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

# NOT JUST ANOTHER ANTIDEPRESSANT

**Auvelity is the first and only oral NMDA receptor antagonist for adults with MDD[1-3]**

## 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.

Actor Portrayal

## PROVEN EFFICACY THAT IS:

# RAPID

### Rapid symptom improvement at Week 1*†

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).[1,4]

### Rapid remission starting at Week 2*‡

Significantly more patients achieved remission at Week 2 with Auvelity vs placebo (key secondary endpoint: 17% [24/142] vs 8% [12/159]; *P*=0.013).[4]

# SUSTAINED

### Sustained symptom improvement at Week 6*†

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).[1,4]

### Sustained clinical response at Week 6*‡

Over half of the patients taking Auvelity achieved clinical response at Week 6 with Auvelity (key secondary endpoint: 54% [67/124] vs 34% with placebo [51/150]; *P*<0.001).[4]

## IMPROVEMENT IN PATIENT-REPORTED FUNCTIONAL AND QUALITY OF LIFE ASSESSMENT SCORES

### Improvements on Sheehan Disability Scale (SDS) scores vs placebo.§

Patients taking Auvelity saw an improvement in SDS scores from Week 1 to Week 6 vs placebo (LS mean change from baseline: 4.6 vs 3.4 at Week 1; 9.0 vs 6.3 at Week 6).[4-6]

### Improvements on Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-SF) scores vs placebo.¶

Patients taking Auvelity saw an increase in Q-LES-Q-SF scores from Week 1 to Week 6 vs placebo (LS mean change from baseline: 9.0 vs 5.8 at Week 1; 19.8 vs 14.4 at Week 6).[4,5,7,8]

**The most common adverse reactions in a 6-week study (≥5% and >2x placebo) were: dizziness, headache, diarrhea, somnolence, dry mouth, sexual dysfunction, and hyperhidrosis.[1]**

## Explore long-term open-label data and full clinical profile at AuvelityHCP.com

*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. Remission defined as MADRS total score ≤10. Response defined as ≥50% improvement in MADRS total score from baseline. The safety population was n=162 Auvelity and n=164 placebo.

†Missing data were not imputed. Endpoints analyzed using MMRM.

‡Missing data were considered failures. Endpoint analyzed using a chi-squared test.

§Functioning was measured in the domains of work/school, social, and family life. *P*-values for comparisons were not adjusted for multiplicity and are therefore not presented.

¶Enjoyment and satisfaction experienced by patients were measured in various areas of daily functioning. *P*-values for comparisons were not adjusted for multiplicity and are therefore not presented.

LS=least squares; MADRS=Montgomery-Åsberg Depression Rating Scale; mITT=modified intent-to-treat; MMRM=mixed model with repeated measures; NMDA=N-methyl-D-aspartate

## 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.

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## 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 $m^2$). 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%).

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.** Machado-Vieira R, Henter ID, and Zarate CA Jr. New targets for rapid antidepressant action. *Prog Neurobiol.* 2017;152:21-37. **3.** FDA Depression Medicines. https://www.fda.gov/media/132665/download. Accessed March 21, 2022. **4.** 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. **5.** Data on File. AXS0020921. **6.** Sheehan Disability Scale (SDS) - Overview. http://memorialparkpsychiatry.com/doc/doc/sheehan_disability_scale.pdf. Accessed September 17, 2023. **7.** Quality of Life Enjoyment and Satisfaction Questionnaire Short Form. https://datashare.nida.nih.gov/instrument/quality-of-life-enjoyment-and-satisfaction-questionnaire-short-form. Accessed June 17, 2021. **8.** Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF). http://www.maternalwellnessclinic.ca/assets/files/Q-LES-Q-SF.pdf. Accessed June 17, 2021.

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**Explore the difference at AuvelityHCP.com**

Actor Portrayal

**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*<br>Coadministration of AUVELITY with drugs that are metabolized by CYP2D6 can increase the exposures of drugs that are substrates of CYP2D6.<br>*Drugs that Require Metabolic Activation by CYP2D6*<br>Drugs that require metabolic activation by CYP2D6 to be effective could have reduced efficacy when administered concomitantly with AUVELITY. |
| *Intervention* | *CYP2D6 Substrates*<br>When used concomitantly with AUVELITY, it may be necessary to decrease the dose of CYP2D6 substrates, particularly for drugs with a narrow therapeutic index.<br>*Drugs that Require Metabolic Activation by CYP2D6*<br>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.

AUV HCP BS 08/2022

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Axsome Therapeutics, Inc. New York, NY 10007

## For ADHD patients 6 years and older


# A novel, nonstimulant ADHD treatment that works![1,2]

ONCE-DAILY
Qelbree®
viloxazine
extended-release capsules
100 mg 150 mg 200 mg

**Rethink ADHD Symptom Control®**

Today's fastest growing ADHD Rx Brand*

***Branded ADHD products launched in last 6 years (as of September 2023).**

### INDICATION

Qelbree is indicated for the treatment of ADHD in adults and pediatric patients 6 years and older.

### IMPORTANT SAFETY INFORMATION

**WARNING: SUICIDAL THOUGHTS AND BEHAVIORS**

**In clinical studies, higher rates of suicidal thoughts and behaviors were reported in patients with ADHD treated with Qelbree than in patients treated with placebo. Closely monitor all Qelbree-treated patients for clinical worsening and for emergence of suicidal thoughts and behaviors.**

### CONTRAINDICATIONS

- Concomitant administration of a monoamine oxidase inhibitor (MAOI), or dosing within 14 days after discontinuing an MAOI, because of an increased risk of hypertensive crisis
- Concomitant administration of sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range

### WARNINGS & PRECAUTIONS

- *Suicidal thoughts and behaviors*: Closely monitor all Qelbree-treated patients 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
- *Heart rate, blood pressure increases*: Qelbree can cause an increase in diastolic blood pressure and heart rate. Assess these measures prior to starting therapy, following increases in dosage, and periodically during therapy
- *Activation of mania or hypomania*: Noradrenergic drugs may induce a manic or mixed episode in patients with bipolar disorder. Prior to initiating treatment with Qelbree, screen patients to determine if they are at risk for bipolar disorder. Screening should include a detailed psychiatric history, including a personal or family history of suicide, bipolar disorder, and depression
- *Somnolence and fatigue*: Patients should not perform activities requiring mental alertness, such as operating a motor vehicle or hazardous machinery, due to potential somnolence (including sedation or lethargy) and fatigue, until they know how they will be affected by Qelbree

### ADVERSE REACTIONS

The most common adverse reactions (≥5% and at least twice the rate of placebo for any dose) in patients 6 to 17 years were somnolence, decreased appetite, fatigue, nausea, vomiting, insomnia, and irritability, and in adults, insomnia, headache, somnolence, fatigue, nausea, decreased appetite, dry mouth, and constipation.

### PREGNANCY

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Qelbree during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Psychiatric Medications at 1-866-961-2388 or by visiting www.womensmentalhealth.org/preg.

Abbreviation: ADHD, attention-deficit/hyperactivity disorder.

**REFERENCES: 1.** Qelbree [package insert]. Rockville, MD: Supernus Pharmaceuticals, Inc. **2.** Food and Drug Administration. Novel drug approvals for 2021. May 13, 2022. Accessed January 7, 2023. https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2021. **3.** Data on file, Supernus Pharmaceuticals.

**Please see the brief summary of full Prescribing Information including Boxed Warning, on adjacent pages, or visit QelbreeHCP.com.**

Supernus® Pharmaceuticals

ONCE-DAILY
Qelbree®
viloxazine
extended-release capsules
100 mg 150 mg 200 mg

**Qelbree® (viloxazine extended-release capsules), for oral use**
**BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION**

For full prescribing information, see package insert.

**WARNING: SUICIDAL THOUGHTS AND BEHAVIORS**

**In clinical studies, higher rates of suicidal thoughts and behavior were reported in patients with ADHD treated with Qelbree than in patients treated with placebo. Closely monitor all Qelbree-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors.**

## INDICATIONS AND USAGE

Qelbree is indicated for the treatment of Attention-Deficit Hyperactivity Disorder (ADHD) in adults and pediatric patients 6 years and older.

## CONTRAINDICATIONS

Qelbree is contraindicated in patients receiving concomitant treatment with monoamine oxidase inhibitors (MAOI), or within 14 days following discontinuing an MAOI, because of an increased risk of hypertensive crisis.

Qelbree should not be taken when receiving concomitant administration of sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range.

## WARNINGS AND PRECAUTIONS

### Suicidal Thoughts and Behaviors

Higher rates of suicidal thoughts and behaviors were reported in pediatric and adult patients with ADHD treated with Qelbree than in patients treated with placebo.

Among 1019 patients exposed to Qelbree 100 mg to 400 mg in short-term trials, a total of nine patients (0.9%) reported suicidal ideation (N=6), behavior (N=1) or both (N=2). Eight patients reported suicidal ideation or behavior on the Columbia Suicide Severity Rating Scale (C-SSRS), a validated scale that assesses suicide risk. An additional patient treated with Qelbree reported suicidal behavior during the clinical trials, but did not report it on the C-SSRS. Among 463 patients treated with placebo in these studies, two patients (0.4%) reported suicidal ideation on the C-SSRS. No patients treated with placebo reported suicidal behavior. No completed suicides occurred in these trials.

Among 189 adults treated with Qelbree, a total of three patients (1.6%) reported suicidal ideation on the C-SSRS, versus 0 of 183 adults treated with placebo. No adults treated with either Qelbree or placebo reported suicidal behavior on the C-SSRS in the study. No attempted or completed suicides occurred in the trial.

Patients treated with Qelbree had higher rates of insomnia and irritability.Although a causal link between the emergence of insomnia and irritability and the emergence of suicidal impulses has not been established, there is a concern that these and other symptoms such as depressed mood, anxiety, agitation, akathisia, mania, hypomania, panic attacks, impulsive behavior, and aggression may represent precursors to emerging suicidal ideation or behavior. Thus, patients being treated with Qelbree should be observed for the emergence of precursor symptoms.

Closely monitor all Qelbree-treated patients 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.

Consider changing the therapeutic regimen, including possibly discontinuing Qelbree, in patients who are experiencing emergent suicidal thoughts and behaviors or symptoms that might be precursors to emerging suicidal ideation or behavior, especially if these symptoms are severe or abrupt in onset, or were not part of the patient's presenting symptoms. Advise family members or caregivers of patients to monitor for the emergence of suicidal ideation or behavior, and to report such symptoms immediately to the healthcare provider.

### Effects on Blood Pressure and Heart Rate

Qelbree can cause an increase in heart rate and diastolic blood pressure.

In a clinical study in patients 6 to 11 years of age, 34/154 (22%) of patients treated with Qelbree 100 mg daily had a ≥20 beat per minute (bpm) increase in heart rate at any time point in the clinical trial, compared to 15/159 (9%) of patients who received placebo. This finding was observed in 84/268 (31%) who received the 200 mg dose, compared to 39/262 (15%) of patients in the placebo group, and in 28/100 (28%) of patients who received the 400 mg dose, compared to 24/103 (23%) of patients who received placebo.

In a clinical study in patients 12 to 17 years of age, 22/99 (22%) of patients treated with Qelbree 200 mg daily had a ≥20 bpm increase in heart rate at any time point in the clinical trial, compared to 15/104 (14%) of patients who received placebo. This finding was observed in 69/205 (34%) who received the 400 mg dose, compared to 35/201 (17%) of patients in the placebo group.

In patients ages 12 to 17 years, 52/205 (25%) of patients treated with Qelbree 400 mg daily had a ≥ 15 mmHg increase in diastolic blood pressure at any time in the clinical trial, compared to 26/201 (13%) of patients in the placebo group.

In a clinical study in adult patients (18 to 60 years of age), 52/178 (29%) of patients treated daily with Qelbree (200 mg to 600 mg) had a ≥20 beat per minute (bpm) increase in heart rate at any time point in the clinical trial, compared to 23/181 (13%) of patients who received placebo. Of patients treated daily with Qelbree (200 to 600 mg), 23/178 (13%) had a ≥ 15 mmHg increase in diastolic blood pressure at any time in the clinical trial, compared to 16/181 (9%) of patients in the placebo group.

Assess heart rate and blood pressure prior to initiating treatment with Qelbree, following increases in dosage, and periodically while on therapy.

### Activation of Mania or Hypomania

Noradrenergic drugs, such as Qelbree, may induce a manic or mixed episode in patients with bipolar disorder. Prior to initiating treatment with Qelbree, screen patients to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a personal or family history of suicide, bipolar disorder, and depression.

### Somnolence and Fatigue

Qelbree can cause somnolence and fatigue. In the short-term, placebo-controlled clinical trials in pediatric patients 6 to 17 years of age with ADHD, somnolence (including lethargy and sedation) was reported in 16% of Qelbree-treated patients compared to 4% of placebo-treated patients. Fatigue was reported in 6% of Qelbree-treated patients compared to 2% of placebo-treated patients.

In adults, somnolence was reported in 6% of Qelbree-treated patients versus 2% in placebo-treated patients. Fatigue was reported in 12% of Qelbree-treated patients versus 3% of placebo-treated patients.

Patients should not perform activities requiring mental alertness, such as operating a motor vehicle or operating hazardous machinery until they know how they will be affected by Qelbree.

## ADVERSE REACTIONS

### Clinical Trials Experience

The safety of Qelbree has been evaluated in 1118 patients 6 to 17 years of age with ADHD exposed to one or more doses in short-term (6 to 8 week), randomized, double-blind, placebo-controlled trials.

A total of 682 pediatric patients were treated for at least 6 months, and 347 pediatric patients for at least 12 months with Qelbree.

The safety of Qelbree has been evaluated in 189 adult patients (18 to 60 years of age) with ADHD exposed to one or more doses in a short-term (6 week), randomized, double-blind, placebo-controlled trial. A total of 277 adult patients with ADHD have been exposed to one or more doses of Qelbree.

Eighty-four adult patients were treated for at least 6 months, and 22 adult patients for at least 12 months.

The data described below reflect exposure to Qelbree in 826 patients (6 to 17 years) who participated in randomized, double-blind, placebo-controlled trials with doses ranging from 100 mg to 400 mg. The population (N=826) was 65% male, 35% female, 54% White, 41% Black, 4% multiracial, and 1% other races.

*Adverse Reactions Leading to Discontinuation of Qelbree Treatment:*
Approximately 3% (n=27) of the 826 patients receiving Qelbree in clinical studies discontinued treatment due to an adverse reaction. The adverse reactions most commonly associated with discontinuation of Qelbree were somnolence (n=5), nausea (n=3), headache (n=2), irritability (n=2), tachycardia (n=2), fatigue (n=2), and decreased appetite (n=2).

*Most Common Adverse Reactions (occurring at ≥5% and at least twice the placebo rate for any dose):* somnolence, decreased appetite, fatigue, nausea, vomiting, insomnia, and irritability.

Tables 1 and 2 below lists adverse reactions that occurred in at least 2% of patients treated with Qelbree and more frequently in Qelbree-treated patients than in placebo-treated patients. Table 1 data represents pooled data from pediatric patients 6-17 years of age who were enrolled in randomized, placebo-controlled trials of Qelbree. Table 2 represents data from adults with ADHD who were enrolled in a flexible-dose, randomized, placebo-controlled trial of Qelbree at doses of 200mg to 600mg.

**Table 1. Adverse Reactions Reported in ≥2% of Pediatric Patients (6 to 17 Years of Age) Treated with Qelbree and at a Rate of Greater than Placebo-Treated Patients in Placebo-Controlled ADHD Studies**

| | | Qelbree | | | |
|---|---|---|---|---|---|
| **Body System Adverse Reaction** | **Placebo N=463 (%)** | **100mg N=154 (%)** | **200mg N=367 (%)** | **400mg N=305 (%)** | **All Qelbree N=836 (%)** |
| **Nervous system disorders** | | | | | |
| **Somnolence*** | 4 | 12 | 16 | 19 | 16 |
| **Headache*** | 7 | 10 | 11 | 11 | 11 |
| **Metabolic and nutritional disorders** | | | | | |
| **Decreased appetite** | 0.4 | 5 | 8 | 8 | 7 |
| **Infections and infestations** | | | | | |
| **Upper respiratory tract infections*** | 6 | 5 | 7 | 8 | 7 |
| **Body as a Whole - General disorders** | | | | | |
| **Fatigue** | 2 | 4 | 5 | 9 | 6 |
| **Pyrexia** | 0.2 | 3 | 2 | 1 | 2 |
| **Gastrointestinal system disorders** | | | | | |
| **Abdominal Pain*** | 4 | 3 | 6 | 7 | 5 |
| **Nausea** | 3 | 1 | 4 | 7 | 5 |
| **Vomiting** | 2 | 5 | 3 | 6 | 4 |

**Table 1. Adverse Reactions Reported in ≥2% of Pediatric Patients (6 to 17 Years of Age) Treated with Qelbree and at a Rate of Greater than Placebo-Treated Patients in Placebo-Controlled ADHD Studies (continued)**

| Body System Adverse Reaction | Placebo N=463 (%) | Qelbree | | | |
|---|---|---|---|---|---|
| | | 100mg N=154 (%) | 200mg N=367 (%) | 400mg N=305 (%) | All Qelbree N=836 (%) |
| **Psychiatric disorders** | | | | | |
| **Insomnia*** | 1 | 2 | 5 | 5 | 4 |
| **Irritability** | 1 | 3 | 2 | 5 | 3 |

*The following items were combined:
**Somnolence:** somnolence, lethargy, sedation
**Headache:** headache, migraine, migraine with aura, tension headache
**Upper respiratory tract infection:** nasopharyngitis, pharyngitis, sinusitis, upper respiratory tract infection, viral sinusitis, viral upper respiratory tract infection
**Abdominal pain:** abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper
**Insomnia:** initial insomnia, insomnia, middle insomnia, poor quality sleep, sleep disorder, terminal insomnia

The data described below reflect exposure to Qelbree in 189 adults with ADHD who participated in the flexible-dose, randomized, double-blind, placebo-controlled trial with doses ranging from 200 mg to 600 mg. The population (N=189) was 56% male, 44% female, 81% White, 12% Black, 3% Asian, 3% other races and 1% multiracial.

*Adverse Reactions Leading to Discontinuation of Qelbree Treatment*: Approximately 9% of the 189 patients receiving Qelbree in clinical studies discontinued treatment due to an adverse reaction. The adverse reactions most commonly associated with discontinuation of Qelbree were fatigue (n=4), insomnia (n=3), constipation (n=3), and headache (n=2).

*Most Common Adverse Reactions (occurring at ≥5% and at least twice the placebo rate of Qelbree)*: insomnia, headache, somnolence, fatigue, nausea, decreased appetite, dry mouth, and constipation.

Listed here are adverse reactions that occurred in at least 2% of patients treated with Qelbree and more frequently in the Qelbree-treated patients than in the placebo-treated patients. Table 2 represents data from adults with ADHD who were enrolled in a flexible-dose, randomized, placebo-controlled trial of Qelbree at doses of 200 mg to 600 mg.

**Table 2. Adverse Reactions Reported in ≥2% of Adults Treated with Qelbree and at a Rate Greater than Placebo-Treated Patients in a Flexible-Dose Placebo-Controlled ADHD Study**

| Body System Adverse Reaction | Placebo N=183 (%) | Qelbree (200 mg to 600 mg) N=189 (%) |
|---|---|---|
| **Psychiatric disorders** | | |
| Insomnia* | 7 | 23 |
| Irritability | 3 | 4 |
| **Nervous system disorders** | | |
| Headache* | 7 | 17 |
| Somnolence* | 2 | 6 |
| Dizziness | 2 | 4 |
| **Gastrointestinal system disorders** | | |
| Nausea | 3 | 12 |
| Dry mouth | 2 | 10 |
| Constipation | 1 | 6 |
| Vomiting | 1 | 4 |
| Gastroesophageal reflux disease | 1 | 2 |
| **Body as a Whole - General disorders** | | |
| Fatigue | 3 | 12 |
| **Metabolic and nutritional disorders** | | |
| Decreased appetite | 3 | 10 |
| **Cardiac disorders** | | |
| Tachycardia | 1 | 4 |

*The following items were combined:
**Somnolence:** somnolence, lethargy, sedation
**Headache:** headache, migraine, migraine with aura, tension headache
**Insomnia:** initial insomnia, insomnia, middle insomnia, poor quality sleep, sleep disorder, terminal insomnia

## DRUG INTERACTIONS

### Drugs Having Clinically Important Interactions with Qelbree

***Monoamine Oxidase Inhibitors (MAOI)***

- Clinical Impact: Concomitant use of Qelbree with an MAOI may lead to a potentially life-threatening hypertensive crisis.
- Intervention: Concomitant use of Qelbree with an MAOI or within 2 weeks after discontinuing an MAOI is contraindicated.

***Sensitive CYP1A2 Substrates or CYP1A2 Substrates with a Narrow Therapeutic Range***

- Clinical Impact: Viloxazine is a strong CYP1A2 inhibitor. Concomitant use of viloxazine significantly increases the total exposure, but not peak exposure, of sensitive CYP1A2 substrates, which may increase the risk of adverse reactions associated with these CYP1A2 substrates.
- Intervention: Coadministration with Qelbree is contraindicated.

***Moderate Sensitive CYP1A2 Substrate***

- Clinical Impact: Viloxazine is a strong CYP1A2 inhibitor. Concomitant use of viloxazine significantly increases the total, but not peak, exposure of sensitive CYP1A2 substrates, which may increase the risk of adverse reactions associated with these CYP1A2 substrates.
- Intervention: Not recommended for coadministration with Qelbree. Dose reduction may be warranted if coadministered.

***CYP2D6 Substrates***

- Clinical Impact: Viloxazine is a weak inhibitor of CYP2D6, and increases the exposure of CYP2D6 substrates when coadministered.
- Intervention: Monitor patients for adverse reactions and adjust dosages of CYP2D6 substrates, as clinically indicated.

***CYP3A4 Substrates***

- Clinical Impact: Viloxazine is a weak inhibitor of CYP3A4 which increases the exposure of CYP3A4 substrates when coadministered.
- Intervention: Monitor patients for adverse reactions and adjust dosages of CYP3A4 substrates, as clinically indicated.

## USE IN SPECIFIC POPULATIONS

### Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Qelbree during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Psychiatric Medications at 1-866-961-2388, or visiting online at www.womensmentalhealth.org/preg.

Risk Summary

Based on findings from animal reproduction studies, viloxazine may cause maternal harm when used during pregnancy. Discontinue Qelbree when pregnancy is recognized unless the benefits of therapy outweigh the potential risk to the mother. Available data from case series with viloxazine use in pregnant women are insufficient to determine a drug-associated risk of major birth defects, miscarriage or adverse maternal outcomes.

In animal reproduction studies, oral administration of viloxazine during the period of organogenesis caused fetal toxicities and delayed fetal development in the rat and maternal toxicities in the rabbit at doses approximately equal to the maximum recommended human dose (MRHD) of 600mg in adults, based on mg/m$^2$. Oral administration of viloxazine to pregnant rats and mice during pregnancy and lactation caused maternal toxicities and deaths and fetal toxicities at doses equal to or less than the MRHD of 600mg in adults, based on mg/m$^2$, respectively.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcome. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

### Lactation

Risk Summary

There are no data on the presence of viloxazine in human milk, the effects on the breastfed infant, or the effects on milk production. Viloxazine is likely present in rat milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Qelbree and any potential adverse effects on the breastfed child from Qelbree or from the underlying maternal condition.

### Geriatric Use

Clinical trials of Qelbree in the treatment of ADHD did not include sufficient numbers of patients aged 65 and older to determine whether or not they respond differently from younger patients.

### Renal Impairment

Dosage reduction is recommended in patients with severe (eGFR of < 30 mL/min/1.73m$^2$ [MDRD]) renal impairment.

No dosage adjustment of Qelbree is recommended in patients with mild to moderate (eGFR of 30 to 89 mL/min/1.73m$^2$ [MDRD]) renal impairment.

The exposure of viloxazine increases in patients with renal impairment.

## OVERDOSAGE

Human Experience

The pre-market clinical trials with Qelbree do not provide information regarding symptoms of overdose.

Literature reports from post marketing experience with immediate-release viloxazine include cases of overdosage from 1000 mg to 6500 mg (1.7 to 10.8 times the maximum recommended daily dose). The most reported symptom was drowsiness. Impaired consciousness, diminished reflexes, and increased heart rate have also been reported.

Treatment and Management

There is no specific antidote for Qelbree overdose. Administer symptomatic and supportive treatment as appropriate. In case of overdose, consult a Certified Poison Control Center (1-800-222-1222 or www.poison.org).