PREMERA HMO

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PHARMACY – 5.01.608

Pharmacologic Treatment of Postpartum Depression

BCBSA Ref. Policy: 5.01.33

		RELATED MEDICAL POLICIES:	
Effective Date:	May 1, 2026	5.01.520	Antidepressants: Pharmacy Medical Necessity Criteria for Brands
Last Revised:	Apr. 27, 2026	5.01.609	Spravato (esketamine) Nasal Spray
Replaces:	N/A		

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POLICY CRITERIA | DOCUMENTATION REQUIREMENTS
RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

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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
Zurzuvae (zuranolone) oral	**Zurzuvae (zuranolone) may be considered medically necessary for the treatment of postpartum depression when the following criteria are met:** • The individual is aged 18 years or older **AND** • Has medical record documentation of DSM-5 diagnostic criteria for Major Depressive Disorder with peripartum onset **AND** • Current episode of depression is moderate to severe as demonstrated by documentation of individual's symptoms and their severity or by one or more standardized depression rating scales **AND** • Is 12 months or less postpartum **AND** • The treatment course is limited to 14 days **All other uses of Zurzuvae (zuranolone) for conditions not outlined in this policy are considered not medically necessary.**

Drug	Investigational
As listed	**The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.** **All other uses of the drugs listed in this policy for conditions not outlined in this policy are considered investigational.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**Non-formulary exception reviews for all drugs listed in this policy may be approved up to 12 months.** **Zurzuvae (zuranolone) may be approved as a 14-day single treatment course per pregnancy.**

Length of Approval	
Approval	**Criteria**
Re-authorization criteria	**Future re-authorization of Zurzuvae (zuranolone) beyond 14 days in a single treatment course per pregnancy is considered not medically necessary.**

Documentation Requirements
The individual'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.

Related Information

Definition of Terms

Diagnostic and Statistical Manual of Metal Disorders (DSM)-5 Diagnostic Criteria for a Major Depressive Episode

- Five (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. Do not include symptoms that are clearly attributable to another medical condition. Criteria A through C represent a major depressive episode. Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgement based on the individual's history and the cultural norms for the expression of distress in the context of loss.

- Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observations made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.)
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
- Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month) or decrease or increase in appetite nearly every day. (NOTE: In children, consider failure to make expected weight gain.)
- Insomnia or hypersomnia nearly every day.
- Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
- Fatigue or loss of energy nearly every day.
- Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
- Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by their subjective account or as observed by others).
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

- The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- The episode is not attributable to the direct physiological effects of a substance or to another medical condition.
- The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
- There has never been a manic or hypomanic episode. This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.

Rating Scales for Severity of Depression in Major Depressive Disorder

Score	Depression Severity
Hamilton Depression Rating Scale (HAM-D)	
<10	Remission
10-13	Mild
14-17	Mild to moderate

Score	Depression Severity
≥18	Moderate to severe
Montgomery-Asberg Depression Rating Scale (MADRS)	
0-6	None
7-19	Mild
20-34	Moderate
≥35	Severe
Quick Inventory of Depressive Symptomatology (QIDS-SR)	
0-5	None
6-10	Mild
11-15	Moderate
16-20	Severe
≥21	Very severe
Patient Health Questionnaire-9 (PHQ-9)	
0-4	None
5-9	Mild
10-14	Moderate
15-19	Moderately severe
≥20	Severe

PHQ-9 Depression Questionnaire

A PHQ-9 score of ≥10 indicates it is likely major depression with a score of 5 to 9 indicating mild, 10 to 14 indicating moderate, 15 to 19 moderately severe and ≥20 severe major depression.

- Over the last two weeks, how often have you been bothered by an of the following (Not at all = 0; Several days = 1; More than half the days = 2; Nearly every day =3):
  - Little interest or pleasure in doing things
  - Feeling down, depressed, or hopeless
  - Trouble falling or staying asleep, or sleeping too much
  - Feeling tired or having little energy
  - Poor appetite or overeating
  - Feeling bad about yourself, or that you are a failure, or that you have let yourself or your family down

- Trouble concentrating on things, such as reading the newspaper or watching television
- Moving or speaking so slowly that other people could have noticed? Or the opposite, being so fidgety or restless that you have been moving around a lot more than usual.
- Thoughts that you would be better off dead, or of hurting yourself in some way

Consideration of Age

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

Benefit Application

Zurzuvae (zuranolone) is managed through the pharmacy benefit.

Evidence Review

Background

Zurzuvae (zuranolone) is a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulators indicated for the treatment of postpartum depression (PPD). Post-partum 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 post-partum 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 extra synaptic 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

Zurzuvae (zuranolone)

Efficacy

Zuranolone was studied in two Phase 3 trials with differing doses. In both studies, zuranolone was significantly more effective than placebo. No comparisons with active treatment are available. Breast feeding was not allowed during the studies and study drug was not administered during pregnancy.

The ROBIN study was a multicenter, randomized, placebo-controlled, double-blind, Phase 3 trial in 153 women with PPD who were ≤6 months postpartum. Individuals met DSM-5 criteria for MDD and a baseline HAMD-17 score ≥26 (severe depression). Individuals were randomized to zuranolone or placebo for 2 weeks followed by an observation period of 45 days. The primary endpoint of change from baseline in Day 15 least squares mean (LSM) HAMD-17 score was -17.8 with zuranolone 30 mg and -13.6 with placebo (effect size 0.53 [medium], p=0.003). While secondary outcomes were not adjusted for multiplicity and p-values were considered nominal, all secondary outcomes favored zuranolone at 15 days. Secondary endpoints noted initial efficacy at 3 days which was maintained to 45 days.

The SKYLARK study was a multicenter, randomized, placebo-controlled, double-blind, Phase 3 trial in 200 women with PPD who were ≤12 months postpartum. Individuals met DMS-5 criteria for MDD; however, a baseline HAMD-17 score required for inclusion was not specified. Like the ROBIN study, study drug was administered for 2 weeks and follow-up was continued for 45 days. In the SKYLARK trial, individuals were randomized to a higher dose of zuranolone (50 mg po QD) or placebo. The primary endpoint of LSM change in HAMD-17 score at day 15 was

significantly improved with zuranolone 50 mg vs placebo (-15.6 vs -11.6; p=0.0007). Efficacy was maintained to 45 days and was initially noted at 3 days. The study is available as data on file only and reporting was incomplete.

Safety

Serious Adverse Events

Serious adverse events occurred in 1.0%-2.8% of individuals across clinical trials with zuranolone. Sedation and loss of consciousness were of interest in zuranolone trials as brexanolone carries a boxed warning for excessive sedation or sudden loss of consciousness and has a Risk Evaluation and Mitigation Strategy (REMS) program requiring continuous monitoring throughout the 60-hour infusion. In the ROBIN trial with zuranolone, one individual discontinued the trial due to sedation and one individual experienced confusion. No loss of consciousness was reported in any of the zuranolone trials. Zuranolone does have a boxed warning regarding driving impairment due to central nervous system (CNS) depressant effects. Individuals are advised not to drive or engage in other potentially hazardous activities until at least 12 hours after administration.

Other Adverse Events

Common adverse events with zuranolone 50 mg included somnolence (26.5%), dizziness (13.3%), sedation (11.2%), and headache (9.2%).

Administration

The recommended dose of Zurzuvae is 50 mg taken orally once daily in the evening for 14 days. If the individual experiences CNS depressant effects within the 14-day period, the dose may be reduced to 40 mg once daily in the evening within the 14-day period. For individuals using a strong CYP3A4 inhibitor, or those with severe hepatic impairment (Child-Pugh C) or severe renal impairment (eGFR <60 mL/min/1.73 m^2) the recommended dose is 30 mg taken orally once daily in the evening for 14 days.

American College of Obstetricians and Gynecologists

In August 2023, after the US Food and Drug Administration-approval of zuranolone for the treatment of postpartum depression, ACOG published a Practice Advisory on the new agent meant to serve as an update to the Clinical Practice Guideline published in June 2023.[31,] In this Advisory, ACOG recommended "consideration of zuranolone in the postpartum period (i.e., within 12 months postpartum) for depression that has onset in the third trimester or within 4 weeks postpartum. The decision to use zuranolone should balance the benefits (e.g.,

significantly improved and rapidly resolved symptoms) with the risks and challenges (e.g., potential suicidal thoughts or behavior, sedation that precludes performing some activities of daily living like driving, and lack of efficacy beyond 45 days)."

American Psychiatric Association

No evidence-based guideline specifically related to the treatment of postpartum depression was identified. Relevant excerpts from "Practice Guideline for the Treatment of Patients with Major Depressive Disorder" published in 2010.

Depression During Pregnancy

- "Depression-focused psychotherapy or other nonmedication therapies may be considered first for some women, and psychotherapy should be considered as part of the treatment plan whenever possible."
- "Although there is little controlled research, psychotherapies appear efficacious in antenatal and postpartum depression, with inter-personal therapy for depression being the best studied."[33,34,]
- "Antidepressant efficacy has not been determined for pregnant women, and questions remain as to whether medications have equivalent efficacy during pregnancy, compared with the nonpregnant state."
- "Electroconvulsive therapy is also recommended as a treatment option for major depressive disorder during pregnancy."

Postpartum Depression

"Antidepressants are often prescribed for postpartum depression, according to the same principles delineated for other types of major depressive disorder, despite a limited number of controlled studies."

US Preventive Services Task Force Recommendations

The US Preventive Services Task Force Recommendations (USPSTF) recommendations apply to pregnant persons and persons who are less than 1 year postpartum who do not have a current diagnosis of depression but are at increased risk of developing depression.

The USPSTF recommends (category B recommendation) screening for depression in the general adult population, including pregnant and postpartum women. The USPSTF also recommends screening for depression in adolescents aged 12 to 18 years and found insufficient evidence to recommend for or against screening in children 11 years or younger.

The USPSTF recommends that clinicians provide or refer pregnant and postpartum persons who are at increased risk of perinatal depression to counseling interventions (category B recommendation).

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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.

2021 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.

2022 Update

Reviewed prescribing information for Zulresso (brexanolone) and updated criteria from 18 years of age or older to 15 years of age or older. Use of Zulresso in individuals 15 to 17 years of age was supported by evidence from adequate and well-controlled studies in adults with PPD, pharmacokinetic data in adults and individuals 15 to 17 years, and safety data in individuals 15 to 17 years. Also, added additional info to define moderate to severe depression which can be demonstrated by documentation of individual's symptoms and their severity or by one or more standardized depression rating scales.

2023 Update

Reviewed prescribing information for Zulresso (brexanolone). No new evidence found that would change this policy.

2024 Update

Reviewed prescribing information for Zulresso (brexanolone) and Zurzuvae (zuranolone). No new evidence found that would change this policy.

2025 Update

Reviewed prescribing information for Zulresso (brexanolone) and Zurzuvae (zuranolone). Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.

2026 Update

Reviewed prescribing information for Zurzuvae (zuranolone). Removed coverage criteria for Zulresso (brexanolone) as product has been removed from the market.

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History

Date	Comments
06/01/19	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.
10/01/20	Annual Review, approved September 1, 2020. No changes to policy statement. Added HCPCS J1632. Removed HCPCS J3490.
11/01/21	Annual Review, approved October 5, 2021. No changes to policy statement.
10/01/22	Annual Review, approved September 26, 2022. Updated criteria from 18 years of age or older to 15 years of age or older and added additional info to define moderate to severe depression. Changed the wording from "patient" to "individual" throughout the policy for standardization.
07/01/23	Annual Review, approved June 26, 2023. No changes to policy statement.
11/01/23	Interim Review, approved October 10, 2023. Added Zurzuvae (zuranolone) for the treatment of postpartum depression in adults.
02/01/24	Annual Review, approved January 22, 2024. Correction made to quantity limit for Zurzuvae (zuranolone).
03/01/25	Annual Review, approved February 24, 2025. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.

Date	Comments
05/01/26	Annual Review, approved, April 27, 2026. Removed coverage criteria for Zulresso (brexanolone) as product has been removed from the market. Removed HCPCS code J1632.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.