AUVELITY® - PUBLIC COMMENT FOR FEB 15, 2023, WEST VIRGINIA DUR BOARD MEETING

We appreciate the opportunity to provide comments on the pending prior authorization criteria for AUVELITY.

AUVELITY (dextromethorphan HBr and bupropion HCl) extended-release tablet is the only oral N-methyl-D-aspartate (NMDA) receptor antagonist approved for the treatment of major depressive disorder (MDD) in adults and the only rapid-acting oral antidepressant with labeling of statistically significant antidepressant efficacy compared to placebo starting at one week.[1]

Suggested Place in Therapy
AUVELITY is an appropriate, differentiated, treatment option for patients who have failed or do not tolerate standard first-line treatment.

Guideline Recommendations[2]
The American Psychiatric Association (APA) recommends either SSRIs, SNRIs, mirtazapine, or bupropion for initial treatment of MDD with the goal of achieving remission of symptoms. After failure of an adequate trial of an antidepressant, options include (but are not limited to) switching to another non-MAOI antidepressant. Making AUVELITY available as a treatment option in those who failed initial antidepressant therapy is consistent with these guideline recommendations.

Clinical Outcomes with Existing Treatment
Data from the STAR*D trial demonstrate that after failure of the SSRI citalopram, switching to either a different SSRI (sertraline), a SNRI (venlafaxine), or to a NDRI (bupropion) was associated with a remission rate of only 20%.[3] The declining remission rates seen in STAR*D may be partially explained by the lack of pharmacological diversity amongst the treatments, e.g., all antidepressants employed are thought to work in generally the same way: monoamine modulation.[4]

Clinical Profile of AUVELITY
AUVELITY is an oral therapy with a novel mechanism of action that has demonstrated statistically and clinically meaningful antidepressant effects that start at Week 1.[1,5,6] Additionally, remission as early as Week 2 is possible with AUVELITY treatment as seen in the pivotal GEMINI study (key secondary endpoint: $P = 0.013$).[5]

In the confirmatory ASCEND trial, 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 ($P < 0.001$). Rates of remission were also increased compared to bupropion starting at Week 2.[7]

Early onset of action, sustained response, and a multimodal mechanism of action may help AUVELITY bridge the existing gaps in treatment of MDD.

Formulation
AUVELITY is a patented, proprietary extended-release formulation. The role of bupropion in AUVELITY is primarily to increase and prolong plasma levels of dextromethorphan via CYP2D6 inhibition.[1] The doses and release profile of the individual components were determined based on extensive PK studies and result in dextromethorphan concentrations that target the Ki values for the relevant neurotransmitter systems. There is no other formulation or combination of dextromethorphan that is approved for the treatment of MDD. Further, there are no generic or therapeutic equivalents to AUVELITY. Given the non-linear pharmacokinetics of AUVELITY, 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.

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. The most common adverse reactions with AUVELITY were dizziness, headache, diarrhea, somnolence, dry

mouth, sexual dysfunction, and hyperhidrosis.[1] Please consult the AUVELITY full Prescribing Information for complete product details including contraindications, warnings and precautions, drug interactions, and adverse reactions available at: https://www.axsome.com/auvelity-prescribing-information.pdf

Thank you for considering these important issues when determining the prior authorization criteria for AUVELITY.

References:

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2. Practice guideline for the treatment of patients with major depressive disorder (revision). American Psychiatric Association. *Am J Psychiatry*. 2000;157(4 Suppl):1-45.
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5. 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
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