Auvelity®

(dextromethorphan HBr and bupropion HCl)
extended-release tablets 45mg/105mg

A Rapid-Acting Antidepressant With Multimodal Activity

INDICATION

Auvelity is indicated for the treatment of major depressive disorder (MDD) in adults.

IMPORTANT SAFETY INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

- **Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients in short-term studies.**
- **Closely monitor all antidepressant-treated patients for clinical worsening, and emergence of suicidal thoughts and behaviors.**
- **Auvelity is not approved for use in pediatric patients.**
- **Please see Important Safety Information in this article and Brief Summary of Prescribing Information, including Boxed Warning for suicidal thoughts and behaviors, on pages xi–xii.**

Early MDD Response May Improve Short and Long-Term Outcomes

Delayed treatment of major depressive disorder (MDD) and longer major depressive episode duration have been associated with poorer short- and long-term outcomes.[1,2] People who experience shorter depressive episodes have better symptomatic outcomes, better functional outcomes, and lower relapse risk. Achieving a clinical response early in the disease trajectory with fewer treatment steps is associated with lower rates of relapse.[3] A meta-analysis showed people with early improvement, defined as a ≥ 20%, ≥ 25%, or ≥ 30% symptom reduction on scales such as Hamilton Depression Rating Scale (HDRS17) and Montgomery–Åsberg Depression Rating Scale (MADRS), in the first 2 weeks, were 8 times more likely to achieve clinical response and 6 times more likely to achieve remission than those without early improvement.[2] In a longitudinal, multicenter, observational study, people who responded to treatment within 6 weeks of initiating antidepressant treatment had approximately 4 times greater chance of achieving a positive outcome at 12 months, suggesting early clinical response (50% decrease from baseline in the 17-item Hamilton Depression Rating Scale [HDRS17] score by Week 6) is associated with improved quality of life and achieving long-term (12 months) remission.[4]

The Role of Glutamate in MDD

Glutamate dysfunction may play a key role in MDD. The pathophysiology of MDD is associated with disruptions of multiple neurotransmitters and receptors, including glutamatergic neurotransmission.[5] Glutamate is the most abundant neurotransmitter in the CNS,[6,7] being released by 40% of neurons in the brain (by contrast, fewer

Auvelity Important Safety Information

CONTRAINDICATIONS

Seizure: Do not use Auvelity in patients with a seizure disorder.

Current or prior diagnosis of bulimia or anorexia nervosa: A higher incidence of seizure was observed in such patients treated with bupropion.

Undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs: Due to risk of seizure.

Monoamine Oxidase Inhibitors (MAOIs): Do not use Auvelity concomitantly with, or within 14 days of stopping, an MAOI due to the risk of serious and possibly fatal drug interactions, including hypertensive crisis and serotonin syndrome. Conversely, at least 14 days must be allowed after stopping Auvelity before starting an MAOI antidepressant. Do not use Auvelity with reversible MAOIs such as linezolid or intravenous methylene blue.

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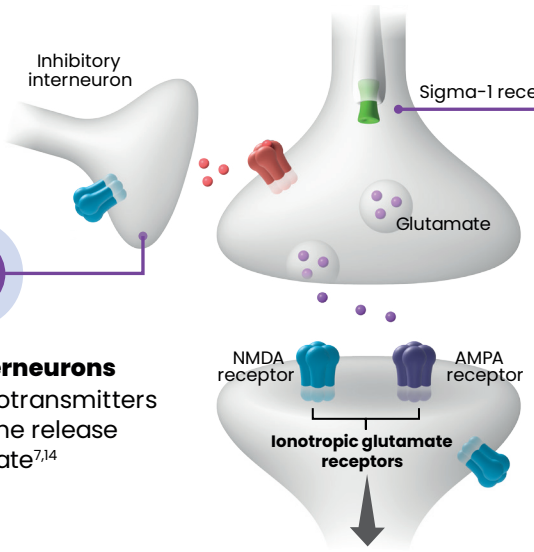
Figure 1. **Glutamate Signaling via Ionotropic Receptors**



Inhibitory interneurons release GABA neurotransmitters which reduce the release of glutamate[7,14]

Sigma-1 receptors within the endoplasmic reticulum (ER) may also modulate glutamate and monoamine release[15]

For illustrative purposes only

Abbreviations: AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, GABA=γ-aminobutyric acid, NMDA=*N*-methyl-D-aspartate.

than 1% of neurons release each of the monoamines–dopamine, norepinephrine, and serotonin–which have also been implicated in the pathophysiology of MDD).[6,8,9] Glutamate signals through metabotropic and ionotropic receptors, with *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) being ionotropic receptors that are suspected targets in antidepressant effects.[10,11]

In vivo studies have found abnormal glutamate levels are common among patients with MDD.[12,13] Modulating glutamate pathways in the brain is an emerging approach to treating MDD. The NMDA receptor in particular has emerged as a potential mediator of MDD pathophysiology.[6,7]

The sigma-1 receptor is thought to be a key modulator of neurobiological processes. Activation of the sigma-1 receptor, within the endoplasmic reticulum, may modulate glutamatergic and monoaminergic signaling, which may be dysregulated in MDD (**Figure 1**).[16]

AUVELITY® Mechanism of Action

AUVELITY is an antidepressant with multimodal activity and is the only antidepressant that modulates both glutamatergic and monoaminergic pathways. AUVELITY is comprised of dextromethorphan and bupropion (see **Figure 2**).[17,18] The exact mechanism of action of AUVELITY is unclear. Dextromethorphan is thought to act as an uncompetitive NMDA receptor antagonist that modulates glutamate signaling by altering the inhibitory tone of interneurons and by direct action on the postsynaptic NMDA receptor. Bupropion is a CYP2D6 inhibitor that increases and prolongs plasma concentrations of dextromethorphan. Bupropion is also a relatively weak inhibitor of norepinephrine and dopamine reuptake. Sigma-1 receptor agonism may additionally modulate glutamate and monoamine signaling (see **Figure 3**).[16–19]

Dextromethorphan has low oral bioavailability due to its rapid and extensive metabolism by the cytochrome P450 (CYP) 2D6 liver enzyme. Dextromethorphan,

Auvelity Important Safety Information

Hypersensitivity: Do not use in patients with known hypersensitivity to dextromethorphan, bupropion, or any component of Auvelity. Anaphylactoid/anaphylactic reactions and Stevens-Johnson syndrome have been reported with bupropion. Arthralgia, myalgia, fever with rash, and other serum sickness-like symptoms suggestive of delayed hypersensitivity have also been reported with bupropion.

WARNINGS AND PRECAUTIONS

Suicidal Thoughts and Behaviors in Pediatrics and Young Adults: Monitor all antidepressant-treated patients for any indication for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy, and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing Auvelity, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

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Figure 2. AUVELITY Exerts Multimodal Activity

AUVELITY is the only antidepressant that modulates both glutamatergic and monoaminergic pathways[17,18]*

Dextromethorphan acts as[17]:

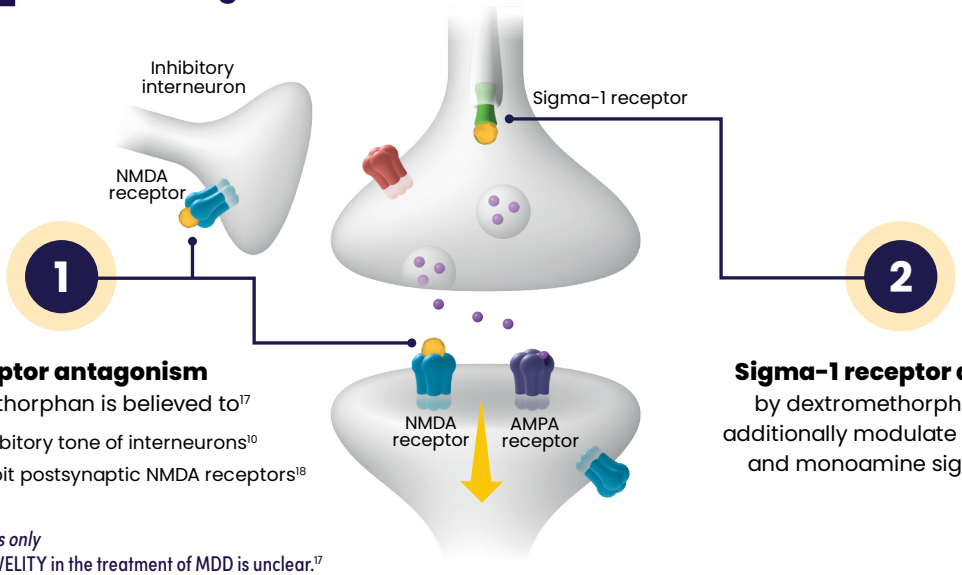
- An uncompetitive antagonist of the **NMDA receptor**
- An agonist of the **sigma-1 receptor**

Bupropion, a CYP2D6 inhibitor[17]

- **Increases and prolongs** plasma concentrations of dextromethorphan
- Is a relatively **weak inhibitor** of norepinephrine and dopamine reuptake

*The mechanism of AUVELITY in the treatment of MDD is unclear.[17]
Abbreviations: CYP2D6=cytochrome P450 2D6; MDD=major depressive disorder; NMDA=*N*-methyl-D-aspartate.

Figure 3. AUVELITY Is Thought to Modulate Glutamatergic Neurotransmission*



NMDA receptor antagonism by dextromethorphan is believed to[17]

- Alter the inhibitory tone of interneurons[10]
- Directly inhibit postsynaptic NMDA receptors[18]

Sigma-1 receptor agonism by dextromethorphan may additionally modulate glutamate and monoamine signaling[15,17]

For illustrative purposes only
*The mechanism of AUVELITY in the treatment of MDD is unclear.[17]
Abbreviations: AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, NMDA=*N*-methyl-D-aspartate.

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Seizure: Bupropion, a component of Auvelity, can cause seizure and the risk is dose related. Because the risk of seizure with bupropion is dose-related, screen patients for use of other bupropion-containing products prior to initiating Auvelity. If concomitant use of Auvelity with other bupropion-containing products is clinically warranted, inform patients of the risk. Discontinue Auvelity and do not restart treatment if the patient experiences a seizure.

Increased Blood Pressure and Hypertension: Treatment with bupropion, a component of Auvelity, can cause elevated blood pressure and hypertension. The risk of hypertension is increased if Auvelity is used concomitantly with MAOIs or other drugs that increase dopaminergic or noradrenergic activity. Assess blood pressure before initiating treatment with Auvelity and monitor periodically during treatment. Monitor blood pressure, particularly in patients who receive the combination of bupropion and nicotine replacement.

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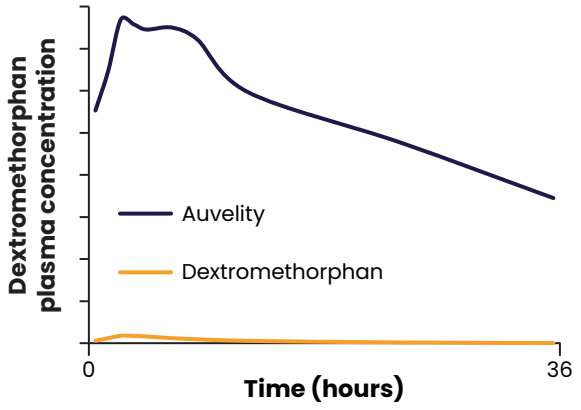
Figure 4. Dextromethorphan Plasma Concentration



For illustrative purposes. Assumes steady state in extensive metabolizers. Data on file, Axsome Therapeutics, Inc., 2022.

Figure 5. ASCEND: Change From Baseline in MADRS Total Score Over Time

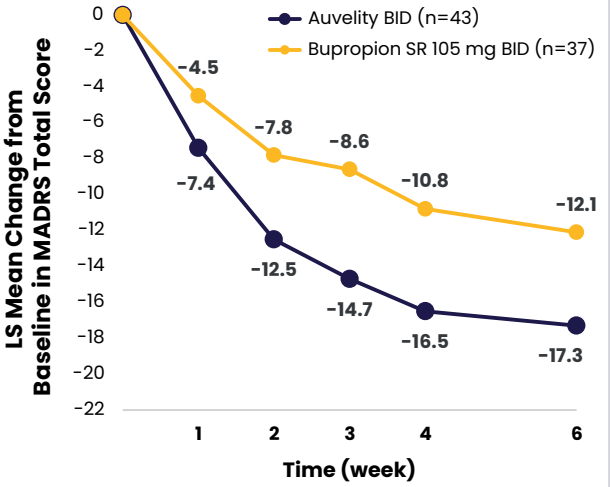


Figure adapted with permission from Tabuteau H et al. *Am J Psychiatry.* 2022;179(7):490-499.[20]
Abbreviations: BID=twice daily, MADRS=Montgomery-Åsberg Depression Rating Scale.

when co-administered with bupropion, displays nonlinear pharmacokinetics, achieving steady-state plasma concentrations within 8 days. The accumulation ratios for dextromethorphan at steady state when given as AUVELITY are 20 and 32, respectively, based on C_{max} and AUC_{0-12}, compared to 1.3 and 1.4, respectively, for dextromethorphan alone (**Figure 4**).

Clinical Program Overview

The efficacy of AUVELITY was demonstrated in two clinical trials: the 6-week randomized, active-controlled, phase 2 ASCEND trial and the 6-week randomized, placebo-controlled, phase 3 GEMINI trial. The safety of AUVELITY was further evaluated in the phase 3, open-label, long-term COMET trial. AUVELITY was approved by the Food and Drug Administration (FDA) in August 2022.[18,20–22]

The ASCEND and GEMINI trials evaluated:[20,21]

- Patients aged 18 to 65 years who met Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for current MDD without psychotic features
- Patients whose Montgomery-Åsberg Depression Rating Scale (MADRS) total score was ≥ 25 at baseline
- Patients whose Clinical Global Impressions-Severity (CGI-S) score was ≥ 4 at baseline

Patients were excluded from the ASCEND and GEMINI trials who:[20,21]

- Had a current or history of bipolar disorder, panic disorder, obsessive-compulsive disorder (OCD), psychotic disorder
- Had alcohol/substance abuse disorder within the past year
- Had a clinically significant risk of suicide
- Had a history of seizure disorder
- Were diagnosed with treatment-resistant depression

The phase 2 ASCEND trial evaluated the efficacy and safety of AUVELITY compared to 105 mg bupropion SR given BID as a control arm in 80 patients diagnosed

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Activation of Mania/Hypomania: Antidepressant treatment can precipitate a manic, mixed, or hypomanic episode. The risk appears to be increased in patients with bipolar disorder or who have risk factors for bipolar disorder. Prior to initiating Auvelity, screen patients for a history of bipolar disorder and the presence of risk factors for bipolar disorder (e.g., family history of bipolar disorder, suicide, or depression). Auvelity is not approved for use in treating bipolar depression.

Psychosis and Other Neuropsychiatric Reactions: Auvelity contains bupropion and dextromethorphan. Depressed patients treated with bupropion have had a variety of neuropsychiatric signs and symptoms, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment. Dextromethorphan overdose can cause toxic psychosis, stupor, coma, and hyperexcitability.

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with moderate to severe MDD.* Overall symptom improvement on the MADRS total score (primary endpoint) was assessed by averaging the change from baseline at each time point (Weeks 1–6). AUVELITY demonstrated statistically significant overall symptom improvement over 6 weeks. The overall LS mean change from baseline in the MADRS total score compared to bupropion SR 105 mg was -13.7 vs. -8.8 ($P < .001$).[20]

ASCEND also looked at the weekly mean change in MADRS total score from baseline over the 6-week treatment period (**Figure 5**). Approximately three times more patients achieved protocol-defined remission (MADRS total score ≤ 10) with AUVELITY compared with bupropion at Week 6 (47% vs 16%, respectively).[20]

Rapid and Sustained Efficacy

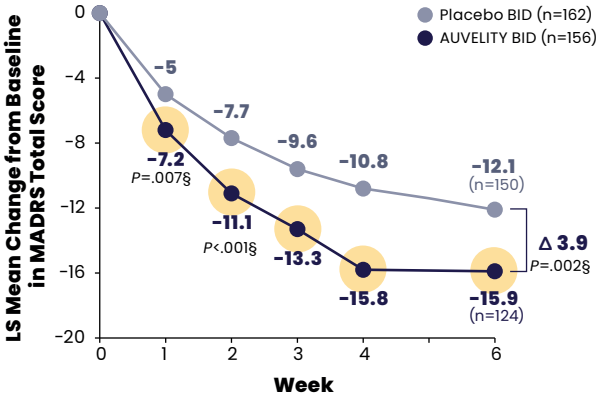
The GEMINI trial evaluated the efficacy and safety of AUVELITY compared to placebo in 327 patients diagnosed with moderate to severe MDD. The primary endpoint was LS mean change from baseline in MADRS total score at Week 6. AUVELITY demonstrated statistically significant symptom improvement as early as Week 1 and continued at Week 2 and Week 6 of therapy, compared to placebo (**Figure 6**). A change in MADRS of approximately 2 points is generally accepted as a minimal clinically important difference (MCID) for this endpoint.[23] The MCID between active treatment and placebo was observed at all timepoints, with a 2.2 difference in MADRS at Week 1 and an increase to a 3.9 difference in MADRS by Week 6 between treatment groups (not an endpoint in the GEMINI trial).[21]

- Week 1: -7.2 in MADRS total score with AUVELITY compared to -5.0 with placebo ($P = .007$).
- Week 6: -15.9 with AUVELITY compared to -12.1 with placebo ($P = .002$).
- Week 1: twice as many patients taking AUVELITY achieved protocol-defined response of ≥ 50% improvement in MADRS total score from baseline compared to placebo (15% vs 7%, respectively).

* N=80 is the modified intention to treat (mITT) population. Patients without a confirmed diagnosis of moderate to severe MDD, as assessed by a blinded independent assessor, but who met all other entry criteria (n=17), were randomized for assessment of safety and were excluded from the efficacy population, as prespecified.

Figure 6.

GEMINI: Change From Baseline in MADRS Total Score Over Time



Symptom Improvement Over Time[21,†,‡]

AUVELITY is a rapid-acting oral antidepressant with proven efficacy at Week 1[21,*]

Primary endpoint: Statistically significant LS mean change from baseline in the MADRS total score at Week 6 vs placebo[21,§]

MCID observed at all timepoints, including Week 1[21,23]

Efficacy across subgroups: Examination of demographic sub-groups by age, sex, and race did not suggest differences in response.[17]

P values for Weeks 3 and 4 were not adjusted for multiplicity and therefore not presented.[21]

*As measured by LS mean change from baseline in MADRS total score vs placebo.[21] †mITT population. ‡Missing data were not imputed [data on file, Axsome Therapeutics, Inc]. §MMRM.[21]
Abbreviations: LS=least-squares, MADRS=Montgomery-Åsberg Depression Rating Scale, mITT=modified intention-to-treat, MCID=minimal clinically important difference, MMRM=mixed model for repeated measures. MCID for MADRS is approximately a 2-point difference between treatment groups.[23]

- Week 6: 54% of patients taking AUVELITY achieved protocol-defined response, compared to 34% receiving placebo ($P < .001$).

Moreover, 17% of patients taking AUVELITY achieved protocol-defined remission (MADRS total score ≤ 10) at Week 2 compared to 8% in the placebo cohort ($P = .013$), with the percentage increasing to 40% with AUVELITY and 17% with placebo at Week 6 (**Figure 7**).

Auvelity Important Safety Information

Psychosis and Other Neuropsychiatric Reactions (continued): Because the risks of neuropsychiatric reactions are dose-related, screen patients for use of other bupropion- or dextromethorphan-containing products prior to initiating Auvelity. If concomitant use of Auvelity with other bupropion- or dextromethorphan-containing products is clinically warranted, monitor patients for neuropsychiatric reactions and instruct patients to contact a healthcare provider if such reactions occur.

Angle-Closure Glaucoma: The pupillary dilation that occurs following use of many antidepressants, including Auvelity, may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy. Avoid use of antidepressants, including Auvelity, in patients with untreated anatomically narrow angles.

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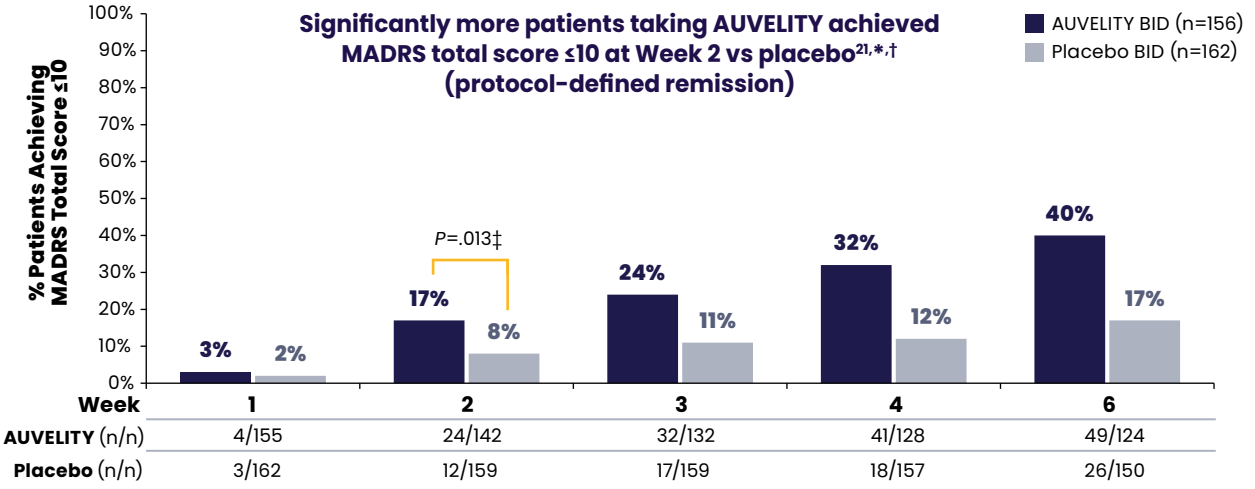
Figure 7. **GEMINI: Protocol-Defined Remission (MADRS Total Score ≤10)**



P values for Weeks 3, 4, and 6 were not adjusted for multiplicity and are therefore not presented.[21]
*mITT population.[21] †Missing data were considered failures [data on file, Axsome Therapeutics, Inc]. ‡Endpoint was analyzed using a chi-square test.
Abbreviations: BID=twice daily, MADRS=Montgomery-Åsberg Depression Rating Scale, mITT=modified intention-to-treat.

Significantly more patients taking AUVELITY reported symptoms that were very much improved or much improved at Week 1 versus placebo using the Clinical Global Impression-Improvement (CGI-I) scale (22% vs 13%, respectively; *P* = .035). This increase was sustained at Week 6, with 58% of patients with AUVELITY having symptom improvement on the CGI-I scale compared to 43% with placebo (*P* = .016).[21]

A post hoc analysis of GEMINI assessed the anhedonic features in patients with moderate to severe MDD. The MADRS anhedonia scale includes 5 items: apparent sadness, reported sadness, concentration difficulties, lassitude, and inability to feel. In the GEMINI trial, baseline MADRS anhedonia scores were 19.8 in patients randomized to receive AUVELITY and 19.6 in patients randomized to receive placebo. At Week 1 and Week 6, 20.6% and 54.4% of patients on AUVELITY achieved response based on a ≥ 50% reduction in MADRS anhedonia subscale, compared to 7.4% and 36.0% of patients on placebo, respectively.[24]

Improvement in Scores Measuring Patient-Reported Functional and Quality of Life Outcomes

AUVELITY was associated with changes in scores that measure quality of life, depressive symptoms, and functionality, as assessed by patient-reported outcome measures. Patient-reported outcome measures were evaluated at Weeks 1, 2, 3, 4 and 6 of treatment with AUVELITY and placebo in the GEMINI study.[21]

Improvement in functional assessment scores using Sheehan Disability Scale (SDS), a well-validated, short, patient-reported scale assessing functional impairment in work or school, family life, and social life, with total scores ranging from 0 to 30, was seen at Week 1 to Week 6. At Week 6, LS mean change from baseline was 9.0 in patients receiving AUVELITY compared to a 6.3 in the placebo cohort. (**Figure 8**).[21,25]

Auvelity Important Safety Information

Dizziness: Auvelity may cause dizziness. Precautions to reduce the risk of falls should be taken, particularly for patients with motor impairment affecting gait or a history of falls. Caution patients about operating hazardous machinery, including motor vehicles, until they are reasonably certain that Auvelity therapy does not affect them adversely.

Serotonin Syndrome: Auvelity contains dextromethorphan. Concomitant use with selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants increases the risk of serotonin syndrome, a potentially life-threatening condition. Prior to initiating therapy with Auvelity, screen patients for use of other dextromethorphan-containing products. If concomitant use of Auvelity with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome, and monitor for symptoms. Discontinue Auvelity and/or concomitant serotonergic drug(s) immediately if symptoms of serotonin syndrome occur and initiate supportive symptomatic treatment.

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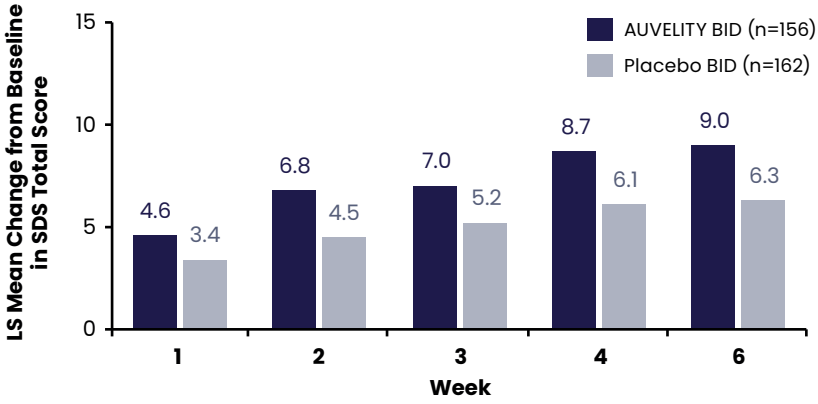
Figure 8. **Improvement on Sheehan Disability Scale (SDS) Score from Week 1 to Week 6 vs Placebo*,†**



Functioning was reported in the domains of work/school, social, and family life.[26]

P values for comparisons were not adjusted for multiplicity and are therefore not presented.[20]

*mITT population [data on file, Axsome Therapeutics, Inc]. †Missing data were not imputed [data on file, Axsome Therapeutics, Inc].
Abbreviations: BID=twice daily; LS=least-squares; mITT=modified intention-to-treat; SDS=Sheehan Disability Scale.

Improved scores on the Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF), a self-report tool designed to measure the degree of enjoyment and satisfaction experienced in various areas of daily functioning, showed a 19.8 LS mean change from baseline with AUVELITY compared to 14.4 with placebo at Week 6.[21,27] A decrease in depressive symptom severity scores was seen starting at Week 1 and continued through Week 6, showing a -7.7 LS mean change from baseline in Quick Inventory of Depressive Symptomatology-Self-Rated (QIDS-SR-16) compared with -5.7 with placebo at Week 6. Moreover, 47% of patients receiving AUVELITY reported being very much/much improved compared to 31% receiving placebo on the Patient Global Impression of Improvement (PGI-I) at Week 6.[21]

Safety and Tolerability

AUVELITY was evaluated for safety in over 1100 patients with MDD at the time of approval. A total of 1114 patients were evaluated from four clinical studies (two 6-week studies in MDD, one 6-week study in another indication, and one long-term study in MDD and another indication[17]). Overall, the GEMINI trial showed 62% of patients receiving AUVELITY experienced any adverse event compared to 45% receiving placebo. The most common adverse reactions (≥ 5% and more than twice as frequently as placebo) include dizziness, headache, diarrhea, somnolence, dry mouth, sexual dysfunction, and hyperhidrosis (**Table 1**[17]).[21]

Four percent of AUVELITY-treated patients discontinued study participation due to an adverse event compared to 0% of placebo-treated patients.[17] At Week 6, AUVELITY was associated with a 0.44 lb weight loss compared to a 0.88 lb weight gain in placebo-treated patients.[21]

Contraindications to taking AUVELITY include:

- Seizure disorder
- Current or prior diagnosis of bulimia or anorexia nervosa
- Undergoing abrupt discontinuation of

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Embryo-fetal Toxicity: Based on animal studies, Auvelity may cause fetal harm when administered during pregnancy. Discontinue treatment in pregnant females and advise the patient about the potential risk to a fetus. Use alternative treatment for females who are planning to become pregnant.

DRUG INTERACTIONS

Strong Inhibitors of CYP2D6: Concomitant use with Auvelity increases plasma concentrations of dextromethorphan. Dosage adjustment is necessary. Monitor patients for adverse reactions potentially attributable to dextromethorphan, such as somnolence and dizziness.

Strong CYP2B6 Inducers: Concomitant use with Auvelity decreases plasma concentrations of dextromethorphan and bupropion and may decrease efficacy of Auvelity. Avoid co-administration of Auvelity.

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Table 1. **Common Adverse Reactions in GEMINI (≥5% and more than twice as frequently as placebo)[17,21]**

Adverse Reaction	AUVELITY BID (n=162)	Placebo BID (n=164)
Dizziness	**16%**	6%
Headache	**8%**	4%
Diarrhea	**7%**	3%
Somnolence	**7%**	3%
Dry mouth	**6%**	2%
Sexual dysfunction*	**6%**	0%
Hyperhidrosis	**5%**	0%

Discontinued study participation due to adverse reactions[17]

- AUVELITY-treated patients: **4%**
- Placebo-treated patients: **0%**

Additional adverse reactions occurring in ≥2% of AUVELITY-treated patients and more frequently than in placebo-treated patients were: nausea (13%); anxiety, constipation, decreased appetite, insomnia (at 4% each); arthralgia, fatigue†, paraesthesia‡, vision blurred (at 3% each).[17]

*Includes abnormal orgasm, erectile dysfunction, decreased libido, anorgasmia.[17] †Includes lethargy.[17] ‡Includes hypoaesthesia.[17]
Abbreviation: BID=twice daily.

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 any component of AUVELITY

Long-Term Safety and Efficacy

COMET was a phase 3, open-label, long-term trial evaluating the safety and efficacy of AUVELITY in 876 patients with moderate to severe MDD.[22] COMET evaluated the efficacy results of 611 newly enrolled patients by MADRS total score change from baseline, MADRS response, remission up to 1 year, CGI-I, and SDS response in functioning. COMET also included 265 patients rolled over from prior controlled trials with AUVELITY. All newly enrolled patients were assessed for efficacy through Week 6, and only patients whose MADRS scores improved by ≥ 25% were eligible to continue in the study. Approximately 6% of patients met discontinuation criteria at Week 6. AUVELITY was generally well-tolerated in the long-term study; 8.4% of patients discontinued the study due to adverse events. The most common adverse events resulting in discontinuation were dizziness (1.3%), nausea (1.1%), and headache (1.0%). There was a mean decrease in MADRS total score of -9.1 at Week 1 and -21.1 at Week 6. The MADRS total score reductions were sustained from Week 6 through Month 12. COMET showed an increase in patients who achieved clinical response (≥ 50% improvement in MADRS) over time, with 19% (n=590) at Week 1, 73% (n=514) at Week 6, and 83% (n=29) at Month 12. There was an increase in patients who achieved remission (MADRS total score ≤ 10) over time, with 53% at Week 6 and 69% at Month 12 (**Figure 9**).[22]

Dosing and Administration

AUVELITY is an oral antidepressant treatment available in one dosage strength with a recommended therapeutic dose by day 4. Prior to starting therapy and during treatment with AUVELITY, it is important to assess blood pressure and monitor periodically during treatment; to screen patients for a personal or family history of bipolar disorder, mania, or hypomania; and to screen for current use of bupropion or dextromethorphan in other medications.[17]

The recommended starting dose of AUVELITY is 1 tablet (45 mg/105 mg dextromethorphan/bupropion) once daily in the morning. After 3 days, increase to 1 tablet twice daily, separated by at least 8 hours, which is the maximum recommended daily dose. Tablets should be swallowed whole and not crushed, divided, or chewed. AUVELITY can be taken with or without food.[17]

Auvelity Important Safety Information

CYP2D6 Substrates: Concomitant use with Auvelity can increase the exposures of drugs that are substrates of CYP2D6. It may be necessary to decrease the dose of CYP2D6 substrates, particularly for drugs with a narrow therapeutic index.

Digoxin: Concomitant use with Auvelity may decrease plasma digoxin levels. Monitor plasma digoxin levels in patients treated concomitantly with Auvelity.

Drugs that Lower Seizure Threshold: Concomitant use with Auvelity may increase risk of seizure. Use Auvelity with caution. Discontinue Auvelity and do not restart treatment if the patient experiences a seizure.

Dopaminergic Drugs: Concomitant use with Auvelity can result in central nervous system toxicity. Use Auvelity with caution.

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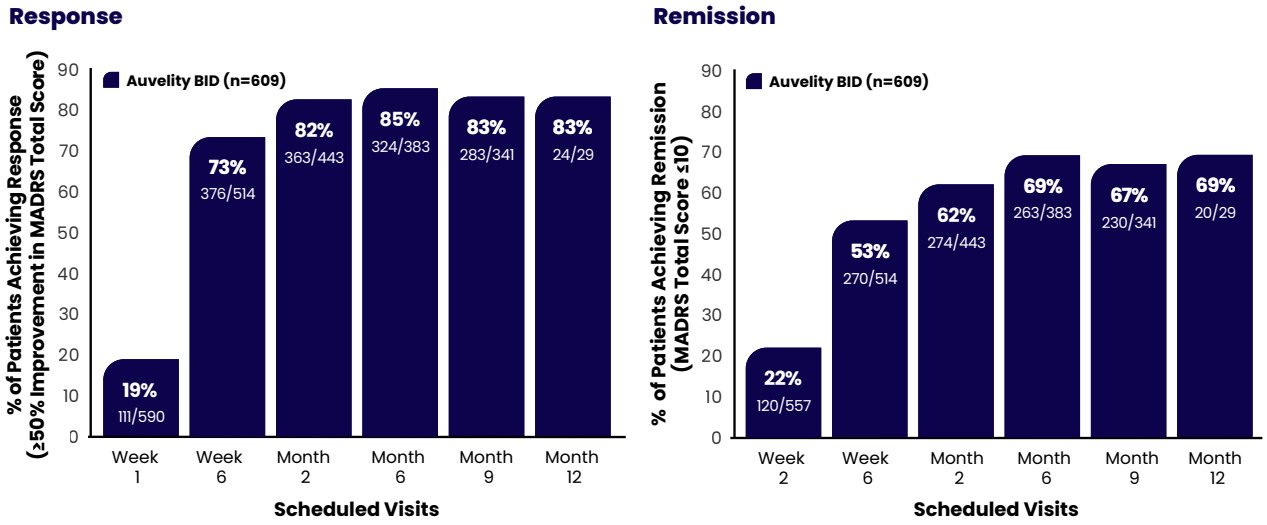
Figure 9. **Protocol-Defined Response and Remission in COMET Trial*,‡**



Adapted from O'Gorman C et al. Poster presented at American Society of Clinical Psychopharmacology virtual annual meeting; June 1-4, 2021.[22]
*AUVELITY-naive ITT population. ‡Missing data were not imputed. Efficacy data from early termination visits were included in the summary of the next scheduled efficacy assessment visit.
Abbreviations: BID=twice a day; ITT=intention-to-treat; MADRS=Montgomery-Åsberg Depression Rating Scale.

The recommended dosage of AUVELITY is reduced to 1 tablet by mouth daily in the morning[17]:

- In poor CYP2D6 metabolizers
- In moderate renal impairment (eGFR 30 to 59 mL/minute/1.73 m^2).
- When co-administered with strong CYP2D6 inhibitors

AUVELITY has the following additional Warnings and Precautions[17]:

- Suicidal thoughts and behaviors in adolescents and young adults
- Seizure
- Increased blood pressure and hypertension
- Activation of mania or hypomania
- Psychosis and other neuropsychiatric reactions
- Angle-closure glaucoma
- Dizziness
- Serotonin syndrome
- Embryo-fetal toxicity

Summary

Glutamatergic dysfunction may play a key role in MDD, and glutamatergic modulation may offer an approach to treating MDD.[7,19] AUVELITY exerts multimodal activity and is the only antidepressant for adults with MDD that modulates both glutamatergic and monoaminergic pathways.[17,18] AUVELITY was evaluated for safety in 1114 patients from four clinical studies (two 6-week studies in MDD, one 6-week study in another indication, and one long-term study in MDD and another indication).[17] In the 6-week randomized, placebo-controlled, phase 3 GEMINI trial, the most common adverse reactions were dizziness (16%), headache (8%), diarrhea (7%), somnolence (7%), dry mouth (6%), sexual dysfunction (6%), and hyperhidrosis (5%).[17,21] Additional safety information for AUVELITY, including its contraindications, can be found in the Important Safety Information throughout this

Auvelity Important Safety Information

USE IN SPECIFIC POPULATIONS

Lactation: Because of the potential for neurotoxicity, advise patients that breast-feeding is not recommended during treatment with Auvelity and for 5 days following final dose.

Renal Impairment: Dosage adjustment is recommended in patients with moderate renal impairment (eGFR 30 to 59 mL/minute/1.73 m^2). Auvelity is not recommended in patients with severe renal impairment (eGFR 15 to 29 mL/minute/1.73 m^2).

Hepatic Impairment: Auvelity is not recommended in patients with severe hepatic impairment.

ADVERSE REACTIONS

Most common adverse reactions (≥5% and twice the rate of placebo): dizziness (16%), headache (8%), diarrhea (7%), somnolence (7%), dry mouth (6%), sexual dysfunction (6%), and hyperhidrosis (5%).

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Please see Important Safety Information in this article and Brief Summary of Prescribing Information, including Boxed Warning for suicidal thoughts and behaviors, on pages xi–xii

article and in the Prescribing Information. In the GEMINI trial, AUVELITY demonstrated efficacy at Week 1 and statistically significant LS mean change from baseline in the MADRS total score at Week 6 vs placebo (primary endpoint).[21] In the COMET trial, a phase 3 open-label, long-term study evaluating safety and efficacy, there was a mean decrease in MADRS total score of -9.1 at Week 1 and -21.1 at Week 6. The MADRS total score reductions, on average, were sustained from Week 6 through Month 12. There was an increase in proportion of patients achieving protocol-defined remission, with 53% at Week 6 increasing to 69% at Month 6, and a comparable proportion maintaining remission at Month 12.[22] AUVELITY is available in one dosage strength with a recommended therapeutic dose by day 4.[17] The recommended starting dose of AUVELITY is one tablet (45 mg/105 mg dextromethorphan/bupropion) once daily in the morning. After 3 days, increase to one tablet twice daily, separated by at least 8 hours, which is the maximum recommended daily dose. Please refer to the Prescribing Information for more details on dosing and administration.[17]

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AUVELITY® (dextromethorphan Hbr-bupropion HCl) extended-release tablets, for oral use

Brief Summary of Prescribing Information
BEFORE PRESCRIBING AUVELITY, PLEASE SEE FULL PRESCRIBING INFORMATION, INCLUDING BOXED WARNING.

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.
- **Antidepressants increased risk of suicidal thoughts and behavior in pediatric and young adult patients in short-term studies.**
- **Closely monitor all antidepressant-treated patients for clinical worsening, and emergence of suicidal thoughts and behaviors.**
- **AUVELITY is not approved for use in pediatric patients.**

INDICATIONS AND USAGE
AUVELITY is indicated for the treatment of major depressive disorder (MDD) in adults.

CONTRAINDICATIONS
AUVELITY is contraindicated in patients:
- with a seizure disorder
- with a current or prior diagnosis of bulimia or anorexia nervosa as a higher incidence of seizures was observed in such patients treated with the immediate release formulation of bupropion
- undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs
- taking, or within 14 days of stopping, MAOIs due to the risk of serious and possibly fatal drug interactions, including hypertensive crisis and serotonin syndrome. Starting AUVELITY in a patient treated with reversible MAOIs such as linezolid or intravenous methylene blue is contraindicated.
- with known hypersensitivity to bupropion, dextromethorphan, or other components of AUVELITY. Anaphylactoid/anaphylactic reactions and Stevens-Johnson syndrome have been reported with bupropion. Arthralgia, myalgia, fever with rash, and other serum sickness-like symptoms suggestive of delayed hypersensitivity have also been reported with bupropion.

WARNINGS AND PRECAUTIONS
Suicidal Thoughts and Behaviors in Adolescents and Young Adults
In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with MDD. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 1.

Table 1: Risk Differences of the Number of Patients of Suicidal Thoughts and Behavior in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric* and Adult Patients

Age Range	Drug-Placebo Difference in Number of Patients of Suicidal Thoughts or Behaviors per 1000 Patients Treated
	Increases Compared to Placebo
<18 years old	14 additional patients
18–24 years old	5 additional patients
	Decreases Compared to Placebo
25–64 years old	1 fewer patient
≥65 years old	6 fewer patients

*AUVELITY is not approved for use in pediatric patients.

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with MDD that antidepressants delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors.

Monitor all antidepressant-treated patients for any indication for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy, and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing AUVELITY, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

Seizure
Bupropion, a component of AUVELITY, can cause seizure. The risk of seizure with bupropion is dose-related.

When a bupropion hydrochloride (HCl) sustained-release tablet was dosed up to 300 mg per day (approximately 1.5 times the maximum recommended daily dosage of AUVELITY), the incidence of seizure was approximately 0.1% (1/1,000) and increased to approximately 0.4% (4/1,000) at the maximum recommended dosage for the sustained-release tablet of 400 mg per day (approximately 2 times the maximum recommended daily dosage of AUVELITY).

The risk of seizures is also related to patient factors, clinical situations, and concomitant medications that lower the seizure threshold. Consider these risks before initiating treatment with AUVELITY. AUVELITY is contraindicated in patients with a seizure disorder, current or prior diagnosis of anorexia nervosa or bulimia, or undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs. The following conditions can also increase the risk of seizure: severe head injury; arteriovenous malformation; CNS tumor or CNS infection; severe stroke; concomitant use of other medications that lower the seizure threshold (e.g., other bupropion products, antipsychotics, tricyclic antidepressants, theophylline, and systemic corticosteroids); metabolic disorders (e.g., hypoglycemia, hyponatremia, severe hepatic impairment, and hypoxia); use of illicit drugs (e.g., cocaine); or abuse or misuse of prescription drugs such as CNS stimulants. Additional predisposing conditions include diabetes mellitus treated with oral hypoglycemic drugs or insulin; use of anorectic drugs; and excessive use of alcohol, benzodiazepines, sedative/hypnotics, or opiates.

Because the risk of seizure with bupropion is dose-related, screen patients for use of other bupropion-containing products prior to initiating AUVELITY. If concomitant use of AUVELITY with other bupropion-containing products is clinically warranted, inform patients of the risk. Discontinue AUVELITY and do not restart treatment if the patient experiences a seizure.

Increased Blood Pressure and Hypertension
AUVELITY contains bupropion, which can cause elevated blood pressure and hypertension. The risk of hypertension is increased if AUVELITY is used concomitantly with MAOIs or other drugs that increase dopaminergic or noradrenergic activity. Assess blood pressure prior to initiating treatment, and periodically monitor blood pressure during treatment with AUVELITY.

Activation of Mania/Hypomania
Antidepressant treatment can precipitate a manic, mixed, or hypomanic episode. The risk appears to be increased in patients with bipolar disorder or who have risk factors for bipolar disorder. Prior to initiating AUVELITY, screen patients for a history of bipolar disorder and the presence of risk factors for bipolar disorder (e.g., family history of bipolar disorder, suicide, or depression). AUVELITY is not approved for use in treating bipolar depression.

Psychosis and Other Neuropsychiatric Reactions
AUVELITY contains bupropion and dextromethorphan. Depressed patients treated with bupropion have had a variety of neuropsychiatric signs and symptoms, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. Some of these patients had a diagnosis of bipolar disorder. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment. Dextromethorphan overdose can cause toxic psychosis, stupor, coma, and hyperexcitability.

Because the risks of neuropsychiatric reactions are dose-related, screen patients for use of other bupropion- or dextromethorphan-containing products prior to initiating AUVELITY. If concomitant use of AUVELITY with other bupropion- or dextromethorphan-containing products is clinically warranted, monitor patients for neuropsychiatric reactions and instruct patients to contact a healthcare provider if such reactions occur.

Angle-Closure Glaucoma
The pupillary dilation that occurs following use of many antidepressant drugs including bupropion, a component of AUVELITY, may trigger an angle-closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy. Avoid use of antidepressants, including AUVELITY, in patients with untreated anatomically narrow angles.

Dizziness
AUVELITY may cause dizziness. In controlled studies of AUVELITY, 14% of patients receiving AUVELITY and 6% of patients on placebo experienced dizziness. Take precautions to reduce the risk of falls, particularly for patients with motor impairment affecting gait or those with a history of falls. Caution patients about operating hazardous machinery, including motor vehicles, until they are reasonably certain that AUVELITY therapy does not affect them adversely.

Serotonin Syndrome
AUVELITY contains dextromethorphan. Concomitant use of AUVELITY with SSRIs or tricyclic antidepressants may cause serotonin syndrome, a potentially life-threatening condition with changes including altered mental status, hypertension, restlessness, myoclonus, hyperthermia, hyperreflexia, diaphoresis, shivering, and tremor.

Prior to initiating AUVELITY, screen patients for use of other dextromethorphan-containing products. If concomitant use of AUVELITY with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome and monitor for symptoms. Discontinue AUVELITY and/or concomitant serotonergic drug(s) immediately if the above symptoms occur and initiate supportive symptomatic treatment.

Embryo-fetal Toxicity
Based on animal studies, AUVELITY may cause fetal harm when administered during pregnancy. In developmental toxicity studies in rats and rabbits, when a combination of dextromethorphan/quinidine was given to pregnant animals, fetal malformations (rabbits) and embryolethality were demonstrated in offspring. Neurotoxicity findings were observed in juvenile rats treated with a combination of dextromethorphan/quinidine on postnatal day (PND) 7, which corresponds to the third trimester of gestation through the first few months of life and may extend through the first three years of life in humans. The separate effect of dextromethorphan on developmental toxicity at the recommended clinical dose is unclear. Discontinue treatment in pregnant females and advise the patient about the potential risk to a fetus. Use alternative treatment for females who are planning to become pregnant.

ADVERSE REACTIONS
Clinical Trials Experience
AUVELITY was evaluated for safety in a total of 1114 patients with MDD or another indication from four studies (two 6-week studies in MDD, one 6-week study in another indication, and one long-term study in MDD and another indication). One 6-week study in MDD employed placebo as a control arm. Two 6-week studies, one in MDD and one in another indication, employed bupropion as a control arm. In the patients treated with AUVELITY in the long-term study (n=876), 597 received at least 6 months of treatment, and 110 received at least 12 months of treatment. The data below are based on the 6-week, placebo-controlled study in which either AUVELITY (n=162) or placebo (n=164) was administered twice daily to patients with MDD (Study 1).

Adverse Reactions Leading to Discontinuation
In the 6-week placebo-controlled study, 4% of patients treated with AUVELITY and 0% of placebo-treated patients discontinued participation due to adverse reactions. The adverse reaction that led to study discontinuation in ≥1% of patients treated with AUVELITY was anxiety (2%).

Most Common Adverse Reactions
In the 6-week placebo-controlled clinical study, the most common (incidence ≥5% for AUVELITY and more than twice as frequently as placebo) adverse reactions were dizziness (16%), headache (8%), diarrhea (7%), somnolence (7%), dry mouth (6%), sexual dysfunction (6%), and hyperhidrosis (5%).

Table 2: Adverse Reactions Occurring in ≥ 2% of Adult Patients with MDD Treated with AUVELITY and More Frequently than in Patients Treated with Placebo in a 6-Week Placebo-Controlled Study (Study 1)

Adverse Reaction	AUVELITY (N=162) %	Placebo (N=164) %
Dizziness	16	6
Nausea	13	9
Headache	8	4
Diarrhea	7	3
Somnolence	7	3
Dry mouth	6	2
Sexual dysfunction[a]	6	0
Hyperhidrosis	5	0
Anxiety	4	1
Constipation	4	2
Decreased appetite	4	1
Insomnia	4	2
Arthralgia	3	0
Fatigue[b]	3	2
Paraesthesia[c]	3	0
Vision blurred	3	0

[a]Sexual dysfunction includes orgasm abnormal, erectile dysfunction, libido decreased, anorgasmia
[b]Fatigue includes fatigue, lethargy
[c]Paraesthesia includes paraesthesia, hypoaesthesia

DRUG INTERACTIONS

Table 3: Clinically Important Drug Interactions with AUVELITY

Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact	The concomitant use of AUVELITY with MAOIs increases the risk of hypertensive crisis and serotonin syndrome.
Intervention	AUVELITY is contraindicated in patients taking MAOIs (including MAOIs such as linezolid or intravenous methylene blue) or in patients who have taken MAOIs within the preceding 14 days. Allow at least 14 days after stopping AUVELITY before starting an MAOI.
Serotonergic Drugs	
Clinical Impact	Concomitant use of AUVELITY with other serotonergic drugs increases the risk of serotonin syndrome.
Intervention	Monitor for symptoms of serotonin syndrome when AUVELITY is used concomitantly with other drugs that may affect the serotonergic neurotransmitter systems. If serotonin syndrome occurs, consider discontinuation of AUVELITY and/or concomitant serotonergic drugs.
Drugs that Lower Seizure Threshold	
Clinical Impact	AUVELITY contains bupropion which can cause seizure. Co-administration with other drugs that lower seizure threshold may increase risk of seizure.
Intervention	Use caution when administering AUVELITY concomitantly with drugs that lower the seizure threshold. Discontinue AUVELITY and do not restart treatment if the patient experiences a seizure.
Strong Inhibitors of CYP2D6	
Clinical Impact	Concomitant use of AUVELITY with strong CYP2D6 inhibitors increases plasma concentrations of dextromethorphan.
Intervention	Dosage adjustment is necessary when AUVELITY is coadministered with strong inhibitors of CYP2D6. Monitor patients for adverse reactions potentially attributable to dextromethorphan, such as somnolence and dizziness.
Strong Inducers of CYP2B6	
Clinical Impact	Concomitant use of AUVELITY with strong CYP2B6 inducers decreases plasma concentrations of dextromethorphan and bupropion and may decrease efficacy of AUVELITY.
Intervention	Avoid co-administration of AUVELITY with strong inducers of CYP2B6. Consider alternatives to strong CYP2B6 inducers if needed.
Drugs Metabolized by CYP2D6	
Clinical Impact	*CYP2D6 Substrates* Coadministration of AUVELITY with drugs that are metabolized by CYP2D6 can increase the exposures of drugs that are substrates of CYP2D6. *Drugs that Require Metabolic Activation by CYP2D6* Drugs that require metabolic activation by CYP2D6 to be effective could have reduced efficacy when administered concomitantly with AUVELITY.
Intervention	*CYP2D6 Substrates* When used concomitantly with AUVELITY, it may be necessary to decrease the dose of CYP2D6 substrates, particularly for drugs with a narrow therapeutic index. *Drugs that Require Metabolic Activation by CYP2D6* Patients treated concomitantly with AUVELITY may require increased doses of drugs that require activation by CYP2D6 to be effective.
Digoxin	
Clinical Impact	Coadministration of AUVELITY with digoxin may decrease plasma digoxin levels.
Intervention	Monitor plasma digoxin levels in patients treated concomitantly with AUVELITY and digoxin.
Dopaminergic Drugs	
Clinical Impact	CNS toxicity was reported when bupropion was co-administered with levodopa or amantadine. Adverse reactions have included restlessness, agitation, tremor, ataxia, gait disturbance, vertigo, and dizziness.
Intervention	Use caution when administering AUVELITY concomitantly with dopaminergic drugs.
Alcohol	
Clinical Impact	AUVELITY contains bupropion which can increase adverse neuropsychiatric events or reduce alcohol tolerance.
Intervention	The consumption of alcohol should be minimized or avoided during treatment with AUVELITY.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including AUVELITY, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Antidepressants at 1-866-961-2388 or online at: https://womensmentalhealth.org/research/pregnancyregistry/antidepressants/

Risk Summary

Based on animal studies, AUVELITY may cause fetal harm when administered during pregnancy. AUVELITY is not recommended during pregnancy. If a female becomes pregnant while being treated with AUVELITY, discontinue treatment and counsel the patient about the potential risk to a fetus.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Women who discontinued antidepressants during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressants. Consider the risks to the mother of untreated depression and potential effects on the fetus when discontinuing or changing treatment with antidepressant medications during pregnancy and postpartum.

Lactation

Risk Summary

Because of the potential for neurotoxicity, advise patients that breast-feeding is not recommended during treatment with AUVELITY and for 5 days following final dose.

Renal Impairment

Dosage adjustment of AUVELITY is recommended in patients with moderate renal impairment (eGFR 30 to 59 mL/minute/1.73 m^2. The pharmacokinetics of AUVELITY have not been evaluated in patients with severe renal impairment. AUVELITY is not recommended in patients with severe renal impairment (eGFR 15 to 29 mL/minute/1.73 m^2).

Hepatic Impairment

No dose adjustment of AUVELITY is recommended in patients with mild (Child-Pugh A) or moderate hepatic impairment (Child-Pugh B). The pharmacokinetics of AUVELITY have not been evaluated in patients with severe hepatic impairment (Child-Pugh C). AUVELITY is not recommended in patients with severe hepatic impairment.

CYP2D6 Poor Metabolizers

Dosage adjustment is recommended in patients known to be poor CYP2D6 metabolizers because these patients have higher dextromethorphan concentrations than extensive/intermediate CYP2D6 metabolizers.

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