Clinical Policy: Dextromethorphan/Bupropion (Auvelity)

Reference Number: CP.PMN.284
Effective Date: 12.01.22
Last Review Date: 11.26
Line of Business: Commercial, HIM/ICHRA, Medicaid Revision Log

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

Description

Dextromethorphan/bupropion (Auvelity®) is an extended-release, fixed-dose combination of dextromethorphan hydrobromide, an uncompetitive N-methyl D-aspartate (NMDA) receptor antagonist and sigma-1 receptor agonist, and bupropion hydrochloride, an aminoketone and CYP450 2D6 inhibitor.

FDA Approved Indication(s)

Auvelity is indicated for the treatment of:

- Major depressive disorder (MDD) in adults.
- Agitation associated with dementia due to Alzheimer's disease (AD).

Limitation(s) of use: Auvelity is not indicated as an as needed ("prn") treatment for agitation associated with dementia due to AD.

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 Auvelity is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Major Depressive Disorder (must meet all)**:**

1. Diagnosis of MDD;
2. Age ≥ 18 years;
3. Member meets one of the following (a or b):
   a. Request is for the treatment of a member in a State with limitations on step therapy in certain mental health settings (*see Appendix D*);
   b. Failure of TWO preferred formulary antidepressants from the following, each tried for ≥ 4 weeks at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated: SSRI, SNRI, bupropion, mirtazapine;*
      **For Illinois HIM requests, the step therapy requirements above do not apply per IL HB 5395*
4. Dose does not exceed both of the following (a and b):
   a. 90 mg dextromethorphan and 210 mg bupropion per day;
   b. 2 tablets per day.

Approval duration: 12 months

B. Alzheimer's Disease Related Agitation (must meet all)**:**
1. Diagnosis of agitation associated with dementia due to AD;
2. Age ≥ 18 years;
3. Auvelity is not prescribed as an as needed ("prn") treatment;
4. Dose does not exceed both of the following (a and b):
   a. 90 mg dextromethorphan and 210 mg bupropion per day;
   b. 2 tablets per day.

Approval duration: 12 months

C. 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/ICHRA) 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/ICHRA, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace/ICHRA) 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/ICHRA, 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/ICHRA, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications In Section I (must meet all)**:**
1. Member meets one of the following (a, b, or c):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Documentation supports that member is currently receiving Auvelity for major depressive disorder and has received this medication for at least 30 days;
   c. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed both of the following (a and b):
   a. 90 mg dextromethorphan and 210 mg bupropion per day;
   b. 2 tablets per day.

Approval duration: 12 months

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/ICHRA) 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/ICHRA, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace/ICHRA) 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/ICHRA, 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/ICHRA, 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/ICHRA, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AD: Alzheimer's disease
FDA: Food and Drug Administration
MAOI: monoamine oxidase inhibitor
MDD: major depressive disorder
SNRI: serotonin norepinephrine reuptake inhibitor
SSRI: selective serotonin reuptake inhibitor

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
bupropion HCl extended-release (Wellbutrin® XL)	150-450 mg PO QAM	450 mg/day
bupropion HCl sustained-release (Wellbutrin SR)	150 mg PO QD or 150-200 mg PO BID	400 mg/day
bupropion HCl	100 mg PO BID or 100-150 mg PO TID	450 mg/day
mirtazapine (Remeron®)	15-45 mg PO QHS	45 mg/day
SSRIs		
citalopram (Celexa®)	20-40 mg PO QD	40 mg/day (≤ 60 years)

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
bupropion HCl extended-release (Wellbutrin® XL)	150-450 mg PO QAM	450 mg/day
bupropion HCl sustained-release (Wellbutrin SR)	150 mg PO QD or 150-200 mg PO BID	400 mg/day
bupropion HCl	100 mg PO BID or 100-150 mg PO TID	450 mg/day
		20 mg/day (> 60 years)
escitalopram (Lexapro®)	10-20 mg PO QD	20 mg/day
fluvoxamine*	50-150 mg PO QD	150 mg/day
fluoxetine (Prozac®)	20-80 mg PO QD	80 mg/day
paroxetine (Paxil®, Paxil CR)	IR: 20-50 mg PO QD CR: 25-62.5 mg PO QD	IR: 50 mg/day CR: 62.5 mg/day
sertraline (Zoloft®)	50-200 mg PO QD	200 mg/day
SNRIs		
desvenlafaxine (Pristiq®)	50-400 mg PO QD	400 mg/day
duloxetine (Cymbalta®)	20-30 mg PO BID or 60 mg PO QD	120 mg/day
venlafaxine (Effexor® XR)	IR: 75 mg PO BID to TID XR: 75 mg PO QD	IR: 375 mg/day XR: 225 mg/day
Fetzima® (levomilnacipran)	40-120 mg PO QD	120 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

- Contraindication(s): seizure disorder; current or prior diagnosis of bulimia or anorexia nervosa; abrupt discontinuation of alcohol, benzodiazepine, barbiturates, and antiepileptic drugs; use with an MAOI or within 14 days of stopping treatment with Auvelity - do not use Auvelity within 14 days of discontinuing an MAOI; hypersensitivity to bupropion, dextromethorphan, or other components of Auvelity
- Boxed warning(s): increased risk of suicidal thoughts and behavior in pediatric and young adult patients taking antidepressants; closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors; not approved for use in pediatric patients

Appendix D: States with Limitations against Redirections in Certain Mental Health Settings

State	Step Therapy Prohibited?	Notes
TX	No	Failure of ONE of the following, used for ≥ 4 weeks at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated: SSRI, SNRI, bupropion, mirtazapine.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
MDD	45 mg/105 mg PO QAM for the first 3 days, then increase to BID given at least 8 hours apart, based on tolerability	2 tablets/day (dextromethorphan 90 mg/ bupropion 210 mg)
Agitation associated with dementia due to AD	30 mg/105 mg PO QAM for the first 7 days, then increase to BID based on tolerability. On day 15, increase to 45 mg/105 mg BID based on tolerability	2 tablets/day (dextromethorphan 90 mg/ bupropion 210 mg)

VI. Product Availability

Extended-release tablets: 30 mg/105 mg, 45 mg/105 mg

VII. References

1. Auvelity Prescribing Information. New York, NY: Axsome Therapeutics, Inc.; June 2026. Available at www.auvelity.com. Accessed July 22, 2026.
2. Clinical Pharmacology [database online]. Philadelphia, PA: Elsevier, Inc.; 2026. Available at: www.clinicalkeys.com/pharmacology.
3. Losifescu 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;83(4):21m14345. https://doi.org/10.4088/JCP.21m14345.
4. Tabuteau H, Jones A, Anderson A, Jacobson M, Losifescu DV. Effect of AXS-05 (dextromethorphan-bupropion) in major depressive disorder: a randomized double-blind controlled trial. *Am J Psychiatry* 2022; 179(7):490-499. https://doi.org/10.1176/appi.ajp.21080800.
5. Gelenberg AJ, Freeman MP, Markowitz JC, et al. Practice guideline for the treatment of patients with major depressive disorder, third edition. Arlington, VA: American Psychiatric Association; May 2010. Available online at: https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Accessed July 22, 2026.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	09.27.22	11.22
Updated initial criteria to include trial of individual components, references reviewed and updated; updated template language for continued therapy and other diagnoses/indication sections.	11.04.22	02.23
Added redirection bypass for members in a State with limitations on step therapy in certain mental health settings along with Appendix D, which includes Texas with requirements for single drug redirection for HIM requests.	07.11.23	
4Q 2023 annual review: clarified that the two antidepressants be preferred formulary antidepressants; removed redirection to individual Auvelity components; references reviewed and updated.	09.06.23	11.23

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Corrected criteria to remove individual Auvelity components use.	01.10.24	
4Q 2024 annual review: no significant changes; in Appendix B, updated dosing regimen for therapeutic alternatives per Clinical Pharmacology; references reviewed and updated.	07.30.24	11.24
4Q 2025 annual review: added step therapy bypass for IL HIM per IL HB 5395; references reviewed and updated.	07.25.25	11.25
RT4: added new indication for treatment of agitation associated with dementia due to AD; revised continued therapy criteria to allow continuity of care for MDD.	05.06.26	
4Q 2026 annual review: added ICHRA line of business; references reviewed and updated.	07.22.26	11.26

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.

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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.

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