Brexanolone (**Zulresso**®)
FDA approved March 2019, Sage Therapeutics Inc.
(Controlled substance Schedule IV)

Indication: Brexanolone is indicated for the treatment of postpartum depression (PPD) in adults

Mechanism of Action: Brexanolone, a neuroactive steroid is an allosteric positive modulator of GABA-A receptors. GABA may play a key role in modulating vulnerability to PPD, however, the mechanism by which brexanolone exerts its antidepressant effect is not fully understood

Dosage	Continuous IV infusion over 60 hours as follows: • 0 to 4 hours: Initiate at 30 mcg/kg/hr • 4 to 24 hours: Increase dosage to 60 mcg/kg/hr • 24 to 52 hours: Increase dosage to 90 mcg/kg/hr (or 60 mcg/kg/hr for clts unable to tolerate 90 mcg/kg/hr) • 52 to 56 hours: Reduce rate to 60 mcg/kg/hr • 56 to 60 hours: Reduce rate to 30 mcg/kg/hr
Administration	• A healthcare provider must be available on site to monitor the client during infusion
Renal impairment	• No dosage adjustments required in mild, moderate, or severe renal impairment • Avoid use in clts with eGFR < 15 mL/min/1.73 m^2 due to potential accumulation of the solubilizing agent
Hepatic impairment	• No dosage adjustment required
How Supplied	• 100 mg/20 mL single-dose vial
Lactation & Pregnancy Considerations	• Use in pregnancy may cause fetal harm (animal studies of other drugs that enhance GABAergic inhibition) • Brexanolone is transferred to breastmilk, however infant exposure is expected to be low (low oral bioavailability)

Drug Drug Interactions

Concomitant Medication	Effect
Benzodiazepines & other CNS depressants	Additive effects, may increase r/o sedation
Antidepressants	Higher incidence of sedation-related events

Adverse Effects

Most frequently reported AEs (≥5% & at least twice of placebo)	Sedation/somnolence, dry mouth, loss of consciousness, & flushing/hot flush
Most frequently reported AEs (≥5% & greater than with placebo)	Sedation/somnolence, dizziness, presyncope, vertigo, dry mouth, hot flush/flushing, & loss of consciousness

Warnings & Precautions

- Black Box warnings
  - Excessive sedation & sudden loss of consciousness during brexanolone administration

        - Clts must be monitored for excessive sedation, sudden loss of consciousness & should have continuous pulse oximetry monitoring
        - Clts must be accompanied during interactions with their children
        - Available only through a restricted REMS program
- **Other warnings**
    - Suicidal thoughts & behaviors

Pharmacokinetics

Metabolism	Extensively metabolized by keto-reduction, glucuronidation, & sulfation to inactive metabolites
Half-life	9 hours
Excretion	47% feces, 42% urine

Clinical Studies

Efficacy of brexanolone was based on the findings of two randomized, double-blind, placebo-controlled studies in a total of 246 women (18 to 45 yo) who were ≤ 6 months postpartum and experienced onset of major depressive symptoms during the 3rd trimester or within 4 weeks of delivery

Study 1 and Study 2 Results		
Regimen	**Score Change at 60 Hours[1]**	**Score Change at 30 Days[1]**
Study 1[2] (n=138); Severe PPD, HAM-D score ≥26		
Brexanolone (max 90 mcg/kg/hr)	-17.7*	-17.6*
Brexanolone (max 60 mcg/kg/hr)	-19.5*	-19.5*
Placebo	-14.0	-13.8
Study 2[2] (n=108); Moderate PPD, HAM-D score 20-25		
Brexanolone (max 90 mcg/kg/hr)	-14.6*	-14.7
Placebo	-12.1	-15.2

*p<0.05 vs placebo. 1. Mean Hamilton Depression Rating Scale (HAM-D) score change from baseline. Mean baseline HAM-D scores were 29 in Study 1 and 23 in Study 2. 2. S Meltzer-Brody et al. Lancet 2018; 392:1058.

- The primary endpoint, mean HAM-D scores were significantly lower at the end of a 60-hour brexanolone infusion compared to placebo in both studies I & 2
    - However at 30 days, HAM-D scores remained significantly lower in the brexanolone group in Study 1, but not in Study 2

- Meltzer-Brody et al defined remission as a HAM-D score ≤ 7 at any given time (subject is symptom-free for that point in time only), however, remission is typically defined as HAM-D score < 7 for a period of up to 4 to 6 months
    - Study 1: 51% of brexanolone treated pts achieved “remission” of symptoms at 60 hours vs. 16% placebo group
    - Study 2: 61% achieved remission at 60 hours (vs. 38% placebo)
    - Integrated data from all 3 RCTs showed remission rates of 50% at 60 hours compared to 28% placebo
        - 94% did not relapse at day 30
        - Significant response rate at 24, 48, 60, and 72 hours and at days 7 & 30 compared to placebo
        - Unknown effect past 30 days or need for maintenance infusions for full remission

Role in Therapy

- Clinical trials suggest that brexanolone, the 1st FDA-approved medication to treat PPD, is modestly more effective compared to placebo in reducing post-infusion depressive symptom scores in moderate to severe PPD
    - may provide rapid relief of depression symptoms, beneficial for women hospitalized with moderate to severe PPD
    - Unclear durability of brexanolone's antidepressant effect
- Novel approach – allopregnanolone, a progesterone metabolite, hasn't previously been a focus to help treat depression
    - Priority review & a Breakthrough Therapy Designation from the FDA
    - Expected to launch in June 2019
- Other treatment options for PPD
    - Mild to moderate PPD: Individual/group psychotherapy, psychosocial support
        - Mild to moderate unipolar major depression
            - Antidepressants (eg, SSRI, SNRI, bupropion, & mirtazapine) are considered a reasonable alternative if psychotherapy is not an option or if the clt has previously responded to antidepressants
            - Pharmacotherapy & psychotherapy combination treatment is useful for some clients
    - Moderate to severe PPD: Psychotherapy in combination with medication
        - Off-label medication options include SSRIs, SNRIs, ER/SR bupropion, and nortriptyline
        - Undetectable levels of sertraline, paroxetine, and nortriptyline in nursing infants
    - Severe PPD: Hospitalization, treatment with adjunctive medications, and ECT
    - Brexanolone's comparative efficacy with other antidepressants which are less expensive and do not require a 60 hour infusion remains to be determined
- Further research
    - Would depressive symptoms return? Intensity of the symptoms (same as prior to treatment)?
    - Any significant long-term neurological effects? Any effect on subsequent pregnancies
    - Unidentified potential risks in real life settings
    - Sage Pharmaceuticals working on injectable and oral formulations of a similar drug
    - Other allopregnanolone derivatives may be effective for depression unrelated to pregnancy/postpartum, may help both men & women
- Abuse potential (schedule IV)
- Off-label & Overutilization Considerations
    - potential for off-label use - for treatment-resistant depression, seizures, and epilepsy

- Logistics and access
    - Require a 60-hour IV infusion (overnight hospitalization)
    - Usually psychiatric inpatient units are not equipped to administer IV infusions
    - Possible mother/baby separation, need for child care during treatment, breastfeeding disruptions?
    - Restricted Distribution System
        - Pharmacies must be certified with the program and must only dispense to certified healthcare facilities. Clts must be enrolled in the Zulresso REMS

Potential candidates

- Clts with suicidal ideation (fast benefit in suicidal patients)
- Clts experiencing severe, ongoing treatment resistant PPD
- Clt's willingness to go into an infusion center

REMS requirements for Healthcare Setting:

- Complete Healthcare setting knowledge assessment and training
- Establish policy and procedure for training of future providers
- Complete patient enrollment forms
- Counsel patient on potential adverse effects
- Facility must have continuous pulse oximetry, fall precaution protocol, intravenous programmable infusion pumps with alarms for malfunctions.
- Healthcare providers to be continuously available on site to monitor and intervene
- During infusion, check patient every 2 hours during non-sleep periods for excessive sedation and loss of consciousness and oxygen saturation using continuous pulse oximetry
- Submit Post Infusion Form and Excessive Sedation and Loss of Consciousness Adverse Event Form

Pricing: Wholesale Acquisition cost for course of Zulresso: $37,250, not including healthcare setting monitoring fees

References

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Formulary Update (CMC only):

- ZULRESSO added w/ PA, QL since it is a protected class drug and requires formulary placement. Quantity limit to prevent fraud, waste, and abuse.

Formulary Update (HealthWorx, Healthy Kids, Medi-Cal, BHRS):

- NONFORMULARY

Prior Authorization (CMC)/Approval Criteria (HealthWorx, Healthy Kids, Medi-Cal) Update:

Covered Uses: All FDA approved indications not otherwise excluded from Part D

Required Medical Information:

A) Patient is ≥ 18 years of age; AND
B) Patient has been diagnosed with severe postpartum depression confirmed by a rating scale such as Montgomery-Åsberg depression rating scale (MADRS) with a score of >34 or the Hamilton Rating Scale for Depression (HAM-D) with a score of >25 or PHQ-9 with a score of >20, performed by a psychiatrist; AND
C) Patient has failed antidepressant medication trials; AND
D) Patient has failed ECT or is not a candidate for ECT; AND
E) Patient meet DSM-V diagnosis of PPD: ≤ 6 months postpartum at screening with a major depressive episode with onset no earlier than the third trimester and no later than 4 weeks after delivery; AND
F) Patient is not currently pregnant; AND
G) Patient does not have active psychosis, history of schizophrenia, bipolar disorder, or Schizoaffective disorder; AND
H) Zulresso is being prescribed by, or in consultation with, a psychiatrist or an obstetrician-gynecologist; AND
I) Zulresso will be administered in a facility that is enrolled in the Zulresso REMS program.

Coverage Duration:

Approved one-time, up to 90mcg/kg/hour x 60-hour infusion, once per postpartum period