PHARMACY COVERAGE GUIDELINE

ZURZUVAE™ (zuranolone) oral
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for therapy:** Zurzuvae (zuranolone) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Psychiatrist
2. Individual is 18 years of age or older
3. Individual has a confirmed diagnosis of severe postpartum depression (PPD) using the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria
4. Onset of depressive symptoms occurred no sooner than the 3rd trimester and no later than 4 weeks after delivery

5. Individual is ≤ 6 months postpartum

6. The diagnosis of PPD used on **ANY** of the following:
    a. Hamilton Rating Scale for Depression (HAM-D) score of at least 20
    b. Edinburgh Postnatal Depression Scale (EPDS) score of at least 13
    c. Montgomery-Asberg Depression Rating Scale (MADRS) score of at least 20
    d. Another validated tool

7. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

8. Individual has documented failure (after at least 6-weeks duration of use), contraindication per FDA label, intolerance, or is not a candidate for **ONE** the following:
    a. Selective serotonin re-uptake inhibitor (SSRI) and Psychotherapy (either cognitive-behavioral therapy (CBT) or interpersonal psychotherapy) [Note: see Definitions section for examples of SSRI]
    b. Selective norepinephrine re-uptake inhibitor (SNRI) and Psychotherapy (either cognitive-behavioral therapy (CBT) or interpersonal psychotherapy) [Note: see Definitions section for examples of SNRI]
    c. Mirtazapine and Psychotherapy (either cognitive-behavioral therapy (CBT) or interpersonal psychotherapy
    d. **TWO** antidepressant agents from **TWO** different antidepressant classes (i.e. SSRI, SNRI, bupropion, or mirtazapine)

9. Individual is not currently taking any other drugs which cause severe adverse reactions or any significant drug interactions requiring discontinuation such as CYP 3A4 inducers (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort)

10. Requested medication will **NOT** be used with or after Zulresso (brexanolone)

11. There is no evidence of active psychosis, bipolar disorder, schizophrenia, schizoaffective disorder or history of suicidal ideation or behaviors

Approval duration:
14 days; safety and effectiveness beyond 14 days in a single treatment course have not been established

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

PHARMACY COVERAGE GUIDELINE

ZURZUVAE™ (zuranolone) oral
Generic Equivalent (if available)

Description:

Zurzuvae (zuranolone) is a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator is indicated for the treatment of postpartum depression (PPD) in adults. PPD is a condition associated with pregnancy. The mechanism of action of zuranolone in the treatment of PPD is not fully understood but is thought to be related to its positive allosteric modulation of GABA receptors.

PPD is characterized by a major depressive episode temporally and pathophysiologically related to pregnancy. It is like other forms of depression and characterized by sadness and/or anhedonia and may present with symptoms such as cognitive impairment, feelings of worthlessness or guilt, or suicidal ideation. PPD should be distinguished from postpartum blues (baby blues) where sadness and anxiety are milder, are time-limited (lasting for a few hours to a few days in the first week postpartum) and have few negative sequelae. The transient symptoms of the "baby blues" - brief crying spells, irritability, nervousness, poor sleep and emotional reactivity. The baby blues affect 75% of new mothers, onset within 1–2 days and resolve by 10 days post-delivery.

Predictors of PPD include previous episodes of major depression, family history of depression, and depression during pregnancy. Other important demographic and clinical data predictive of PPD are recent immigrant status, increased stressful life events, history of childhood sexual abuse and decision to stop antidepressant therapy during pregnancy.

PPD is a temporal major depressive episode that may occur during pregnancy or within 4 weeks of delivery with an estimated prevalence of approximately 12% of births. The onset of symptoms of PPD generally occurs at a discrete time point in the third trimester of pregnancy or after childbirth. As per estimates by Sage Therapeutics, the sponsor of brexanolone, PPD may affect 1 in 9 women who give birth in the U. S. per year, which translates to 400,000 incident cases annually.

The most common measure to screen for depression related to childbearing is the Edinburgh Postnatal Depression Scale (EPDS). This self-report instrument contains ten items ranked from 0-3 that reflect the patient's experience over the past week. The EPDS has been validated extensively for use in the postpartum period and during pregnancy. An EPDS ≥ 13 is an acceptable cut-point for identifying women at risk for major depression in clinical settings. An EPDS ≥ 13 also corresponds with a Hamilton Rating Scale for Depression (HAM-D) ≥ 20 which suggests a high probability for a major depressive episode. For clinicians who wish to implement antenatal screening, the recommended cut-point is an EPDS ≥ 15. The higher threshold is clinically justified since increased scores may be explained by transient stress unrelated to a depressive disorder but related to normative experiences of pregnancy.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Antidepressant medications: (not a complete list)

Selective serotonin re-uptake inhibitors (SSRI)	Serotonin-norepinephrine re-uptake inhibitors (SNRI)
Citalopram (e.g., Celexa)	Desvenlafaxine (e.g., Pristiq)
Escitalopram (e.g., Lexapro)	Duloxetine (e.g., Cymbalta)
Fluoxetine (e.g., Prozac)	Levomilnacipran (e.g., Fetzima)

Fluvoxamine	Milnacipran (e.g., Savella)
Paroxetine (e.g., Paxil)	Venlafaxine (e.g., Effexor, Effexor XR)
Sertraline (e.g., Zoloft)	

Depression Screening Tools:

Depression Screening Tools				
Screening Tool	Number of items	Time to Complete (min)	Sensitivity & Specificity	Available in Spanish
Edinburgh Postnatal Depression Scale	10	< 5	Sensitivity: 59-100% Specificity: 49-100%	Yes
Postpartum Depression Scale	35	5-10	Sensitivity: 91-94% Specificity: 72-98%	Yes
Patient Health Questionnaire 9	9	< 5	Sensitivity: 75% Specificity: 90%	Yes
Beck Depression Inventory-I	21	5-10	Sensitivity: 47.6-82% Specificity: 85.9-89%	Yes
Beck Depression Inventory-II	21	5-10	Sensitivity: 56-57% Specificity: 97-100%	Yes
Center for Epidemiologic Studies Depression Scale	20	5-10	Sensitivity: 60% Specificity: 92%	Yes
Zung Self-Rating Depression scale	20	5-10	Sensitivity: 45-89% Specificity: 77-88%	No

Diagnostic Criteria for a Major Depressive Episode:

A. Five or more symptoms for 2 weeks (one of which must be either depressed mood or anhedonia)
   1. Depressed mood most of the day nearly every day
   2. Anhedonia most of the day nearly every day
   3. Significant weight loss or gain
   4. Insomnia or hypersomnia
   5. Psychomotor agitation or retardation
   6. Fatigue or loss of energy
   7. Feelings of worthlessness or excessive guilt
   8. Diminished ability to think or concentrate, indecisiveness
   9. Recurrent thoughts of death; suicidal ideation or attempt

B. Symptoms cause clinically significant distress or functional impairment
C. The episode is not attributable to the physiological effects of a substance or another medical condition
D. The episode is not better explained by a psychotic illness
E. There has never been a manic or hypomanic episode

Edinburgh Postnatal Depression Scale (EPDS)	
Check the answer that comes closest to how you felt in the past 7 days Each answer is scored from 0-3. The maximum score is 30.	
I have been able to laugh and see the funny side of things	0 = As much as I always could 1 = Not quite so much now 2 = Definitely not so much now 3 = Not at

I have looked forward with enjoyment to things	0 = As much as I ever did 1 = Rather less than I used to 2 = Definitely less than I used to 3 = Hardly at all
I have blamed myself unnecessarily when things went wrong	3 = Yes, most of the time 2 = Yes, some of the time 1 = Not very often 0 = No, never
I have been anxious or worried for no good reason	0 = No, not at all 1 = Hardly ever 2 = Yes, sometimes 3 = Yes, very often
I have felt scared or panicky for no very good reason	3 = Yes, quite a lot 2 = Yes, sometimes 1 = No, not much 0 = No, not at all
Things have been getting on top of me	3 = Yes, most of the time I haven't been able to cope at all 2 = Yes, sometimes I haven't been coping as well as usual 1 = No, most of the time I have coped quite well 0 = No, I have been coping as well as ever
I have been so unhappy that I have had difficulty sleeping	3 = Yes, most of the time 2 = Yes, sometimes 1 = Not very often 0 = No, not at all
I have felt sad or miserable	3 = Yes, most of the time 2 = Yes, quite often 1 = Not very often 0 = No, not at all
I have been so unhappy that I have been crying	3 = Yes, most of the time 2 = Yes, quite often 1 = Only occasionally 0 = No, never
The thought of harming myself has occurred to me	3 = Yes, quite often 2 = Sometimes 1 = Hardly ever 0 = Never
A score of more than 13 suggests minor or major depression may be present. Further evaluation is recommended	

Hamilton Rating Scale for Depression (HAM-D)	
Depressed Mood (sadness, hopeless, helpless, worthless)	**Anxiety - Psychic**
0 = Absent 1 = These feeling states indicated only on questioning 2 = These feeling states spontaneously reported verbally 3 = Communicates feeling states nonverbally, i.e., through facial expression, posture, voice and tendency to weep 4 = Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and nonverbal communication	0 = No difficulty 1 = Subjective tension and irritability 2 = Worrying about minor matters 3 = Apprehensive attitude apparent in face or speech 4 = Fears expressed without questioning
Feelings of Guilt	**Anxiety - Somatic**

0 = Absent 1 = Self-reproach, feels he has let people down 2 = Ideas of guilt or rumination over past errors or sinful deeds 3 = Present illness is a punishment. Delusions of guilt 4 = Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations	0 = Absent Physiological concomitants of anxiety such as: 1 = Mild Gastrointestinal - dry mouth, wind, indigestion, 2 = Moderate diarrhea, cramps, belching 3 = Severe Cardiovascular – palpitations, headaches 4 = Incapacitating Respiratory - hyperventilation, sighing Urinary frequency Sweating
Suicide	**Somatic Symptoms - Gastrointestinal**
0 = Absent 1 = Feels life is not worth living 2 = Wishes he were dead or any thoughts of possible death to self 3 = Suicide ideas or gesture 4 = Attempts at suicide (any serious attempt rates 4)	0 = None 1 = Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen. 2 = Difficulty eating without staff urging. Requests or requires laxatives or medications for bowels or medication for GI symptoms.
Insomnia – Early	**Somatic Symptoms - General**
0 = No difficulty falling asleep 1 = Complains of occasional difficulty falling asleep i.e., more than ½ hour 2 = Complains of nightly difficulty falling asleep	0 = None 1 = Heaviness in limbs, back or head, backaches, headache, muscle aches, loss of energy and fatigability 2 = Any clear-cut symptom rates 2
Insomnia – Middle	**Genital Symptoms**
0 = No difficulty 1 = Patient complains of being restless and disturbed during the night 2 = Waking during the night – any getting out of bed rates 2 (except for purposes of voiding)	0 = Absent 0 Not ascertained 1 = Mild Symptoms such as: loss of libido, 2 = Severe menstrual disturbances
Insomnia – Late	**Hypochondriasis**
0 = No difficulty 1 = Waking in early hours of the morning but goes back to sleep 2 = Unable to fall asleep again if gets out of bed	0 = Not present 1 = Self-absorption (bodily) 2 = Preoccupation with health 3 = Frequent complaints, requests for help, etc. 4 = Hypochondriacal delusions
Work and Activities	**Loss of Weight**
0 = No difficulty 1 = Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies 2 = Loss of interest in activity; hobbies or work – either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities) 3 = Decrease in actual time spent in activities or decrease in productivity. In hospital, rate 3 if patient does not spend at least three hours a day in activities (hospital job or hobbies) exclusive of ward chores. 4 = Stopped working because of present illness. In hospital, rate 4 if patient engages in no activities except ward chores, or if patient fails to perform ward chores unassisted.	A. When Rating by History: 0 = No weight loss 1 = Probable weight loss associated with present illness 2 = Definite (according to patient) weight loss B. On Weekly Ratings by Ward Psychiatrist, When Actual Changes are Measured: 0 = Less than 1 lb. weight loss in week 1 = Greater than 1 lb. weight loss in week 2 = Greater than 2 lb. weight loss in week
Retardation (slowness of thought and speech; impaired ability to concentrate; decreased motor activity)	**Insight**
0 = Normal speech and thought	0 = Acknowledges being depressed and ill

1 = Slight retardation at interview 2 = Obvious retardation at interview 3 = Interview difficult 4 = Complete stupor	1 = Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc. 2 = Denies being ill at all
Agitation	
0 = None 1 = "Playing with" hand, hair, etc. 2 = Hand-wringing, nail-biting, biting of lips	
0-7: Normal, not depressed 8-16: Mild depression 17-23: Moderate depression ≥ 24: Severe depression	HAM-D response = ≥ 50% reduction from baseline in score HAM-D remission = ≤ 7 HAM-D score

Montgomery–Åsberg Depression Rating Scale (MADRS):
A ten-item diagnostic questionnaire that measures the severity of depressive episodes in patients with mood disorders.

The rating is based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones that allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5) and then report the appropriate number. The items should be rated with regard to the state of the patient over the past week. Score can range from 0-60, with higher scores indicating more severe depression. Total score can range from 0 to 60, with higher scores indicating more severe depression. Usual cut-points are: score 0-6 = no depression; score 7-19 = mild depression; score 20-34 = moderate depression; and score 35-60 = severe depression.

1 - APPARENT SADNESS - Representing despondency, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.		
	0	No sadness.
	1	
	2	Looks dispirited but does brighten up without difficulty.
	3	
	4	Appears sad and unhappy most of the time.
	5	
	6	Looks miserable all the time. Extremely despondent.
2 - REPORTED SADNESS - Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.		
	0	Occasional sadness in keeping with the circumstances.
	1	
	2	Sad or low but brightens up without difficulty.
	3	
	4	Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
	5	
	6	Continuous or unvarying sadness, misery or despondency.
3 - INNER TENSION - Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.		
	0	Placid. Only fleeting inner tension.
	1	

	2	Occasional feelings of edginess and ill-defined discomfort.
	3	
	4	Continuous feelings of inner tension or intermittent panic that the patient can only master with some difficulty.
	5	
	6	Unrelenting dread or anguish. Overwhelming panic.
4 - REDUCED SLEEP - Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.		
	0	Sleeps as usual.
	1	
	2	Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
	3	
	4	Sleep reduced or broken by at least two hours.
	5	
	6	Less than two or three hours sleep.
5 - REDUCED APPETITE - Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.		
	0	Normal or increased appetite.
	1	
	2	Slightly reduced appetite.
	3	
	4	No appetite. Food is tasteless.
	5	
	6	Needs persuasion to eat at all.
6 - CONCENTRATION DIFFICULTIES - Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.		
	0	No difficulties in concentrating.
	1	
	2	Occasional difficulties in collecting one's thoughts.
	3	
	4	Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
	5	
	6	Unable to read or converse without great difficulty.
7 - LASSITUDE - Representing a difficulty getting started or slowness initiating and performing everyday activities.		
	0	Hardly any difficulties in getting started. No sluggishness.
	1	
	2	Difficulties in starting activities.
	3	
	4	Difficulties in starting simple routine activities that are carried out with effort.
	5	
	6	Complete lassitude. Unable to do anything without help.
8 - INABILITY TO FEEL - Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.		
	0	Normal interest in the surroundings and in other people.
	1	
	2	Reduced ability to enjoy usual interests.
	3	
	4	Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.

	5	
	6	The experience of being emotionally paralyzed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.
9 - PESSIMISTIC THOUGHTS - Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.		
	0	No pessimistic thoughts.
	1	
	2	Fluctuating ideas of failure, self-reproach or self-depreciation.
	3	
	4	Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.
	5	
	6	Delusions of ruin, remorse and unredeemable sin. Self-accusations which are absurd and unshakable.
	0	No pessimistic thoughts.
	1	
	2	Fluctuating ideas of failure, self-reproach or self-depreciation.
	3	
	4	Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.
	5	
	6	Delusions of ruin, remorse and unredeemable sin. Self-accusations which are absurd and unshakable.
10 - SUICIDAL THOUGHTS - Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.		
	0	Enjoys life or takes it as it comes.
	1	
	2	Weary of life. Only fleeting suicidal thoughts.
	3	
	4	Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
	5	
	6	Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

Resources:

Zurzuvae (zuranolone) product information, revised by Biogen MA Inc. 07-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 27, 2024.

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Deligiannidis KM, Meltzer-Brody S, Gunduz-Bruce H, et al.: Effect of Zuranolone vs Placebo in Postpartum Depression A Randomized Clinical Trial. JAMA Psychiatry. 2021;78(9):951-959. doi:10.1001/jamapsychiatry.2021.1559. Accessed November 21, 2023. Re-evaluated January 09, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT04442503: A Randomized, Double-Blind, Placebo-controlled Study Evaluating the Efficacy and Safety of SAGE-217 in the Treatment of Adults With Severe Postpartum Depression. Available from: http://clinicaltrials.gov. Last update posted June 22, 2023. Last verified June 2023. Accessed November 21, 2023. Re-evaluated January 09, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT02978326: A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-217 in the Treatment of Adult Female Subjects With Severe Postpartum Depression. Available from: http://clinicaltrials.gov. Last update posted February 10, 2022. Last verified February 2022. Accessed November 21, 2023. Re-evaluated January 09, 2025.