09-J3000-36

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Subject: Brexanolone (Zulresso®) IV Infusion

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Brexanolone (Zulresso) is a neuroactive steroid GABA-A (gamma-aminobutyric acid-A) receptor positive modulator approved by the Food and Drug Administration (FDA) in March 2019 for the treatment of postpartum depression (PPD) in adults. Prior to approval, the FDA granted the Zulresso application Priority Review and Breakthrough Therapy designation status. Brexanolone is an analog of allopregnanolone, an endogenous steroid hormone metabolite that increases during pregnancy and then declines abruptly after birth. In some women, this decline is thought to trigger depression and anxiety. Brexanolone is the first drug to be approved by the FDA for the specific treatment of PPD. However, oral antidepressants have been historically used off-label for the treatment of PPD with varying degrees of success.

There are several terms that encompass mood disorders that occur during pregnancy and soon after delivery. These mood disorders can be broadly categorized as: (1) postpartum blues (“the baby blues”), (2) perinatal depression (encompassing prenatal and postpartum depression), and (3) postpartum psychosis. Many women have the baby blues in the days following childbirth (approximately 50% to 80% of all mothers). For most women, the baby blues are temporary and ranges from a few days to up to 2 weeks after childbirth. Symptoms are not usually severe and there are effective ways to handle them. The symptoms of perinatal depression last longer than the baby blues and are more severe. A very small number of women (1 or 2 in 1,000) suffer a rare and severe form of depression called postpartum psychosis that is considered a medical emergency. An estimated 9 to 12% of women experience some degree of PPD and it is one of the most common complications of pregnancy and the postpartum period. It is well established that perinatal depression can result in adverse short- and long-term effects on both the mother and child. Risk factors for PPD include personal or family history of anxiety or depression, sociological factors (e.g., low income, social conflict, physical or psychological abuse, recent stressful life events, single marital status, etc.), and factors that negatively impact newborn care (e.g.,

lack of social support, premature or low-birth-weight infant, breastfeeding problems, infant temperament, etc.). It is thought that fewer than half of PPD cases are diagnosed in clinical practice, and there has been a more intense focus on screening and prevention. The American Academy of Pediatricians (AAP) recommend integrating PPD screening and surveillance at the 1-, 2-, 4-, and 6-month well-child visits. The American College of Gynecologists (ACOG) recommend all obstetrician–gynecologists and other obstetric care providers complete a full assessment of mood and emotional well-being, including screening for postpartum depression and anxiety with a validated instrument, during the comprehensive postpartum visit for each patient (which ACOG states should occur no later than 12 weeks after birth).

Clinical diagnosis of PPD is based on Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) criteria for Major Depressive Disorder (MDD) with peripartum onset. Criteria include five or more depressive symptoms present for ≥ 2 weeks, for most of nearly every day and cause clinically significant distress or impairment in social, occupational, or other important areas of function. The duration of the peripartum or postpartum period varies among references. The DSM-5 defines MDD with peripartum onset as an episode of major depression with onset during pregnancy or within four weeks of delivery. The ACOG define perinatal depression to include major and minor depressive episodes that occur during pregnancy or in the first 12 months after delivery. The most current guidelines from the American Psychiatric Association (APA) for the treatment of MDD (October 2010) do not address the use of brexanolone, but do address the treatment of PPD. Treatment of PPD depends on the severity of depressive symptoms and includes psychotherapy and/or antidepressant medication. Selective serotonin reuptake inhibitors (SSRIs) are typically the drugs of choice. Sertraline is often recommended as first-line therapy because it passes minimally through breast milk. In patients with more severe symptoms, additional drug therapy (e.g., benzodiazepines, adjunctive antipsychotic agents) may be needed to treat severe anxiety or depression with psychotic features. For patients with suicidal intent or psychosis, hospitalization may be required. Electroconvulsive therapy (ECT) may be appropriate in some situations due to its more immediate effect.

The safety and efficacy of brexanolone leading to FDA-approval for the treatment of PPD was demonstrated in two multicenter, randomized, double-blind, placebo-controlled studies in women (18 to 45 years) with PPD who met the DSM-5 for a major depressive episode with onset of symptoms in the third trimester or within 4 weeks of delivery. Patient also had to be less than six months postpartum at screening, not have active psychosis, not attempted suicide associated with index case of postpartum depression, and not have medical history of schizophrenia, bipolar disorder, or schizoaffective disorder. In these studies, patients received a 60-hour continuous IV infusion of brexanolone or placebo and were then followed for 4 weeks. 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/hr was evaluated in both studies, and a titration to a target dosage of 60 mcg/kg/hr was also evaluated in Study 1. 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%) and the average age 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. The primary endpoint was the mean change from baseline in depressive symptoms as measured by the HAM-D total score at the end of the infusion (Hour 60). A pre-

specified secondary efficacy endpoint was the mean change from baseline in HAM-D total score at Day 30. Brexanolone significantly improved the HAM-D total score compared placebo in both studies (see Table).

Table: Results for the Primary Endpoint – HAM-D Total Score (Studies 1 and 2)

Study Number	Treatment Group (# of ITT subjects)	Primary Endpoint: Change from Baseline in HAM-D Total Score at Hour 60		
		Mean Baseline Score (SD)	Mean Change from Baseline (SE)	Mean Change from Baseline (SE)
1 (severe PPD)	Brexanolone target dose 90 mcg/kg/hr (N=41)*	28.4 (2.5)	-17.7 (1.2)	-3.7 (-6.9, -0.5), p=0.0252
	Placebo (n=43)	28.6 (2.5)	-14 (1.1)	
	Brexanolone target dose 60 mcg/kg/hr (N=38)*	29 (2.7)	-19.5 (1.2)	-5.5 (-8.8, -2.2), p=0.0013
	Placebo (n=43)	28.6 (2.5)	-14 (1.1)	
2 (moderate PPD)	Brexanolone target dose 90 mcg/kg/hr (N=51)*	22.6 (1.6)	-14.6 (0.8)	-2.5 (-4.5, -0.5), p=0.0160
	Placebo (n=53)	22.7 (1.6)	-12.1 (0.8)	

*HAM-D: Hamilton depression rating scale; ITT: intention to treat; SD: standard deviation; LS: least squares; SE: standard error; CI: confidence interval; * statistically significant after multiplicity adjustments*

Regarding other secondary outcomes, HAM-D remission (HAM-D total score of 7 or less) rate was significantly improved with 60 mcg/kg/hr at 48, 60 (OR, 6 [95% CI, 2.1 to 17.8]), and 72 hours in study 1 and with 90 mcg/kg/hr at 48, 60 (OR, 3.4 [95% CI, 1.5 to 7.9]), and 72 hours and day 7 in study 2 only. HAM-D response (50% or greater reduction in total score) rate and Clinical Global Impression-Improvement (CGI-I) were significantly improved with both doses of brexanolone compared with placebo at hour 60 and day 30 in study 1 and were significantly improved at hour 60 and day 7 in study 2. The most common treatment-related adverse events with brexanolone and placebo were headache (50% and 54% vs 51% [study 1]; 49% vs 45% [study 2]), dizziness (16% and 15% vs 2% [study 1]; 10% vs 8% [study 2]), and somnolence (18% and 5% vs 7% [study 1]; 8% vs 4% [study 2]).

In June 2022, the FDA approved brexanolone (Zulresso) for patients 15 years of age and older. The approval was based on an open-labeled study in patients 15 to 17 years. Twenty patients with PPD were titrated to a target dosage of 90 mcg/kg/hour and were then followed for 4 weeks. Adverse reactions reported in the clinical study were generally similar to those observed in adult patients with PPD.

POSITION STATEMENT:

Administration of brexanolone (Zulresso) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "8"):

1. Member is 15 years of age or older

2. Member has a confirmed diagnosis of moderate or severe postpartum depression, defined as having a major depressive episode that began no earlier than the third trimester and no later than the first 4 weeks following delivery – the date (or approximate time frame) of the onset of the major depressive episode must be provided
3. Treatment with brexanolone will be initiated no later than 6 month following the member's delivery date – the member's child's date of birth must be provided
4. Brexanolone is prescribed by, or in consultation with, a psychiatrist
5. Member does **NOT** have end stage renal disease (ESRD) [i.e., an eGFR of <15 mL/minute/1.73m^2]
6. Brexanolone will be administered at a healthcare facility that is certified in the ZULRESSO REMS program and the facility must have appropriate monitoring equipment with a licensed healthcare provider available on site to continuously monitor the patient, and intervene as necessary, for the duration of the infusion
7. Member has **NOT** previously received brexanolone or zuranolone following their most recent childbirth
8. The amount of brexanolone prepared for the 60-hour infusion does not exceed the following based on the member's body weight:
    - ≤92 kg (203 lbs) - 500 mg (five 100-mg vials to make 5 infusion bags)
    - >92 kg (203 lbs) to 138 kg (304 lbs) – 600 mg (six 100-mg vials to make 6 infusion bags)
    - >138 kg (304 lbs) to 166 kg (366 lbs) – 700 mg (seven 100-mg vials to make 7 infusion bags)
    - >166 kg (366 lbs) – add an additional 100 mg for each 24 kg (53 lbs) increment of weight over 166 kg (e.g., >166 to 190 kg – 800 mg, >190 to 214 kg – 900 mg, etc.)

Approval duration: 30 days (to allow for a single 60-hour infusion)

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Brexanolone is approved for the treatment of postpartum depression (PPD) in adults
- The recommended dose is administered as a continuous IV infusion over 60 hours 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 (a reduction in dosage to 60 mcg/kg/hour may be considered during this time period for patients 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

If excessive sedation occurs at any time during the infusion, stop the infusion until the symptoms resolve. The infusion may be resumed at the same or lower dose as clinically appropriate.

- Brexanolone must be diluted before administration and can be used for only 12 hours at room temperature. As such, each 60-hour infusion will require the preparation of at least five infusion bags. Additional bags will be needed for patients weighing 92 kg (203 lbs) or more. Refer to the package labeling for complete administration information.
- A healthcare provider must be available on site to continuously monitor the patient, and intervene as necessary, for the duration of the infusion. Monitor patients for hypoxia using continuous pulse oximetry equipped with an alarm. Assess for excessive sedation every 2 hours during planned, non-sleep periods. Initiate treatment early enough during the day to allow for recognition of excessive sedation. Refer to the package labeling for complete monitoring recommendations.
- Brexanolone is a Schedule IV controlled substance (CIV) under the Controlled Substances Act

Dose Adjustments

- Renal impairment - Avoid use in patients with end stage renal disease (ESRD) with eGFR of <15 mL/minute/1.73m^2 because of the potential accumulation of the solubilizing agent, betadex sulfobutyl ether sodium. No dosage adjustment is recommended in patients with mild (eGFR 60 to 89 mL/minute/1.73m^2), moderate (eGFR 30 to 59 mL/minute/1.73 m^2) or severe (eGFR 15 to 29 mL/minute/1.73 m^2) renal impairment.
- Hepatic impairment - Dosage adjustment is not necessary.

Drug Availability

- Supplied as 100 mg brexanolone in 20 mL (5 mg/mL) single-dose vials containing a sterile, preservative-free, clear, colorless solution.
- Store the undiluted product at 2°C to 8°C (36°F to 46°F). Do not freeze. Store protected from light.
- The diluted product in the infusion bag can be used at room temperature for up to 12 hours. If the diluted product is not used immediately after dilution, store under refrigerated conditions for up to 96 hours.

PRECAUTIONS:

Boxed Warning

WARNING: EXCESSIVE SEDATION AND SUDDEN LOSS OF CONSCIOUSNESS

- Patients treated with Zulresso 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, Zulresso is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ZULRESSO REMS

Contraindications

- None

Precautions/Warnings

- **Excessive Sedation and Sudden Loss of Consciousness** - In clinical studies, brexanolone caused sedation and somnolence that required dose interruption or reduction in some patients (5% vs. 0% of placebo-treated patients). Some patients were also reported to have loss of consciousness or altered state of consciousness (4% vs. 0% of placebo-treated patients). Time to full recovery from loss or altered state of consciousness, after dose interruption, ranged from 15 to 60 minutes. All patients with loss of or altered state of consciousness recovered with dose interruption. Not all patients who experienced a loss or alteration of consciousness reported sedation or somnolence before the episode.
    - During the infusion, monitor patients for sedative effects every 2 hours during planned, non-sleep periods. Immediately stop the infusion if there are signs or symptoms of excessive sedation. After symptoms resolve, the infusion may be resumed at the same or lower dose as clinically appropriate. Immediately stop the infusion if pulse oximetry reveals hypoxia. After hypoxia, the infusion should not be resumed.
    - Patients should be cautioned against engaging in potentially hazardous activities requiring mental alertness, such as driving after infusion until any sedative effects have dissipated.
    - Patients must be accompanied during interactions with their child(ren) while receiving the infusion because of the potential for excessive sedation and sudden loss of consciousness.
    - Concomitant use of opioids, antidepressants, or other CNS depressants such as benzodiazepines or alcohol may increase the likelihood or severity of adverse reactions related to sedation
- **Zulresso Risk Evaluation and Mitigation Strategy (REMS) –** Brexanolone 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.
- **Suicidal Thoughts and Behaviors** - In pooled analyses of placebo-controlled trials of chronically administered antidepressant drugs (SSRIs and other antidepressant classes), the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. Brexanolon e does not directly affect monoaminergic systems. Because of this and the comparatively low number of exposures to brexanolone the risk of developing suicidal thoughts and behaviors with brexanolone is unknown. Consider changing the therapeutic regimen, including discontinuing brexanolone, in patients whose depression becomes worse or who experience emergent suicidal thoughts and behaviors.
- **Pregnancy -** Based on findings from animal studies of other drugs that enhance GABAergic inhibition, brexanolone may cause fetal harm. There are no available data on brexanolone use in pregnant women to determine a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.
- **Lactation -** Available data from a lactation study in 12 women indicate that brexanolone is transferred to breastmilk in nursing mothers. However, the relative infant dose is low, 1% to 2% of the maternal weight-adjusted dosage. Also, as brexanolone has low oral bioavailability (<5%) in adults, infant exposure is expected to be low. There are no data on the effects of brexanolone on a breastfed

infant. Available data on the use of brexanolone during lactation do not suggest a significant risk of adverse reactions to breastfed infants. 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.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J1632	Injection, brexanolone, 1 mg

ICD-10 Diagnoses Codes That Support Medical Necessity

F53.0	Postpartum depression

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of guideline creation.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 03/13/24.

GUIDELINE UPDATE INFORMATION:

06/15/19	New Medical Coverage Guideline.
01/01/20	Revision: HCPCS code updates. Added C9055.
04/15/20	Review and revision to guideline consisting of updating the position statement, dosage/administration section and references.
10/01/20	Revision: Added HCPCS code J1632 and removed codes C9055 and J3490.
04/15/21	Review and revision to guideline consisting of updating the references.
04/15/22	Review and revision to guideline consisting of updating the references.
04/15/23	Review and revision to the guideline consisting of revising the position statement to include members 15 years of age and older and updating the references.
04/15/24	Review and revision to guideline consisting of revising the position statement to exclude zuranolone use with brexanolone and updating the references.