INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Postpartum Depression***
-November 2024-

Background:
Zuranolone, a novel treatment for postpartum depression (PPD), was evaluated at the Fall 2024 meeting of the Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC). Zuranolone is now recommended in the American College of Obstetricians and Gynecologists 2023 practice advisory on treatment of postpartum depression.[1] Following the clinical review, zuranolone was not added to the NCF due to little clinical data for its use beyond the studies presented to the FDA for its approval. Additionally, there is no clinical experience or utilization within the Agency. Ultimately, **no modifications** were made to the NCF.

Discussion:
PPD has incidence estimates between 9 and 12% in the US. No American Indian / Alaska Native-specific incidence data exist, however PPD is among the top 3 most common pregnancy complications.[2] Maternal suicide is the most common cause of maternal death.[3] The impacts of PPD are wide ranging and include depersonalization, insomnia, irritability for mothers; difficulty with bonding and breastfeeding for mothers and their babies; delay in developmental milestones for babies; and relationship difficulties for whole families.

Zuranolone is the first oral medication to be FDA approved specifically for PPD.[4] It resides within a novel class of drugs called neuroactive steroids and works primarily on the gamma-aminobutyric acid (GABA)-A receptor. It has unique properties that make it ideal for treatment of PPD, including a short duration of time from initiation to impact on symptoms with a significant number of patients noticing improvement within 3 days. Zuranolone's most common side effect is sedation. Further complicating the matter, PPD also has a high prevalence of associated insomnia. Zuranolone has dependency potential similar to benzodiazepines, which also act on GABA-A receptors and is labeled by the US Drug Enforcement Agency as a schedule IV controlled substance. Zuranolone is administered orally at 50 mg PO daily for 14 days at bedtime. Dose adjustment is recommended for excessive sedation, in the case of renal or hepatic impairment, or if drug interaction dictates. Zuranolone is metabolized through the CYP 3A4 system and co-administration with CYP 3A4 inhibitors may require dose adjustment. It is also not recommended for co-administration with CYP 3A4 inducers. A Black Box Warning cautions not to drive or operate machinery within 12 hours of a dose due to sedation.

FDA approval of zuranolone was based on 2 studies with a total of 346 participants. The primary endpoint was improvement of depression scores at day 15. Secondary endpoints were change in depression scores at days 3, 28, and 45. Both studies demonstrated a clinically relevant and statistically significant improvement in depression scores at all timepoints when compared to placebo. Remission at day 45 was 44% vs 29% with placebo (OR 2.1, 95% CI: 1.1-3.9).[5] Fifteen percent (15%) of participants were on chronic selective serotonin receptor inhibitor (SSRI) treatment during their participation in the zuranolone studies, thus SSRI coadministration with zuranolone is acceptable.

Findings:
Zuranolone was FDA approved for PPD in August 2023 and is the only oral medication specifically approved for PPD. Zuranolone is considered a neuroactive steroid and has a novel mechanism of action thought to be exerted primarily at the GABA-A receptor. Zuranolone is administered orally at 50 mg daily at bedtime for 14 days. Time to onset of improvement in depressive symptoms is short in contrast to SSRI. Zuranolone has little post-marketing safety and effectiveness data and there is limited clinical experience with this agent in IHS. Local adoption is encouraged at sites where clinical expertise supports its use.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

References:
1. American College of Obstetricians and Gynecologists. ACOG Practice Advisory for Treatment of Postpartum Depression. Accessed Oct 26, 2024.
2. Law A, McCoy M, Lynen R, et al. The prevalence of complications and healthcare costs during pregnancy. J Med Econ. 2015;18(7):533-41.
3. US Centers for Disease Control and Prevention. Press Release: Four in Five Pregnancy-Related Deaths are Preventable. Accessed Oct 26, 2024.
4. Zuranolone package insert. ZURZUVAE (zuranolone) capsules, for oral use. C-IV. Initial US Approval: 2023.
5. Deligiannidis KM, Meltzer-Brody S, et al. Zuranolone for the Treatment of Postpartum Depression. Am J Psychiatry 2023;180(9):668–75.