Drug Coverage Policy

Effective Date..... 8/1/2025
Coverage Policy Number IP0270
Policy Title ..... Zulresso

Psychiatry – Zulresso

- Zulresso® (brexanolone intravenous infusion – Sage Therapeutics)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

Zulresso, a neuroactive steroid gamma-aminobutric acid (GABA) A receptor positive modulator, is indicated for the **treatment of postpartum depression** in patients ≥ 15 years of age.[1] As of January 1, 2025, Zulresso will no longer be commercially available in the US.[4]

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] Approximately 40% to 80% of cases of postpartum depression are considered moderate to severe.[2]

Clinical Efficacy
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] Eligible patients were diagnosed with a major depressive episode, which had an onset no earlier than the third trimester of pregnancy and no later than 4 weeks after delivery.

Dosing Information
Zulresso is administered as a continuous intravenous infusion over 60 hours.[1] If excessive sedation occurs during the infusion, the infusion should be stopped until the symptoms resolve, then the infusion may be restarted at the same or a lower dose as clinically appropriate. The dose titration schedule for Zulresso is provided in Table 1.

Table 1. Dose Titration Schedule of Zulresso.[1]

Time	Infusion rate
0 to 4 hours	30 mcg/kg/hour
4 to 24 hours	60 mcg/kg/hour
24 to 52 hours	90 mcg/kg/hour (a reduction in dose 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	60 mcg/kg/hour
56 to 60 hours	30 mcg/kg/hour

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 Risk Evaluation and Mitigation Strategy program.[1,4]

Coverage Policy

POLICY STATEMENT

Prior Authorization is required for benefit coverage of Zulresso. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. 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. 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.

Note: 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.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, claims records, and/or other information.

Zulresso is considered medically necessary when the following criteria are met:

FDA-Approved Indication

1. **Postpartum Depression.** Approve for 1 month if the patient meets the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 15 years of age; AND
   - **B)** Patient has been diagnosed with moderate to severe depression with symptom onset during the third trimester of pregnancy or up to 4 weeks post-delivery **[Documentation Required]**; 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.

   Dosing. Approve up to 90 mcg/kg/hour given intravenously as a one-time, 60-hour infusion once per postpartum period.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Zulresso for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

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

Coding Information

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.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J1632	Injection, brexanolone, 1 mg

References

1. Zulresso® intravenous infusion [prescribing information]. Cambridge, MA: Sage Therapeutics; June 2022.
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. Drug trials snapshots: Zulresso. Last updated on March 18, 2021. Available at: Drug Trials Snapshots: ZULRESSO | FDA. Accessed on May 30, 2025.
4. Food and Drug Administration. Zulresso Risk Evaluation and Mitigation Strategy (REMS). Last updated: January 23, 2025. Available at: https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=387. Accessed on May 30, 2025.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	**Updated** coverage policy title from *Brexanolone* to *Psychiatry – Zulresso*. **Postpartum Depression.** **Added** criterion requirement screening patient is not currently pregnant. **Added** dosing to medical necessity criteria stem.	10/1/2024
Annual Revision	Documentation required added to diagnosis of Postpartum Depression.	8/1/2025

The policy effective date is in force until updated or retired.

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