

Clinical Policy: Brexanolone (Zulresso)

Reference Number: ERX.SPA.327

Effective Date: 06.01.19

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Line of Business: Commercial, Medicaid

[Revision Log](#)

See **Important Reminder** at the end of this policy for important regulatory and legal information.

Description

Brexanolone (Zulresso™) is a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator.

FDA Approved Indication(s)

Zulresso is indicated for the treatment of postpartum depression (PPD) in patients 15 years and older.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Zulresso is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Postpartum Depression (must meet all):

1. Diagnosis of a major depressive episode that began no earlier than the third trimester and no later than the first 12 weeks following delivery, as diagnosed by Structured Clinical Interview for DSM-5;
2. Prescribed by or in consultation with psychiatrist;
3. Age ≥ 15 years;
4. Member meets one of the following (a, b, c, or d):
 - a. HAM-D score is ≥ 24 (severe depression) (*see Appendix D*);
 - b. MADRS score is ≥ 34 (severe depression) (*see Appendix D*);
 - c. PHQ-9 score is ≥ 20 (severe depression) (*see Appendix D*);
 - d. Failure of an 8-week trial of one of the following oral antidepressants at up to maximally indicated dose but no less than the commonly recognized minimum therapeutic dose, unless clinically significant adverse effects are experienced or all are contraindicated: selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), tricyclic antidepressant (TCA), bupropion, mirtazapine (*see Appendix B*);
5. No more than 6 months have passed since member has given birth;
6. Dose does not exceed 90 mcg/kg per hour over 60 hours (2.5 days) as follows:
 - a. 0 to 4 hours: Initiate with a dosage of 30 mcg/kg per hour;
 - b. 4 to 24 hours: Increase dosage to 60 mcg/kg per hour;
 - c. 24 to 52 hours: Increase dosage to 90 mcg/kg per hour (alternatively consider a dosage of 60 mcg/kg per hour for those who do not tolerate 90 mcg/kg per hour);
 - d. 52 to 56 hours: Decrease dosage to 60 mcg/kg per hour;
 - e. 56 to 60 hours: Decrease dosage to 30 mcg/kg per hour.

Approval duration: 30 days (one time infusion per pregnancy)

B. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Postpartum Depression

1. Re-authorization is not permitted. Members must meet the initial approval criteria.

Approval duration: Not applicable

B. Other diagnoses/indications (must meet 1 or 2):

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.

Approval duration: Duration of request or 6 months (whichever is less); or

2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

- A.** Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration

HAM-D: Hamilton Rating Scale for Depression

MADRS: Montgomery-Åsberg Depression Rating Scale

PHQ-9: Patient Health Questionnaire

PPD: postpartum depression

SNRI: serotonin-norepinephrine reuptake inhibitor

SSRI: selective serotonin reuptake inhibitor

TCA: tricyclic antidepressant

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
SSRIs		
citalopram (Celexa®)	20 mg PO QD; may increase to 40 mg PO QD after one week	40 mg/day (≤ 60 years) 20 mg/day (> 60 years)
escitalopram (Lexapro®)	10 mg PO QD; may increase to 20 mg PO QD after 1 week	20 mg/day
fluoxetine (Prozac®, Prozac Weekly®)	Prozac: 20 mg PO QD; may increase by 10-20 mg after several weeks Prozac Weekly: 90 mg PO q week beginning 7 days after the last daily dose	Prozac: 80 mg/day Prozac Weekly: 90 mg/week
paroxetine (Paxil®, Paxil CR®, Pexeva®)	Paxil, Pexeva: 20 mg PO QD; may increase by 10 mg every week as needed Paxil CR: 25 mg PO QD; may increase by 12.5 mg every week as needed	Paxil, Pexeva: 50 mg/day Paxil CR: 62.5 mg/day
sertraline (Zoloft®)	50 mg PO QD; may increase every week as needed	200 mg/day
SNRIs		
duloxetine (Cymbalta®)	20 mg PO BID or 30 mg PO BID or 60 mg PO QD	120 mg/day
venlafaxine (Effexor®, Effexor XR®)	Effexor: 75 mg/day PO in 2-3 divided doses; may increase by 75 mg every 4 days as needed	Effexor: 225 mg/day (outpatient) or 375 mg/day (inpatient)

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Effexor XR: 75 mg PO QD; may increase by 75 mg every 4 days as needed	Effexor XR: 225 mg/day
desvenlafaxine (Pristiq [®] , Khedezla [®])	50 mg PO QD	400 mg/day
Fetzima [®] (levomilnacipran)	20 mg PO QD for 2 days, then 40 mg PO QD; may increase by 40 mg every 2 days	120 mg/day
TCAs		
amitriptyline (Elavil [®])	25 to 50 mg/day PO QD or divided doses	150 mg/day
amoxapine	25 to 300 mg/day PO in divided doses	400 mg/day (300 mg/day if geriatric)
clomipramine* (Anafranil [®])	12.5 to 150 mg/day PO QD	250 mg/day (200 mg/day if pediatric)
desipramine (Norpramin [®])	25 to 300 mg/day PO QD	300 mg/day (100 mg/day if pediatric)
doxepin (Sinequan [®])	25 to 300 mg/day PO QD	300 mg/day
imipramine HCl (Tofranil [®])	25 to 200 mg/day PO QD or divided doses	200 mg/day (150 mg/day if geriatric or pediatric)
imipramine pamoate (Tofranil PM [®])	25 to 200 mg/day PO QD or divided doses	200 mg/day (100 mg/day if geriatric or pediatric)
nortriptyline (Pamelor [®])	25 to 150 mg/day PO QD	150 mg/day
protriptyline (Vivactil [®])	10 to 60 mg/day PO in divided doses	60 mg/day (30 mg/day if geriatric or pediatric)
trimipramine (Surmontil [®])	25 to 200 mg/day PO QD	200 mg/day (100 mg/day if geriatric or pediatric)
Miscellaneous Antidepressants		
bupropion (Aplenzin [®] , Budeprion SR [®] , Budeprion XL [®] , Forfivo XL [®] , Wellbutrin [®] , Wellbutrin SR [®] , Wellbutrin XL [®])	Varies	Immediate-release: 450 mg/day (300 mg/day if pediatric) Sustained-release: 400 mg/day Extended-release (HCl): 450 mg/day Extended-release (HBr): 522 mg/day
mirtazapine (Remeron [®])	15 to 15 mg PO QD	45 mg/day

Therapeutic alternatives are listed as Brand name[®] (generic) when the drug is available by brand name only and generic (Brand name[®]) when the drug is available by both brand and generic.

*Off-label

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): none reported
- Boxed warning(s): Excessive sedation and sudden loss of consciousness during administration. Patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. Because of these risks, Zulresso is available only through a restricted program under a REMS program.

Appendix D: General Information

- HAM-D scale is a 17-item depression assessment scale to assess severity of, and change in, depressive symptoms.

HAM-D Score	Depression Rating
0 – 7	Normal, absence or remission of depression
8 – 16	Mild depression
17 – 23	Moderate depression
> 24	Severe depression

- MADRS is a 10-item diagnostic questionnaire used to measure the severity of depressive episodes in patients with mood disorders.

MADRS Score	Depression Rating
0 – 6	Normal/symptom absent
7 – 19	Mild depression
20 – 34	Moderate depression
> 34	Severe depression

- PHQ-9 is a 9-item multiple choice questionnaire used for diagnosis, screening, monitoring and measuring the severity of depression.

PHQ-9 Score	Depression Severity
5 – 9	Minimal symptoms
10 – 14	Minor depression Major depression, mild
15 – 19	Major depression, moderately severe
> 20	Major depression, severe

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
PPD	Administered as a continuous intravenous infusion over 60 hours (2.5 days) as follows: <ul style="list-style-type: none"> 0 to 4 hours: Initiate with a dosage of 30 mcg/kg per hour 4 to 24 hours: Increase dosage to 60 mcg/kg per hour 24 to 52 hours: Increase dosage to 90 mcg/kg per hour (alternatively consider a dosage of 60 mcg/kg per hour for those who do not tolerate 90 mcg/kg per hour) 52 to 56 hours: Decrease dosage to 60 mcg/kg per hour 56 to 60 hours: Decrease dosage to 30 mcg/kg per hour 	90 mcg/kg per hour

VI. Product Availability

Vial for injection, single-dose: 100 mg/20 mL (5 mg/mL)

VII. References

- Zulresso Prescribing Information. Cambridge, MA: Sage Therapeutics, Inc.; June 2022. Available at: www.zulresso.com. Accessed July 18, 2022.
- Meltzer-Brody S, Colquhoun H, Riesenberger R, et al. Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet*. 2018 Sep 22;392(10152):1058-1070.
- American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder, third edition. November 2010. Available at: <http://psychiatryonline.org/guidelines.aspx>. Accessed February 6, 2022.
- Sharp, Rachel. The Hamilton rating scale for depression. *Occupational Medicine*. 2015; 65(4):340
- Montgomery-Åsberg Depression Rating Scale. Available at: http://www.liquisearch.com/montgomery%E2%80%93%C3%85sberg_depression_rating_scale/interpolation. Accessed February 6, 2022.

6. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606–613.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created.	04.16.19	05.19
2Q 2020 annual review: added prescriber requirement; revised diagnosis with DSM-V definition of postpartum depression; revised criteria to allow members with severe depression without trial of other antidepressants; references reviewed and updated.	03.04.20	05.20
2Q 2021 annual review: no significant changes; references reviewed and updated.	03.01.21	05.21
2Q 2022 annual review: no significant changes; references reviewed and updated.	02.06.22	05.22
RT4: per updated prescribing information, updated indication and age requirements from adults (18 years) to 15 years of age or older.	07.18.22	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

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