Clinical Policy: Zuranolone (Zurzuvae)

Reference Number: CP.PHAR.650
Effective Date: 12.01.23
Last Review Date: 05.25
Line of Business: Commercial, HIM, Medicaid

Revision Log

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

Description

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

FDA Approved Indication(s)

Zurzuvae is indicated for the treatment of postpartum depression (PPD) in adults.

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 Zurzuvae 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 ≥ 18 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 psychiatrist or obstetrician-gynecologist clinical interview;
   g. 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 a 14 day treatment course and both of the following (a and b):
   a. 50 mg per day;
   b. 2 capsules per day.

Approval duration: 30 days (one 14 day treatment course 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®)	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: 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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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®)	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	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®)	25 mg PO QD for 3 days, then 50 mg PO QD, and then 75 mg/day (25 mg in the morning and 50 mg in the evening)	150 mg/day
desipramine (Norpramin®)	100 to 200 mg/day PO QD or in divided doses	300 mg/day (150 mg/day if geriatric)
doxepin	75 to 300 mg/day PO QD	300 mg/day
imipramine HCl	30 to 200 mg/day PO QD or divided doses	200 mg/day (100 mg/day if geriatric)
imipramine pamoate	75 to 200 mg/day PO QD or divided doses	200 mg/day (100 mg/day if geriatric)
nortriptyline (Pamelor®)	30 to 150 mg/day PO QD or in divided doses	150 mg/day (50 mg/day if geriatric)
protriptyline	15 to 60 mg/day PO in divided doses	60 mg/day (30 mg/day if geriatric)
trimipramine	50 to 200 mg/day PO QD	200 mg/day (100 mg/day if geriatric)
Other Antidepressants		
bupropion (Aplenzin®, Forfivo XL®, Wellbutrin SR®, Wellbutrin XL®)	Varies	Immediate-release: 450 mg/day Sustained-release: 400 mg/day Extended-release (HCl): 450 mg/day Extended-release (HBr): 522 mg/day
mirtazapine (Remeron®, Remeron Soltab)	15 to 45 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

- Boxed warning(s): impaired ability to drive or engage in other potentially hazardous activities
- 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	50 mg PO QD in the evening for 14 days Dosage may be reduced to 40 mg once daily if CNS depressant effects occur	50 mg/day

VI. Product Availability

Capsules: 20 mg, 25 mg, 30 mg

VII. References

1. Zurzuvae Prescribing Information. Cambridge, MA: Biogen, Inc.; July 2024. Available at: https://documents.sage-biogen.com/us/zurzuvae/pi.pdf. Accessed February 18, 2025.
2. 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.
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4. Montgomery–Åsberg Depression Rating Scale. Available at: https://www.mdcalc.com/calc/4058/montgomery-asberg-depression-rating-scale-madrs. Accessed February 18, 2025.
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Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	08.16.23	11.23
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.	03.14.24	05.24
2Q 2025 annual review: in Appendix B per Clinical Pharmacology, updated dosing regimens and removed commercially unavailable branded therapeutic alternatives; references reviewed and updated.	01.22.25	05.25

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.