BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

AUVELITY® (dextromethorphan & bupropion) extended release tablets 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/or 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.

Medical Necessity Requirements for AUVELITY (dextromethorphan & bupropion)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by a Psychiatrist or is in consultation with a Psychiatrist

Indication
- Major depressive disorder (MDD) without psychotic features meeting Diagnostic and Statistical Manual of Mental Disorders criteria

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Age Requirement

- 18 years or older

Baseline Clinical Evaluation

- Completed the following tests before starting treatment and will have continued monitoring as clinically appropriate:
  - **BOTH** of the following:
    1. Montgomery Asberg Depression Rating Scale (MADRS) of at least 25
    2. Clinician global impression severity (CGI S) scale of at least 4
  - Major depressive episode has persisted for a minimum of 4 weeks
  - Blood pressure

Alternative Therapies

- Failure (trial for at least three months duration), contraindication, intolerance, or is not a candidate for **ALL** of the following:
  - A trial of maximally tolerated doses of bupropion
  - A trial of a serotonin reuptake inhibitor
  - A trial of serotonin norepinephrine reuptake inhibitor

Brand Specific Criteria

- Have failure, contraindication, or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the United States Food and Drug Administration (FDA) (see Definitions section)

Safety

- There are **NONE** of the following:
  - Use of other medications that contain bupropion and dextromethorphan
  - Personal or family history of bipolar disorder, mania or hypomania
  - Bipolar depression
  - Untreated angle closure glaucoma
  - Seizure disorder
  - Current or prior diagnosis of bulimia or anorexia nervosa
  - Concurrent use with or within 14 days of stopping a mono amine oxidase inhibitor (MAOI) including use of linezolid or methylene blue
  - Hypersensitivity to bupropion or dextromethorphan
  - Undergoing abrupt discontinuation of alcohol, benzodiazepine, barbiturates, and antiepileptic medications
  - Use with strong CYP2B6 inducers (e.g., ritonavir, lopinavir, efavirenz)
  - Severe renal impairment (estimated glomerular filtration rate 15 to 29 mL per minute per 1.73 square meters
  - Severe hepatic impairment (Child Pugh Class C)
  - Recent history of myocardial infarction or unstable cardiac disease

- Woman of childbearing potential who is pregnant or planning to become pregnant

Documentation Requirements

- A completed request form must be submitted including:
  - Chart notes
  - Lab results (creatinine clearance, hepatic function)
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration

- 6 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy):

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy.

Prescriber Qualifications

- Continues to be seen by a Psychiatrist or is in consultation with a Psychiatrist

Clinical Response

- Achieved and maintains improvement in **ONE** of the following:
  - Clinical response shown by a Montgomery Asberg Depression Rating Scale (MADRS) reduction of at least 50 percent from baseline
  - Clinical remission shown by a Montgomery Asberg Depression Rating Scale (MADRS) of less than or equal to 10

Adherence

- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- There are **NONE** of the following:
  - Use of other medications that contain bupropion and dextromethorphan
  - Personal or family history of bipolar disorder, mania or hypomania
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- Use with strong CYP2B6 inducers
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- Severe hepatic impairment (Child Pugh Class C)
- Recent history of myocardial infarction or unstable cardiac disease
- Woman of childbearing potential who is pregnant or planning to become pregnant
- Hypertension (resting, sitting systolic blood pressure of greater than or equal to 150 mmHg or diastolic blood pressure greater than or equal to 95 mmHg)
- Activation of mania or hypomania
- Serotonin syndrome
- Worsening depression or experiencing emergent suicidal thoughts or behaviors

Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement
- Lab values confirming safe continued use

Continuation Therapy Criteria Approval Duration

- 12 months OR end of plan year

Criteria for Off-Label Use Requests:

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

Description:

Auvelity is a combination of dextromethorphan, an uncompetitive N-methyl D-aspartate (NMDA) receptor antagonist and sigma-1 receptor agonist, and bupropion, an aminoketone and CYP450 2D6 inhibitor, indicated for the treatment of major depressive disorder (MDD) in adults.

Dextromethorphan is an uncompetitive antagonist of the NMDA receptor (an ionotropic glutamate receptor) and a sigma-1 receptor agonist. The mechanism of dextromethorphan in the treatment of MDD is unclear. The mechanism of action of bupropion in the treatment of MDD is unclear; however, it may be related to noradrenergic

and/or dopaminergic mechanisms. Bupropion increases plasma levels of dextromethorphan by competitively inhibiting cytochrome P450 2D6, which catalyzes a major biotransformation pathway for dextromethorphan. Bupropion is a relatively weak inhibitor of the neuronal reuptake of norepinephrine and dopamine and does not inhibit monoamine oxidase or the reuptake of serotonin.

Auvelity is available as round bilayer tablets. Each tablet contains 45 mg dextromethorphan hydrobromide (equivalent to 32.98 mg dextromethorphan base) in an immediate-release formulation and 105 mg bupropion hydrochloride (equivalent to 91.14 mg bupropion base) in an extended-release formulation.

Definitions:

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

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Montgomery-Asberg Depression Rating Scale (MADRS)
The rating should be 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 to 60, with higher scores indicating more 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.

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.

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Clinical global impression – severity scale (CGI-S)

1	Normal, not at all ill
2	Borderline mentally ill
3	Mildly ill
4	Moderately ill
5	Markedly ill
6	Severely ill
7	Among the most extremely ill patients

Clinical global impression – improvement scale (CGI-I)

1	Very much improved
2	Much improved
3	Minimally improved
4	No change
5	Minimally worse
6	Much worse
7	Very much worse

Resources:

Auvelity (dextromethorphan hydrobromide and bupropion hydrochloride) extended release tab product information, revised by Axsome Therapeutics, Inc. 12-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 16, 2026.

Iosifescu DV, Jones A, O'Gorman C, et al.: Efficacy and Safety of AXS-05 (Dextromethorphan-Bupropion) in Patients With Major Depressive Disorder: A Phase 3 Randomized Clinical Trial (GEMINI). J Clin Psychiatry 2022 July/Aug;83(4):21m14345. Accessed February 16, 2026.

Tabuteau H, Jines A, Anderson A, et al.: Effect of AXS-05 (Dextromethorphan-Bupropion) in Major Depressive Disorder: A Randomized Double-Blind Controlled Trial. Am J Psychiatry 2022 July; 179:490–499; doi: 10.1176/appi.ajp.21080800. Accessed February 16, 2026.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT04019704: AXS-05-MDD-301: A Randomized, Double-Blind, Placebo-Controlled Trial of AXS-05 in Subjects With Major Depressive Disorder. Available from: http://clinicaltrials.gov. Last update posted October 12, 2022. Last verified September 2022. Accessed February 16, 2026.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT03595579: A Randomized, Double-Blind, Active-Controlled Trial of AXS-05 Administered Orally to Subjects With Major Depressive Disorder. Available from: http://clinicaltrials.gov. Last update posted September 09, 2024. Last verified September 2021. Accessed February 16, 2026.