Iowa Medicaid
IOWA HHS

PDL DRUG REVIEW

Proprietary Name: Zurzuvae®
Common Name: zuranolone
PDL Category: Antidepressants

Comparable Products	Preferred Drug List Status
SSRIs	Preferred
Zulresso	Medical

Pharmacology/Usage: Zuranolone, the active ingredient of Zurzuvae®, is a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator. The mechanism of action of zuranolone in the treatment of postpartum depression is not fully understood, but is thought to be related to its positive allosteric modulation of GABA-A receptors.

Zurzuvae® is a Schedule IV controlled substance under the Controlled Substances Act. Zuranolone has abuse potential with associated risks of misuse, abuse, and substance use disorder including addiction. Zurzuvae® may produce physical dependence.

Indication: For the treatment of postpartum depression (PPD) in adults.

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings from animal studies, Zurzuvae® may cause fetal harm. Advise pregnant women of the potential risk to a fetus. Available data on use in pregnant women from the clinical development program are not sufficient to assess for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Advise female patients of reproductive potential to use effective contraception during treatment with Zurzuvae® and for one week after the final dose. There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including Zurzuvae®, during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or visiting online at https://womensmentalhealth.org/research/pregnancyregistry/antidepressants. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Capsules: 20mg, 25mg, 30mg.

Recommended Dosage: Take 50mg PO QD in the evening for 14 days. Administer with fat-containing food (e.g., 400 to 1000 calories, 25% to 50% fat). If patients experience CNS depressant effects within the 14-day period, consider reducing the dosage to 40mg QD in the evening within the 14-day period. Zurzuvae® can be used alone or as an adjunct to oral antidepressant therapy. The safety and efficacy of use beyond 14 days in a single treatment course have not been established. If a Zurzuvae® evening dose is missed, take the next dose at the regular time the following evening. Do not take extra capsules on the same day to make up for the missed dose. Continue taking Zurzuvae® QD until the remainder of the 14-day treatment course is completed.

The recommended dosage in patients with mild or moderate hepatic impairment is the same as those in patients with normal hepatic function. The recommended dosage in patients with severe hepatic impairment is 30mg PO QD in the evening for 14 days. The recommended dosage in patients with mild renal impairment is the same as those in

patients with normal renal function. The recommended dosage in patients with moderate or severe renal impairment is 30mg PO QD in the evening for 14 days.

Drug Interactions: If use with another CNS depressant is unavoidable, consider dosage reduction. Caution should be used when Zurzuvae® is administered in combination with other CNS drugs or alcohol.

Reduce the Zurzuvae® dosage when used with a strong CYP3A4 inhibitor. Reduce the Zurzuvae® dosage to 30mg PO QD in the evening for 14 days when used concomitantly with a strong CYP3A4 inhibitor. Dosage modification is not recommended when Zurzuvae® is concomitantly used with a moderate CYP3A4 inhibitor.

Avoid the concomitant use of Zurzuvae® with CYP3A4 inducers.

Box Warning: This product has a box warning regarding impaired ability to drive or engage in other potentially hazardous activities. Zurzuvae® 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 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 Zurzuvae®.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Zurzuvae®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included somnolence (30%), dizziness (4%), diarrhea (4%), fatigue (3%), urinary tract infection (1%), memory impairment (3%), abdominal pain (3%), tremor (2%), hypoesthesia (2%), muscle twitching (2%), myalgia (2%), COVID-19 (2%), anxiety (1%), and rash (1%).

Zurzuvae® can cause CNS depressant effects such as somnolence and confusion. Because Zurzuvae® can cause CNS depressant effects, patients may be at higher risk of falls. To reduce the risk of CNS depressant effects and/or mitigate CNS depressant effects that occurs with Zurzuvae® treatment:

- If patients develop CNS depressants effects, consider dosage reduction or discontinuation of treatment.
- If use with another CNS depressant is unavoidable, consider dosage reduction.
- Reduce the Zurzuvae® dosage in patients taking strong CYP3A4 inhibitors.

In pooled analyses of placebo-controlled trials of chronically administered antidepressant drugs that included about 77,000 adults and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients aged 24 years and younger was greater than in placebo-treated patents. There was variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. Zurzuvae® does not directly affect monoaminergic systems. Consider changing the therapeutic regimen, including discontinuing Zurzuvae®, in patients whose depression becomes worse or who experience emergent suicidal thoughts and behaviors.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Biogen Inc.

Analysis: The efficacy of Zurzuvae® for the treatment of PPD in adults was demonstrated in two randomized, placebo-controlled, double-blind, multicenter studies (Study 1 and Study 2) that included women with PPD who met the DSM-5 criteria for a major depressive episode 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 HAMD-17 scores ≥26 at baseline.

In Study 1, patients received Zurzuvae® 50mg (N=98) or placebo (N=97) QD in the evening with fat-containing food for 14 days, with the option to reduce the dosage based on tolerability to 40mg QD of Zurzuvae® or placebo. The patients were followed for a minimum of 4 weeks after the 14-day treatment course.

In Study 2, patients received another zuranolone capsule formulation (approximately equivalent to 40mg of Zurzuvae®; N=76) or placebo (N=74) QD in the evening with food for 14 days. The patients were followed for a minimum of 4 weeks after the 14-day treatment course.

Baseline demographics were similar between treatment groups in both studies. In Study 1, patients had a mean age of 30 years (range 19 to 44), while 70% were white and 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 to 44), while 56% were white and baseline use of stable oral antidepressants was reported in 19% of patients.

The primary endpoint for both studies was the change from baseline in depressive symptoms as measured by the HAMD-17 total score at day 15. In these studies, patients in the Zurzuvae® groups experienced statistically significantly greater improvement on the primary endpoint compared to patients in the placebo group. Results are presented in the table below, which was adapted from the prescribing information.

Study number	Treatment group	N	Mean Baseline Score	LS mean change from baseline	Placebo-subtracted difference
1	50mg Zurzuvae®	98	28.6	-15.6	-4.0
	Placebo	97	28.8	-11.6	
2	Zuranolone * (another cap formulation)	76	28.4	-17.8	-4.2
	Placebo	74	28.8	-13.6	

*This capsule formulation of zuranolone is approximately equivalent to 40mg of Zurzuvae®.

Two randomized, double-blind, placebo- and active-controlled four-way crossover studies (Study 3 and Study 4) assessed the effects of nighttime Zurzuvae® administration on next-morning driving performance, 9 hours after dosing, using a computer-based driving simulation.

In Study 3, 50mg of Zurzuvae® was administered for six consecutive nights and on the seventh night a single dose of 50mg or 100mg (two times the recommended dose) was administered. The primary driving performance outcome measure was the change in Standard Deviation of Lateral Position (SDLP; a measure of driving impairment) in the Zurzuvae® group compared to the placebo group on days 2 and 8 (after a single dose and repeat doses, respectively).

This study included healthy participants (N=67), with a median age of 45 years (range from 22 to 81 years; 7 participants were ≥65 years of age). In addition, 38 were males and 88% were white. A single dose of Zurzuvae® 50mg caused statistically significant impairment in next-morning driving performance compared to placebo. Statistically significant effects on driving were also observed on day 8 following daily administration of 50mg Zurzuvae®. Administration of 100mg of Zurzuvae® on the final night increased impairment in driving ability. The exposure-response analysis for driving impairment in this study suggested that the projected mean placebo-adjusted SDLP at 12 hours post-dose would be less than the threshold associated with driving impairment.

In Study 4, 30mg of Zurzuvae® was administered for four consecutive nights and on the fifth night a single dose of 30mg or 60mg was administered. The primary driving performance outcome measure was the change in SDLP in the Zurzuvae® group compared to the placebo group on days 2 and 6 (after a single dose and repeat doses, respectively). This study included participants (N=60) with a median age of 41 years (range 22 to 62), while 60% were male and 90% were white.

A single 30mg dose of Zurzuvae® caused a statistically significant impairment in next-morning driving performance compared to placebo. The mean effect on driving performance was not statistically significantly different following 30mg of Zurzuvae® compared to placebo on day 6; however, driving ability was impaired in some participants taking

Zurzuvae®. Administration of 60mg of Zurzuvae® on the final night caused statistically significant impairment in next-morning driving performance compared to placebo.

Place in Therapy: Zurzuvae® is a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator indicated for the treatment of postpartum depression (PPD) in adults. This once daily in the evening dosing for 14 days should be administered with fat-containing food and can be used alone or as an adjunct to oral antidepressant therapy. Zurzuvae® does have a box warning regarding the impaired ability to drive or engage in other potentially hazardous activities. It causes driving impairment due to CNS depressant effects, and thus patients should be advised not to drive or engage in other potentially hazardous activities until at least 12 hours after Zurzuvae® administration for the duration of the 14-day treatment course.

The safety and efficacy of Zurzuvae® were assessed in 2 randomized, double-blind, placebo-controlled trials that included women with PPD who met criteria for a major depressive episode with onset of symptoms in the third trimester or within 4 weeks of delivery. Note that in Study 2, patients received another zuranolone capsule formulation (about equivalent to 40mg Zurzuvae®). The primary efficacy endpoint for each study was the change from baseline in depressive symptoms as measured by the HAMD-17 total score at day 15. Results suggested that patients in the Zurzuvae® groups experienced statistically significantly greater improvement on the primary endpoint compared to patients in the placebo group. Zurzuvae® is the first oral medication FDA approved for the treatment of PPD in adults, taken for 14 days. Note that the safety and efficacy of Zurzuvae® use beyond 14 days in a single treatment course have not been established.

There is no evidence at this time to support that Zurzuvae® is safer or more effective than the other currently preferred, more cost-effective medications. It is therefore recommended that Zurzuvae® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Zurzuvae [package insert]. Cambridge, MA: Biogen Inc; 2023.