PRIOR AUTHORIZATION POLIC

POLICY: Psychiatry – Zulresso™ (brexanolone injection for intravenous use – Sage Therapeutics)

DATE REVIEWED: 05/13/2020

OVERVIEW

Zulresso, a neuroactive steroid gamma-aminobutric acid (GABA) A receptor positive modulator, is indicated for the treatment of postpartum depression in adults.[1] Zulresso was approved under a priority review by the FDA and was granted a breakthrough therapy designation. The active ingredient of Zulpressa, brexanolone, is chemically identical to endogenous allopregnanolone. Plasma concentrations of allopregnanolone increase during pregnancy and decrease substantially after childbirth in both rodents and humans, and fluctuations in allopregnanolone have demonstrated effects on anxiety and depression in animal models.[2] The mechanism of action of Zulresso is not fully understood but it has been shown to modulate GABA-mediated currents from recombinant human $GABA_A$ receptors in mammalian cells expressing $\alpha_1\beta_2\gamma_2$, $\alpha_4\beta_3\delta$, and $\alpha_6\beta_3\delta$ receptor subunits.[1]

The efficacy of Zulresso was established in two Phase III, US-only, randomized, double-blind, placebo-controlled, multicenter, pivotal studies in patients with moderate to severe postpartum depression initiating treatment within 6 months of delivery.[2] Zulresso is administered as a one-time, continuous intravenous (IV) infusion over 60 hours.[1]

Disease Overview

Postpartum (or peripartum) depression is a major depressive episode with onset during pregnancy or within 4 weeks of delivery that can have serious effects on the maternal-infant bond and later infant development.[3] Postpartum depression is estimated to affect 10% to 20% of women who give birth worldwide and occurs in low- to high-income countries.[2] Approximately 40% to 80% of cases of postpartum depression are considered moderate to severe. In the US, the estimated prevalence of postpartum depression in new mothers varies by state from 8% to 20%, with an overall prevalence of approximately 12%.

Postpartum depression is symptomatically indistinguishable from major depression.[3] However, the timing of its onset has led to the acknowledgement of it potentially being a unique illness. As with other forms of depression, it is characterized by sadness and/or loss of interest in activities that one used to enjoy and a decreased ability to feel pleasure and may present with symptoms such as cognitive impairment, feelings of worthlessness or guilt, or suicidal ideation.[4] Because of the risk of suicide, postpartum depression is considered a life-threatening condition.[3]

Abuse and Misuse

Zulresso is a CIV controlled substance.[1] In a human abuse potential study, 3% of volunteers administered Zulresso 90 mcg/kg and 13% of volunteers administered Zulresso 270 mcg/kg (three times the maximum recommended infusion rate) reported euphoric mood compared with no volunteers administered placebo over a 1 hour infusion.

Safety

Based on findings from animal studies of other drugs that enhance GABAergic inhibition, Zulresso may cause fetal harm.[1] Currently, 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. A pregnancy exposure registry is available to monitor pregnancy outcomes in women exposed to antidepressants during pregnancy.

Zulresso has a Boxed Warning regarding excessive sedation and sudden loss of consciousness.[1] 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 children. During the infusion, patients must be monitored for sedative effects every 2 hours during planned, non-sleep periods. If there are signs or symptoms of excessive sedation, the infusion must be stopped immediately. After symptom resolution, the infusion may be restarted at the same or a lower dose.

Due to the risks of serious adverse events resulting from excessive sedation and sudden loss of consciousness, Zulresso is only available through a restricted distribution system under a REMS.[1,5] The Zulresso REMS requires healthcare facilities be enrolled in the program and ensure that Zulresso is only administered to patients enrolled in the program. Pharmacies are required to be certified and can only dispense Zulresso to certified healthcare facilities. Patients must enroll in the program prior to administration of Zulresso. The REMS requires the prescriber and the patient sign the Patient Enrollment Form that clearly states that the patient understands the risk of excessive sedation and loss of consciousness associated with Zulresso. A healthcare provider must be available on site to monitor the patient for the duration of the infusion. Patients must be monitored for hypoxia using continuous pulse oximetry and for excessive sedation every 2 hours during planned, non-sleep periods.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Zulresso. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zulresso as well as the monitoring required for adverse events and long-term efficacy, approval requires Zulresso to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Note that a 1-month (30 days) approval duration is applied to allow for the scheduling and administration of the one-time, 60-hour infusion of Zulresso.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zulresso is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Postpartum Depression.** Approve for 1 month if the patient meets the following criteria (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has been diagnosed with moderate to severe depression; AND
   - **C)** Patient is ≤ 6 months postpartum; AND
   - **D)** Patient is not currently pregnant; AND

E) Zulresso is being prescribed by, or in consultation with, a psychiatrist or an obstetrician-gynecologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Zulresso has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Previous Treatment with Zulresso During the Current Episode of Postpartum Depression**.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Zulresso™ injection for intravenous use [prescribing information]. Cambridge, MA: Sage Therapeutics; June 2019.
2. Meltzer-Brody S, Colquhoun H, Riesenberg R, et al. Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet*. 2018;392(10152):1058-1070.
3. FDA briefing document for Zulresso. Psychopharmacologic Drugs Advisory Committee (PDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee Meeting on November 2, 2018. Available at: https://www.fda.gov/media/121345/download. Accessed on May 8, 2020.
4. FDA News Release. FDA approves first treatment for post-partum depression. Published on March 19, 2019. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm633919.htm. Accessed on May 8, 2020.
5. Food and Drug Administration. Zulresso Risk Evaluation and Mitigation Strategy (REMS). Last updated: December 13, 2019. Available at: https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=387. Accessed on May 8, 2020.

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Aspirus Health Plan, Inc.
PO Box 1062
Minneapolis, MN 55440
Phone: 1.866.631.5404 (TTY: 711)
Fax: 763.847.4010
Email: customerservice@aspirushealthplan.com

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U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1-800-368-1019, 800-537-7697 (TDD)

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