

# Zuranolone

Zurzuvae

First oral neuroactive steroid for postpartum depression, given as a single 14-day course with onset of benefit within about 3 days.

## USUAL ADULT RANGE

50 mg PO daily for 14 days

## HALF-LIFE

19-23 h; Tmax 5-6 h

## METABOLISM

CYP3A4 (major)

## ONSET

Day 3; effect held to day 45

## ⚠️ FDA BOXED WARNING

Impaired ability to drive or engage in other potentially hazardous activities: zuranolone causes driving impairment because of central nervous system depressant effects. Patients should not drive or operate heavy machinery for at least 12 hours after each dose, and may be unable to assess their own impairment.

## 🕒 INDICATIONS

- FDA-approved in August 2023 for the treatment of postpartum depression in adults, as a discrete 14-day oral course.
- The pivotal trials enrolled women with severe postpartum depression whose symptoms began in the third trimester or within 4 weeks of delivery.
- Not approved for major depressive disorder outside the postpartum period; the FDA issued a complete response letter for that indication.
- Improvement in depressive symptoms appeared by day 3 in trials and was maintained through day 45, well past the end of dosing.
- May be used alone or alongside an existing oral antidepressant, and it does not require an ongoing maintenance prescription.
- Safety and effectiveness in patients under 18 years of age have not been established for this indication.

## 🕒 DOSING & TITRATION

- Give **50 mg PO once daily in the evening for 14 days**, taken with a fat-containing meal of roughly 400 to 1000 calories.
- Dose in the evening to align peak sedation with sleep, and instruct the patient not to drive for at least **12 hours** after each dose.
- Reduce to **30 mg once daily** if central nervous system depressant effects such as excessive sedation are problematic.
- Use **30 mg once daily** in severe hepatic impairment and in moderate or severe renal impairment with eGFR below 60 mL/min/1.73 m<sup>2</sup>.
- Reduce to **30 mg once daily** when a strong CYP3A4 inhibitor cannot be avoided, and avoid strong CYP3A4 inducers entirely.
- No taper is required because treatment is a fixed 14-day course; a repeat course may be given if symptoms recur.

## ⚙️ MECHANISM OF ACTION

- A synthetic analogue of allopregnanolone, the endogenous neuroactive steroid metabolite of progesterone that falls abruptly after delivery.
- Acts as a positive allosteric modulator at both synaptic and extrasynaptic GABA-A receptors, enhancing phasic and tonic inhibition.
- Extrasynaptic delta-subunit receptor modulation is the key difference from benzodiazepines, which act only at synaptic sites.
- Restoring GABAergic tone after the postpartum allopregnanolone withdrawal is the proposed basis for rapid symptom relief.
- The same GABA-A potentiation produces the sedation and driving impairment that dominate the safety profile of the drug.

## 🧪 PHARMACOKINETICS

- Peak plasma concentrations occur about 5 to 6 hours after dosing, and a fat-containing meal substantially increases absorption.
- Terminal half-life is roughly 19 to 23 hours, which supports once-daily evening dosing across the 14-day treatment course.
- Metabolized predominantly by CYP3A4, so strong inhibitors and inducers of that enzyme meaningfully alter exposure.
- Highly protein bound with negligible renal excretion of unchanged drug; elimination is largely as inactive metabolites.
- Exposure rises in severe hepatic impairment and in moderate to severe renal impairment, both of which require a lower dose.

## ⚠️ ADVERSE EFFECTS

- Somnolence occurs in roughly 36 percent of patients and dizziness in about 13 percent, both concentrated in the first days of dosing.
- Sedation, fatigue, diarrhea, and headache are the other common adverse effects reported in the postpartum depression trials.
- Driving impairment is the central safety concern and patients frequently cannot recognize the degree of their own impairment.
- Additive central nervous system depression with alcohol, opioids, or benzodiazepines can produce profound sedation or respiratory risk.
- Suicidal thoughts and behavior have been reported, so depression severity must still be monitored throughout the 14-day course.
- Embryo-fetal toxicity was seen in animal studies, requiring effective contraception during and for 1 week after treatment.

## 📈 MONITORING

- Confirm at each contact that the patient is not driving or operating machinery within **12 hours** of a dose during the course.
- Assess depression severity and suicidality before starting, during the course, and again after day 15 when dosing has ended.
- Counsel women of reproductive potential to use effective contraception during treatment and for 1 week after the last dose.
- Verify renal and hepatic function before starting, since both severe hepatic and moderate renal impairment require **30 mg** dosing.
- Review concurrent central nervous system depressants and CYP3A4 modulators before the first dose and at any dose change.

## 🔄 INTERACTIONS & CAUTIONS

- Strong CYP3A4 inhibitors such as ketoconazole, clarithromycin, and ritonavir raise exposure and require reduction to **30 mg daily**.
- Strong or moderate CYP3A4 inducers including rifampin, carbamazepine, and St. John's wort reduce exposure and should be avoided.
- Alcohol, opioids, benzodiazepines, and sedating antihistamines produce additive sedation and increase the risk of accidental injury.
- Zuranolone can raise exposure to P-glycoprotein substrates with narrow therapeutic index, such as digoxin, so monitor closely.
- No monoamine oxidase inhibitor contraindication exists, but combined sedation with any central depressant is the main practical hazard.

## 👤 SPECIAL POPULATIONS

- Indicated specifically in postpartum women, though it may cause fetal harm and should not be used during an ongoing pregnancy.
- Zuranolone is present in human milk at low levels; a decision to continue breastfeeding should weigh benefit against infant sedation.
- Not established as safe or effective under 18 years, so adolescent postpartum patients require individualized risk discussion.
- Geriatric data are absent because the indication is postpartum, and no age-based dose adjustment has been defined.
- Use **30 mg daily** in severe hepatic impairment and in moderate to severe renal impairment; no adjustment is needed for mild impairment.

## ☆ PRESCRIBING PEARLS

- A 14-day course, not a maintenance drug; benefit persisted to day 45 after dosing stopped.
- Must be taken with a fatty meal in the evening; food materially raises absorption.
- No driving for **12 hours** after each dose, and patients often misjudge their own impairment.

# References

- American College of Obstetricians and Gynecologists. (2023). *Treatment and management of mental health conditions during pregnancy and postpartum* (Clinical Practice Guideline No. 5). <https://www.acog.org/clinical/clinical-guidance/clinical-practice-guideline>
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- Deligiannidis, K. M., Meltzer-Brody, S., Gunduz-Bruce, H., Doherty, J., Jonas, J., Li, S., Sankoh, A. J., Silber, C., Campbell, A. D., Werneburg, B., Kanes, S. J., & Lasser, R. (2021). Effect of zuranolone vs placebo in postpartum depression: A randomized clinical trial. *JAMA Psychiatry*, 78(9), 951-959. <https://doi.org/10.1001/jamapsychiatry.2021.1559>
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- National Institute for Health and Care Excellence. (2020). *Antenatal and postnatal mental health: Clinical management and service guidance* (Clinical Guideline CG192). <https://www.nice.org.uk/guidance/cg192>
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## NOTE

References follow APA 7th edition style. Dosing, boxed warnings, and interaction data change; confirm every clinical decision against the current FDA prescribing information (DailyMed) and your institution's formulary. This sheet is an educational quick reference and does not replace the full label or clinical judgment.