

MAJOR DEPRESSIVE DISORDER SYMPTOM RELIEF THAT WORKS

FAST &



FAST

Rapid symptom improvement as early as Week 1 vs placebo^{1,2*}

Statistically significant improvement from baseline in MADRS total score at Week 1 with AUVELITY vs placebo (key secondary endpoint: LS mean change of -7.2 vs -5.0; $P=0.007$)^{1,2,3†§¶}

Substantial symptom improvement (MADRS total score ≤ 10 ; protocol-defined remission) as early as Week 2 vs placebo^{2*}

Significantly more patients achieved a MADRS total score of <10 at Week 2 with AUVELITY vs placebo (key secondary endpoint: 17% [24/142] vs 8% [12/159]; $P=0.013$)^{2†#||}

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 additional Important Safety Information and the Brief Summary of Prescribing Information on the following pages, including **Boxed Warning** for suicidal thoughts and behaviors.

LASTS



LASTS

Sustained symptom improvement at Week 6 vs placebo^{1,2*}

Statistically significant improvement from baseline in MADRS total score at Week 6 with AUVELITY vs placebo (primary endpoint: LS mean change of -15.9 vs -12.1; $P=0.002$)^{1,2,3†§¶}

Substantial symptom improvement ($\geq 50\%$ improvement in MADRS total score from baseline; protocol-defined response) at Week 6 vs placebo^{2*}

Over half of the patients taking AUVELITY achieved 50% improvement in MADRS total score from baseline at Week 6 with AUVELITY (key secondary endpoint: 54% [67/124] vs 34% with placebo [51/150]; $P<0.001$)^{2†#||}



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*GEMINI Phase 3 study evaluated AUVELITY vs placebo in 327 patients (N=163 AUVELITY and N=164 placebo) with MDD for 6 weeks. N denotes randomized patients. The mITT population, defined as all randomized patients who took at least 1 dose of study drug and had at least 1 post-baseline assessment, was n=156 AUVELITY and n=162 placebo. Response protocol-defined as $\geq 50\%$ improvement in MADRS total score from baseline. The safety population was n=162 AUVELITY and n=164 placebo.

¹mITT population.

²Missing data were not imputed.

³Minimal clinically important difference (MCID) estimates for MADRS ranged from 1.6 to 1.9 between treatment groups.⁴

[†]Endpoints analyzed using MMRM.

[‡]Endpoint analyzed using a chi-squared test.

[§]Missing data were considered failures.

^{||}LS=least squares; MADRS=Montgomery-Åsberg Depression Rating Scale; mITT=modified intent-to-treat.

IMPORTANT SAFETY INFORMATION (CONT'D)

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.

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.

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.

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. 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.

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.

WARNINGS AND PRECAUTIONS (CONT'D)

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.

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.

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 m²). AUVELITY is not recommended in patients with severe renal impairment (eGFR 15 to 29 mL/minute/1.73 m²).

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%).

Please see Brief Summary of Prescribing Information on the following pages, including **Boxed Warning** for suicidal thoughts and behaviors.

AUV HCP ISI 10/2022

References: 1. AUVELITY [Prescribing Information]. Axsome Therapeutics, Inc.: New York, NY. 2. 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. 3. Data on File. AXS0010921. 4. Duru G and Fantino B. The clinical relevance of changes in the Montgomery-Åsberg Depression Rating Scale using the minimum clinically important difference approach. *Curr Med Res Opin*. 2008;24(5):1329–35.

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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

^aSexual dysfunction includes orgasm abnormal, erectile dysfunction, libido decreased, anorgasmia

^bFatigue includes fatigue, lethargy

^cParaesthesia includes paraesthesia, hypoaesthesia

DRUG INTERACTIONS

Table 3: Clinically Important Drug Interactions with AUVELITY

Monoamine Oxidase Inhibitors (MAOIs)	
<i>Clinical Impact</i>	The concomitant use of AUVELITY with MAOIs increases the risk of hypertensive crisis and serotonin syndrome.
<i>Intervention</i>	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	
<i>Clinical Impact</i>	Concomitant use of AUVELITY with other serotonergic drugs increases the risk of serotonin syndrome.
<i>Intervention</i>	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	
<i>Clinical Impact</i>	AUVELITY contains bupropion which can cause seizure. Co-administration with other drugs that lower seizure threshold may increase risk of seizure.
<i>Intervention</i>	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	
<i>Clinical Impact</i>	Concomitant use of AUVELITY with strong CYP2D6 inhibitors increases plasma concentrations of dextromethorphan.
<i>Intervention</i>	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	
<i>Clinical Impact</i>	Concomitant use of AUVELITY with strong CYP2B6 inducers decreases plasma concentrations of dextromethorphan and bupropion and may decrease efficacy of AUVELITY.
<i>Intervention</i>	Avoid co-administration of AUVELITY with strong inducers of CYP2B6. Consider alternatives to strong CYP2B6 inducers if needed.

Drugs Metabolized by CYP2D6	
<i>Clinical Impact</i>	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.
<i>Intervention</i>	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	
<i>Clinical Impact</i>	Coadministration of AUVELITY with digoxin may decrease plasma digoxin levels.
<i>Intervention</i>	Monitor plasma digoxin levels in patients treated concomitantly with AUVELITY and digoxin.
Dopaminergic Drugs	
<i>Clinical Impact</i>	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.
<i>Intervention</i>	Use caution when administering AUVELITY concomitantly with dopaminergic drugs.
Alcohol	
<i>Clinical Impact</i>	AUVELITY contains bupropion which can increase adverse neuropsychiatric events or reduce alcohol tolerance.
<i>Intervention</i>	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 m²). 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 m²).

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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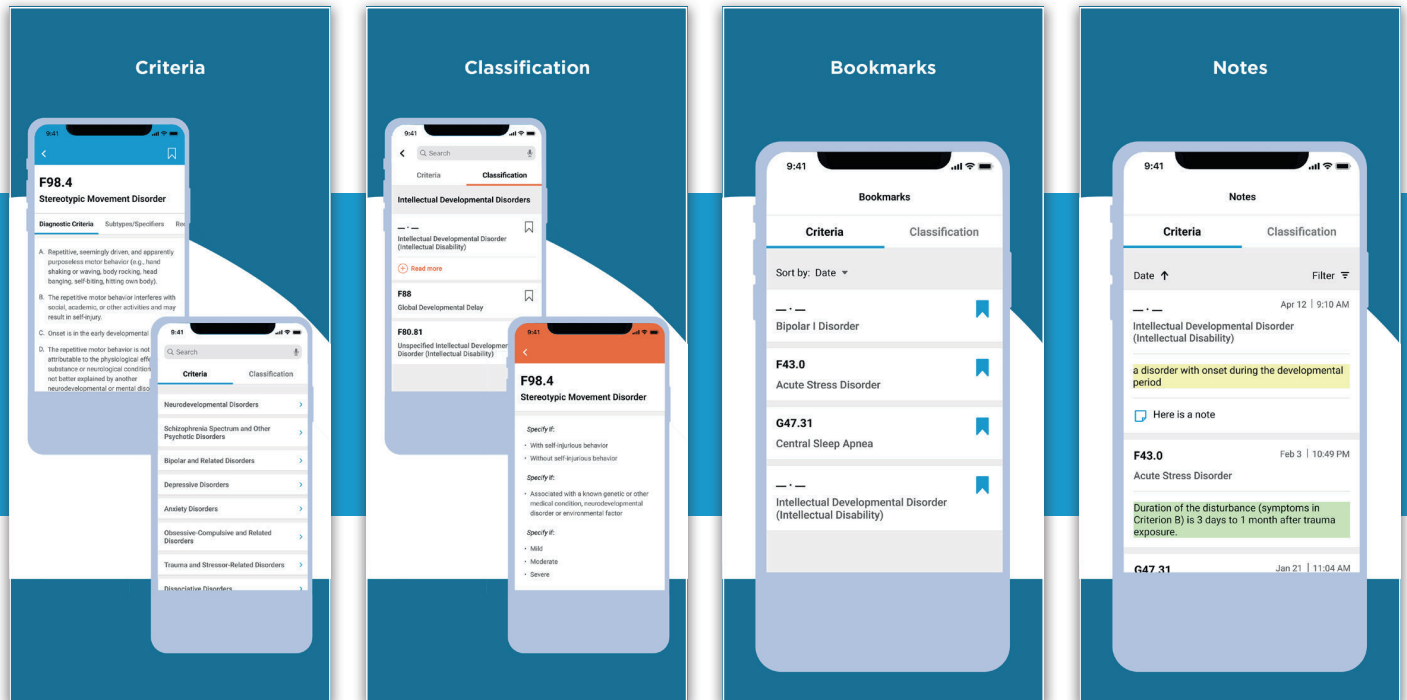
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