Auvelity (dextromethorphan hydrobromide / bupropion hydrochloride)

- Extended-release tablets
- Titration pack

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Auvelity (dextromethorphan hydrobromide and bupropion hydrochloride), is an oral combination product indicated for the treatment of major depressive disorder (MDD) or for the treatment of agitation associated with dementia due to Alzheimer's disease in adults.

Major depressive disorder is a mental health disorder that causes symptoms of sadness, hopelessness, and loss of interest in things. It can disrupt relationships and everyday activities, such as work, school, and activities that are usually pleasant. There are many medications from several classes that are available to treat major depressive disorder including selective serotonin-reuptake inhibitors (SSRIs), serotonin- and norepinephrine-reuptake inhibitors (SNRIs), tricyclic antidepressants, monoamine oxidase (MAO) inhibitors, and other antidepressants (e.g., bupropion, mirtazapine, trazodone).

Agitation associated with dementia due to Alzheimer's disease (AD) is characterized by emotional distress combined with excessive, repetitive, or aggressive behaviors. It is an expression of confusion, fear, or discomfort when the brain loses the ability to communicate needs normally. This distress manifests outwardly as non-aggressive physical restlessness (e.g., continuous pacing or wandering), verbal aggression (e.g., screaming or shouting), or physical aggression (e.g., hitting, pushing, or resisting necessary care). It can be triggered by underlying physical pain, urinary tract infections, overstimulating environments, or "sundowning".

Definitions

"Agitation associated with dementia due to Alzheimer's disease (AD)" is a behavioral syndrome characterized by increased, often undirected, motor activity, restlessness, aggressiveness, and emotional distress in those with dementia.

"Documentation" refers to written information, including but not limited to:

- Up-to-date chart notes, relevant test results, and/or relevant imaging reports to support diagnoses; or
- Prescription claims records, and/or prescription receipts to support prior trials of formulary alternatives.

"Major depressive disorder", also known as (MDD), is a psychiatric condition characterized by persistent low mood, low energy, or loss of interest in enjoyable activities causing substantial impairment in daily life. MDD is thought to be caused by a combination of genetic, environmental and psychological factors. Risk factors include family history, major life changes, certain medications, chronic health problems, and substance use disorders.

"Neurotransmitter" is a molecule that sends signals from neurons to different parts of the body (e.g., muscles).

"[s]" indicates state mandates may apply.

Clinical Indications

Medical Necessity Criteria for Clinical Review

General Medical Necessity Criteria

The Plan considers **Auvelity (dextromethorphan and bupropion)** medically necessary when **ALL** of the following criteria are met:

1. The member is 18 years of age or older; ***AND***
2. **IF** the request is for the Auvelity (dextromethorphan and bupropion) titration pack, its use is for agitation associated with dementia due to Alzheimer's disease***; AND***
3. Auvelity (dextromethorphan and bupropion) is being prescribed at a dose and frequency that is within FDA approved labeling **OR** is supported by compendia or evidence-based published dosing guidelines for the requested indication***; AND***

   The requested medication is being used within the Plan's Quantity Limit of the following:

   - *Extended-release tablets: 60 tablets every 30 days; or*
   - *Titration pack: 51 tablets per lifetime.*
4. The member meets the applicable General Medical Necessity Criteria - Indication-Specific Criteria listed below.

<u>Agitation Associated with Dementia due to Alzheimer's Disease (AD)</u>

The Plan considers **Auvelity (dextromethorphan and bupropion)** medically necessary when **ALL** of the following criteria are met:

5. The member meets the above General Medical Necessity Criteria; ***AND***
6. Prescribed by a specialist[⇅] in Alzheimer's disease or a psychiatrist; ***AND***

   [⇅]*To ensure member access to appropriate pharmacotherapy when clinical criteria are met but specialist availability is limited, an exception to the Auvelity (dextromethorphan and bupropion) specialist requirement may be considered if there is inadequate access to specialists in the member's location. In such cases, Auvelity (dextromethorphan and bupropion) may be prescribed by the member's primary care provider or other qualified clinician experienced in safely using this medication for agitation in Alzheimer's disease dementia, provided all other clinical criteria are documented and met.*
7. The member has a diagnosis of Alzheimer's disease with documented agitation; ***AND***
8. The member has has tried and failed **TWO** non-pharmacological treatments for agitation, including but not limited to[s]:
   a. Caregiver education and support; *and/or*
   b. Cognitive stimulation; *and/or*
   c. Exercise programs; *and/or*
   d. Group therapy; *and/or*
   e. Music therapy; *and/or*
   f. Redirecting; *and/or*
   g. Occupational therapy; ***AND***

9. The member exhibits agitation behaviors (i.e., symptoms are severe, dangerous, and/or cause significant distress) warranting pharmacotherapy; *AND*
10. Auvelity (dextromethorphan and bupropion) is NOT being used as an "as needed" treatment.

If the above prior authorization criteria are met, the requested medication will be approved for up to a lifetime.[s]

Major Depressive Disorder (MDD)

The Plan considers Auvelity (dextromethorphan and bupropion) medically necessary when ALL of the following criteria are met:

5. The member meets the above General Medical Necessity Criteria; *AND*
6. The member has a diagnosis of major depressive disorder (MDD); *AND*
7. The member is unable to use or has tried and failed TWO (2) therapies, each from a different drug class for at least six (6) weeks each[s]:
    a. Noradrenergic and dopaminergic antidepressants (bupropion)*; and/or*
    b. Noradrenergic and specific serotonin antidepressants (e.g., mirtazapine)*; and/or*
    c. Selective serotonin reuptake inhibitors (e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline)*; and/or*
    d. Serotonin-norepinephrine reuptake inhibitors (e.g., duloxetine, venlafaxine IR/ER)*; and/or*
    e. Tricyclic antidepressants (e.g., amitriptyline, nortriptyline).

If the above prior authorization criteria are met, the requested medication will be approved for up to a lifetime.[s]

Experimental / Investigational, or unproven[s]

Auvelity (dextromethorphan and bupropion) for any other use is considered experimental, investigational, or unproven. Non-covered uses include, but are not limited to, the following:

- Smoking cessation. There is not enough evidence to support the safety and efficacy of Auvelity (Dextromethorphan and Bupropion) for the management of smoking cessation. One unpublished study (NCT03471767) with 58 participants did not find a statistically significant difference in the primary outcome of change in smoking behavior.

References

1. Akbar D, Rhee TG, Ceban F, et al. Dextromethorphan-Bupropion for the Treatment of Depression: A Systematic Review of Efficacy and Safety in Clinical Trials. CNS Drugs. 2023 Oct;37(10):867-881. doi: 10.1007/s40263-023-01032-5. Epub 2023 Oct 4.
2. American Geriatrics Society Beers Criteria® Alternatives Panel; Steinman MA. Alternative Treatments to Selected Medications in the 2023 American Geriatrics Society Beers Criteria®. J Am Geriatr Soc. 2025 Jul 23:10.1111/jgs.19500. doi: 10.1111/jgs.19500. Epub ahead of print.
3. American Psychiatric Association: Practice Guideline for the Treatment of Patients with Major Depressive Disorder, 3rd edition, 2010. Available at:

https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Published October 2010. Accessed October 2022.
4. Ashwin JV, Shahi MK, Singh A, Kumar ST. Efficacy and safety of dextromethorphan-bupropion combination (AXS-05) in the treatment of depression: A systematic review and network meta-analysis. Indian J Pharmacol. 2025 Jul 1;57(4):262-268. doi: 10.4103/ijp.ijp_907_24. Epub 2025 Jul 21.
5. Auvelity (dextromethorphan and bupropion) [prescribing information]. New York, NY: Axsome Therapeutics Inc; June 2026.
6.
7. Bauer M, Pfennig A, Severus E, Whybrow PC, Angst J, Möller HJ; World Federation of Societies of Biological Psychiatry Task Force on unipolar depressive disorders. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders. Part 1: update 2013 on the acute and continuation treatment of unipolar depressive disorders. World J Biol Psychiatry. 2013;14(5):334-385. doi: 10.3109/15622975.2013.804195.
8. Bauer M, Severus E, Köhler S, Whybrow PC, Angst J, Möller HJ; WFSBP Task Force on treatment guidelines for unipolar depressive disorders. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders. Part 2: maintenance treatment of major depressive disorder-update 2015. World J Biol Psychiatry. 2015;16(2):76-95. doi:10.3109/15622975.2014.1001786.
9. Carrarini C, Russo M, Dono F, Barbone F, Rispoli MG, Ferri L, Di Pietro M, Digiovanni A, Ajdinaj P, Speranza R, Granzotto A, Frazzini V, Thomas A, Pilotto A, Padovani A, Onofrj M, Sensi SL, Bonanni L. Agitation and Dementia: Prevention and Treatment Strategies in Acute and Chronic Conditions. Front Neurol. 2021 Apr 16;12:644317. doi: 10.3389/fneur.2021.644317. PMID: 33935943; PMCID: PMC8085397.
10. Cummings JL, Lyketsos CG, Peskind ER, et al. Effect of Dextromethorphan-Quinidine on Agitation in Patients With Alzheimer Disease Dementia: A Randomized Clinical Trial. JAMA. 2015 Sep 22-29;314(12):1242-54. doi: 10.1001/jama.2015.10214.
11. Daniel Lee, Emily D. Clark, Inga M. Antonsdottir & Anton P. Porsteinsson (2023) A 2023 update on the advancements in the treatment of agitation in Alzheimer's disease, Expert Opinion on Pharmacotherapy, 24:6, 691-703, DOI: 10.1080/14656566.2023.2195539.
12. Garriga M, Pacchiarotti I, Kasper S, et al. Assessment and management of agitation in psychiatry: expert consensus. World J Biol Psychiatry. 2016;17(2):86-128. doi:10.3109/15622975.2015.1132007.
13. 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;83(4):21m14345. doi:10.4088/JCP.21m14345.
14. Mauri MC, Fiorentini A, Paletta S, Altamura AC. Pharmacokinetics of antidepressants in patients with hepatic impairment. Clin Pharmacokinet. 2014;53(12):1069-1081. doi:10.1007/s40262-014-0187-5.
15. Mullish BH, Kabir MS, Thursz MR, Dhar A. Review article: depression and the use of antidepressants in patients with chronic liver disease or liver transplantation. Aliment Pharmacol Ther. 2014;40(8):880-892. doi:10.1111/apt.12925.
16. Qaseem A, Owens DK, Etxeandia-Ikobaltzeta I, et al; Clinical Guidelines Committee of the American College of Physicians. Nonpharmacologic and Pharmacologic Treatments of Adults in the Acute Phase of Major Depressive Disorder: A Living Clinical Guideline From the American College of Physicians. Ann Intern Med.2023;176:239-252. [Epub 24 January 2023]. doi:10.7326/M22-2056.
17. Reus VI, Fochtmann LJ, Eyler AE, et al. The American Psychiatric Association practice guideline on the use of antipsychotics to treat agitation or psychosis in patients with dementia. Am J Psychiatry. 2016;173(5):543-546. doi:10.1176/appi.ajp.2015.173501.
18. Stahl SM. Dextromethorphan/bupropion: a novel oral NMDA (N-methyl-d-aspartate) receptor antagonist with multimodal activity-Addendum. CNS Spectr. 2020;25(6):803. doi:10.1017/S109285291900155X.

19. Tabuteau H, Jones A, Anderson A, Jacobson M, Iosifescu 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. doi:10.1176/appi.ajp.21080800.
20. VA/DoD Clinical Practice Guideline. (2022). The Management of Major Depressive Disorder. Washington, DC: U.S. Government Printing Office.
21. World Federation of Societies of Biological Psychiatry; Ihl R, Frölich L, Winblad B, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of Alzheimer's disease and other dementias. World J Biol Psychiatry. 2011;12(1):2-32. doi:10.3109/15622975.2010.538083.

Clinical Guideline Revision / History Information

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