Introduction

Depression after the birth of a baby – postpartum depression – affects up to 20 percent of women. It’s common to have mood swings for a few weeks after giving birth. This is commonly called “the baby blues.” Postpartum depression, however, is longer lasting and is considered a major depressive episode. Postpartum depression can affect women of all ages and economic classes. Between 40 percent to 80 percent of postpartum depression cases are considered moderate to severe. The cause of postpartum depression is unknown. The symptoms of postpartum depression include sadness, loss of interest in activities, and a lower ability to feel pleasure. Other symptoms may be feelings of worthlessness or guilt, difficulty with thinking, or thoughts of suicide. This policy describes when medication for postpartum depression may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria
**Drug** | **Medical Necessity**
--- | ---
Zulresso™ (brexanolone) | Zulresso™ (brexanolone) may be considered medically necessary for the treatment of postpartum depression when the following criteria are met:
• Patient is ≥ 18 years of age
AND
• Patient has medical record documentation of DSM-5 diagnostic criteria for Major Depressive Disorder with peripartum onset
AND
• Patient’s current episode of depression is moderate to severe
AND
• Patient is 6 months or less postpartum
AND
• Zulresso™ (brexanolone) is administered as a one-time 60-hour infusion per pregnancy

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

**Length of Approval**

<table>
<thead>
<tr>
<th>Approval</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial authorization</td>
<td>Zulresso™ (brexanolone) may be approved as a one-time infusion per pregnancy.</td>
</tr>
<tr>
<td>Re-authorization criteria</td>
<td>Future re-authorization of Zulresso™ (brexanolone) beyond a one-time infusion per pregnancy is considered not medically necessary.</td>
</tr>
</tbody>
</table>

**Documentation Requirements**

The patient’s medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:
• Office visit notes that contain the relevant history and physical evaluation information.

**Coding**
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>HCPCS</td>
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</tr>
<tr>
<td>J1632</td>
<td>Injection, brexanolone, 1 mg (Zulresso™) (New code effective 10/1/20)</td>
</tr>
</tbody>
</table>

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## Related Information

### Consideration of Age

Age limits specified in this policy are determined according to FDA-approved indications where applicable.

### Benefit Application

This policy is managed through the Medical benefit.

## Evidence Review

### Background

Zulresso™ (brexanolone) is a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator indicated for the treatment of postpartum depression (PPD) in adults. Postpartum depression is the most common complication of childbirth and can result in considerable suffering for mothers, children, and families. Postpartum depression is estimated to affect 10–20% of women who give birth worldwide, and occurs in low-income, middle-income, and high-income countries. Approximately 40–80% of cases of post-partum depression are considered moderate to severe. In the USA, the estimated prevalence of post-partum depression in new mothers varies by state from 8–20%, with an overall mean prevalence of 11.5%.

The pathogenesis of postpartum depression is unknown. It is also not known to what degree the underpinnings of postpartum depression differ from those of nonperinatal depression, and
whether postpartum depression represents a distinct (reproductive) subtype of depression. Factors involved in postpartum depression may include genetic susceptibility, epigenetic phenomena (e.g., DNA methylation), and hormonal changes, as well as psychological and social problems and stressful life events.

The hypothalamic-pituitary-adrenal (HPA) axis, perinatal hormonal fluctuations, and γ-aminobutyric acid (GABA) signaling have been implicated in the pathophysiology of postpartum depression, and previous studies have identified associations between these potential mechanisms. In mouse models of GABA dysfunction, mice were found to have postpartum depression-like maternal behaviors and defects in HPA axis regulation, indicating an association between GABA and HPA regulation. Additionally, plasma concentrations of allopregnanolone, a potent positive allosteric modulator of synaptic and extrasynaptic GABA type A (GABA-A) receptors, which are an endogenous progesterone metabolite, decrease considerably following childbirth, indicating an association between perinatal hormonal fluctuations and GABA regulation.

### Summary of Evidence

**Zulresso™ (brexanolone)**

**Efficacy**

The efficacy of brexanolone was evaluated in 138 postpartum women in two moderate quality, phase 3, randomized, double blinded, placebo-controlled clinical trials: Hummingbird 202B and 202C. Eligible patients were randomized (1:1:1) to receive brexanolone 90 ug/kg, brexanolone 60 ug/kg, or placebo. The primary endpoint was the change from baseline in the 17-item Hamilton Depression Rating Score (HAM-D) total score at 60 hours, assessed in all patients who started infusion of study drug 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).

Results from Hummingbird202B showed a least-squares mean reduction in HAM-D total score from baseline of 19.5 points in brexanolone 60 ug/kg, 17.7 points in brexanolone 90 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; -3.7 [95% CI -6.9 to -0.5], p=0.0252 for brexanolone 90 ug/kg). In Hummingbird 202C, the least-squares mean reduction in HAM-D total score at 60 hours from baseline was 14.6 points (SE 0.8) in the brexanolone 90 ug/kg group compared with 12.1 points (SE 0.8) for the placebo group (difference –2.5 [95% CI –4.5 to –0.5], p=0.0160).
The efficacy of brexanolone was also evaluated in 21 postpartum women in a moderate quality, phase 2, randomized, double blinded, active-controlled clinical trial. Eligible women were randomly assigned (1:1), via a computer-generated randomization program, to receive either a single, continuous intravenous dose of brexanolone or placebo for 60 hours. The primary efficacy endpoint was the change from baseline in the 17-item HAM-D total score at 60 hours. Secondary endpoints included mean HAM-D total score and least-squares mean change from baseline; CGI-I response; and change in baseline of MADRS.

Results from this phase 2 study showed a reduction in HAM-D total score from baseline was 21.0 points (SE 2.9) in the brexanolone group compared with 8.8 points (SE 2.8) in the placebo group (difference –12.2, 95% CI –20.77 to –3.67; p=0.0075; effect size 1.2) at 60 hours.

**Safety**

**Serious Adverse Events**

In the phase 3 trials, the most impactful serious adverse event reported was suicidal ideation and intentional overdose in one patient on brexanolone. Across groups, 4 patients receiving brexanolone experienced excessive sedation and loss of consciousness without respiratory and hemodynamic compromise. In three cases, the infusion was continued and completed without recurrence.

**Other Adverse Events**

In Hummingbird 202B, 19 patients in the brexanolone 60 ug/kg group and 22 patients in the brexanolone 90 ug/kg group had adverse events compared with 22 patients in the placebo group. In study 2, 25 patients in the brexanolone 90 ug/kg group had adverse events compared with 24 patients in the placebo group. The most common treatment emergent adverse events in the brexanolone groups were headache (n=7 brexanolone 60 ug/kg group and n=6 brexanolone 90 ug/kg group vs n=7 placebo group for study 1; n=9 brexanolone 90 ug/kg group vs n=6 placebo group for study 2), dizziness (n=6 brexanolone 60 ug/kg group and n=6 brexanolone 90 ug/kg group vs n=1 placebo group for study 1; n=5 brexanolone 90 ug/kg group vs n=4 placebo group for study 2), and somnolence (n=7 brexanolone 60 ug/kg group and n=2 brexanolone 90 ug/kg group vs n=3 placebo group for study 1; n=4 brexanolone 90 ug/kg group vs n=2 placebo group for study 2).
Tolerability

Of 147 patients included in the ALL-brexanolone study results, the most common adverse events were: headache (n=22), dizziness (n=19), and somnolence (n=15). These events were typically mild in severity and did not commonly lead to discontinuation of treatment.

2020 Update

Reviewed prescribing information for Zulresso™ (brexanolone) and conducted a literature search for the treatment of postpartum depression. No new evidence found that would change this policy.

References


History

<table>
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<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>06/01/19</td>
<td>New policy, approved May 14, 2019. Add to Prescription Drug section. Zulresso™ (brexanolone) may be considered medically necessary when criteria are met, considered not medically necessary when criteria are not met.</td>
</tr>
</tbody>
</table>
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Email AppealsDepartmentInquiries@Premera.com

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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at

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Oromo (Cushite):
Lakkoofsa bibiliba 800-722-1471 (TTY: 800-842-5357) ti bibiliba.

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Deutsche (German):

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Ilokano (Ilocano):
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Chiama 800-722-1471 (TTY: 800-842-5357).