Auvelity™ (dextromethorphan/bupropion) – New drug approval

- On August 19, 2022, Axsome Therapeutics announced the FDA approval of Auvelity (dextromethorphan/bupropion), for the treatment of major depressive disorder (MDD) in adults.

- Auvelity contains dextromethorphan, a N-methyl D-aspartate (NMDA) receptor antagonist and a sigma-1 receptor agonist. The bupropion component of Auvelity is an aminoketone and CYP2D6 inhibitor which serves to increase and prolong the blood levels of dextromethorphan.

    - Auvelity is the first oral NMDA antagonist-containing product approved for MDD.
    - Single-ingredient bupropion formulations are available generically for the treatment of MDD.

- The efficacy of Auvelity was established in a randomized, placebo-controlled clinical study (Study 1) in 318 adult patients (18 to 65 years of age) with MDD. Patients were randomized to receive Auvelity or placebo for 6 weeks. The primary endpoint was the change from baseline to week 6 in the total score of the Montgomery-Asberg Depression Rating Scale (MADRS). Scores on the MADRS range from 0 to 60, with higher scores indicating more severe depression. The change in MADRS total score from baseline to week 1 and from baseline to week 2 were pre-specified secondary endpoints.

    - At week 6, the least-squares (LS) mean change from baseline in the MADRS total score was -15.9 with Auvelity vs. -12.1 with placebo (LS mean difference -3.9, 95% CI: -6.4, -1.4).
    - The difference between Auvelity and placebo in change from baseline in MADRS total score was statistically significant at week 1 and at week 2.

- In addition to Study 1, confirmatory evidence was demonstrated in a second study comparing Auvelity to monotherapy with bupropion (Study 2). The primary endpoint was calculated by assessing the change from baseline in total MADRS score at each on-site visit from week 1 to week 6 and then taking the average of those scores. The results of the study demonstrated that dextromethorphan contributes to the antidepressant properties of Auvelity.

- Auvelity carries a boxed warning for suicidal thoughts and behaviors.

- Auvelity is contraindicated in patients:

    - With a seizure disorder
    - With a current or prior diagnosis of bulimia or anorexia nervosa
    - Undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs
    - Taking, or within 14 days of stopping, monoamine oxidase inhibitors (MAOIs)
    - With known hypersensitivity to bupropion, dextromethorphan, or other components of Auvelity.

- Additional warnings and precautions for Auvelity include seizure; increased blood pressure and hypertension; activation of mania or hypomania; psychosis and other neuropsychiatric reactions; angle-closure glaucoma; dizziness; serotonin syndrome; and embryo-fetal toxicity.

- The most common adverse reactions (≥ 5% and more than twice as frequently as placebo) with Auvelity use were dizziness, headache, diarrhea, somnolence, dry mouth, sexual dysfunction, and hyperhidrosis.

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- The recommended starting dosage of Auvelity (45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride) is one tablet once daily in the morning. After 3 days, the dosage should be increased to the recommended maximum of one tablet twice daily, given at least 8 hours apart. Two doses should not be exceeded within the same day. Prior to initiating and during treatment with Auvelity:

    — Blood pressure should be assessed and monitored periodically during treatment
    — Patients should be screened for a personal or family history of bipolar disorder, mania, or hypomania
    — Patients should be screened to determine if they are receiving any other medications that contain bupropion or dextromethorphan.

- Axsome Therapeutics plans to launch Auvelity in the fourth quarter 2022. Auvelity will be available as a 45 mg/105 mg dextromethorphan hydrobromide/bupropion hydrochloride extended-release tablet.

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