Clinical Policy: Brexanolone (Zulresso)

Reference Number: CP.PHAR.417
Effective Date: 06.01.19
Last Review Date: 05.24
Line of Business: Commercial, HIM, Medicaid

Coding Implications
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.

It is the policy of health plans affiliated with Centene Corporation® 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 4 weeks following delivery, as diagnosed by Structured Clinical Interview for DSM-5;
2. Prescribed by or in consultation with psychiatrist or obstetrician-gynecologist;
3. Age ≥ 15 years;
4. Member meets ONE of the following (a, b, c, d, e, f, or g):
   a. HAMD score is ≥ 24 (severe depression) (*see Appendix D*);
   b. MADRS score is ≥ 35 (severe depression) (*see Appendix D*);
   c. PHQ-9 score is ≥ 20 (severe depression) (*see Appendix D*);
   d. EPDS score is ≥ 20 (severe depression) (*see Appendix D*);
   e. BDI score is ≥ 29 (severe depression) (*see Appendix D*);
   f. If member does not have severe depression as demonstrated by at least one of the depression scores above (a, b, c, d, or e), documentation of severe depression as evidenced by a psychiarist or obstetrician-gynecologist clinical interview;
   g. Failure of an 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 6 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 (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business:

CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

BDI: Beck Depression Inventory
EPDS: Edinburgh Postnatal Depression Scale
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
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, Pexeva: 50 mg/day Paxil CR: 62.5 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Paxil CR: 25 mg PO QD; may increase by 12.5 mg every week as needed	
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 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
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)
Other Antidepressants		
bupropion (Aplenzin®, Budeprion SR® ,	Varies	Immediate-release: 450 mg/day (300 mg/day if pediatric)

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Budeprion XL®, Forfivo XL®, Wellbutrin®, Wellbutrin SR®, Wellbutrin XL®)		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.

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
> 23	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
> 19	Major depression, severe

- EPDS is a 10-item multiple choice questionnaire used to screen and assist in identifying possible symptoms of depression in the postnatal period.

EPDS Score	Depression Severity
5 – 9	Minimal symptomatology
10 – 14	Mild symptomatology
15 – 19	Moderate symptomatology
> 19	Severe symptomatology

- BDI is a 21-item, self-reported rating inventory that measures characteristic attitudes and symptoms of depression.

BDI Score	Depression Severity
0 – 13	Minimal depression
14 – 19	Mild depression
20 – 28	Moderate depression
> 28	Severe depression

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
PPD	Administered as a continuous intravenous infusion over 60 hours (2.5 days) as follows: • 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 April 4, 2024.
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 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: https://www.mdcalc.com/calc/4058/montgomery-asberg-depression-rating-scale-madrs. Accessed April 4, 2024.
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.
9. Screening and Diagnosis of Mental Health Conditions During Pregnancy and Postpartum: ACOG Clinical Practice Guideline No. 4. Obstet Gynecol. 2023 Jun 1; 141(6):1232-1261.
10. Gordon Jackson-Koku. Beck Depression Inventory. Occupational Medicine. 2016 March; 66(2): 174–175.

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
2Q 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 and PHQ-9; revised HIM-Medical Benefit line of business to HIM; references reviewed and updated.	03.04.20	05.20
2Q 2021 annual review: no significant changes; revised HIM.PHAR.21 to HIM.PA.154; 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	
Template changes applied to other diagnoses/indications.	09.23.22	
2Q 2023 annual review: shortened the trial durations of antidepressant agent from 8 weeks to 4 weeks; references reviewed and updated.	02.07.23	05.23
Revised criterion for diagnosis of major depressive episode that began no later than the first 4 weeks following delivery per updated	08.25.23	11.23

Reviews, Revisions, and Approvals	Date	P&T Approval Date
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 depression as demonstrated by at least one of the depression scores, documentation of severe depression as evidenced by a psychiarist clinical interview.		
2Q 2024 annual review: Added obstetrician-gynecologist as an additional prescriber specialty and specialist that can perform a clinical interview to confirm severe depression; per competitor analysis, added BDI and EPDS scales as additional methods to identify severe depression.	04.04.24	05.24

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.