Subject: Zulresso (brexanolone)	**Original Effective Date:** 05/29/2019
Policy Number: MCP-345	**Revision Date(s):**
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DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.

SUMMARY OF EVIDENCE/POSITION

This policy addresses **Zulresso (brexanolone)** is a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator indicated for the treatment of postpartum depression (PPD) in adult women when appropriate criteria are met.

Postpartum depression (PPD), also known as major depressive disorder with peripartum onset, is defined by the onset of depressive symptoms, unipolar major depressive disorder, or mood disorder in the postpartum period (onset 4-6 weeks following delivery for up to 1 year).

- The Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM-5) classifies peripartum depression as a major depressive disorder that is identified during pregnancy or within four weeks postpartum, although some experts extend this to within one year postpartum. The DSM-5 does not recognize PPD as a separate diagnosis; rather, PPD patients meet the criteria for a major depressive episode and the criteria for peripartum onset. The DSM-5 criteria for major depressive disorder are listed in **Appendix 1.**
- It is estimated that PPD affects approximately 10-20 percent of women giving birth globally. In the United States, estimates of new mothers identified with PDD each year vary by state from 8-20 percent, with an overall average of 11.5 percent (Sage Therapeutics). The Centers for Disease Control and Prevention estimates that 1 in 9 women, and possibly as many as 1 in 5, experience PPD.
- The etiology of PPD is unknown, but a rapid decline in reproductive hormone levels after delivery is thought to trigger mood disorder in susceptible women. Risk factors include personal or family history of antenatal or postpartum depression. Preventive therapy is recommended for at-risk women, including prenatal and postpartum counseling, psychotherapy, and/or previously used antidepressant medication.
- Primary care clinicians (including obstetricians, gynecologists, or pediatricians) should screen all postpartum women for depression at least once during the perinatal period (at the postpartum visit or 2-month well-child visit) with the Edinburgh Postnatal Depression Scale (EDPS) or other screening tool.
- Generally, PPD has been treated with counseling and/or antidepressants, according to the National Institute of Mental Health. Treatment of PPD depends on the severity of symptoms and the level of functional impairment.

- 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. Cognitive behavior therapy has the most evidence supporting its effectiveness.
- The management of PPD has included psychological therapy as a first-line option, with no defined time to response, followed by pharmacologic options for patients with moderate to severe PPD or for those who failed to respond to psychological treatment.
- *Pharmacologic Treatment* Pharmacological treatment options included: SSRIs, Serotonin and norepinephrine reuptake inhibitors (SNRIs), Monoamine oxidase inhibitors (MAOIs), or Tricyclic antidepressants (TCAs). (Molyneaux E, et al.)
- *SSRIs* are the most commonly prescribed antidepressant (Langan et al., 2016). However, SSRI agents are not specifically FDA-approved for the treatment of PPD, and can often take weeks to months to be effective in alleviating symptoms of depression. No substantial evidence supports the use of one SSRI over another, although there are a few factors to consider when selecting an agent for postpartum women including sensitivity to medications due to hormone effects on liver enzymes, increased volume of distribution, and increased levels of drug-binding proteins; therefore, some experts recommend starting a medication at one-half of the regular dose and titrating slowly. Generally, Celexa (citalopram), Lexapro (escitalopram), or Zoloft (sertraline) is recommended first-line during pregnancy or while breastfeeding, due to minimal risks to the fetus/neonate. However, 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.
- While the use of pharmacotherapy during breastfeeding is a concern, the risks must be weighed against the risks of untreated PPD to the woman and her children, including suicide risk and impaired maternal-infant bonding.

Zulresso (brexanolone) is the first treatment to receive FDA approval for specific treatment of postpartum depression (PPD). The mechanism of action differs from that of currently available antidepressants; however mechanism of action is not fully understood. Brexanolone is chemically identical to endogenous allopregnanolone, a hormone that decreases after childbirth, which acts as a positive allosteric modulator of γ-aminobutyric-acid type A ($GABA_A$) receptors, which become dysregulated in the postpartum period. The efficacy of Zulresso in the treatment of PPD was demonstrated in 2 phase III pivotal trials (Meltzer-Brody et al., 2018). The trials were randomized, double-blind, randomized, placebo-controlled, phase 3 trials, at 30 clinical research centers and specialized psychiatric units in the U.S. (Studies 1 and 2).

Study 1 randomly assigned participants to one of three groups to receive: Zulresso 90 micrograms per kilogram (μg/kg) per hour (BRX90; n=45), Zulresso 60 μg/kg per hour (BRX60; n=47), or placebo (n=46) for 60 hours **(study 202B; n=122).** Study 2 compared brexanolone titrated up to 90 mcg/kg per hour with placebo; BRX90 (n=54) or matching placebo (n=54) for 60 hours in **study 202C (Study 2; n=104).**

The primary efficacy endpoint was the change from baseline in the 17-item HAM-D total score at 60 hours, assessed in all patients who started infusion of study drug or placebo, had a valid HAM-D baseline assessment, and had at least 1 post-baseline HAM-D assessment. The safety population included all randomized patients who started infusion of study drug or placebo. Patients were followed up until day 30.

Summary of Clinical Evidence:
- Clinically, the first-line treatment for moderate to severe PPD will remain selective-serotonin reuptake inhibitors (SSRIs) combined with psychosocial interventions. Zulresso presents an alternative to SSRIs for first-line treatment of PPD due to its rapid onset of action, robust response rate, and low side effect profile.
- Brexanolone significantly improved Hamilton Rating Scale for Depression (HAM-D) total score at the end of 60-hour infusion consistently compared with placebo in 3 randomized trials in women with moderate to severe postpartum depression, with a majority of patients maintaining response after 30 days (Meltzer-Brody S)(Kanes S, et al)
- There is insufficient published evidence to evaluate the long-term safety and efficacy of Zulresso for the treatment of PPD. Follow-up in published trials was limited to 30 days; therefore, the durability of treatment effect beyond 30 days

is unknown. To date, there are no trials comparing Zulresso with currently available agents used for the treatment of PPD, and the long-term efficacy of Zulresso compared with currently available oral antidepressants remains unclear.
- The most significant limitation with Zulresso as a treatment option is the 60-hour infusion in an inpatient/overnight facility for appropriate monitoring, and accessibility a 'certified healthcare facilities' specified by the REMS.

FDA INDICATIONS

Postpartum Depression: For the treatment of postpartum depression (PPD) in adult women

Available as: 100 mg/20 mL solution (5 mg/mL) in single-dose vials

FDA Approved: March 2019
Previously granted Priority Review and Breakthrough Therapy designations

Black Box Warnings: Excessive sedation and sudden loss of consciousness. Because of the risk of serious harm in patients treated with brexanolone, monitoring for excessive sedation and sudden loss of consciousness and continuous pulse oximetry is required. Patients must be accompanied during interactions with their child(ren).

Risk evaluation and mitigation strategy (REMS): To mitigate the risk of serious harm resulting from excessive sedation and sudden loss of consciousness during Zulresso infusion by ensuring that Zulresso is administered only to patients in a medically-supervised setting that provides monitoring during administration; pharmacy and health care settings that dispense Zulresso are certified; patients are informed of the adverse events of excessive sedation and loss of consciousness and the need for monitoring during administration; and all patients are enrolled in the REMS program to ensure and support safe-use conditions. A list of certified health care facilities is available at https://www.zulressorems.com.

PHARMACOLOGIC CATEGORY: Gamma-Aminobutyric Acid (GABA) A Receptor Positive Modulator

RECOMMENDATIONS/COVERAGE CRITERIA

Zulresso (brexanolone) may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty [ALL]

- ❒ Prescribed by, or in consultation with, a board-certified **Psychiatrist and OB/GYN.** Submit consultation notes if applicable.

- ❒ Zulresso REMS Program requirements are met. Documentation of the following required: [BOTH]
  - ❍ Health care facility and dispensing pharmacy must be certified with the REMS program and patient (Molina member) enrollment in the program *prior to* administration
    AND
  - ❍ Completed Patient Enrollment Form with the health care provider and documentation that member has been counseled on signs and symptoms of excessive sedation, loss of consciousness, and the importance of immediately reporting to a health care provider any signs and symptoms of excessive sedation using the Patient Information Guide.

2. **Diagnosis/Indication [ALL]**
Documentation of diagnosis required and may include clinical notes from the member's medical records including any relevant labs and/or tests, supporting the diagnosis **[ALL]**

- ❒ Diagnosis of moderate or severe Postpartum Depression based on the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria for a major depressive episode

- ❒ Peripartum onset: Onset of depression occurring between the 3rd trimester of pregnancy and four weeks postpartum (after delivery). Documented diagnosis and all supporting clinical records required.

  - *APPENDIX 1: DSM-5 Diagnostic criteria for a major depressive episode*

- ❒ **Moderate to severe postpartum depression** documented by a rating scale such as the Hamilton Rating Scale for Depression (HAM-D) or Montgomery-Åsberg Depression Rating Scale (MADRS) with a **score of ≥ 20,** OR as documented by a *comparable standardized rating scale that reliably measures depressive symptoms

  *Refer to APPENDIX 2: Common Screening Tests for Peripartum Depression. May use other standard PPD scales including: Edinburgh postnatal Depression Scale (EPDS), Patient Health Questionnaire-9 (PHQ-9), Beck Depression Inventory (BDI-II)]

- ❒ Member is 6 months or less postpartum
  - *In clinical studies for postpartum depression, treatment was started within 6 months after delivery.*

- ❒ Other diagnoses such as postpartum blues, postpartum psychosis, bipolar disorder, and hypo- or hyperthyroidism have been ruled out AND the following blood tests to rule out: [BOTH]
  - ❍ Thyroid disorders which may cause depressive symptoms: Assess levels of thyroid-stimulating hormone and free thyroxine
    AND
  - ❍ Postpartum anemia leading to fatigue

3. **Age/Gender/Restrictions [ALL]**

- ❒ 18 to 45 years of age
  - *Safety and efficacy has not been established in patients outside of this age range*

- ❒ Member has ceased lactating, OR if still lactating or actively breastfeeding, then member agrees to cease breastfeeding at the start of the infusion and for FOUR (4) days after the infusion ended. Documentation of lactation status or agreement to temporarily cease breastfeeding required.
  - *APPENDIX 3: Considerations for Breastfeeding Women*

- ❒ Negative pregnancy test and member agrees to use contraception during therapy and for 30 days after completion of the brexanolone infusion
  - *In clinical studies for postpartum depression, treatment was started within 6 months after delivery. Study participants were required to have a negative pregnancy test and use contraception during therapy and for 30 days after completion of the brexanolone infusion (Meltzer-Brody 2018)*
  - *Based on findings from animal studies of other drugs that enhance GABAergic inhibition, Zulresso may cause fetal harm; however there are no available data on Zulresso use in pregnant women to determine a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.*

4. Conventional Therapy/Concurrent Therapy/Other Requirements [ALL]

- ❒ Member meets ONE of the following. Documentation required: [ONE]
  - ❍ Inadequate response to a compliant 8-week trial of a generic oral antidepressant at a maximally tolerated therapeutic dose: selective serotonin reuptake inhibitor (SSRI) (e.g. paroxetine, sertraline, citalopram); serotonin-norepinephrine reuptake inhibitor (SNRI) (e.g. desvenlafaxine, duloxetine, venlafaxine), tricyclic antidepressant (TCA) (e.g. nortriptyline), bupropion; mirtazapine; OR
  - ❍ Intolerance or FDA labeled contraindication to ALL classes of antidepressants; OR
  - ❍ Other clinical rationale supporting an exception of an oral antidepressant trial as determined by Prescriber (i.e. member is a potential risk of harm to self and/or others as determined by the treating provider)

- ❒ Treatment plan includes: Initiation of oral therapy within 7 days post-infusion AND discharge on oral antidepressant(s) regimen as prescribed by psychiatrist, or in consult with psychiatrist. Treatment plan must be submitted for review.
  - ◆ *APPENDIX 3: Considerations for Breastfeeding Women*

- ❒ For members who have received Zulresso therapy for a previous pregnancy/post-partum period: Prior therapy with Zulresso (brexanolone) resulted in improvement of depressive symptoms AND did not experience serious adverse effects, including: excessive sedation or sudden loss of consciousness during administration; worsening depression or emergent suicidal thoughts and behaviors; hypoxia

5. Contraindications/Exclusions

**There are no contraindications listed in the manufacturer's labeling. The following conditions are *key exclusion criteria from pivotal trials which must be excluded for authorization of treatment.*

Authorization will not be granted if ANY of the following conditions apply [ANY]

- ❒ Non-FDA approved indications
- ❒ Known hypersensitivity to brexanolone or allopregnanolone progesterone or any component of the formulation, including betadex sulfobutyl ether sodium
- ❒ End stage renal disease (ESRD) with eGFR less than 15 mL/minute/1.73 m^2
  - ◆ *Due to the potential accumulation of the solubilizing agent, betadex sulfobutyl ether sodium*
- ❒ Active psychosis
  - ◆ *Antipsychotics are the treatment of choice for women with psychosis during pregnancy or the postpartum period, despite a lack of high-quality evidence to support their effectiveness (Langan et al., 2016).*
- ❒ Attempted suicide associated with index case of postpartum depression NOTE: Suicidal ideation is not an exclusion
  - ◆ *Patients with active suicidal thoughts, thoughts of harming their newborns, or psychosis should have same-day psychiatric consultation for possible inpatient treatment (American Psychiatric Association, 3rd edition)*
- ❒ Medical history of bipolar disorders, schizophrenia, and/or schizoaffective disorder
- ❒ Current substance or alcohol use disorder (Melzer-Brody et al, 2018)

NOTE: No studies were conducted to evaluate the effects of other drugs on Zulresso

6. **Labs/Reports/Documentation required [ALL]**
All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

   - ❒ Member's current weight (within the past 30 days) for dosage review as consistent with FDA-approved labeling

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

CONTINUATION OF THERAPY

Zulresso (brexanolone) will <u>not</u> be authorized for continuation of therapy.

Authorizations are granted for one treatment per postpartum period, per delivery.

Repeat treatment for one postpartum period is not proven by clinical trials and supported by medical literature, or by approved compendia; therefore, is not considered medically necessary.

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.

1. **Recommended Dosage [ALL]**

   - ❒ Administer as a continuous IV infusion over a total of 60 hr (2.5 days) in a monitored health setting that is able to intervene as necessary with continuous pulse oximetry. Recommended dosing also requires several infusion rate changes as follows:
     - 0-4 hours: Initiate at 30 mcg/kg/hr
     - 4-24 hours: Increase to 60 mcg/kg/hr
     - 24-52 hours: Increase to 90 mcg/kg/hr (consider reducing to 60 mcg/kg/hr if not tolerating 90 mcg/kg/hr)
     - 52 to 56 hours: Decrease to 60 mcg/kg/hr
     - 56 to 60 hours: Decrease to 30 mcg/kg/hr

   - ❒ Dosage requested is consistent with member's current weight and FDA-approved labeling

2. **Authorization Limit [ALL]**

   - ❒ Quantity Limit: One treatment per postpartum period (per delivery)

   - ❒ One treatment generally requires five infusion bags. Additional bags may be needed for patients weighing ≥ 90 kg.

3. Route of Administration [ALL]
**All authorizations are subject to utilization of the most cost-effective site of care*

- ❒ Prescriber/physician attestation that brexanolone will be administered under direct supervision of a healthcare professional at a treatment facility that is certified through the Zulresso REMS program.
  - Zulresso (brexanolone) is considered as a **provider-administered** and in the hospital setting or identified "Centers of Excellence" able to **meet REMS requirements** and have the capabilities to prepare, administer and monitor therapy.
  - A healthcare provider must be available on site to continuously monitor the patient, and intervene as necessary, for the duration of the Zulresso infusion; patients must be monitored for hypoxia using continuous pulse oximetry equipped with an alarm.

COVERAGE EXCLUSIONS

This policy addresses Zulresso (brexanolone), a Gamma-Aminobutyric Acid (GABA) A Receptor Positive Modulator, indicated for the treatment of postpartum depression (PPD) in adult women when appropriate criteria are met.

All other uses of Zulresso (brexanolone) that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered not medically necessary. This is subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

SUMMARY OF EVIDENCE

PIVOTAL TRIALS

There are 2 phase III pivotal trials (Meltzer-Brody et al., 2018) published in a single report. There is also a published phase II 202A study (Kanes et al., 2017a) and a published proof-of-concept study in 4 women with PPD (Kanes et al., 2017b).

A Study to Evaluate SAGE-547 in Patients with Severe Postpartum Depression (PPD)
A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-547 Injection in the Treatment of Adult Female Subjects with Severe PPD and Adult Female Subjects with Moderate PPD

Meltzer-Brody and colleagues conducted two large, multicenter, randomized, controlled trials (RCTs) at 30 clinical sites. **Study 1 (NCT02942004)** included patients with severe PPD (Hamilton Depression Rating Scale (HAM-D) score ≥ 26), and **Study 2 (NCT02942017)** included patients with moderate PPD (HAM-D score of 20 to 25). A titration to the recommended target dosage of 90 mcg/kg/hour (BRX90) was evaluated in both studies (patients received 30 mcg/kg/hour for 4 hours, 60 mcg/kg/hour (BRX60) for 20 hours, 90 mcg/kg/hour for 28 hours, followed by a taper to 60 mcg/kg/hour for 4 hours and then 30 mcg/kg/hour for 4 hours). A titration to a target dosage of 60 mcg/kg/hour (patients received 30 mcg/kg/hour for 4 hours, 60 mcg/kg/hour for 52 hours, then 30 mcg/kg/hour for 4 hours) was also evaluated in Study 1.

Subjects received a 60-hour continuous intravenous infusion of Zulresso or placebo and were then followed for 4 weeks.

Eligible subjects were women (18 to 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. Study 1 included patients with severe PPD (Hamilton Depression Rating Scale (HAM-D) score ≥ 26), and Study 2 included patients with moderate PPD (HAM-D score of 20 to 25).

Demographic and baseline disease characteristics were generally similar across treatment groups in the pooled Studies 1 and 2. Most patients were White (63%) or Black (34%); 18% of patients identified as Hispanic or Latina; the average age

of women receiving Zulresso was 28 years. Most patients (76%) had onset of PPD symptoms within 4 weeks after delivery, with the remainder having onset during the third trimester. Baseline oral antidepressant use was reported for 23% of patients.

Study 1 (NCT02942004)

- 138 adult women ≤ 45 years old (mean age 27 years) with depression ≤ 6 months postpartum were randomized to 1 of 3 IV infusions over 60 hours
  - BRX90 consisted of brexanolone 30 mcg/kg/hour (0-4 hours), 60 mcg/kg/hour (4-24 hours), 90 mcg/kg/hour (24-52 hours), 60 mcg/kg/hour (52-56 hours), and 30 mcg/kg/hour (56-60 hours)
  - BRX60 consisted of same schedule except for receiving brexanolone 60 mcg/kg/hour at 24-52 hours
  - placebo
- all women had 17-item Hamilton Rating Scale for Depression (HAM-D) score ≥ 26 (range 0-52 points)
- at baseline, mean HAM-D score was about 28.7 points for all groups
- 88% included in analysis
- mean reduction in HAM-D scores at 60 hours
  - 17.7 points with BRX90 (95% CI for mean difference vs. placebo -0.5 to -6.9), significant, but CI includes differences that may not be clinically important
  - 19.5 points with BRX60 (95% CI for mean difference vs. placebo -2.2 to -8.8), significant, but CI includes differences that may not be clinically important
  - 14 points with placebo
- consistent results for mean reduction in HAM-D score at 30 days
- rates of remission defined as HAM-D score ≤ 7 points
  - 32% (estimated from figure) with BRX90 (not significant vs. placebo)
  - 51% with BRX60 (p = 0.0011 vs. placebo, NNT 3)
  - 16% with placebo
- no significant differences in rates of remission at 30 days
- rates of women receiving new or changed antidepressant therapy after end of treatment
  - 12.2% with BRX90
  - 10.5% with BRX60
  - 7% with placebo
- rates of women with Clinical Global Impression-Improvement (CGI-I) rating of 1 or 2 at 60 hours
  - 82% with BRX90 (p = 0.0095, NNT 4)
  - 84% with BRX60 (p = 0.013, NNT 4)
  - 56% with placebo
- rates of treatment discontinuation due to adverse event
  - 0% with BRX90
  - 3% with BRX60
  - 2% with placebo
- 1 patient in BRX60 group had suicidal ideation and intentional overdose attempt

Study 2 (NCT02942017)

- 108 women with depression (HAM-D score 20-25) ≥ 6 months postpartum were randomized to BRX90 infusion vs. placebo for 60 hours
- at baseline mean HAM-D score was 22.6 points
- 96% included in analysis
- comparing BRX90 vs. placebo
  - mean reduction in HAM-D scores at 60 hours 14.6 points vs. 12.1 points (95% CI for mean difference -0.5 to -4.5) significant, but CI includes differences that may not be clinically important
  - mean reduction in HAM-D scores at 30 days 14.7 points vs. 15.2 points (not significant)
  - remission at 60 hours in 61% vs. 38% (p = 0.0033, NNT 5)
  - CGI-I of 1 or 2 at 60 hours in 79.6% vs. 55.8% (p = 0.0005, NNT 5)

- discontinuation due to adverse event in 4% vs. 0% (no p value reported)
- 1 patient in BRX90 group had altered state of consciousness and syncope

The primary efficacy endpoint of the clinical study was the mean change from baseline in the 17-item HAM-D total score in subjects who received brexanolone compared with subjects who received placebo at the 60-hour time point, at the end of the infusion. A pre-specified secondary efficacy endpoint was the mean change from baseline in HAM-D total score at Day 30. In both placebo-controlled studies, titration to a target dose of Zulresso 90 mcg/kg/hour was superior to placebo in improvement of depressive symptoms. In a group of 38 patients in Study 1, a Zulresso titration to a target dose of 60 mcg/kg/hour was also superior to placebo in improvement of depressive symptoms. Other secondary outcome measures were Edinburgh Postnatal Depression Scale (EPDS), Patient Health Questionnaire-9, Generalized Anxiety Disorder 7-item scale, and Clinical Global Impression scale-improvement subscale.

- Brexanolone achieved the primary endpoint in all trials at all doses–a significant mean reduction from baseline in the Hamilton Rating Scale for Depression total score at 60 hours compared to placebo. In addition, a reduction of symptoms was seen as early as 24 hours, and the drug maintained its effect through the 30-day follow-up.
- Most common (in ≥ 3 women) adverse events included headache, dizziness, somnolence, infusion site pain, nausea, dry mouth, and fatigue

CLINICAL PRACTICE GUIDELINES

No guidelines were identified at the time of this writing, in April 2019, that recommend the use of Zulresso for treatment of moderate to severe postpartum depression.

DEFINITIONS

Hamilton Rating Scale for Depression (HAM-D) is a validated 17-item rating scale used to determine the severity level of depression in a patient before, during, and after treatment. This scale is an accepted regulatory endpoint for depression. The scale is used to rate the severity of a patient's depression by probing mood, feelings of guilt, suicide ideation, insomnia, agitation, anxiety, weight loss, and somatic symptoms. The total score ranges from 0 to 52, with the score corresponding to the following classifications:

- 0-7: No depression (normal)
- 8-16: Mild depression
- 17-23: Moderate depression
- ≥24: Severe depression

APPENDIX

APPENDIX 1: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5): Diagnostic criteria for a major depressive episode

A.	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.
	NOTE: Do not include symptoms that are clearly attributable to another medical condition.
	1) 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.)
	2) 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)
	3) 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.)

4) Insomnia or hypersomnia nearly every day
5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
6) Fatigue or loss of energy nearly every day
7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by their subjective account or as observed by others)
9) 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
B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. The episode is not attributable to the direct physiological effects of a substance or to another medical condition.
NOTE: Criteria A through C represent a major depressive episode.
NOTE: 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.
D. 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.
E. There has never been a manic or hypomanic episode.
NOTE: 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.
Specify:
With anxious distress
With mixed features
With melancholic features
With atypical features
With psychotic features
With catatonia
With peripartum onset
With seasonal pattern

Reference: Langan, R. Identification and Management of Peripartum Depression. Am Fam Physician. 2016 May 15;93(10):852-858. https://www.aafp.org/afp/2016/0515/p852.html --Reprinted with permission from the American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013:160–161.

APPENDIX 2: Common Screening Tests for Peripartum Depression

- American Academy of Family Physicians (AAFP) recommend screening at the postpartum visit, or 2-month well-child visit (Am Fam Physician 2010 Oct 15;82(8):926)
- American College of Obstetricians and Gynecologists (ACOG) Committee Opinion 757 on screening for perinatal depression

- Screen women at least once during perinatal period for depression and anxiety using a validated, standardized screening tool
- Close monitoring, evaluation, and assessment is recommended in women with: current depression or anxiety, history of perinatal mood disorders, risk factors for mood disorders

Edinburgh Postnatal Depression Scale (EPDS) was published over 30 years ago and is a self-reported scale used internationally to assess depression during pregnancy and postpartum

- EPDS is most frequently used tool in research and clinical settings; available in 50 different languages and can be completed in < 5 minutes. Criteria supported by ACOG Committee Opinion 757 on screening for perinatal depression (ACOG 2018 Oct PDF)
- 10-item questionnaire, with each question scored from 0 to 3, and a maximum score of 30
- can be used as early as 3 days postpartum with a score > 9.5 indicating possible depression
- likely major or minor depression indicated by score > 12 in pregnancy, or > 10 in postpartum period
- Calculator available at: https://psychology-tools.com/test/epds

Reference: Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry. 1987 Jun;150:782-6. PMID:3651732

Hamilton Rating Scale for Depression (HAM-D) is a validated 17-item rating scale used to determine the severity level of depression in a patient before, during, and after treatment. This scale is an accepted regulatory endpoint for depression. The scale is used to rate the severity of a patient's depression by probing mood, feelings of guilt, suicide ideation, insomnia, agitation, anxiety, weight loss, and somatic symptoms. The total score ranges from 0 to 52, with the score corresponding to the following classifications:

- 0-7: No depression (normal)
- 8-16: Mild depression
- 17-23: Moderate depression
- ≥24: Severe depression

https://qxmd.com/calculate/calculator_146/hamilton-depression-rating-scale-ham-d-or-hdrs

Montgomery-Asberg Depression Rating Scale (MADRS) is a 10-item diagnostic questionnaire used to measure the severity of depressive episodes in patients with mood disorders.

MADRS Score	Depression Severity
0 – 6	Normal/symptom absent
7 – 19	Mild depression
20 – 34	Moderate depression
> 34	Severe depression

https://www.mdcalc.com/montgomery-asberg-depression-rating-scale-madrs

Patient Health Questionnaire-9 (PHQ-9) is a 9-item multiple choice questionnaire used for diagnosis, screening, monitoring and measuring the severity of depression.

PHQ-9	Depression Severity
5 – 9	Minimal symptoms
10 – 14	Minor depression Major depression, mild
15 – 19	Major depression, moderately severe
> 20	Major depression, severe

APPENDIX 3: Considerations for Breastfeeding Women

American College of Obstetricians and Gynecologists (ACOG) recommendations for use of psychiatric medications during lactation

- Benefits of breastfeeding should be weighed against risks to the neonate associated with exposure to medication in breast milk. Certain antidepressants considered safer for use in breastfeeding women than others, but long-term outcomes for exposed babies are unknown
- Antidepressants categorized as low lactation risk include: sertraline, paroxetine, nortriptyline
- Antidepressants categorized as moderately safe lactation risk include: fluoxetine (in neonates, considered safer in older infants), citalopram, venlafaxine, escitalopram (in older infants)
- Possibly hazardous lactation risk with lithium; monitor infant complete blood count, thyroid-stimulating hormone levels, and lithium levels

Reference: ACOG Practice Bulleting 92 on use of psychiatric medications during pregnancy and lactation (Obstet Gynecol 2008 Apr;111(4):1001, reaffirmed 2016)

Academy of Breastfeeding Medicine protocol on use of antidepressants in nursing mothers

- If mother has history of successful treatment with a particular selective serotonin reuptake inhibitor, tricyclic antidepressant, or serotonin–norepinephrine uptake inhibitor, particularly during pregnancy, review data for this specific antidepressant and consider it as first-line treatment if no contraindications
- If mother has no history of antidepressant treatments, an antidepressant such as sertraline, which has evidence of lower levels in breast milk and infant serum and few side effects, is considered appropriate for first choice (ABM II-2)
    - recommended starting dose 25 mg for 5-7 days, then increased to 50 mg/day
- Serum levels are not indicated on a regular basis without a clinical indication or concern
- Suggest that mother take medication immediately after feedings to decrease infant exposure (ABM III)

Reference: Breastfeed Med 2015 Jul-Aug;10(6):290 full-text

Selective serotonin reuptake inhibitors (SSRIs) in nursing mothers occur in varying levels in breast milk

- Based on systematic review of observational studies
- Systematic review of 57 studies evaluating antidepressant levels in maternal serum/plasma, breast milk, and/or infant serum/plasma from nursing mother-infant pairs
- Authors determined infant plasma level > 10% of mother's plasma level to be of potential clinical significance
- Nortriptyline, paroxetine, and sertraline usually produce undetectable levels in infant plasma
- Fluoxetine produces the highest proportion (22%) of infant levels that are elevated above 10% of the average maternal level
- Citalopram associated with elevated levels in 17% of infants
- Database included 238 infants plus an additional 6 identified in case reports due to adverse events
- 9 case reports of possible adverse effects identified but authors unable to make conclusions about adverse effects

Reference: Am J Psychiatry 2004 Jun;161(6):1066

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CPT	Description
NA	

HCPCS	Description
C9055	Injection, brexanolone, 1 mg

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Policy History	P&T
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**All content, clinical evidence, coverage criteria, practice guidelines, appendices and reference sections reviewed and revised with the most recent medical literature and available evidence for both 'Annual Reviews' and 'Policy Revisions.' Annual Reviews without notable changes to coverage criteria or position may not require Peer Review. Policy Revisions include notable content updates or revisions that which may have affected criteria or requires review by a practicing specialist, Peer Reviewer.*

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