Policy Number	**RX501.106**
Policy Effective Date	**12/15/2024**

Brexanolone for Postpartum Depression

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted

study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Zulresso™ (brexanolone) **may be considered medically necessary** for one-time use per pregnancy for individuals meeting **all** of the following criteria:

1. Individual is 15 years of age or older and ≤ 6 months postpartum at the time of infusion.
2. Individual meets the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria for a major depressive episode (**see Table 1 in Description**) by a structured clinical interview for DSM-5 disorders.
3. Individual has an onset of depressive episode between the 3rd trimester through 4 weeks postpartum.
4. Individual has a diagnosis of postpartum depression based on either of the following:
   - Hamilton Rating Scale for Depression (HAM-D) score ≥ 20 (**see NOTE 1**), OR
   - Edinburg Postnatal Depression Scale (EPDS) score ≥ 13 (**see NOTE 2**).
5. Individual meets **ONE** of the following:
   - Has a documented intolerance or U.S. Food and Drug Administration (FDA) labeled contraindication to major classes of antidepressant agents; OR
   - Shows a potential risk of immediate harm to self and/or others as determined by the treating physician and supported by documentation.
6. Individual does **NOT** have any FDA labeled contraindications to the requested agent and is intended to be used consistently with the FDA approved label (**see NOTE 3**).
7. The prescriber is a specialist in the area of the individual's diagnosis (e.g., psychiatrist) or the prescriber has consulted with a specialist in the area of the individual's diagnosis.
8. Will not be utilized concomitantly with zuranolone (Zurzuvae™) for the treatment of postpartum depression.

Zulresso (brexanolone) **is considered experimental, investigational and/or unproven** in all other situations.

NOTE 1: Hamilton Rating Scale for Depression (HAM-D)
HAM-D is a 17-item rating scale to determine the severity level of depression in an individual before, during and after treatment. The total score ranges from 0 to 52, with the score corresponding to the following classifications:

- 0-7: No depression (normal)
- 8-13: Mild depression
- 14-18: Moderate depression
- 19-22: Severe Depression
- ≥ 23: Very Severe depression

NOTE 2: Edinburgh Postnatal Depression Scale (EPDS)
EPDS is a self-report instrument containing ten items that are ranked from 0 to 3 that reflect the individual's experience over the past week. The total score ranged from 0 to 30. An EPDS ≥ 13 is an acceptable cut-point for identifying women at risk for major depression in clinical settings.

NOTE 3: Brexanolone should be administered as a continuous intravenous infusion over 60 hours (2.5 days) as follows:

- 0 to 4 hours: Initiate with a dosage of 30 mcg/kg/hour
- 4 to 24 hours: Increase dosage to 60 mcg/kg/hour
- 24 to 52 hours: Increase dosage to 90 mcg/kg/hour (alternatively consider a dosage of 60 mcg/kg/hour for those who do not tolerate 90 mcg/kg/hour)
- 52 to 56 hours: Decrease dosage to 60 mcg/kg/hour
- 56 to 60 hours: Decrease dosage to 30 mcg/kg/hour

Brexanolone has a black box warning because individuals are at risk of excessive sedation or sudden loss of consciousness during administration. Individuals must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. Individuals must be accompanied during interactions with their child(ren). In addition, a healthcare provider must be available on site to continuously monitor the individual and intervene as necessary for the duration of the infusion.

NOTE 4: Risk Evaluation and Mitigation Strategy (REMS) Program
Brexanolone is available only through a restricted program called the ZULRESSO REMS. Notable requirements include the following:

- Healthcare facilities must enroll in the program and ensure that brexanolone is only administered to individuals who are enrolled in the ZULRESSO REMS.
- Pharmacies must be certified with the program and must only dispense brexanolone to healthcare facilities who are certified in the ZULRESSO REMS.
- Individuals must be enrolled in the ZULRESSO REMS prior to administration of brexanolone.
- Wholesalers and distributors must be registered with the program and must only distribute to certified healthcare facilities and pharmacies.

Because of the low amounts of brexanolone secreted in milk and low oral bioavailability, brexanolone would not be expected to cause any adverse effects in breastfed infants. There are no data on the effects of brexanolone on a breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for brexanolone and any potential adverse effects on the breastfed child from brexanolone or from the underlying maternal condition.

Policy Guidelines

None.

Description

Postpartum Depression

Postpartum depression (PPD) is a temporal major depressive episode that may occur during pregnancy or within 4 weeks of delivery with an estimated prevalence of approximately 12% of births. (1) As per estimates by Sage Therapeutics, the sponsor of brexanolone, PPD may affect 1 in 9 women who give birth in the U.S. per year which translates to 400,000 incident cases annually. (2, 3)

Postpartum depression is similar to other forms of depression and characterized by sadness and/or anhedonia (the inability to feel pleasure) and may present with symptoms such as cognitive impairment, feelings of worthlessness or guilt, or suicidal ideation (see Table 1 for the diagnostic criteria for a major depressive episode). However, PPD is distinguishable from postpartum blues (baby blues) where sadness and anxiety are milder, are time-limited (lasting for a few hours to a few days in the first week postpartum) and have few negative sequelae. (4) Postpartum depression can have serious implications as suicide is the leading cause of maternal death after childbirth in the developed world. This condition has been reported to be one of the strongest predictors of suicidal ideation in new mothers (5) and carries an increased risk for suicide. (6, 7) Recent studies suggest that postpartum suicidal ideation occurs in 19% to 30% of women with PPD. (8, 9)

Table 1. Diagnostic Criteria for a Major Depressive Episode

	Criteria	
A	Five of more symptoms for 2 weeks (one of which must be either depressed mood or anhedonia)	1. Depressed mood most of the day nearly every day 2. Anhedonia most of the day nearly every day 3. Significant weight loss or gain 4. Insomnia or hypersomnia 5. Psychomotor agitation or retardation 6. Fatigue or loss of energy 7. Feelings of worthlessness or excessive guilt 8. Diminished ability to think or concentrate; indecisiveness 9. Recurrent thoughts of death; suicidal ideation or attempt
B	Symptoms cause clinically significant distress or functional impairment	
C	The episode is not attributable to the physiological effects of a substance or another medical condition	
D	The episode is not better explained by a psychotic illness	
E	There has never been a manic or hypomanic episode	

Adapted from FDA Briefing Document (10) and Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed., American Psychiatry Association, 2013. (7)

Current Treatment

The following therapies are currently being used to manage patients with PPD.

Psychotherapy alone is considered first-line treatment for mild to moderate peripartum depression, whereas psychotherapy is often combined with medication in patients with severe symptoms. (11) Cognitive behavior therapy has the most evidence supporting its effectiveness. (12) Evidence is equivocal regarding the use of exercise to treat peripartum depression, (13) and hypnosis has no demonstrated benefit. (14) In patients with severe peripartum depression that is refractory to medication or who have contraindications to medication use, electroconvulsive therapy is effective. (11)

No drugs had been specifically approved by the U.S. Food and Drug Administration (FDA) for treatment of PPD prior to the approval of brexanolone. (10) Drugs generally approved for the treatment of major depression are used to treat PPD, but data on their effectiveness is limited. Non-drug treatments such as electroconvulsive therapy, repetitive transcranial magnetic stimulation, and psychotherapy are also used. All available depression treatments show a delayed effectiveness response. Antidepressant drugs typically take four to six weeks to demonstrate efficacy. Similarly, a course of electroconvulsive therapy is typically twice per week for 4 or 5 weeks, transcranial magnetic stimulation is given daily for 4 to 6 weeks, and psychotherapy usually involves 8 to 20 weekly sessions. (3)

De Crescenzo et al. (2014) published a systematic review of randomized controlled trials (RCTs) comparing selective serotonin reuptake inhibitors to placebo and/or other treatments for PPD that included 6 RCTs with 595 patients. (15) Comparators included cognitive-behavioral intervention, psychosocial community-based intervention, psychodynamic therapy, a second-generation tricyclic antidepressant, and placebo. Limitations in the evidence precluded meta-analytic pooling of data and included small sample size, heterogeneity in interventions, outcomes, duration of follow-up, and a high dropout rate. The response was defined as a reduction of at least 50% from baseline on the Hamilton Rating Scale for Depression (HAM-D) or Edinburgh Postnatal Depression Scale (EPDS) and calculated on the primary endpoint. Only one of the six included studies reported a statistically significant difference in response rate with selective serotonin reuptake inhibitors vs the comparator.

Molyneaux et al. (2018) published a Cochrane systematic review of antidepressants for preventing postnatal depression. (16) The authors identified 2 RCTs trials with a total of 81 participants. The first trial compared nortriptyline with placebo and did not find any evidence that nortriptyline was effective in preventing postnatal depression. (17) In this study, 23% (6/26) of women who took nortriptyline and 24% (6/25) of women who took placebo experienced postnatal depression (relative risk 0.96, 95% confidence interval 0.36 to 2.59, very low-quality evidence) in the first 17 weeks postpartum. The second study compared sertraline with placebo. (18) In this study, 7% (1/14) of women who took sertraline developed postnatal depression in the first 17 weeks postpartum compared with 50% (4/8) of women who took a placebo. It is uncertain whether sertraline reduces the risk of postnatal depression (relative risk 0.14, 95% confidence interval 0.02 to 1.07, very low-quality evidence). Authors failed to draw

any clear conclusions about the effectiveness of antidepressants for the prevention of postnatal depression because of the limited sample size in both the trials.

Regulatory Status
On March 19, 2019, brexanolone (Zulresso) injection for intravenous use was approved by the U.S. Food and Drug Administration for the treatment of postpartum depression in adults. On June 16, 2022, the labeled indication was expanded to patients 15 years and older.

Rationale

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

The clinical development program for brexanolone is summarized in Table 2.

Table 2. Summary of the Clinical Development Program for Brexanolone

Trial	Phase	NCT	N	Dose	Status
Women with severe postpartum depression (HAM-D ≥ 26)					
Kanes et al., 2017 (19) (Study 202A)	2	NCT02614547	21	90µg/kg/h	Completed and published
Meltzer et al. 2018 (20) (Study 202B)	3	NCT02942004	122	60 and 90 µg/kg/h	Completed and published
Women with moderate postpartum depression (HAM-D 20 to 25)					

Meltzer et al. 2018 (20) (Study 202C)	3	NCT02942017	104	90µg/kg/h	Completed and published

HAM-D; Hamilton Rating Scale for Depression; NCT: National Clinical Trial.

Brexanolone

Clinical Context and Therapy Purpose

The purpose of brexanolone in patients who have postpartum depression (PPD) is to provide a treatment option that is an improvement on existing therapies. Potential benefits of this therapy may include the following:

- Treatment offers a novel mechanism of action or approach that may allow successful treatment of many patients for whom other available treatments have failed.
- Successful treatment may reduce the potential for significant morbidity and mortality and allow more positive interactions with mother and baby.
- Treatment offers an opportunity to alleviate symptoms faster (known response within 60 hours) than conventional treatments (weeks to months with selective serotonin reuptake inhibitors or non-drug treatments).

The following PICO was used to select literature to inform this policy.

Populations

The relevant populations of interest is individuals with a diagnosis of PPD (See Table 1).

Interventions

The therapy being considered is brexanolone, which is chemically identical to endogenous allopregnanolone, a positive allosteric modulator of γ-aminobutyric acid-ligand gated chloride (GABAA) channel receptors.

Allopregnanolone is an endogenous hormone derived from progesterone and formed in the brain and corpus luteum, and during pregnancy, in the placenta. Levels of allopregnanolone increase during pregnancy, reach a peak during the third trimester, and then fall abruptly after delivery. Although the mechanism of action is unknown, it is thought to be related to positive allosteric modulator of both synaptic and extrasynaptic GABAA receptors. (21)

Comparators

The relevant comparators are standard medical management (psychotherapy and /or pharmacotherapy).

Outcomes

The general outcomes of interest are change in disease status, functional outcomes, quality of life, treatment-related mortality and treatment-related morbidity. The primary efficacy outcomes measure used in the 3 clinical trials of brexanolone was the 17-item Hamilton Rating Scale for Depression (HAM-D). It is a validated instrument used to rate the severity of depression in patients who are already diagnosed as depressed (22) and has been used in a

number of registration studies of approved oral antidepressants. (2) It is summarized in Table 3. Sage Therapeutics also collected information on other secondary outcomes using the Clinical Global Impression, the Montgomery-Asberg Depression Rating Scale and Edinburgh Postnatal Depression Scale (EPDS). While Clinical Global Impression is a validated measure often utilized in clinical trials to allow clinicians to integrate several sources of information into a single rating of the patient's condition, it is not a disease-specific measure and was only used to corroborate the results of the primary outcome measure. (3) Therefore, such outcome measures are not summarized further in this policy. The onset of symptoms of PPD generally occurs at a discrete time point in the third trimester of pregnancy or after childbirth. The intention of a one-time infusion of brexanolone postpartum for the onset of PPD during pregnancy or after delivery is to achieve acute relief from depressive symptoms. Therefore, assessment of early efficacy outcomes after completion of the 60-hour infusion is appropriate. Further, to assess the durability of efficacy at 30 days is also appropriate.

Table 3. Health Outcome Measures Relevant to Postpartum Depression

Outcome	Description	Relevance
HAM-D	• Clinician 's assessment of depression, traditionally utilized on a weekly or biweekly basis. • Comprises individual ratings related to the following symptoms: depressed mood (sadness, hopeless, helpless, worthless), feelings of guilt, suicide, insomnia (early, middle, late), work and activities, retardation (slowness of thought and speech; impaired ability to concentrate; decreased motor activity), agitation, anxiety (psychic and somatic), somatic symptoms (gastrointestinal and general), genital symptoms, hypochondriasis, loss of weight, and insight. • Previously published trials of oral antidepressant medications have reported mean baseline HAM-D total scores of 13.9 to 24.7 in studies of postpartum depression. (16)	• Each item scored in a range of 0 to 2 or 0 to 4, with higher scores indicating a greater degree of depression. • Scores range from 0 to 48. • Scores as low as 17 are associated with moderate depression and those at or above 24 are associated with severe depression. (23) • In clinical trials of brexanolone, HAM-D response was defined as having a 50% reduction in HAM-D score from baseline, and HAM-D remission was defined as having a HAM-D score ≤ 7.
EPDS	• Self-report instrument containing ten items ranked from 0 to 3 that reflect the patient's experience over the past week with higher scores indicating a greater degree of depression.	• Maximum score is 30 • An EPSD ≥13 is an acceptable cut-point for identifying women at risk

	• This tool is more frequently used for screening depression among postpartum women.	for major depression in clinical setting. • An EPDS ≥13 corresponds with a HAM-D =20 (24) which suggests a high probability for a major depressive episode. (25)

HAM-D: Hamilton Depression Rating Scale; EPSD: Edinburgh Postnatal Depression Scale

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for randomized controlled trials.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought;
- Studies with duplicative or overlapping populations were excluded.

Postpartum Depression

The clinical development program of brexanolone for patients with PPD is summarized in Table 3 and includes three randomized, placebo-controlled trials. Trial characteristics and results are summarized in Table 4 and 5 respectively. All three trials were independent but conducted under an umbrella protocol with similar trial designs. There were some differences and similarities. These are summarized below:

- While all 3 trials randomized patients to a 60-hour infusion of brexanolone IV or placebo and included the proposed 90 µg/kg/h dose regimen, trial 202B also included an arm to evaluate a 60 µg/kg/h dose regimen.
- Trials 202A and 202B enrolled patients with severe PPD (baseline HAM-D score of ≥ 26) while trial 202C enrolled patients with moderate PPD (baseline HAM-D score of 20 to 25).
- The primary endpoint in all 3 trials was the change from baseline in the HAM-D total score at the end of infusion (hour 60).
- Pre-specified key secondary endpoints varied between the trials and included a change from baseline in HAM-D total score at the end of day 30, HAM-D change over time, change in HAM-D individual items, HAM-D response, HAM-D remission, and Clinical Global Impression-I.

A total of 267 patients were randomized in the 3 trials but 20 were not dosed and withdrew for personal reasons (n = 10) or were withdrawn because they no longer met study criteria in the time between randomization and scheduled treatment (n = 10). Overall, 94.7% of all patients completed the study. All 3 trials demonstrated a statistically and clinically significant difference

in the least mean square change in HAM-D score at 60 hours after the infusion. However, the larger phase 3 trials (202B and 202C) revealed a smaller treatment effect than what was observed in the initial phase 2 trial (202A) (3.7 and 2.5 vs 12.2 respectively). The placebo-subtracted difference in HAM-D scores for both the 60 and 90 µg/kg/h doses (-5.5 and -3.7, respectively) are consistent with the efficacy results of other approved antidepressants. Clinically significant improvements in depression were also observed in the placebo arm. This was likely due to increased attention and care received from trained health professionals, as well as supportive care for babies while staying in the hospital.

Post hoc analyses of pooled data of 127 patients from pivotal 202B and 202C studies showed that the baseline health-related quality of life and health utility as assessed with the Short Form-36 Health Survey version 2 (SF-36-v2) among patients with PPD was significantly below normative values and those patients who respond to treatment also experienced rapid improvement in health-related quality of life to levels similar to those observed in the general population. (26) Excluding the physical summary measure, the mean improvement in scores ranged from 4.76 to 25.44 points on day 7 and from 6.20 to 29.56 on day 30, which are all larger than the minimal important change in scores established for these SF-36v2 scales. Score improvements of this magnitude are in the moderate to large effect size range. Since SF-36v2 was added to the trials as an exploratory endpoint by protocol amendment, data was only available for a subset of patients in the clinical trials.

Overall, the incidence of adverse events was similar between brexanolone and placebo arms (50% vs 50.5% respectively). Two cases of serious adverse events were reported in brexanolone treated patients compared to none in placebo. In one patient in the 202B trial, a patient who received brexanolone 60 µg/kg/h reported suicidal ideation 2 days after infusion while another patient in the 202C trial who received brexanolone 90 µg/kg/h suffered from syncope/altered consciousness. In general, the incidence of sedation-related adverse events was observed at a higher frequency in brexanolone vs placebo-treated patients which is reflective of the primary pharmacology of brexanolone. The incidence of sedation/somnolence was 6% and 15% in patients treated with placebo and brexanolone (any dose) respectively. The incidence of dizziness, lightheadedness, presyncope or vertigo was 7% and 12% respectively.

The major safety concern observed with brexanolone was six participants experienced loss of consciousness/syncope/presyncope during infusion. Of these six, one fainted with blood draw (fear of needles), one suffered presyncope /vertigo standing which was resolved after sitting and four appeared to have suddenly fallen asleep. These effects were resolved with dose interruption and all patients recovered in 10 to 60 minutes after loss of consciousness. As per the U.S. Food and Drug Administration (FDA), (10) the loss of consciousness can be abrupt, there is no known way to predict the risk of loss of consciousness which could result in serious harm, accident, or injury to the mother and, potentially to the infant. The observed incidence of loss of consciousness occurred in a clinical trial setting that required overnight accommodations for patients for approximately 72 hours, IV infusion capabilities, and the presence of a healthcare professional on site at all times. While the healthcare professional credentials varied between sites such as emergency medical technicians, nurses, and physicians, the majority of

patients (85%) were dosed in a variety of non-hospital clinical research environments and 15% were dosed at units that were part of a hospital environment. (27) In order to mitigate the risk of sudden loss of consciousness, the FDA has mandated a Risk Evaluation and Mitigation Strategy (REMS) that requires administration of brexanolone only in medically-supervised settings and is detailed in section "Tentative Inclusion Guidelines".

Table 4. Summary of Key Randomized Trials of Brexanolone

					Description of Interventions	
Study	**Countries**	**Sites**	**Dates**	**Participants**	**Active**	**Comapator**
Kanes et al. 2017 (19) (Study 202A)	U.S.	4	2015-2016	• Ages 18 to 45 years • ≤ 6 months post-partum • Major depressive episode (DSM criteria) • Onset 3rd trimester through 4 weeks postpartum • HAM-D ≥ 26 (202A and 202B) or 20 to 25 (Study 202C)	Brexanolone 90 µg/kg/h (n=10)	Placebo (n=11)
Meltzer et al. 2018 (20) (Study 202B)	U.S.	32	2016 to 2017		Brexanolone 60 µg/kg/h (n=38) Brexanolone 90 µg/kg/h (n=41)	Placebo (n=43)
Meltzer et al. 2018 (20) (Study 202C)	U.S.	32	2016 to 2017		Brexanolone 90 µg/kg/h (n=51)	Placebo (n=53)

DSM: Diagnostic and Statistical Manual of Mental Disorders; HAM-D: Hamilton Rating Scale for Depression

Table 5. Summary of Key Randomized Trials of Brexanolone

	LS Difference in Mean HAM-D[a]		**HAM-D Remission[b]**		**HAM-D Response[b]**	
Study	**Hour 60**	**Day 30**	**Hour 60**	**Day 30**	**Hour 60**	**Day 30**
Kanes et al. 2017 (19) (Study 202A)						
N	21	21	21	21	21	21
Brexanolone (±SE)	-21·0 (±2·94)	-20·77 (NR)	70% (NR)	70% (NR)	70% (NR)	70% (NR)

Placebo (±SE)	-8·8 (±2·80)	- 8·84 (NR)	9%(NR)	18%(NR)	36% (NR)	27% (NR)
Diff (95% Cl)	-12·2 (-20·8 to -3·7)	-11·9 (4·1)	61% (NR)	52% (NR)	34% (NR)	43% (NR)
P value	<.05	<.05	NA	NA	NA	NA
Meltzer et al. 2018 (20) (Study 202B)						
N	122	122	122	122	122	122
Brexanolone 60 (±SE)	-19·5 (±1·23)	-19·5 (±1·44)	51% (NR)	49% (NR)	87% (NR)	83% (NR)
Brexanolone 90 (±SE)	-17·7 (±1·19)	-17·6 (±1·40)	31% (NR)	39% (NR)	74% (NR)	69% (NR)
Placebo (±SE)	-14·4 (±1·15)	-13·8 (±1·32)	16% (NR)	31% (NR)	56% (NR)	50% (NR)
Diff 60 (95% Cl)	-5·5 (-8·8 to -2·2)	-5·6 (-9·5, -1·8)	35% (NR)	18%(NR)	31% (NR)	33% (NR)
Diff 90 (95% Cl)	-3·7 (-6·9 to -0·5)	-3·8 (-7·6, -0·0)	15% (NR)	8%(NR)	18% (NR)	19% (NR)
P value	<.05	<.05	NA	NA	NA	NA
Meltzer et al. 2018 (20) (Study 202C)						
N	104	104	104	104	104	104
Brexanolone (±SE)	-14·6 (0·78)	-14·7 (0.96)	61% (NR)	48% (NR)	76% (NR)	71% (NR)
Placebo (±SE)	-12·1 (0·77)	-15·2 (0.93)	39% (NR)	62% (NR)	60% (NR)	79% (NR)
Diff (95% Cl)	-2·5 (-4·5, -0·5)	0·5 (-2·0, 3·1)	22% (NR)	-14% (NR)	16% (NR)	-8% (NR)
P value	<0.05	.67	NA	NA	NA	NA

Cl: confidence interval; HAM-D: Hamilton Rating Scale for Depression; LS: least square; NA: not applicable; NR: not reported; SE: standard error

[a] HAM-D remission is ≤ 7 HAM-D total score

[b] HAM-D response is ≥ 50% reduction from baseline in HAM-D total score.

The purpose of the study limitations table (see Table 6) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of the evidence supporting the position statement. No limitations in study design and conduct were noted. Notable relevance limitations include a relatively short follow-up of 30 days and exposure of drugs in a limited number of patients under controlled setting to adequately characterize the safety of brexanolone. The FDA has proposed the creation of a registry to enroll all patients treated with brexanolone to better characterize the risk of loss of consciousness and management of the risk.

Table 6. Study Relevance Limitations

Study	Population [a]	Intervention [b]	Comparator [c]	Outcomes [d]	Follow-Up [e]
Kanes et al. 2017 (19) (Study 202A); Meltzer et al. 2018 (20) (Study 202B and 202C)					2. Not sufficient duration for harms.

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinical significant difference not supported.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Section Summary: Postpartum Depression (PPD)

The evidence for use of brexanolone for PPD consists of 3 RCTs in which 247 patients were randomized to brexanolone 60 µg/kg/h (n=38), brexanolone 90 µg/kg/h (n=102) and placebo (n=107). The primary efficacy endpoint of change from baseline in the HAM-D total score at 60 hours resulted in significant and clinically meaningful reductions in HAM-D total score compared with placebo. Brexanolone was associated with a greater frequency of sedation-related side effects than placebo including sudden loss of consciousness in six patients. Therefore, brexanolone has been approved with a Risk Evaluation and Mitigation Strategy program to monitor and manage the risk of loss of consciousness. Notable relevance gaps include a relatively short follow-up of 30 days and exposure of drugs in a limited number of patients under controlled setting to adequately characterize the safety of brexanolone.

Summary of Evidence

For individuals with postpartum depression who receive brexanolone, the evidence includes 3 randomized, placebo-controlled trials in which 247 patients with Hamilton Rating Scale for Depression (HAM-D) scores ≥20 were randomized to brexanolone 60 µg/kg/h (n=38), brexanolone 90 µg/kg/h (n=102) and placebo (n=107). The relevant outcomes are change in disease status, functional outcomes, quality of life, and treatment-related mortality and morbidity. The primary efficacy endpoint of change from baseline in the 17-item HAM-D total score at 60 hours resulted in significant and clinically meaningful reductions in the total score

compared with placebo. Brexanolone was associated with a greater frequency of sedation-related side effects than placebo including sudden loss of consciousness in six patients. Characterization of the safety of brexanolone was inadequate due to notable study limitations. These include exposure to study drug in a limited number of patients in a controlled setting and a relatively short follow-up of 30 days. The observed loss of consciousness during drug infusion is part of the basis for a Risk Evaluation and Mitigation Strategy requirement. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

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 (28) are summarized here.

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." (29, 30)
- "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."

U.S. Preventive Services Task Force (USPSTF) Recommendations

- The USPSTF recommendations apply to pregnant persons and persons who are less than one year postpartum who do not have a current diagnosis of depression but are at increased risk of developing depression. (31)
- 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).

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 7.

Table 7. Summary of Key Clinical Trials

NCT Number	Study Title	Planned Enrollment	Completion Date
Ongoing			
NCT04468360	Facilitation of Extinction Retention and Reconsolidation Blockade in PTSD	256	Mar 2024
Unpublished			
NCT03665038[a]	A study to assess the safety and efficacy of brexanolone in the treatment of adolescent female subjects with postpartum depression	28	Completed
NCT02477618	A study with SAGE-547 for super-refractory status epilepticus	132	Completed
NCT02285504	Evaluate SAGE-547 in female patients with severe postpartum depression	4	Completed
NCT02277106	Evaluate SAGE-547 in patients with essential tremor	25	Completed
NCT02052739	Study to evaluate SAGE-547 injection as adjunctive therapy for the treatment of super-refractory status epilepticus	25	Completed
NCT05059600	A study to assess the safe-use conditions for administration of Zulresso® in a home setting	42	Completed

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J1632

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
12/15/2024	Reviewed. No changes.
03/15/2024	Document updated with literature review. The following changes were made to the Coverage: 1) Added: "Will not be utilized concomitantly with zuranolone (Zurzuvae™) for the treatment of postpartum depression" to the medically necessary statement for Zulresso™ (brexanolone) for one-time use per pregnancy; 2) Revised rating scale /classifications listed under NOTE 1 for Hamilton Rating Scale for Depression (HAM -D); 3) Removed "moderate to severe" from statement 4: Individual has a diagnosis of moderate to severe postpartum depression based on either of the following. No references were added, some references were updated.
02/01/2023	Document updated with literature review. The following change was made to the Coverage: Revised age of individual from 18 years to 15 years of age or older. No new references added; some updated and one reference removed.
01/01/2022	Document updated with literature review. Coverage unchanged. The following reference was added: 26, other references were updated.
10/15/2020	Reviewed. No changes.
06/01/2020	New medical document. Brexanolone (Zulresso) may be considered medically necessary for one time use per pregnancy when criteria indicated in coverage are met. Zulresso (brexanolone) is considered experimental, investigational and/or unproven in all other situations.