# Zulresso (brexanolone)

## BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This medical policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

## DESCRIPTION

The indications below including FDA-approved indications and compendial uses are considered covered benefits provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications
Treatment of postpartum depression (PPD) in adults.

Limitations of Use

- The safety and effectiveness of more than one Zulresso (brexanolone) infusion has not been evaluated.
- The use of Zulresso (brexanolone) for any other indication has not been evaluated.

## POLICY

Required Documentation
The following information is necessary to initiate the prior authorization review:

1. Medical records (e.g. office notes) documenting relevant history, physican evaluation information, and rating scale/diagnostic criteria for major depression with peripartum onset
2. Medical records documenting inadequate response with antidepressant or intolerance or contraindication to antidepressants (if applicable)
3. Medical records documenting urgent need for treatment negating the step through antidepressant agent (if applicable)

Criteria for Approval

A. Authorization of 1 infusion may be granted for treatment of moderate to severe postpartum depression in members 18 years of age or older when all of the following criteria are met:
    1. Member has had a major depressive episode that began no earlier than the third trimester of pregnancy and no later than the first 4 weeks following delivery, documented by standardized rating scales that reliably measure depressive symptoms (e.g., Beck Depression Scale [BDI], Hamilton Depression Rating Scale [HDRS], Montgomery-Asberg Depression Rating Scale [MADRS], etc.)
    2. Must be prescribed by, or in consultation with, a psychiatrist
    3. Member is 6 months postpartum or less

4. Lactation has ceased or breastmilk produced will not be used for feedings during the infusion and up to 4 days following infusion completion
5. Member does not have current substance or alcohol use disorder
6. Member will not receive more than one 60-hour infusion per pregnancy/childbirth
7. Provider, member, facility, and pharmacy must be enrolled in the Zulresso REMS (Risk Evaluation and Mitigation Strategy) program
8. Member's current episode of depression is moderate to severe
9. Member meets one of the following:
    a) Has tried and had an inadequate response to at least one antidepressant agent (i.e. SSRIs, SNRIs, TCAs, bupropion, or mirtazapine) at a maximally tolerated therapeutic dose for a minimum duration of 2 months

    **OR**

    b) Has a documented intolerance or FDA labeled contraindication, to ALL classes of antidepressant agents

    **OR**

    c) Shows a potential risk of harm to self and/or others as determined by the treating provider and supported by documentation

B. All other uses of Zulresso (brexanolone) for conditions not outlined in this policy are considered **not medically necessary**.

Dosage and Administration

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

Quantity Limit

One-time, 60-hour intravenous infusion up to 90mcg/kg/hour per postpartum period.

## CLINICAL RATIONALE

Background

Postpartum depression (PPD) is the most prevalent complication of childbirth and may lead to great suffering for mothers, children, and families. Approximately 10% to 20% of women who give birth worldwide experience postpartum depression, and about 40% to 80% of the cases are considered severe. The American Psychiatric Association (APA)'s DSM-5 defines postpartum depression as a major depressive episode with peripartum onset if onset of mood symptoms occurs during pregnancy or within 4 weeks after delivery. However, postpartum depression that occurs up to 12 months after childbirth or does not meet the full criteria for a major depressive episode may still lead to harm and require treatment. Symptoms include sleep disturbance beyond that associated with taking care of the baby, anxiety, irritability, feelings of being overwhelmed, and obsessional preoccupation with the baby's health and feeding. Although the exact pathogenesis of postpartum depression in unknown, the rapid drop in reproductive hormone levels after childbirth may play a role in susceptible women. The greatest risk factor for postpartum depression is a history of depression and anxiety; other risk factors include lack of social support, marital difficulties, violence involving the intimate partner, history of abuse, and negative life events.

Postpartum depression may resolve within weeks after onset on its own, but it can last beyond the first year after delivery in 20% of women and after 2 years in 13% of women; relapses during subsequent pregnancies or on other occasions unrelated to pregnancy occur in about 40% of women. Consequences of postpartum depression include maternal suffering and diminished functioning, increased risks of marital conflict, impaired infant-caregiver attachment, increased risks of impaired emotional, social and cognitive development in the child, and rarely suicide or infanticide. Treatment usually starts with psychological treatment/interventions based on severity of symptoms and functional status (e.g., support groups, nurse

in home visits, formal psychotherapy, cognitive behavioral therapy, interpersonal therapy). An antidepressant is recommended when psychological treatment alone does not resolve symptoms, when symptoms are severe and require prompt treatment, or when preferred by the patient. An SSRI, usually Celexa (citalopram), Lexapro (escitalopram), or Zoloft (sertraline) is recommended first-line during pregnancy or while breastfeeding, due to minimal risks to the fetus/neonate. When these agents cannot be used or are ineffective, alternatives include bupropion, Pristiq (desvenlafaxine succinate ER), Cymbalta (duloxetine DR), Prozac (fluoxetine), Remeron (mirtazapine), venlafaxine, and TCAs.

Zulresso (brexanolone), a gamma-aminobutyric acid (GABA) modulator, is the first treatment that is FDA approved specifically for postpartum depression and received FDA Breakthrough Therapy designation.

Efficacy

The efficacy of Zulresso (brexanolone) was demonstrated in two phase 3, randomized, double-blind, multicenter, placebo-controlled clinical trials in women (age 18-45 years) with PPD who met the Diagnostic and Statistical Manual of Mental Disorders criteria for a major depressive episode (DSM-IV) with onset of symptoms in the third trimester or within 4 weeks of delivery. Eligible patients were randomized (1:1:1) to receive brexanolone 90 ug/kg, brexanolone 60 ug/kg, or placebo. The primary endpoint was the mean change from baseline in depressive symptoms as measured by the 17-item Hamilton Depression Rating Score (HAM-D) total score at the end of the infusion (Hour 60), assessed in all patients who started infusion of Zulresso (brexanolone) or placebo. Secondary endpoints included mean HAM-D total score and least-squares mean change from baseline; Clinical Global Impression-Improvement (CGI-I) response; and change in baseline of Montgomery-Asberg Depression Rating Scale (MADRS). In both placebo-controlled studies, titration to a target dose of Zulresso (brexanolone) 90 mcg/kg/hour was superior to placebo in improvement of depressive symptoms. Results from Study 1 showed a least-squares mean reduction in HAM-D total score from baseline of 17.7 points in brexanolone 90 ug/kg, compared with 14.0 points in placebo (difference of -3.7 [95% CI -6.9 to -0.5], p=0.0252 for brexanolone 90 ug/kg). In Study 2, the least-squares mean reduction in HAM-D total score at 60 hours from baseline was 14.6 points in the brexanolone 90 ug/kg group compared with 12.1 points for the placebo group (difference –2.5 [95% CI –4.5 to –0.5], p=0.0160). In a group of 38 patients in Study 1, Zulresso (brexanolone) titration to a target dose of 60 mcg/kg/hour was also superior to placebo in improvement of depressive symptoms showing a least-squares mean reduction in HAM-D total score from baseline of 19.5 points in brexanolone 60 ug/kg compared with 14.0 points in placebo (difference of -5.5, [95% CI -8.8 to -2.2], p=0.0013 for brexanolone 60 ug/kg).

Safety

Zulresso (brexanolone) may cause sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush. In addition, Zulresso (brexanolone) will be available only through the Zulresso REMS Program that requires the drug be administered by a health care provider in a certified health care facility. Zulresso (brexanolone) is administered as a continuous IV infusion over 60 hrs (2.5 days). Because of the risk of serious harm due to the sudden loss of consciousness, patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. While receiving the infusion, patients must be accompanied during interactions with their children. The product labeling for Zulresso (brexanolone) carries a boxed warning regarding the REMS program. Concomitant use of Zulresso (brexanolone) with CNS depressants (e.g., opioids, benzodiazepines) or antidepressants may increase the likelihood or severity of adverse reactions related to sedation.

## PROCEDURES AND BILLING CODES

**To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.**

- C9055 Zulresson (brexanolone)
- J1632 Zulresson (brexanolone)

## REFERENCES


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*Some content reprinted from CVSHealth

## POLICY HISTORY

**Policy #:** 05.02.76
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