

Clinical Policy: Brexanolone (Zulresso)

Reference Number: PA.CP.PHAR.417

Effective Date: 01/2020

Last Review Date: 10/2023

[Coding Implications](#)

[Revision Log](#)

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.

It is the policy of PA Health & Wellness® 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 \geq 15 years;
4. Member meets one of the following (a, b, c, d or e):
 - a. HAMD score is \geq 17 (moderate to severe depression) (*see Appendix D*);
 - b. MADRS score is \geq 20 (moderate to severe depression) (*see Appendix D*);
 - c. PHQ-9 score is \geq 15 (moderate to severe depression) (*see Appendix D*);
 - d. If member does not have moderate to severe depression as demonstrated by at least one of the depression scores above (a, b, or c), documentation of moderate to severe depression as evidenced by a psychiatrist clinical interview;
 - e. Failure of a 4-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 12 months have passed since member has given birth;
6. Member has not received prior treatment with Zulresso or Zurzuvae™ for the current pregnancy;
7. 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 PA.CP.PMN.53

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 PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies.

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

2. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

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 policies – PA.CP.PMN.53.

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 for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
SSRI		
citalopram (Celexa [®])	20 mg PO QD; may increase to 40 mg PO QD after one week	40 mg/day (\leq 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: initial dosing = 37.5-75 mg/day. Doses $>$ 37.5 mg administered in 2-3 divided doses; may increase by 75 mg every 4 days as needed Effexor XR: 75 mg PO QD; may increase by 75 mg every 4 days as needed	Effexor: 225 mg/day (outpatient) or 375 mg/day (inpatient) 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
TCA's		
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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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)
Other Antidepressants		
<i>bupropion</i> (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
<i>mirtazapine</i> (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.

Appendix C: Contraindications/Boxed Warnings

- 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.
- Contraindication(s): none reported

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. Please note that MADRS severity gradations

vary by reference. The following severity gradations are suggestions based on the reference cited below, and may not be universally agreed upon.

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
> 19	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

1. Zulresso Prescribing Information. Cambridge, MA: Sage Therapeutics, Inc.; June 2022. Available at: www.zulresso.com. Accessed February 6, 2023.
2. Meltzer-Brody S, Colquhoun H, Riesenber 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.
3. 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>.

4. Sharp, Rachel. The Hamilton rating scale for depression. *Occupational Medicine*. 2015; 65(4):340
5. Montgomery–Åsberg Depression Rating Scale. Available at: http://www.liquisearch.com/montgomery%E2%80%93%C3%85sberg_depression_rating_scale/interpretation. 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.
7. Stewart DE, Vigod SN. Postpartum Depression: Pathophysiology, Treatment, and Emerging Therapeutics. *Annu Rev Med*. 2019;70:183-196.
8. Treatment and management of mental health conditions during pregnancy and postpartum: ACOG Clinical Practice Guideline No. 5. *Obstet Gynecol*. 2023 Jun 1;141(6):1262-1288. Accessed August 25, 2023.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J1632	Injection, brexanolone, 1 mg

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	01/2020	
1Q 2020 annual review: added prescriber requirement; revised diagnosis with DSM-V definition of postpartum depression; revised criteria to allow bypass of 8-week antidepressant trial if member has severe depression as evidenced by HAMD, MADRS, or PHQ-9 score; updated HAM-D scale; references reviewed and updated.	01/2021	
2Q 2021 annual review: no significant changes; references reviewed and updated.	04/2021	
2Q 2022 annual review: references reviewed and updated.	04/2022	
RT4: per updated prescribing information, updated indication and age requirements from adults (18 years) to 15 years of age or older.	08/2022	
2Q 2023 annual review: shortened the trial durations of antidepressant agent from 8 weeks to 4 weeks; references reviewed and updated.	04/2023	
Revised criterion for diagnosis of major depressive episode that began no later than the first 4 weeks following delivery per updated ACOG guidance; added requirement that member has not received prior treatment with Zulresso or Zurzuvae for the current pregnancy; corrected MADRS score to ≥ 35 for severe depression; added additional approval pathway if member does not have severe	10/2023	

CLINICAL POLICY
Brexanolone



Reviews, Revisions, and Approvals	Date	P&T Approval Date
depression as demonstrated by at least one of the depression scores, documentation of severe depression as evidenced by a psychiatrist clinical interview.		