BlueCross BlueShield of North Carolina

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Corporate Medical Policy

Brexanolone (Zulresso™) **"Notification"**

File Name:	brexanolone_zulresso
Origination:	7/2019
Last CAP Review:	n/a
Next CAP Review:	6/2020
Last Review:	12/2019

Policy Effective March 24, 2020

Description of Procedure or Service

Brexanolone (Zulresso™) is a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator that is indicated for the treatment of postpartum depression (PPD) in adult patients.

PPD is a disabling but treatable serious mood disorder that can occur in women during pregnancy or after giving birth, and is characterized by clinically significant depressive symptoms post-delivery, often accompanied by symptoms of anxiety. PPD is estimated to affect 10-20% of women who give birth, and approximately 40-80% of cases of PPD are considered moderate to severe. Severe PPD can be defined as a major depressive episode in the postpartum period with marked impairment in functioning. While the exact pathogenesis of PPD is unknown, peripartum changes in serum concentrations of several reproductive hormones (e.g. progesterone, estrogen) are thought to be a contributing factor. Impairment of maternal functioning due to PPD is connected to poor nutrition and health of the child and can interfere with breastfeeding, bonding between the mother and infant, infant care, and the mother's interpersonal relationships. In addition, PPD has been associated with abnormal development, cognitive impairment, and mental and behavioral disorders in the children.

Treatment for PPD is dependent upon symptom severity and level of functional impairment, and can include psychosocial strategies, psychological therapy, and/or pharmacotherapy. Standard treatment for severe PPD has generally consisted of pharmacological treatment with antidepressants, with selective serotonin reuptake inhibitors (SSRIs) as first-line. However, many patients do not achieve adequate response or full remission of symptoms with the present pharmacological treatments used for PPD.

Brexanolone (Zulresso) was approved by the U.S. Food and Drug Administration (FDA) in March 2019 for the treatment of adults with postpartum depression. While the mechanism of brexanolone in PPD treatment is not fully understood, its action is thought to be related to positive allosteric modulation of $GABA_A$ receptors.

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for brexanolone (Zulresso™) when it is determined to be medically necessary because the medical criteria and guidelines noted below are met.

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Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Brexanolone (Zulresso) is covered

Brexanolone (Zulresso) is considered medically necessary for the treatment of adult patients (≥18 years old) with postpartum depression when the following criteria are met:

1. The patient has a confirmed diagnosis of a major depressive episode using DSM criteria; AND
2. The patient has moderate to severe postpartum depression with a HAM-D total score of at least 20, or as scored by a comparable standardized rating scale that reliably measures depressive symptoms (see Policy Guidelines); AND
3. The patient has onset of depressive symptoms no sooner than the third trimester of pregnancy and no later than within 4 weeks after delivery; AND
4. The patient is ≤ 6 months postpartum; AND
5. The patient does not have active psychosis; AND
6. The patient is not lactating or actively breastfeeding upon initiation and during brexanolone treatment; AND
7. Brexanolone is prescribed by or in consultation with a psychiatrist; AND
8. There is 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 (see Policy Guidelines).

*The infusion facility must be equipped and staffed with continuous pulse oximetry and staffed with healthcare professionals trained to handle possible excessive sedation and/or sudden loss of consciousness, including acute airway management.

Authorization: One infusion per pregnancy

When Brexanolone (Zulresso) is not covered

Brexanolone (Zulresso) is considered **investigational** and therefore not covered when the above criteria are not met.

Policy Guidelines

Zulresso is administered as a continuous intravenous infusion over 60 hours (2.5 days) with the following recommended dosing schedule:

- 0 to 4 hours: Initiate with a dose of 30 mcg/kg/hour
- 4 to 24 hours: Increase dose to 60 mcg/kg/hour
- 24 to 52 hours: Increase dose to 90 mcg/kg/hour (an alternate dose of 60 mcg/kg/hour may be considered for patients who are unable to tolerate 90 mcg/kg/hour)
- 52 to 56 hours: Decrease dose to 60 mcg/kg/hour

- 56 to 60 hours: Decrease dose to 30 mcg/kg/hour

Zulresso treatment carries a black box warning for risk of excessive sedation or sudden loss of consciousness during administration. Due to this risk of serious harm, patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. Additionally, as a result of such risk, Zulresso is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Zulresso REMS. According to the Zulresso REMS program, a healthcare provider must be available on site to provide continuous monitoring of the patient and intervention when necessary for the duration of the infusion. The patient should be monitored for hypoxia using continuous pulse oximetry equipped with an alarm. The patient should also be assessed for excessive sedation every 2 hours during planned, non-sleep periods.

The Hamilton Rating Scale for Depression (HAM-D) is a 17-item rating scale to determine the severity level of depression in a patient 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)
- 8-16: Mild depression
- 17-23: Moderate depression
- ≥24: Severe depression

Clinical Trial Evidence

The use of brexanolone in the treatment of PPD was initially evaluated in a multicenter, double-blind, randomized, placebo-controlled phase 2 clinical trial (NCT02614547) assessing 21 women (18 to 45 years of age) with severe PPD. Patients included in the trial had a major depressive episode that began no earlier than the third trimester and no later than the first 4 weeks after deliver as diagnosed by the Diagnostic and Statistical Manual of Mental Disorders criteria for a major depressive episode (DSM-IV), and had a baseline HAM-D total score of ≥ 26. Eligible patients were also within 6 months postpartum at time of enrollment. Participants in the trial were randomly assigned 1:1 to receive either a single, continuous intravenous dose of brexanolone (n=10) or placebo (n=11) for 60 hours. The primary efficacy endpoint was the change from baseline in the 17-item HAM-D total score at 60 hours, which was a mean reduction of 21.0 points (SE 2.9) in the brexanolone group versus 8.8 points (SE 2.8) in the placebo group (difference -12.2, 95% CI -20.77 to -3.67; p=0.0075; effect size 1.2). Follow up occurred in patients until day 30. Authors of the study concluded that that brexanolone treatment resulted in a significant and clinically meaningful reduction in HAM-D total score compared with placebo in women with severe PPD.

The efficacy of brexanolone (Zulresso) for the treatment of PPD in women 18 to 45 years of age was further evaluated in two randomized, multicenter, double-blind, placebo-controlled, pivotal phase 3 clinical trials (Study 1 and Study 2). Patients included in the trials met the DSM-IV diagnostic criteria and had symptom onset in the third trimester of pregnancy or within 4 weeks of delivery. Eligible patients were also 6 months postpartum or less at study entry. Participants in both studies received a 60-hour continuous intravenous infusion of brexanolone or placebo and were subsequently followed for 30 days. Study 1 (NCT02942004) included patients (N=138) with severe PPD defined by a Hamilton Depression Rating Scale (HAM-D) score ≥26, and Study 2 (NCT02942017) included patients (N=108) with moderate PPD defined by a HAM-D score of 20 to 25. Both studies assessed a titration to the recommended target brexanolone dose of 90 mcg/kg/hour (patients received 30 mcg/kg/hour for 4 hours, 60 mcg/kg/hour 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). Study 1 also evaluated a titration to a target dose 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). The average age of women receiving brexanolone was 28 years, and 76% of patients had PPD symptom onset within 4 weeks after delivery versus the remaining patients having onset during the third trimester. Baseline oral antidepressant use was reported for 23% of patients.

The primary efficacy endpoint was mean change from baseline in depressive symptoms, which was measured by the HAM-D total score at the end of the 60-hour infusion. For both clinical trials, a titration to a target brexanolone dose of 90 mcg/kg/hour was superior to placebo in improvement of depressive symptoms. In addition, for a subset of patients in Study 1 (n=38), a titration to a target brexanolone dose of 60 mcg/kg/hour was superior to placebo in improvement of depressive symptoms.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: *C9055, C9399, J3490*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

Sage Therapeutics, Inc. Zulresso (brexanolone) injection for intravenous use. Highlights of prescribing information. March 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211371lbl.pdf. Last accessed June 2019.

U.S Food and Drug Administration. FDA approves first treatment for post-partum depression. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-post-partum-depression. Last accessed June 2019.

Kanes S, Colquhoun H, Gunduz-Bruce H, et al. Brexanolone (SAGE-547 injection) in post-partum depression: a randomized controlled trial. Lancet. 2017;390:480-489.

Meltzer-Brody S, Colquhoun H, Riesenberg R, et al. Brexanolone injection in post-partum depression: two multicenter, double-blind, randomized, placebo-controlled, phase 3 trials. Lancet. 2018;392:1058-1070.

Stewart CM and Vigod S. Postpartum depression. N Engl J Med. 2016;375:2177-2186.

American Psychiatric Association (APA). Postpartum depression: What is postpartum depression? Reviewed March 2017. Available at: https://www.psychiatry.org/patients-families/postpartum-depression/what-is-postpartum-depression. Last accessed June 2019.

Medical Director review 6/2019

Medical Director review 12/2019

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Policy Implementation/Update Information

7/1/19 New policy developed. Zulresso is considered medically necessary for the treatment of adult patients (≥18 years old) with postpartum depression (PPD). Added HCPCS codes C9399 and J3490 to Billing/Coding section. References added. Medical Director review 6/2019. (krc)

12/31/19 Added HCPCS code C9055 to Billing/Coding section effective 1/1/2020. (krc)

1/14/20 Added the following criteria to "When Covered" section: "There is 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 (see Policy Guidelines)." Added the following clarification to "When Covered" section: "The infusion facility must be equipped and staffed with continuous pulse oximetry and staffed with healthcare professionals trained to handle possible excessive sedation and/or sudden loss of consciousness, including acute airway management." Medical Director review 12/2019. **Notification given 1/14/2020 for effective date 3/24/2020**. (krc)