Dextromethorphan and bupropion (Auvelity™) Drug Bulletin

August 2022

Drug Name	dextromethorphan/bupropion (Auvelity)
Manufacturer	Axsome Therapeutics
FDA Approval Information	505(b)(2) NDA approval 8/18/22; Breakthrough Therapy, Priority Review
Market Availability	Availability anticipated in 4th quarter 2022
Drug Class & Indication	▪ Uncompetitive N-methyl D-aspartate (NDMA) receptor antagonist/sigma-1 receptor agonist and aminoketone/cytochrome P450 2D6 (CYP2D6) inhibitor ▪ Indicated in the treatment of major depressive disorder (MDD) in adults[1]
Dosage Strength/Form	Extended-release (ER) tablets: 45 mg/105 mg dextromethorphan hydrobromide/ bupropion hydrochloride
Dosage Regimen	▪ Prior to initiating treatment assess blood pressure and monitor periodically during treatment and screen patients for a personal or family history of bipolar disorder, mania, or hypomania and to determine if receiving other bupropion or dextromethorphan-containing medications ▪ Recommended starting dosage is 1 tablet by mouth once daily in the morning. After 3 days, increase to 1 tablet by mouth twice daily, separated by at least 8 hours. Maximum recommended dose is 2 tablets per day. ▪ Moderate renal impairment (eGFR 30 to 59 mL/minute/1.73 m2), poor CYP2D6 metabolizers, or concomitant use with strong CYP2D6 inhibitors: recommended dose is 1 tablet by mouth once daily in the morning
Clinical Comments	▪ First and only oral NMDA receptor antagonist FDA-approved for MDD; first and only rapid-acting oral antidepressant with clinical efficacy, as evidenced by Montgomery-Asberg Depression Rating Scale (MADRS), starting at 1 week[2] ▪ Multiple other oral dextromethorphan products are available on the market; however, all other dextromethorphan products are indicated only for the temporary relief of cough. Other ER oral bupropion products (Aplenzin®, Forfivo XL®, Wellbutrin XL®, Wellbutrin SR®) are available and are also indicated for the treatment of MDD in adult patients.[3] Symptom improvement can be seen within the first 2 weeks of starting antidepressants but it typically takes 4 to 8 weeks for benefit.[4] ▪ Safety profile aligns with that expected of bupropion and dextromethorphan ▪ Like other antidepressants, dextromethorphan/bupropion carries a boxed warning regarding the risks of suicidal thoughts and behaviors) ▪ Guidelines from the American Psychological Association recommend psychotherapy or second-generation antidepressants for the initial treatment of adult patients with MDD[5]

Clinical Comments *(continued)*	▪ The efficacy of dextromethorphan/bupropion was demonstrated in a placebo-controlled trial of 327 adults with MDD (NCT04019704, GEMINI). At week 6, dextromethorphan/bupropion showed an improvement of depressive symptoms compared to placebo as measured by a decrease in MADRS total score (least square mean difference, -3.9; 95% confidence interval [CI], -6.4 to -1.4). The change from baseline in MADRS total score was statistically significant as early as week 1.[6] ▪ Dextromethorphan/bupropion was compared to ER bupropion (105 mg) in a phase-2, double-blind, multicenter, randomized, parallel-group trial (NCT03595579) of 97 adults with MDD. Over weeks 1 through 6, dextromethorphan/bupropion showed an improved overall treatment effect compared to bupropion as measured by the mean change from baseline in MADRS score (-13.7 versus -8.8; least square mean difference,-4.9; 95% CI, -3.1 to -6.8).[7,8]

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	Antidepressants, Other
Clinical Edit	**Initial Approval Criteria** ▪ Patient age ≥ 18 years of age; **AND** ▪ Diagnosis of major depressive disorder; **AND** ▪ Patient must not have hypersensitivity to bupropion, dextromethorphan, or any component of the product; **AND** ▪ Patient is not pregnant, breastfeeding, or planning to become pregnant; **AND** ▪ Patient must not have diagnosis of seizure disorder, or current or prior diagnosis of bulimia or anorexia nervosa; **AND** ▪ Patient is not taking, or within 14 days of stopping, monoamine oxidase inhibitors (MAOIs); **AND** ▪ Patient is not undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs; **AND** ▪ Prescriber attestation that patient has been screened for personal or family history of bipolar disorder, mania, and hypomania; **AND** ▪ Prescriber attestation that patient has been screened for use of other medications that contain bupropion or dextromethorphan; **AND** ▪ Prescriber attestation that blood pressure has been assessed prior to initiation of treatment and will be monitored periodically during treatment. **Renewal Criteria** ▪ Patient must continue to meet the above criteria; **AND** ▪ Patient must have disease improvement and/or stabilization; **AND** ▪ Patient has not have experienced any treatment-restricting adverse effects (e.g., seizure, hypertension, psychosis, serotonin syndrome, angle-closure glaucoma)

Suggested Utilization Management (continued)

Quantity Limit	60 tablets/30 days; max dose 2 tablets per day
Duration of Approval	Initial: 1 year Renewal: 1 year
Drug to Disease Hard Edit	Seizure disorder, bulimia, anorexia nervosa

REFERENCES

1 Auvelity [package insert]. New York, NY; Axsome Therapeutics; August 2022.
2 Auvelity [package insert]. New York, NY; Axsome Therapeutics; August 2022.
3 Clinical Pharmacology. Available at: http://www.clinicalpharmacology-ip.com/default.aspx. Accessed August 31, 2022.
4 Drugs for Depression. Med Lett Drugs Ther. 2020 Feb;62(1592):25-32.
5 American Psychological Association. Clinical practice guideline for the treatment of depression across three age cohorts. 2019. Available at: https://www.apa.org/depression-guideline. Accessed August 31, 2022.
6 Auvelity [package insert]. New York, NY; Axsome Therapeutics; August 2022.
7 Auvelity [package insert]. New York, NY; Axsome Therapeutics; August 2022.
8 Tabuteau H, Jones 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 Jul;179(7):490-499.