**Auvelity® (dextromethorphan HBr and bupropion HCl) Public Comments for West Virginia DUR Board Meeting November 13, 2024**

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| **Epidemiology and Unmet Need** | • MDD is a potentially life-threatening condition and is also the leading cause of disability worldwide.[1,2]<br>• More than two-thirds of individuals with MDD have severe functional impairment.[3]<br>• Despite numerous treatment options for MDD, many challenges exist including delayed therapeutic effect, low rates of remission, and intolerable side effects.[4]<br>• Early clinical improvement with antidepressant therapy has emerged as an important treatment consideration, as it has been associated with significantly improved prognosis, remission, and long-term outcomes.[5,6]<br>• Prior to approval of Auvelity, traditional oral MDD therapies have shared similar mechanisms of monoaminergic modulation.[7]<br>• Importantly, after ineffective SSRI treatment, the likelihood of remission with switching to another monoamine-based treatment, whether another SSRI, an SNRI, or bupropion, is only ~20% based on the STAR*D study.[8]<br>• The lack of pharmacologic diversity among oral treatments has been a well-recognized area of unmet need and a focus of drug development for over 20 years. |
| **Mechanism of Action** | • Auvelity is the first and only oral N-methyl D-aspartate (NMDA) receptor antagonist approved for the treatment of MDD and represents the first oral treatment whose mechanism is not primarily monoaminergic.<br>• Dextromethorphan is an antagonist of the NMDA receptor and a sigma-1 receptor agonist.[9] NMDA receptor antagonism and sigma-1 receptor agonism modulate glutamatergic neurotransmission.<br>• The role of bupropion in AUVELITY is primarily to increase and prolong plasma levels of dextromethorphan, by inhibiting its CYP2D6-mediated metabolism. Bupropion is also a relatively weak inhibitor of the dopamine and norepinephrine transporters.[9] |
| **Clinical Development of Auvelity** | • Breakthrough therapy designation was granted to Auvelity in 2019 by the FDA and it was approved in August 2022 based on a clinical development program of over 1100 patients.<br>• In the pivotal, placebo-controlled, Phase 3, **GEMINI study:**<br>  ○ Auvelity achieved the primary outcome: Change from baseline to week 6 in MADRS total score was -15.9 points in the Auvelity group and -12.1 in the placebo group (*P*=0.002).[9,10]<br>  ○ Statistically significant improvement in the MADRS was demonstrated starting at Week 1,[9,10] a time frame consistent with the draft FDA guidance for rapid-acting antidepressants.[11]<br>  ▪ No other oral antidepressant has FDA-approved labeling stating improvement in depressive symptoms starting at Week 1.<br>  ○ The improvements seen with Auvelity were greater than the minimum clinically important threshold on the MADRS, which ranges from 1.6-1.9 points, at all timepoints measured.[10,12]<br>  ○ The key secondary endpoint of remission (MADRS Total Score ≤10) at Week 2 was also achieved, with Auvelity demonstrating a statistically significant greater remission rate compared to placebo (Auvelity 17%, Placebo 8%; *P* = 0.013).[10]<br>  ▪ Symptom remission is considered the desired goal in depression treatment, because it is associated with better daily functioning and better long-term prognosis.[13] |

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| | • In the confirmatory, active-controlled, Phase 2, **ASCEND study:**<br>  ○ Auvelity achieved the primary outcome by demonstrating statistically significant improvement in change from baseline in MADRS total score over weeks 1-6 compared to bupropion 105 mg dosed twice daily (Auvelity -13.7 points, Bupropion -8.8 points; *P* < 0.001).[14]<br>  ○ Rates of remission were also increased compared to bupropion starting at Week 2.[14] |
| **Adverse Events and Other Important Safety Information** | • Auvelity has a boxed warning for increased risk of suicidal thoughts and behaviors in pediatric and young adult patients.[9]<br>• The most common (incidence ≥5% for AUVELITY and more than twice as frequently as placebo) adverse reactions with Auvelity were dizziness, headache, diarrhea, somnolence, dry mouth, sexual dysfunction, and hyperhidrosis.[9]<br>• Please consult the Auvelity full Prescribing Information (https://www.axsome.com/auvelity-prescribing-information.pdf) for complete product details including contraindications, warnings and precautions, drug interactions, and adverse reactions. |
| **Treatment Guideline** | • Auvelity is now among the recommended first line treatments in the recently updated Florida Best Practice Psychotherapeutic Medication Guidelines for Adults with MDD.[15] |
| **Formulation and Other Considerations** | • Auvelity is a patented, proprietary, extended-release formulation.<br>• There is no other formulation or combination of dextromethorphan that is approved for the treatment of MDD and there are no generic or therapeutic equivalents for Auvelity.<br>• The doses and release profile of the individual components of Auvelity were determined based on extensive pharmacokinetic studies and result in dextromethorphan concentrations that target the Ki (inhibitory constant) values for the relevant neurotransmitter systems.<br>• Given the non-linear pharmacokinetics of Auvelity,[9] alterations in the dose or recommendations that patients attempt to take the components separately are not advisable and have not been proven to be safe or effective.<br>• Poor adherence is perhaps the largest contributor to pharmacotherapy failures. In the case of using the individual components, patients would be required to take a minimum of 8 tablets through the day, versus 1 tablet of Auvelity in the morning and 1 at night.<br>• Through misunderstanding or human error, patients may not take the correct doses of the individual components, critically impacting safety as well as efficacy.<br>• In the December 2022 issue of the *Pharmacist's Letter,* the authors caution providers to "…steer away from using Rx bupropion plus OTC dextromethorphan separately for depression...it's a recipe for mishaps."[16]<br>• Requiring a trial of the individual components is not consistent with evidence-based practice and has not been shown to be safe and efficacious |
| **Summary** | • Auvelity is a oral, rapid-acting antidepressant that addresses important unmet clinical needs in MDD. We respectfully ask the committee to reconsider the individual component requirement and allow Auvelity for Medicaid beneficiaries in the state of West Virginia after trial and failure of two preferred agents. |

**References**: **1.** World Health Organization. Depression and Other Common Mental Disorders: Global Health Estimates. Geneva: World Health Organization; 2017. **2**. Borentain S, et al. Patient-reported outcomes in major depressive disorder with suicidal ideation: a real-world data analysis using PatientsLikeMe platform. *BMC Psychiatry*. 2020;20:384. **3.** SAMHSA. (2021). Key substance use and mental health indicators in the United States: Results from the 2020 National Survey on Drug Use and Health (HHS Publication No. PEP21-07-01-003, NSDUH Series H-56). Rockville, MD: Center for Behavioral Health Statistics and Quality, SAMHSA. **4.** Rush AJ, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006;163:1905-17. **5.** Ciudad A, et al. Early response and remission as predictors of a good outcome of a major depressive episode at 12-month follow-up: a prospective, longitudinal, observational study. *J Clin Psychiatry*. 2012;73(2):185-191. **6.** Belanger HG, et al. Early response to antidepressant medications in adults with major depressive disorder: A naturalistic study and odds of remission at 14 weeks. *J Clin Psychopharmacol*. 2023;43(1):46-54. **7.** Machado-Vieira R, et al. New targets for rapid antidepressant action. *Prog Neurobiol*. 2017;152:21-37. **8.** Rush AJ, et al. What to Expect When Switching to a Second Antidepressant Medication

Following an Ineffective Initial SSRI: A Report from the Randomized Clinical STAR*D Study. *J Clin Psychiatry*. 2020;81(5):19m12949. **9.** Auvelity [Prescribing Information]. New York, NY: Axsome Therapeutics Inc. **10.** Iosifescu DV, 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. **11.** FDA. Major Depressive Disorder: Developing Drugs for Treatment Guidance for Industry: DRAFT GUIDANCE. June 2018. Revision **12.** Duru G, Fantino B. The clinical relevance of changes in the Montgomery-Asberg Depression Rating Scale using the minimum clinically important difference approach. *Curr Med Res Opin*. 2008;24(5): 1329-1335. **13.** Rush AJ, et al. ACNP Task Force. Report by the ACNP Task Force on response and remission in major depressive disorder. *Neuropsychopharmacology*. 2006;31:1841-1853. **14.** Tabuteau H, et al. Effect of AXS-05 (dextromethorphan-bupropion) in major depressive disorder: a randomized double-blind controlled trial. *Am J Psychiatry*. 2022;179(7):490-499. **15.** 2023–2024 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults (2023). The University of South Florida, Florida Center for Behavioral Health Improvements and Solutions. Available at: https://floridabhcenter.org/wp-content/uploads/2023/07/2023-06-Medication-Guidelines-%E2%80%93-Adults-Final_06.30.2023.pdf. **16**. Pharmacist's Letter. December 2022. No 381205.