NEUROACTIVE STEROID | C-IV

Brexanolone

Zulresso

Intravenous allopregnanolone given as a single 60-hour titrated infusion for postpartum depression, only in certified REMS facilities.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
30-90 mcg/kg/h IV over 60 h	About 9 h	Non-CYP: reduction, conjugation	Within 24-48 h of infusion

⚠ FDA BOXED WARNING

Excessive sedation and sudden loss of consciousness: patients must be monitored for excessive sedation and sudden loss of consciousness with continuous pulse oximetry. Because of these risks, brexanolone is available only through the restricted ZULRESSO REMS program at certified facilities.

INDICATIONS

- FDA-approved for the treatment of postpartum depression in patients 15 years of age and older, given as a single infusion course.
- Originally approved in March 2019 for adults, with the age range extended down to 15 years by the FDA in June 2022.
- Reserved for moderate to severe postpartum depression given the resource intensity of a 60-hour supervised inpatient infusion.
- Antidepressant effect appears within the first day or two of infusion and was sustained through day 30 in the phase 3 trials.
- Not indicated for major depressive disorder outside the postpartum period or for any other psychiatric condition.
- May be given alone or with an existing oral antidepressant, which is typically continued unchanged through the infusion.

DOSING & TITRATION

- Administer as a single continuous intravenous infusion over **60 hours**, using titration steps rather than a fixed rate.
- Give **30 mcg/kg/hour for hours 0-4**, then **60 mcg/kg/hour for hours 4-24**, then **90 mcg/kg/hour for hours 24-52**.
- Taper with **60 mcg/kg/hour for hours 52-56** and **30 mcg/kg/hour for hours 56-60**, then stop the infusion.
- If **90 mcg/kg/hour** is not tolerated, the hours 24 to 52 segment may be run at 60 mcg/kg/hour instead.
- Dilution is required and the diluted solution must be used within specified time limits; each vial is single dose only.
- Avoid entirely in end-stage renal disease with eGFR below **15 mL/min/1.73 m2** because of vehicle accumulation.

MECHANISM OF ACTION

- A chemically identical formulation of allopregnanolone, the endogenous progesterone metabolite that drops sharply after delivery.
- Acts as a positive allosteric modulator of GABA-A receptors at both synaptic and extrasynaptic delta-containing receptor sites.
- Extrasynaptic tonic inhibition is enhanced in a way that benzodiazepines cannot achieve, which is the pharmacologic rationale.
- Rapid restoration of GABAergic tone after postpartum allopregnanolone withdrawal is the proposed basis for the fast response.
- The same receptor action produces dose-dependent sedation and the abrupt loss of consciousness described in the boxed warning.

PHARMACOKINETICS

- Given only intravenously because oral bioavailability is negligible; steady state is reached within hours of starting the infusion.
- Terminal half-life is approximately 9 hours, so plasma concentrations fall quickly once the 60-hour infusion is completed.
- Metabolized by non-CYP pathways including keto-reduction, glucuronidation, and sulfation, which limits metabolic drug interactions.
- More than 95 percent protein bound, and metabolites are excreted in feces and urine with negligible unchanged drug in urine.
- The betadex sulfobutyl ether sodium solubilizing agent accumulates in end-stage renal disease, so eGFR below 15 is a contraindication.

ADVERSE EFFECTS

- Sedation and somnolence affect roughly 21 percent of patients and are the reason continuous monitoring is mandatory.
- Sudden loss of consciousness or altered consciousness occurred in about 5 percent of treated patients in clinical trials.
- Dry mouth, flushing or hot flush, and infusion site pain are the other commonly reported adverse effects.
- Excessive sedation can occur without warning, so the infusion must be stopped and can be restarted only after full resolution.
- Suicidal thoughts and behaviors have been reported, and depression must be reassessed throughout and after the infusion.
- Loss of consciousness while caring for an infant is the specific hazard behind the requirement for a continuous attendant.

MONITORING

- Use continuous pulse oximetry with an alarm for the entire **60-hour** infusion, with a health care provider immediately available.
- Assess for excessive sedation at least every 2 hours during planned non-sleep periods throughout the infusion course.
- Stop the infusion immediately for excessive sedation and resume only at the same or a lower rate once the patient is fully alert.
- Require that a caregiver or attendant be present whenever the patient interacts with her child during the infusion period.
- Reassess depression severity and suicidality at baseline, during infusion, and at follow-up after the course is complete.

INTERACTIONS & CAUTIONS

- Additive central nervous system depression occurs with opioids, benzodiazepines, alcohol, and sedating antihistamines.
- Concomitant antidepressants may be continued, but any added sedative markedly increases the risk of excessive sedation.
- Metabolic drug interactions are minimal because clearance does not depend on cytochrome P450 enzymes to a meaningful degree.
- Contraindicated in end-stage renal disease with eGFR below 15 because the solubilizing vehicle cannot be cleared adequately.
- Available only through the restricted ZULRESSO REMS, so prescribers, pharmacies, and facilities must all be certified.

SPECIAL POPULATIONS

- Indicated for postpartum patients from age 15 years, with the same monitoring and REMS requirements applied to adolescents.
- Brexanolone is present in human milk at very low relative infant dose, and breastfeeding may generally continue with monitoring.
- Use in pregnancy is not the labeled indication, though the infusion has been given late in pregnancy in limited settings.
- Geriatric experience is essentially absent given the postpartum indication and no age-based adjustment has been defined.
- No hepatic dose adjustment is specified; avoid in end-stage renal disease and use caution in significant renal impairment.

PRESCRIBING PEARLS

- A single **60-hour** inpatient IV course, not an ongoing prescription; effect held through day 30.
- Continuous pulse oximetry with an alarm is mandatory for the entire infusion.
- An attendant must be present whenever the mother interacts with her infant during dosing.

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

Kanes, S., Colquhoun, H., Gunduz-Bruce, H., Raines, S., Arnold, R., Schacterle, A., Doherty, J., Epperson, C. N., Deligiannidis, K. M., Riesenberg, R., Hoffmann, E., Rubinow, D., Jonas, J., Paul, S., & Meltzer-Brody, S. (2017). Brexanolone (SAGE-547 injection) in post-partum depression: A randomised controlled trial. *The Lancet, 390*(10093), 480-489. https://doi.org/10.1016/S0140-6736(17)31264-3

Meltzer-Brody, S., Colquhoun, H., Riesenberg, R., Epperson, C. N., Deligiannidis, K. M., Rubinow, D. R., Li, H., Sankoh, A. J., Clemson, C., Schacterle, A., Jonas, J., & Kanes, S. (2018). Brexanolone injection in post-partum depression: Two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. *The Lancet, 392*(10152), 1058-1070. https://doi.org/10.1016/S0140-6736(18)31551-4

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

Sage Therapeutics, Inc. (2022). *Zulresso (brexanolone) injection [Prescribing information]*. U.S. Food and Drug Administration. https://dailymed.nlm.nih.gov/dailymed/

Stahl, S. M. (2021). *Stahl's essential psychopharmacology* (5th ed.). Cambridge University Press.

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.