References

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