NEW DRUG APPROVAL

Brand Name	Auvelity™
Generic Name	dextromethorphan hydrobromide and bupropion hydrochloride
Drug Manufacturer	Axsome Therapeutics, Inc

New Drug Approval

FDA approval date: August 18, 2022

Review designation: Priority

Type of review: Type 3 - New Dosage Form; Type 4 - New Combination; New Drug Approval (NDA): 215430

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Disease Definition

The cardinal feature of a major depressive episode is either a depressed mood or loss of interest or pleasure in usual activities that persists over a period of at least 2 weeks and is accompanied by a constellation of depressive symptoms such as changes in eating or sleeping patterns, fatigue, difficulty concentrating, indecision, thoughts of death or suicide, or feelings of worthlessness, helplessness, or hopelessness. It is important to note that these symptoms must represent a change from the individual's usual self and cause clinically significant distress or impairment. In addition, they cannot be attributable to bereavement or another disorder, including a substance-induced condition or a general medical condition. In some individuals, hallucinations or delusions may occur in the context of a major depressive episode, in which case the episode would be specified as "Severe with Psychotic Features." When psychotic features are present, they may either be mood congruent (typically involving themes such as guilt, punishment, personal inadequacy, or disease) or mood incongruent. Although not a part of the DSM-IV-TR criteria, anxiety and somatic symptoms (particularly muscular, respiratory, and genitourinary) can also be seen in the context of major depressive disorder. Episodes of major depression may also be distinguishable by their longitudinal course (e.g., chronic if symptoms are present for at least 2 years, postpartum onset if symptoms occur within 4 weeks postpartum, seasonal pattern if the timing of episodes is regularly associated with a specific time of year) and characteristic subsets of episode features.

Epidemiology

Information on the current prevalence of major depressive disorder comes from two large community surveys, the National Comorbidity Survey Replication (NCS-R) study and the National Epidemiologic Survey of Alcoholism and Related Conditions (NESARC). In the NCS-R, the lifetime prevalence of major depressive disorder among the 9,090 adult participants was 16.2%, with a 12-month prevalence of 6.6%. The NESARC, which included more than 43,000 adults found slightly lower prevalence rates than the NCS-R (13.25% lifetime and 5.28% 12-month), perhaps because the sample included previously omitted groups of individuals with lower prevalence rates. A number of sociodemographic factors appears to be associated with an increased prevalence of major depressive disorder, including female sex, being middle-aged, being never or previously married, having a low income, being unemployed, or being disabled, In the NESARC, being Native American increased risk relative to being Caucasian, whereas being Asian, Hispanic, or black decreased risk.

The impact of major depressive disorders on individuals and their families is substantial. Virtually all individuals in the NCS-R who had a major depressive episode in the preceding 12-month period experienced significant levels of symptom severity as assessed by an independent rating scale. For more than 50% of individuals, symptoms were rated at severe or very severe and were associated with substantial role impairment.

Major depressive disorder rarely occurs in isolation; anxiety disorders, substance use disorders, personality disorders, and impulse control disorders commonly co-occur with major depressive disorder in community samples as well as in individuals in psychiatric treatment. In the NCS-R, major depressive disorder was found to cooccur with at least one other DSM-IV disorder in two thirds of those surveyed, but from a temporal standpoint major depressive disorder was the primary diagnosis in only about 12% of these individuals. In contrast, in a study of patients in psychiatric treatment in the United States, 84% of major depressive disorder patients had at least one co-occurring condition: 61% had a co-occurring Axis I condition, 30% a co-occurring Axis II condition, and 58% a co-occurring Axis III condition. Anxiety disorders were the most common co-occurring disorder in the prior 12 months in both the NCS-R (57.5% of the sample) and the NESARC (36.1% of the sample). Of the anxiety disorders, the greatest association was seen with generalized anxiety disorder and the weakest association with specific phobia. Substance use disorders in the preceding 12-month period were less common in the NCS-R (8.5%) than in the NESARC, in which 14.1% of the individuals with major depressive disorder had an alcohol use disorder, 26.0% had nicotine dependence, and 4.6% had another substance use disorder. Personality disorders were present in 37.9% of individuals with major depressive disorder in the NESARC. Obsessive-compulsive, paranoid, schizoid, and avoidant personality disorders were most common among subjects with major depressive disorder; avoidant, dependent, paranoid, and schizoid personality disorders had greater odds ratios for association with major depressive disorder than other personality disorders.

Treatment of major depressive disorder does not always occur and may be delayed. The average time to treatment in the NESARC was approximately 3 years, and only about 60% of the sample with major depressive disorder received treatment. The NCS-R also evaluated history and adequacy of treatment for major depressive disorder. Of respondents who reported having had a major depressive episode in the last year, just more than one-half had received treatment but less than one-half of these individuals (about one-fifth of the total) received adequate treatment. These findings highlight the need for changes in the delivery of mental health services to enhance the timeliness and quality of care for major depressive disorder.

Efficacy

The efficacy of Auvelity™ for the treatment of MDD in adults was demonstrated in a placebo-controlled clinical study (Study 1, NCT04019704) and confirmatory evidence which included a second study comparing Auvelity™ to bupropion hydrochloride sustained-release tablets (Study 2, NCT03595579).

In Study 1, adult patients (18 to 65 years of age) who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for MDD were randomized to receive Auvelity™ (45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride) twice daily (N=156) or placebo twice daily (N=162) for 6 weeks. Patients in Study 1 had a median age of 41 years and were 67% female, 55% Caucasian, 35% Black, and 5% Asian.

The primary outcome measure was the change from baseline to Week 6 in the total score of the Montgomery-Asberg Depression Rating Scale (MADRS). The MADRS is a clinician-rated scale used to assess the severity of depressive symptoms. Patients are rated on 10 items to assess feelings of sadness, inner tension, reduced sleep or appetite, difficulty concentrating, lassitude, lack of interest, pessimism, and suicidality. Scores on the MADRS range from 0 to 60, with higher scores indicating more severe depression. Auvelity™ was statistically significantly superior to placebo in improvement of depressive symptoms as measured by decrease in MADRS total score at Week 6.

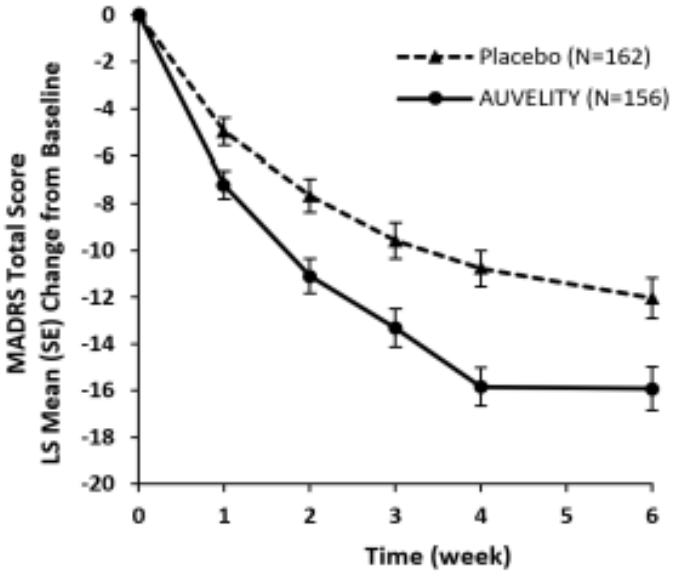
Table 1. Primary Efficacy Results for Change from Baseline in MADRS Total Score at Week 6 in Adult Patients with MDD

Study	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	LS Mean Difference[a] (95% CI)
Study 1	Auvelity™ (N = 156)	33.6 (4.4)	-15.9 (0.9)	-3.9 (-6.4, -1.4)
	Placebo (N = 162)	33.2 (4.4)	-12.1 (0.9)	---

SD=standard deviation; SE=standard error; LS Mean=least-squares mean; CI=confidence interval.
[a] drug – placebo

The change from baseline in MADRS total score by week in Study 1 is displayed in Figure 1. The change in MADRS total score from baseline to Week 1 and from baseline to Week 2 were pre-specified secondary efficacy endpoints. The difference between Auvelity™ and placebo in change from baseline in MADRS total score was statistically significant at Week 1 and at Week 2.

Figure 1. Change from Baseline in MADRS Total Score by Week (Study 1)



SE = Standard Error

Examination of demographic subgroups by age, sex, and race did not suggest differences in response.

In Study 2, patients with MDD were randomized to receive Auvelity™ or bupropion hydrochloride sustained-release tablets 105 mg twice daily for 6 weeks. The primary outcome measure 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™.

Safety

ADVERSE EVENTS

Most common adverse reactions (≥5% and more than twice as frequently as placebo): dizziness, headache, diarrhea, somnolence, dry mouth, sexual dysfunction, and hyperhidrosis.

WARNINGS & PRECAUTIONS

- Seizure: Risk is dose related. Discontinue if seizure occurs.
- Increased Blood Pressure and Hypertension: Auvelity™ can increase blood pressure and cause hypertension. Assess blood pressure before initiating treatment and monitor periodically during treatment.
- Activation of Mania or Hypomania: Screen patients for bipolar disorder.
- Psychosis and Other Neuropsychiatric Reactions: Instruct patients to contact a healthcare provider if such reactions occur.
- Angle-Closure Glaucoma: Angle-closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants.
- Dizziness: Auvelity™ may cause dizziness. Take precautions to reduce falls and use caution when operating machinery.
- Serotonin Syndrome: Use of Auvelity™ with selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants increases the risk. Discontinue if occurs.
- Embryo-fetal Toxicity: May cause fetal harm. Advise pregnant females of the potential risk to a fetus. Discontinue treatment in pregnant females and use alternative treatment for females who are planning to become pregnant.

CONTRAINDICATIONS

- Seizure disorder.
- Current or prior diagnosis of bulimia or anorexia nervosa.
- Abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs.
- Use with an MAOI or within 14 days of stopping treatment with Auvelity™. Do not use Auvelity™ within 14 days of discontinuing an MAOI.
- Known hypersensitivity to bupropion, dextromethorphan, or other components of Auvelity™.

Clinical Pharmacology

MECHANISMS OF ACTION

Dextromethorphan is an uncompetitive antagonist of the NMDA receptor (an ionotropic glutamate receptor) and a sigma-1 receptor agonist. The mechanism of dextromethorphan in the treatment of MDD is unclear.

The mechanism of action of bupropion in the treatment of MDD is unclear; however, it may be related to noradrenergic and/or dopaminergic mechanisms. Bupropion increases plasma levels of dextromethorphan by competitively inhibiting cytochrome P450 2D6, which catalyzes a major biotransformation pathway for dextromethorphan. Bupropion is a relatively weak inhibitor of the neuronal reuptake of norepinephrine and dopamine and does not inhibit monoamine oxidase or the reuptake of serotonin.

Dose & Administration

ADULTS

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, increase to the maximum recommended dosage of one tablet twice daily, given at least 8 hours apart. Do not exceed two doses within the same day.

Administer Auvelity™ orally with or without food. Swallow tablets whole, do not crush, divide, or chew.

Switching a Patient to or from a Monoamine Oxidase Inhibitor (MAOI) Antidepressant
At least 14 days must elapse between discontinuation of an MAOI intended to treat depression and initiation of therapy with Auvelity™. Conversely, at least 14 days must be allowed after stopping Auvelity™ before starting an MAOI antidepressant

PEDIATRICS

The safety and effectiveness of Auvelity™ have not been established in pediatric patients.

GERIATRICS

The safety and effectiveness of Auvelity™ have not been established in geriatric patients.

RENAL IMPAIRMENT

The recommended dosage of Auvelity™ for patients with moderate renal impairment (eGFR 30 to 59 mL/minute/1.73 m^2) is one tablet once daily in the morning. Auvelity™ is not recommended in patients with severe renal impairment (eGFR 15 to 29 mL/minute/1.73 m2).

HEPATIC IMPAIRMENT

No dose adjustment of Auvelity™ is recommended in patients with mild (Child-Pugh A) or moderate hepatic impairment (Child-Pugh B). Auvelity™ is not recommended in patients with severe hepatic impairment.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Extended-release tablets: 45 mg/105 mg dextromethorphan hydrobromide/ bupropion hydrochloride.