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Policy Number: C16319-A

Zulresso (brexanolone)

PRODUCTS AFFECTED

Zulresso (brexanolone)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.
This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Postpartum Depression

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review.

A. POSTPARTUM DEPRESSION
1. Documented diagnosis of moderate to severe Postpartum Depression (PPD)
   AND
2. Documentation of Peripartum onset: Onset of depressive episode occurring between the 3rd trimester of pregnancy and four weeks postpartum (after delivery). [DOCUMENTATION REQUIRED]
   AND

3. Prescriber attestation that the member's baseline moderate to severe postpartum depression (PPD) symptoms are measured and 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
   AND
4. Member is 6 months or less postpartum at initiation of Zulresso (brexanolone) therapy
   AND
5. Prescriber attests other diagnoses such as postpartum blues, postpartum psychosis, bipolar disorder, hypo- or hyperthyroidism, and postpartum anemia have been ruled out
   AND
6. Member has ceased lactating OR prescriber attests if still lactating or actively breastfeeding, member has been counseled on risk
   AND
7. Documentation of negative pregnancy test
   AND
8. Prescriber attests that member agrees to use contraception during therapy and for 30 days after completion of the brexanolone infusion
   AND
9. (a) Documentation of inadequate response (8 week trial) serious side effects, or contraindication to ONE of the following at a maximally tolerated therapeutic dose:
   i. Selective serotonin reuptake inhibitor (SSRI) (e.g., paroxetine, sertraline, citalopram)
   ii. Serotonin- norepinephrine reuptake inhibitor (SNRI) (e.g., desvenlafaxine, duloxetine, venlafaxine)
   iii. Tricyclic antidepressant (TCA) (e.g., nortriptyline)
   iv. Bupropion
   v. Mirtazapine

   OR

   (b) 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)
   AND
10. 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.
    AND
11. 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
    AND
12. Documentation of member's current weight (within the past 30 days)

CONTINUATION OF THERAPY:
Zulresso (brexanolone) will not be authorized for continuation of therapy. Authorizations are granted for one treatment per postpartum period, per delivery.

DURATION OF APPROVAL:
Initial authorization: 6 months

PRESCRIBER REQUIREMENTS:
Prescribed by or in consultation with a board-certified Psychiatrist or OB/GYN. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:
15 to 45 years of age

QUANTITY:
One treatment per postpartum period (per delivery). Administer as a continuous IV infusion over a total of 60 hr (2.5 days) in a monitored health setting that can 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.

PLACE OF ADMINISTRATION:
The recommendation is that infused medications in this policy will be for medical benefit coverage administered in a place of service that is a non-inpatient hospital facility-based location.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Intravenous Infusion

DRUG CLASS:
Gamma-Aminobutyric Acid (GABA) A Receptor Positive Modulator

FDA-APPROVED USES:
Indicated for the treatment of postpartum depression (PPD) in patients 15 years and older.

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:

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**

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.

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)
- 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

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

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 %of women giving birth globally. In the United States, estimates of new mothers identified with PDD each year vary by state from 8-20 %, with an overall average of 11.5 % (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. Management of PPD
- Treatment of PPD depends on the severity of symptoms and the level of functional impairment. 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 (National Institute of Mental Health).
- 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.
- *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.

The FDA approved brexanolone (Zulresso) injection for intravenous (IV) use for the treatment of postpartum depression (PPD) in adult women based on the results of **Study 1** and **Study 2** (FDA, 2019).

Brexanolone infusion was evaluated as a treatment option for moderate to severe PPD in two multicenter, randomized, double-blind, placebo-controlled phase 3 trials (Meltzer-Brody et al., 2018). Both trials enrolled ambulatory female participants **(Study 1, n=138; Study 2, n=108)** aged 18 to 45 years who had an onset of a major depressive episode no earlier than the third trimester of pregnancy and no later than4 weeks after delivery (as determined by DSM-IV Axis I Disorders (SCID-I)), had a qualifying Hamilton Rating Scale for Depression (HAM-D) total score (≥ 26 for study 1 for severe PPD; 20–25 for study 2 for moderate PPD), were 6 months postpartum or less at screening, and had stopped lactating or ceased breastfeeding while receiving the study drug until 4 days after the end of the infusion. 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.

Participants were excluded if they had hemoglobin less than 10 g/dL, renal failure requiring dialysis, fulminant hepatic failure, active psychosis, medical history of schizophrenia, bipolar disorder, or schizoaffective disorder, had attempted suicide during the current episode of PPD, a history of alcohol or drug abuse in the previous 12 months, or electroconvulsive (ECT) therapy within last 14 days before screening. Participants taking prescribed psychotropic medication at baseline were required to be at a stable dose 14 days before screening until completion of the 72 h assessments (Melzer-Brody et al, 2018).

Study 1 (NCT02942004) included patients with severe PPD (HAM-D score ≥ 26), and Study 2 (NCT02942017) included patients with moderate PPD (HAM-D score of 20 to 25). A total of 246 participants were treated in a medically supervised setting for 72 hours (60 hours of infusion and 12 additional hours for assessment completion) in both studies.
In study 1, participants were randomly assigned to receive either a single intravenous (IV) infusion of:

- brexanolone 90 µg/kg/h (BRX90) (n=45),
- brexanolone 60 µg/kg/h (BRX60) (n=47), or
- matching placebo (n=46) for a single 60-hour infusion in study 1 (severe PPD), orIn study 2 BRX90 or placebo was infused as a single 60-hour infusion (moderate PPD).

The primary efficacy endpoint was the change from baseline in the 17-item HAM-D total score at 60 hours. This was assessed in all patients who started infusion of brexanolone or placebo, had a valid HAM-D baseline assessment, and had at least one post-baseline HAM-D assessment.
Summary
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 HAM-D total score at 60 hours compared to placebo. In addition, a reduction of symptoms was noted as early as 24 hours, and the drug maintained its effect through the 30-day follow-up.
  In study 1, at 60 hours, the least-squares (LS) mean reduction in HAM-D total score from baseline was
  19.5 points (SE 1.2) in the BRX60 group and 17.7 points (1.2) in the BRX90 group compared with 14.0 points (1.1) in the placebo group (difference -5.5 [95% CI -8.8 to -2.2], p=0.0013 for the BRX60 group; - 3.7 [95% CI -6.9 to -0.5], p=0.0252 for the BRX90 group). In study 2, at 60 hours, the LS mean reduction in HAM-D total score from baseline was 14.6 points (SE 0.8) in the BRX90 group compared with 12.1 points (SE 0.8) for the placebo group (difference -2.5 [95% CI -4.5 to -0.5], p=0·0160). The authors conclude that brexanolone for PPD resulted in significant and clinically meaningful reductions in HAM-D total score at 60 hours compared with placebo, with rapid onset of action and durable treatment response during the study period. In summary, the results suggest that brexanolone injection is a pharmacologic option that is likely to improve

treatment for women with this PPD.

Common adverse reactions (≥5% and at least twice the rate of placebo) include dry mouth, flushing, sedation/somnolence, and loss of consciousness, of which the latter two are included in the Black Box warning.

Zulresso Risk Evaluation and Mitigation Strategy (REMS)

Zulresso is available only through a restricted program under a REMS called the Zulresso REMS because excessive sedation or sudden loss of consciousness can result in serious harm.

Notable requirements of the Zulresso REMS include the following:

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

Further information, including a list of certified healthcare facilities, is available at www.zulressorems.com or 1-844-472-4379.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Zulresso (brexanolone) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Zulresso (brexanolone) include: pregnancy, and use in patient with end stage renal disease (ESRD).

OTHER SPECIAL CONSIDERATIONS:

Black Box Warning: Excessive sedation and sudden loss of consciousness

Patients treated with brexanolone are at risk of excessive sedation or sudden loss of consciousness during administration. Because of the risk of serious harm, patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. Patients must be accompanied during interactions with their child(ren). Because of these risks, brexanolone is available only through a restricted program called the Zulresso REMS.

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
J1632	Injection, brexanolone, 1 mg

AVAILABLE DOSAGE FORMS:

Zulresso SOLN 100MG/20ML

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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Prescriber Requirements Age Restrictions FDA-Approved Uses Background Contraindications/Exclusions/Discontinuation Other Special Considerations	Q1 2023
Q2 2022 Established tracking in new format	Historical changes on file