

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use QELBREE™ safely and effectively. See full prescribing information for QELBREE™.

QELBREE™ (viloxazine extended-release capsules), for oral use
Initial U.S. Approval: 2021

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

In clinical trials, higher rates of suicidal thoughts and behavior were reported in pediatric patients treated with Qelbree than in patients treated with placebo. Closely monitor for worsening and emergence of suicidal thoughts and behaviors (5.1).

INDICATIONS AND USAGE

Qelbree is a selective norepinephrine reuptake inhibitor indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in pediatric patients 6 to 17 years of age (1)

DOSAGE AND ADMINISTRATION

- *Pediatric patients 6 to 11 years of age:* Recommended starting dosage is 100 mg once daily. May titrate in increments of 100 mg weekly to the maximum recommended dosage of 400 mg once daily (2.2)
- *Pediatric patients 12 to 17 years of age:* Recommended starting dosage is 200 mg once daily. May titrate after 1 week, by an increment of 200mg, to the maximum recommended dosage of 400 mg once daily (2.2)
- Capsules may be swallowed whole or opened and the entire contents sprinkled onto applesauce (2.3)
- Severe Renal Impairment: Initial dosage is 100 mg once daily. Titrate in weekly increments of 50 mg to 100 mg to a maximum recommended dosage of 200 mg once daily (2.4, 8.6)

DOSAGE FORMS AND STRENGTHS

Extended-release capsules: 100 mg, 150 mg and 200 mg (3)

CONTRAINDICATIONS

- Concomitant administration of monoamine oxidase inhibitors (MAOI), or dosing within 14 days after discontinuing an MAOI (4, 7.1)
- Concomitant administration of sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range (4, 7.1)

WARNINGS AND PRECAUTIONS

- Blood Pressure and Heart Rate Increases: Assess heart rate and blood pressure prior to initiating treatment, following increases in dosage, and periodically while on therapy (5.2)
- Activation of Mania or Hypomania: Screen patients for bipolar disorder (5.3)
- Somnolence and Fatigue: Advise patients to use caution when driving or operating hazardous machinery due to potential somnolence (including sedation and lethargy) and fatigue (5.4)

ADVERSE REACTIONS

Most commonly observed adverse reactions ($\geq 5\%$ and at least twice the rate of placebo) were: somnolence, decreased appetite, fatigue, nausea, vomiting, insomnia, and irritability (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Supernus Pharmaceuticals at 1-866-398-0833 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Moderate sensitive CYP1A2 substrates: Not recommended for coadministration with Qelbree. Dose reduction may be warranted (7.1)

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause maternal harm; discontinue when pregnancy is recognized (8.1)
- Hepatic Impairment: Not recommended (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised:4/2021

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FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

In clinical studies, higher rates of suicidal thoughts and behavior were reported in pediatric 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 [see Warnings and Precautions (5.1)].

1 INDICATIONS AND USAGE

Qelbree is indicated for the treatment of Attention-Deficit Hyperactivity Disorder (ADHD) in pediatric patients 6 to 17 years of age.

2 DOSAGE AND ADMINISTRATION

2.1 Important Considerations Prior to Initiating Treatment

- Assess heart rate and blood pressure prior to initiating treatment with Qelbree, following increases in dosage, and periodically while on therapy [see Warnings and Precautions (5.2)].
- Prior to initiating treatment with Qelbree, screen patients for a personal or family history of suicide, bipolar disorder, and depression [see Warnings and Precautions (5.3)].

2.2 Recommended Dosage

Pediatric patients 6 to 11 years of age

The recommended starting dosage for pediatric patients 6 to 11 years of age is 100 mg orally once daily. Dosage may be titrated in increments of 100 mg at weekly intervals to the maximum recommended dosage of 400 mg once daily, depending on response and tolerability.

Pediatric patients 12 to 17 years of age

The recommended starting dosage for pediatric patients 12 to 17 years of age is 200 mg orally once daily. After 1 week, dosage may be titrated by an increment of 200 mg to the maximum recommended dosage of 400 mg once daily, depending on response and tolerability.

Pharmacological treatment of ADHD may be needed for extended periods. Periodically reevaluate the long-term use of Qelbree and adjust dosage as needed.

2.3 Administration Information

Administer Qelbree orally with or without food [see Clinical Pharmacology (12.3)]. Do not cut, crush, or chew the capsules.

Swallow Qelbree capsules whole or open the capsule and sprinkle the entire contents over a teaspoonful of applesauce. Consume all the sprinkled applesauce in its entirety, without chewing, within 2 hours; do not store for future use.

2.4 Dosage Recommendations in Patients with Renal Impairment

In patients with severe renal impairment (eGFR < 30 mL/min/1.73m²), the recommended starting dosage is 100 mg once daily. Dosage may be titrated in weekly increments of 50 to 100 mg once daily, to a maximum recommended dosage of 200 mg once daily.

No dosage adjustment is recommended in patients with mild to moderate (eGFR of 30 to 89 mL/min/1.73m²) renal impairment [see Use in Specific Populations (8.6)].

3 DOSAGE FORMS AND STRENGTHS

Qelbree (viloxazine extended-release capsules) are available as:

100 mg: yellow opaque body and cap (printed “SPN” on the cap, “100” on the body)

150 mg: lavender opaque body and cap (printed “SPN” on the cap, “150” on the body)

200 mg: light green opaque body and cap (printed “SPN” on the cap, “200” on the body)

4 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 [*see Drug Interactions (7.1)*].
- receiving concomitant administration of sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range [*see Drug Interactions (7.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Suicidal Thoughts and Behaviors

In clinical studies, higher rates of suicidal thoughts and behavior were reported in pediatric 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.

Patients treated with Qelbree had higher rates of insomnia and irritability [*see Adverse Reactions (6.1)*]. Although a causal link between the emergence of such symptoms 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 such 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.

5.2 Blood Pressure and Heart Rate Increases

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 daily dosage, compared to 39/262 (15%) of patients in the placebo group, and in 28/100 (28%) of patients who received the 400 mg daily dosage, 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 daily dosage, compared to 35/201 (17%) of patients in the placebo group. In patients ages 12 to 17 years of age, 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.

Assess heart rate and blood pressure prior to initiating treatment with Qelbree, following increases in dosage, and periodically while on therapy [see *Dosage and Administration (2.1)*].

5.3 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 [see *Dosage and Administration (2.1)*].

5.4 Somnolence and Fatigue

Qelbree can cause somnolence and fatigue. In the short-term, placebo-controlled clinical trials in pediatric patients 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 [see *Adverse Reactions (6.1)*].

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.

6 ADVERSE REACTIONS

The following serious adverse reactions are described in other sections of the labeling:

- Suicidal Thoughts and Behaviors [see *Warnings and Precautions (5.1)*]
- Blood Pressure and Heart Rate Increases [see *Warnings and Precautions (5.2)*]
- Activation of Mania or Hypomania [see *Warnings and Precautions (5.3)*]
- Somnolence and Fatigue [see *Warnings and Precautions (5.4)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, and may not reflect the rates observed in practice.

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 data described below reflect exposure to Qelbree in 826 patients 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% 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, nausea, headache, irritability, tachycardia, fatigue, and decreased appetite.

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

Table 1 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 to 17 years of age who were enrolled in randomized, placebo-controlled trials of Qelbree.

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

Body System Adverse Reaction	Placebo N=463 (%)	Qelbree			
		100mg N=154 (%)	200mg N=367 (%)	400mg N=305 (%)	All Qelbree N=826 (%)
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 infection*	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
Psychiatric disorders					
Insomnia*	1	2	5	5	4
Irritability	1	3	2	5	3

*The following terms 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

Effects on Weight: In short-term, controlled studies (6 to 8 weeks), Qelbree-treated patients 6 to 11 years of age gained an average of 0.2 kg, compared to a gain of 1 kg in same-aged patients who received placebo. Qelbree-treated patients 12 to 17 years of age lost an average of 0.2 kg, compared to a weight gain of 1.5 kg in same-aged patients who received placebo. In a long-term open-label extension safety trial, 1097 patients received at least 1 dose of Qelbree. Among the 338 patients evaluated at 12 months, the mean change from baseline in weight-for-age z-score was -0.2 (standard deviation of 0.5). In the absence of a control group, it is unclear whether the weight change observed in the long-term open-label extension was attributable to the effect of Qelbree.

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with Qelbree

Table 2: Clinically Important Drug Interactions with Qelbree

<i>Monoamine Oxidase Inhibitors (MAOI)</i>	
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 [see <i>Contraindications (4)</i>].
Examples	Selegiline, isocarboxazid, phenelzine, tranylcypromine, safinamide, rasagiline
<i>Sensitive CYP1A2 Substrates or CYP1A2 Substrates with a Narrow Therapeutic Range</i>	
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 [see <i>Clinical Pharmacology (12.3)</i>], which may increase the risk of adverse reactions associated with these CYP1A2 substrates.
Intervention	Coadministration with Qelbree is contraindicated [see <i>Contraindications (4)</i>].
Examples	Alosetron, duloxetine, ramelteon, tasimelteon, tizanidine, theophylline
<i>Moderate Sensitive CYP1A2 Substrate</i>	
Clinical Impact	Viloxazine is a strong CYP1A2 inhibitor. Concomitant use of viloxazine significantly increases the total, but not peak, exposure of sensitive CYP1A2 substrates [see <i>Clinical Pharmacology (12.3)</i>], 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.
Examples	Clozapine, pirlfenidone

<i>CYP2D6 Substrates</i>	
Clinical Impact	Viloxazine is a weak inhibitor of CYP2D6, and increases the exposure of CYP2D6 substrates when coadministered [see <i>Clinical Pharmacology (12.3)</i>].
Intervention	Monitor patients for adverse reactions and adjust dosages of CYP2D6 substrates, as clinically indicated.
Examples	Atomoxetine, desipramine, dextromethorphan, nortriptyline, metoprolol, nebivolol, perphenazine, tolterodine, venlafaxine, and risperidone
<i>CYP3A4 Substrates</i>	
Clinical Impact	Viloxazine is a weak inhibitor of CYP3A4 which increases the exposure of CYP3A4 substrates when coadministered [see <i>Clinical Pharmacology (12.3)</i>].
Intervention	Monitor patients for adverse reactions and adjust dosages of CYP3A4 substrates, as clinically indicated.
Examples	Alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil, and lurasidone

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed 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 to pregnant rats and rabbits during the period of organogenesis did not cause significant maternal toxicity but caused fetal toxicities and delayed fetal development in the rat at doses up to 2 times the maximum recommended human dose (MRHD) of 400 mg, based on mg/m². In the rabbit, viloxazine caused maternal toxicity without significant fetal toxicity at doses ≥ 7 times the MRHD based on mg/m². The no observed adverse effect levels (NOAELs) for fetal toxicity are approximately equal to and 11 times the MRHD, based on mg/m² in the rat and rabbit, respectively. Oral administration of viloxazine to pregnant rats and mice during pregnancy and lactation caused maternal toxicities and deaths at doses approximately 2 and 1 time the MRHD, based on mg/m², respectively (*see Data*). At these maternally toxic doses, viloxazine caused offspring toxicities. The NOAEL for maternal and developmental toxicity is approximately equal to or less than the MRHD, based on mg/m², in the rat and mouse, respectively (*see Data*).

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 outcomes. 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.

Data

Animal Data

Viloxazine was administered orally to pregnant rats during the period of organogenesis at doses of 13, 33, and 82 mg/kg/day, which are less than, equal to, and 2 times the MRHD of 400 mg, based on mg/m², respectively. Viloxazine did not cause maternal toxicity at doses up to 82 mg/kg/day. Viloxazine at 82 mg/kg/day increased early and late resorption, delayed fetal development, and possibly caused low incidences of fetal malformations or anomalies (craniorachischisis, missing cervical vertebrae, and morphological changes associated with hydranencephaly). The NOAEL for fetal toxicity and malformation is 33 mg/kg/day, which is approximately equal to the MRHD, based on mg/m².

Viloxazine was administered orally to pregnant rabbits during the period of organogenesis at doses of 43, 87, and 130 mg/kg/day, which are approximately 4, 7, and 11 times the MRHD of 400 mg, based on mg/m², respectively. Viloxazine decreased maternal body weight, weight gain, or food consumption at doses \geq 87 mg/kg/day but did not cause fetal toxicity at doses up to 130 mg/kg/day. The NOAELs for maternal and fetal toxicity is 43 and 130 mg/kg/day, respectively, which is approximately 4 and 11 times the MRHD, based on mg/m², respectively.

Viloxazine was administered orally to pregnant rats during gestation and lactation at doses of 43, 87, and 217 mg/kg/day, which are approximately 1, 2, and 5 times the MRHD of 400 mg, based on mg/m², respectively. Viloxazine caused maternal toxicity of decreased body weight, weight gain, and food consumption at doses \geq 87 mg/kg/day and maternal deaths near term at 217 mg/kg/day. At these maternally toxic doses, viloxazine caused lower live birth, decreased viability, and delayed growth and sexual maturation without affecting learning and memory in the offspring. The NOAEL for maternal and developmental toxicity is 43 mg/kg/day, which is approximately equal to the MRHD, based on mg/m².

Viloxazine was administered orally to pregnant mice during gestation and lactation at doses of 13, 33, and 82 mg/kg/day, which are approximately less than or equal to the MRHD of 400 mg, based on mg/m², respectively. Viloxazine treatment at 82 mg/kg/day during the gestation period caused maternal deaths and decreased body weight in the offspring. The NOAEL for both maternal and developmental toxicity is 33 mg/kg/day, which is less than the MRHD, based on mg/m².

8.2 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.

8.4 Pediatric Use

The safety and effectiveness of Qelbree in pediatric patients 6 to 17 years of age with ADHD have been established based on randomized, placebo-controlled studies in pediatric patients [*see Adverse Reactions (6.1) and Clinical Studies (14)*].

The safety and effectiveness of Qelbree have not been established in pediatric patients younger than 6 years old.

Patients treated with Qelbree should be monitored for suicidal thoughts and behavior [*see Warnings and Precautions (5.1)*], and for changes in weight [*see Adverse Reactions (6.1)*].

Juvenile Animal Toxicity Data

Viloxazine was administered orally to juvenile rats from postnatal day (PND) 23 through PND 79 at doses of 43, 130, and 217 mg/kg/day, which are approximately 1, 2, and 3 times the MRHD of 400 mg, based on mg/m² in

children, respectively. Viloxazine decreased body weight, weight gain, and food consumption in both sexes at 217 mg/kg/day. Sexual maturation, reproductive capacity, and learning and memory were not affected. The NOAEL for juvenile toxicity is 130 mg/kg/day, which is approximately 2 times the MRHD, based on mg/m² in children.

8.5 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.

8.6 Renal Impairment

Dosage reduction is recommended in patients with severe (eGFR of < 30 mL/min/1.73m² [MDRD]) renal impairment [see *Dosage and Administration (2.4)*].

No dosage adjustment of Qelbree is recommended in patients with mild to moderate (eGFR of 30 to 89 mL/min/1.73m² [MDRD]) renal impairment.

The exposure of viloxazine increases in patients with renal impairment [see *Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of viloxazine is unknown [see *Clinical Pharmacology (12.3)*]. Qelbree is not recommended in patients with hepatic impairment.

10 OVERDOSAGE

Human Experience

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

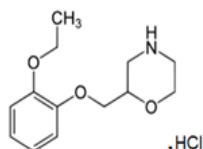
Literature reports from post marketing experience with immediate-release viloxazine include cases of overdose from 1000 mg to 6500 mg (2.5 to 16.25 times the maximum recommended daily dose). The most reported symptom was drowsiness. Impaired consciousness, diminished reflexes, and increased heart rate 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).

11 DESCRIPTION

Qelbree contains viloxazine, a selective norepinephrine reuptake inhibitor. Viloxazine is (±)-2-[(2-ethoxyphenoxy)methyl]morpholine hydrochloride. The molecular formula is C₁₃H₂₀NO₃Cl and its molecular weight is 273.8 (HCl salt) with the following structural formula:



Viloxazine hydrochloride is a white to off-white powder. Viloxazine hydrochloride is soluble in water, 0.1N HCl and aqueous solutions of pH 9.5 and lower. Viloxazine hydrochloride is sparingly soluble in methanol, very slightly soluble in acetonitrile, acetic acid and isopropyl alcohol, and practically insoluble in ethyl acetate.

Qelbree extended-release capsules are intended for oral administration. Each extended-release capsule contains 100 mg, 150 mg, and 200 mg of viloxazine free base equivalent to 115mg, 173mg, and 231mg, respectively, of viloxazine hydrochloride salt.

The inactive ingredients are: Ammonium hydroxide, black iron oxide, butyl alcohol, corn starch, ethylcellulose, FD&C Blue #1, FD&C Red #28, FD&C Yellow #5, FD&C Yellow #6, FD&C Yellow #10, gelatin, hypromellose, isopropyl alcohol, lactose monohydrate, medium chain triglycerides, oleic acid, polyethylene glycol, potassium hydroxide, propylene glycol, shellac, strong ammonia solution, sucrose, talc, triacetin, titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of viloxazine in the treatment of ADHD is unclear; however, it is thought to be through inhibiting the reuptake of norepinephrine.

12.2 Pharmacodynamics

Viloxazine binds to the norepinephrine transporter (NET, $K_i = 0.63 \mu\text{M}$) and inhibits the reuptake of norepinephrine ($\text{IC}_{50} = 0.2 \mu\text{M}$).

Cardiac Electrophysiology

At a dose 4.5 times the maximum recommended dose, Qelbree did not prolong the QT interval to any clinically relevant extent. There was no effect of Qelbree on the PR interval or QRS duration in healthy volunteers. However, nonclinical studies suggest the potential for Qelbree to inhibit cardiac sodium channels.

12.3 Pharmacokinetics

Viloxazine C_{max} and AUC increase proportionally over a dosage range from 100 mg to 400 mg once daily. Steady-state was reached after two days of once-daily administration, and no accumulation was observed.

Absorption

The relative bioavailability of viloxazine extended-release relative to an immediate-release formulation was about 88%. The median (range) time to peak plasma concentration of viloxazine (T_{max}) was approximately 5 hours, with a range of 3 to 9 hours, following a single 200 mg dose.

Effect of Food

Administration of 200 mg viloxazine extended-release with a high-fat meal (800 to 1000 calories) decreased viloxazine C_{max} and AUC by about 9% and 8%, respectively. Viloxazine T_{max} increased by about 2 hours after administration with a high-fat meal. Sprinkling the contents of a capsule on applesauce decreased viloxazine C_{max} and AUC by about 10% and 5%, respectively.

Distribution

Viloxazine is 76-82% bound to human plasma proteins over the blood concentration range of 0.5 mcg/mL to 10 mcg/mL.

Elimination

The mean (\pm SD) half-life of viloxazine was $7.02 \pm (4.74)$ hours).

Metabolism

Viloxazine is primarily metabolized by CYP2D6, UGT1A9, and UGT2B15. The major metabolite detected in plasma is 5-hydroxy-viloxazine glucuronide.

Excretion

Renal excretion is the primary route of excretion of viloxazine. After administration of radiolabeled viloxazine, 90% of the dose was recovered in urine within the first 24 hours post-dose. Less than 1% of the dose is excreted in the feces.

Specific Populations

Geriatric Patients

No studies were conducted to evaluate pharmacokinetics in the geriatric population.

Pediatric Patients

The estimated steady-state C_{max} and AUC_{0-t} of viloxazine and its major metabolite, at doses ranging from 100 mg to 400 mg, were approximately 40-50% higher in pediatric patients 6 to 11 years of age than in pediatric patients 12 to 17 years of age.

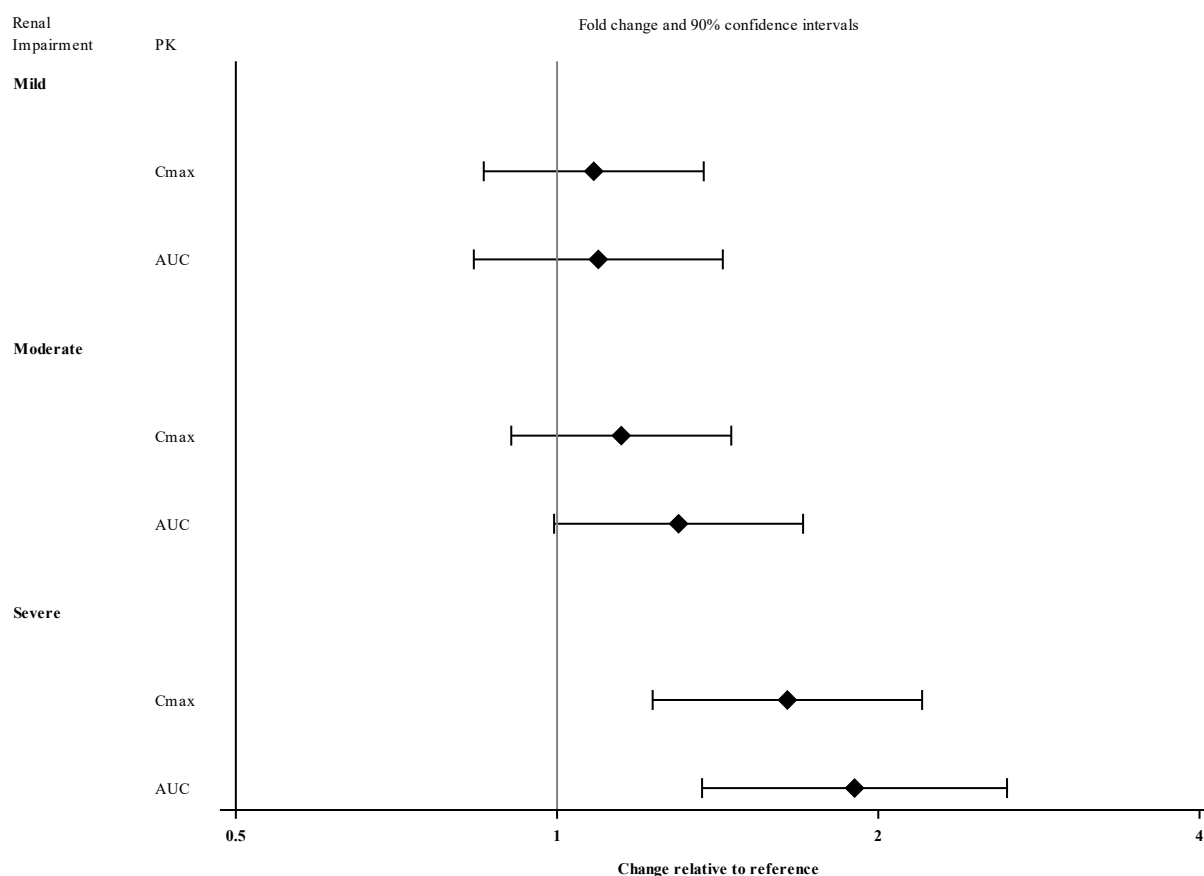
Male or Female Patients and Racial or Ethnic Groups

No clinically significant differences in the pharmacokinetics of viloxazine was observed based on race and sex.

Patients with Renal Impairment

Exposures of viloxazine in patients with renal impairment are summarized in Figure 1 [see *Dosage and Administration (2.4) and Use in Specific Populations (8.6)*]

Figure 1: Effect of Renal Impairment on Viloxazine Pharmacokinetics



Patients with Hepatic Impairment

The pharmacokinetics of viloxazine have not been evaluated in hepatic impairment [see *Use in Specific Populations (8.7)*].

CYP2D6 Metabolism

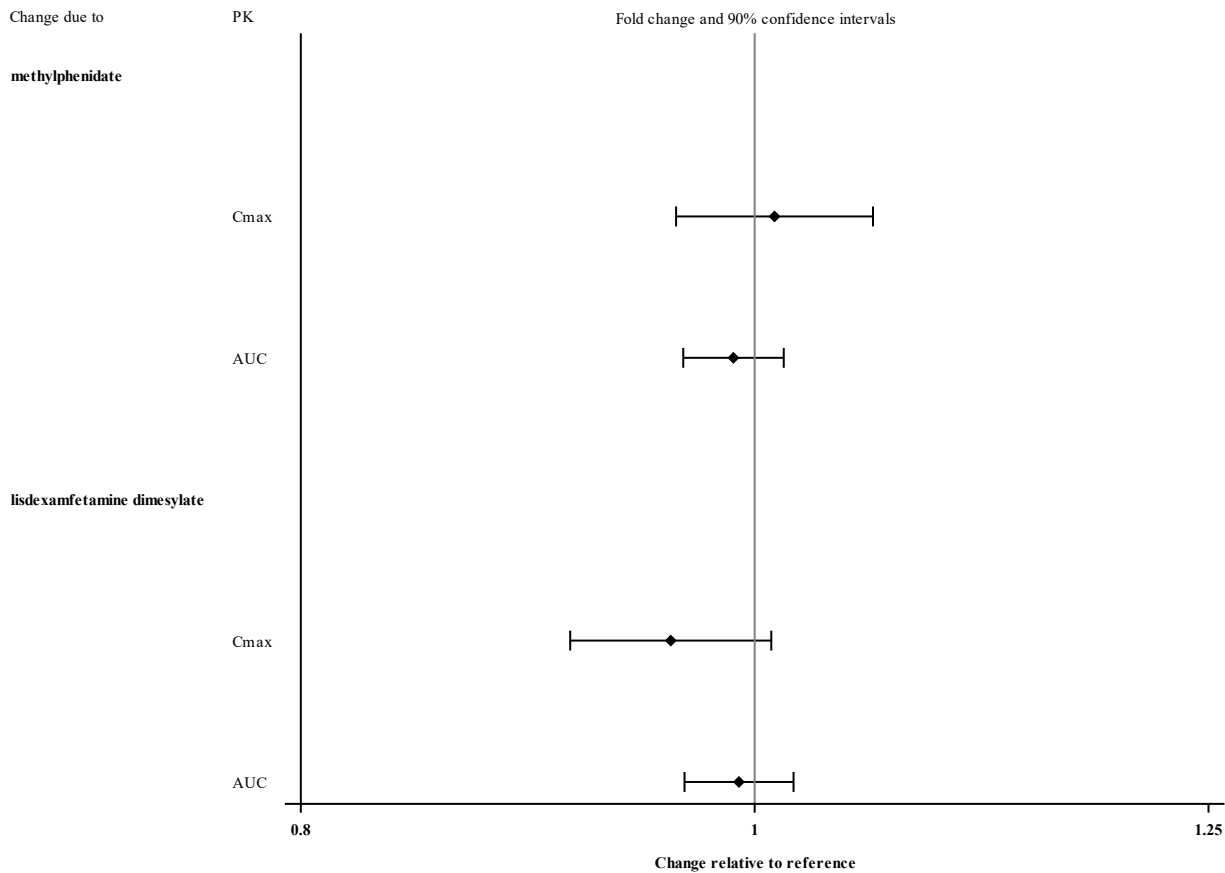
A multiple-dose study was conducted with Qelbree 900 mg once-daily in healthy volunteers to compare the effect of CYP2D6 poor metabolizers (PMs) and extensive metabolizers (EMs) on the PK of viloxazine. At steady state, viloxazine geometric means for C_{max} and AUC_{0-24} were 21% and 26%, respectively, higher in CYP2D6 PMs compared to EMs.

Drug Interaction Studies

Alcohol: There was no significant effect on viloxazine C_{max} and AUC when 200 mg viloxazine ER was administered with orange juice containing 4% and 20% alcohol. However, when administered with orange juice containing 40% alcohol, C_{max} and AUC of viloxazine decreased by about 32% and 19%, respectively.

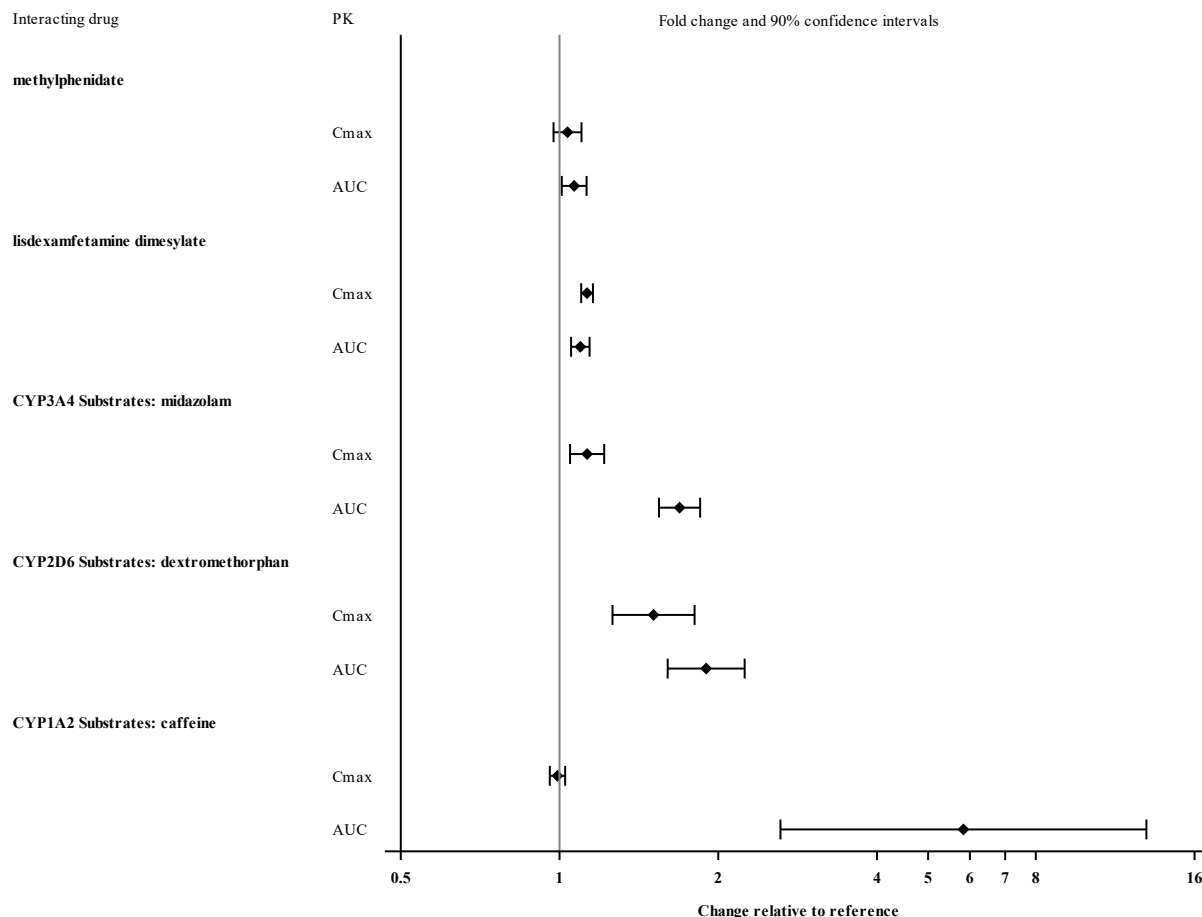
The effect of other drugs on the pharmacokinetics of viloxazine is presented in [Figure 2](#).

Figure 2: Effects of Other Drugs on Viloxazine Pharmacokinetics



The effect of viloxazine on the pharmacokinetics of other drugs is presented in [Figure 3](#) [see *Drug Interactions (7.1)*].

Figure 3: Effect of Viloxazine on the Pharmacokinetics of Other Drugs



In Vitro Studies

Based on *in vitro* data, drugs that inhibit CYP isozymes 1A1, 1A2, 2B6, 2D6, 2C8, 2C9, 2C19, and 2E1 are not expected to have significant impact on the pharmacokinetic profile of viloxazine.

Viloxazine does not inhibit CYP2C8, 2C9 or 2C19 activities. Viloxazine is a reversible inhibitor of P450-1A2, 2B6, 2D6 and 3A4/5. Viloxazine is a potential inducer of CYP1A2 and CYP2B6.

Viloxazine is not a inhibitor of P-gp, BCRP, MATE2-K, OATP1B1*1a, and OATP1B3 transporters. Viloxazine appears to be a weak inhibitor of the MATE1. Viloxazine is not a substrate of either OATP1B1*1a or OATP1B3 transporters.

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis

Viloxazine did not increase the incidence of tumors in rats treated for 2 years at oral doses of 22, 43, and 87 mg/kg/day. The high dose of 87 mg/kg/day is approximately equal to the MRHD of 400 mg, based on mg/m² in children.

Viloxazine did not increase the incidence of tumors in Tg.rasH2 mice treated for 26 weeks at oral doses of 4.3, 13, and 43 mg/kg/day.

Mutagenesis

Viloxazine was not genotoxic in a battery of genotoxicity tests. It was not mutagenic in the *in vitro* bacterial reverse mutation (Ames) assay or clastogenic in the *in vitro* mammalian chromosomal aberration assay or in the *in vivo* rat bone marrow micronucleus assay.

Impairment of Fertility

Viloxazine was orally administered to male and female rats prior to and throughout mating and continued until completion of the second littering at doses of 13, 33, and 82 mg/kg/day, which are less than, equal to, and 2 times the MRHD of 400 mg, based on mg/m², respectively. Viloxazine did not affect male or female fertility parameters in the rat. The NOAEL for male and female fertility is 82 mg/kg/day, which is approximately 2 times the MRHD, based on mg/m².

13.2 Animal Toxicology and/or Pharmacology

In animal studies, viloxazine treatment caused dose-dependent convulsions at oral doses of ≥ 130 , ≥ 173 , and ≥ 39 mg/kg/day in the rat, mouse, and dog, respectively, which are approximately equal to or slightly higher than the MRHD of 400 mg, based on mg/m² in children.

14 CLINICAL STUDIES

The efficacy of Qelbree in the treatment of ADHD in pediatric patients 6 to 17 years of age was evaluated in three short-term, randomized, placebo-controlled monotherapy trials (Studies 1, 2, and 3).

Study 1 (NCT03247530) was a multicenter, randomized, double-blind, three-arm placebo-controlled, parallel group monotherapy trial in patients 6 to 11 years of age with ADHD. Total duration of treatment was 6 weeks, including a 1-week titration period (starting at 100 mg once daily) and 5-week maintenance phase. Patients were randomized to receive 100 mg, 200 mg, or placebo, given once daily as a single dose. The primary endpoint was the change from baseline to the end of study on the total score on the ADHD Rating Scale (ADHD-RS-5), an 18-question scale that assesses hyperactivity, impulsivity, and inattentive symptoms. Higher ADHD-RS-5 scores reflect more severe symptoms. The Clinical Global Impression-Improvement (CGI-I) score at the end of the study was a secondary endpoint.

A total of 477 patients were randomized in Study 1; 399 completed the study, and 78 discontinued. The change from baseline (reduction) in ADHD-RS-5 total score was statistically significantly greater in patients treated with Qelbree 100 mg or with Qelbree 200 mg than in patients on placebo (see [Table 3](#)). Compared with patients on placebo, a statistically significantly greater reduction (improvement) in CGI-I score at the end of the study was observed both in patients treated with Qelbree 100 mg and in patients treated with Qelbree 200 mg.

Study 2 (NCT03247543) was a multicenter, randomized, double-blind, three-arm, placebo-controlled, parallel-group monotherapy trial in patients 6 to 11 years of age with ADHD. Total duration of treatment was 8 weeks, including a 3-week titration period (starting at 100 mg once daily), and a 5-week maintenance phase. Patients were randomized to receive Qelbree 200 mg, Qelbree 400 mg, or placebo, given once daily as a single dose. The primary endpoint was the change from baseline to the end of study on the total score on the ADHD Rating Scale (ADHD-RS-5). The Clinical Global Impression-Improvement (CGI-I) score at the end of the study was a secondary endpoint.

A total of 313 patients were randomized in Study 2; 251 completed the study, and 62 discontinued. The change from baseline (reduction) in ADHD-RS-5 total score was statistically significantly greater in patients treated with Qelbree 200 mg or with Qelbree 400 mg than in patients on placebo (see [Table 3](#)). Compared with patients on placebo, a statistically significantly greater reduction (improvement) in CGI-I score at the end of the study was observed both in patients treated with Qelbree 200 mg and in patients treated with Qelbree 400 mg.

Study 3 (NCT03247517) was a multicenter, randomized, double-blind, three-arm, placebo-controlled, parallel-group monotherapy trial in patients 12 to 17 years of age with ADHD. Total duration of treatment was 6 weeks, including 1-week titration period (starting at 200mg once daily) and a 5-week maintenance phase. Patients were randomized to receive Qelbree 200 mg, Qelbree 400 mg, or placebo, given once daily as a single dose. The primary endpoint was the change from baseline to the end of study on the total score on the ADHD Rating Scale (ADHD-RS-5). The Clinical Global Impression-Improvement (CGI-I) score at the end of the study was a secondary endpoint.

A total of 310 patients were randomized in Study 3; 266 completed and 44 discontinued. The change from baseline (reduction) in ADHD-RS-5 total score was statistically significantly greater in patients treated with Qelbree 200 mg or with Qelbree 400 mg than in patients on placebo (see Table 3). Compared with patients on placebo, a statistically significantly greater reduction (improvement) in CGI-I score at the end of the study was observed both in patients treated with Qelbree 200 mg and in patients treated with Qelbree 400 mg.

Table 3. Primary Efficacy Results for Change from Baseline in ADHD-RS-5 Total Score in Pediatric Patients (6 to 17 years) with ADHD (Studies 1, 2, 3)

Study Number (Age range)	Treatment Group	Primary Efficacy Measure: ADHD-RS-5 Total Score			
		n	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference ^a (95% CI)
Study 1 (6 to 11 years)	100 mg/day*	147	45.0 (6.53)	-16.6 (1.16)	-5.8 (-8.9, -2.6)
	200 mg/day*	158	44.0 (6.80)	-17.7 (1.12)	-6.9 (-10.0, -3.8)
	Placebo	155	43.6 (7.05)	-10.9 (1.14)	--
Study 2 (6 to 11 years)	200 mg/day*	107	43.8 (6.54)	-17.6 (1.43)	-6.0 (-10.0, -1.9)
	400 mg/day*	97	45.0 (6.55)	-17.5 (1.52)	-5.8 (-9.9, -1.7)
	Placebo	97	43.5 (6.79)	-11.7 (1.48)	--
Study 3 (12 to 17 years)	200 mg/day*	94	39.9 (7.22)	-16.0 (1.45)	-4.5 (-8.4, -0.6)
	400 mg/day*	103	39.4 (7.59)	-16.5 (1.38)	-5.1 (-8.9, -1.3)
	Placebo	104	40.5 (6.79)	-11.4 (1.37)	--

ADHD-RS-5 = Attention-Deficit/Hyperactivity Disorder Rating Scale 5th Edition; n: sample size; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval, not adjusted for multiple comparisons

^a Difference (drug minus placebo) in least-squares mean change from baseline

* Doses that are statistically significantly superior to placebo after multiplicity adjustment

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Qelbree (viloxazine extended-release capsules) are available in the following strengths and colors:

100mg (yellow capsule printed with “SPN” on capsule cap and “100” on capsule body with edible black ink).

Bottles of 100 capsules.....NDC 17772-131-01

Bottles of 90 capsules.....NDC 17772-131-90

Bottles of 60 capsules.....NDC 17772-131-60

Bottles of 30 capsules.....NDC 17772-131-30

150mg (lavender capsule printed with “SPN” on capsule cap and “150” on capsule body with edible black ink).

Bottles of 100 capsules.....NDC 17772-132-01

Bottles of 90 capsules.....NDC 17772-132-90

Bottles of 60 capsules.....NDC 17772-132-60

Bottles of 30 capsules.....NDC 17772-132-30

200mg (light green capsule printed with “SPN” on capsule cap and “200” on capsule body with edible black ink).

Bottles of 100 capsules.....NDC 17772-133-01

Bottles of 90 capsules.....NDC 17772-133-90

Bottles of 60 capsules.....NDC 17772-133-60

Bottles of 30 capsules.....NDC 17772-133-30

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Suicidal Thoughts and Behaviors

Advise patients and caregivers to monitor for the emergence of suicidal thoughts or behaviors or symptoms that might be precursors to emerging suicidal ideation or behavior, especially early during treatment and when the dosage is adjusted up or down. Instruct patients and caregivers to report such symptoms to the healthcare provider [*see Boxed Warning and Warnings and Precautions (5.1)*].

Concomitant Use with Monoamine Oxidase Inhibitors (MAOI)

Caution patients about the concomitant use of Qelbree and monoamine oxidase inhibitors (MAOI), or within 14 days after discontinuing an MAOI, because of an increased risk of hypertensive crisis [*see Contraindications (4) and Drug Interactions (7.1)*].

Blood Pressure and Heart Rate Increases

Instruct patients that Qelbree can cause elevations of their blood pressure and pulse rate and they should be monitored for such effects [*see Warnings and Precautions (5.2)*].

Activation of Mania/Hypomania

Advise patients and their caregivers to look for signs of activation of mania/hypomania [*see Warnings and Precautions (5.3)*].

Somnolence and Fatigue

Advise patients about the potential for somnolence (including sedation and lethargy) and fatigue. Advise patients to use caution when performing activities requiring mental alertness, such as driving a motor vehicle or operating hazardous machinery, until they know how they will be affected by Qelbree [*see Warnings and Precautions (5.4)*].

Effects on Weight

Advise patients and their caregivers that Qelbree may affect weight and that weight should be monitored while using Qelbree [*see Adverse Reactions (6.1)*].

Pregnancy

Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to Qelbree during pregnancy. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy to discuss if Qelbree should be discontinued [*see Use in Specific Populations (8.1)*].

Administration Instructions

Advise patients to take the capsule whole or sprinkled on a teaspoonful of applesauce and consume within 2 hours. Do not cut, chew or crush the capsule [*see Dosage and Administration (2.3)*].

Qelbree is manufactured by: Catalent Pharma Solutions, LLC, 1100 Enterprise Drive Winchester, KY 40391.

Distributed by: Supernus Pharmaceuticals, Inc. Rockville, MD 20850 USA

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