

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 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.

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 (See Above)

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. 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.

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.

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 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.

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 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.

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. Data represents pooled data from pediatric patients ages 6 to 17 years who were enrolled in randomized, placebo-controlled trials of Qelbree.

Adverse Reactions Reported in $\geq 2\%$ of Pediatric Patients (Ages 6 to 17 Years) Treated with Qelbree and at a Greater Rate than Placebo-Treated Patients in Placebo-Controlled ADHD Studies Placebo (N=463); All Qelbree (N=826). **Nervous system disorders:** Somnolence*; Headache*. **Metabolic and nutritional disorders:** Decreased appetite. **Infections and infestations:** Upper respiratory tract infection*. **Body as a Whole - General disorders:** Fatigue; Pyrexia. **Gastrointestinal system disorders:** Abdominal Pain*; Nausea; Vomiting. **Psychiatric disorders:** Insomnia*; Irritability.

*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.

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.
- Examples: Selegiline, isocarboxazid, phenelzine, tranylcypromine, safinamide, rasagiline

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 viloxazine is contraindicated.
- Examples: Alosetron, duloxetine, ramelteon, tasimelteon, tizanidine, theophylline

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, which may increase the risk of adverse reactions associated with these CYP1A2 substrates.

- Intervention: Not recommended for coadministration with viloxazine. Dose reduction may be warranted if coadministered.

Drugs Having Clinically Important Interactions with Qelbree (continued)

Moderate Sensitive CYP1A2 Substrate (continued)

- Examples: Clozapine, piperfenidone

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.
- Examples: Atomoxetine, desipramine, dextromethorphan, nortriptyline, metoprolol, nebivolol, perphenazine, tolterodine, venlafaxine, and risperidone

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.
- Examples: Alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibuprofen, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil, and lurasidone

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

Report pregnancies to the National Pregnancy Registry for Psychiatric Medications at 1-866-961-2388, and at the website (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 \geq 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).

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 (craniochischisis, 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.

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.

Pediatric Use

The safety and effectiveness of Qelbree in pediatric patients ages 6 to 17 years of age with ADHD have been established based on randomized, placebo-controlled studies in pediatric patients.

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, and for changes in weight.

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.

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/1.73m² [MDRD]) renal impairment.

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.

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of viloxazine is unknown. Qelbree is not recommended in patients with hepatic 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 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).

NON-CLINICAL TOXICOLOGY

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.

Animal Toxicology and/or Pharmacology

In animal studies, viloxazine treatment caused dose-dependent convulsions at oral doses of \geq 130, \geq 173, and \geq 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.



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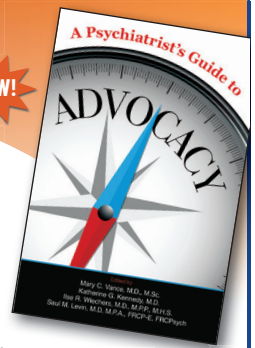
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Kenneth S. Kendler, M.D. [EDITORIAL](#)

The views our forebears in psychiatry had on inherited transmission of mental illness, based largely on clinical observation and family histories, can usefully complement our views today on key issues in the field.

509 Neuroimaging Biomarkers in Schizophrenia

Nina V. Kraguljac, M.D., et al.

This important review of data on the biology of mental illnesses focuses on research in schizophrenia, evaluating evidence concerning a range of clinically useful biomarkers. Overall, the data suggest that clinically useful biomarkers have yet to emerge for schizophrenia. Nevertheless, these data provide clues from where such markers may emerge.

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ARTICLES

522 Elevated C-Reactive Protein in Patients With Depression, Independent of Genetic, Health, and Psychosocial Factors: Results From the UK Biobank

Maria C. Pitharouli, M.Sc., et al. [EDITORIAL](#)

Increased inflammation in depression is only partially explained by clinical and sociodemographic factors. The polygenic risk score for major depression is positively associated with C-reactive protein levels, but the association loses significance after adjusting for body mass index and smoking status.

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530 Functional Connectome Prediction of Anxiety Related to the COVID-19 Pandemic

Li He, M.Sc., et al. EDITORIAL • CME • VIDEO

Evidence from resting-state fMRI shows that the pre-pandemic functional connectome predicted individuals' anxiety level during the COVID-19 pandemic, with this identified "anxiety connectome" discriminating generalized anxiety disorder from depressive disorder and schizophrenia.

541 Mood Disorders and Outcomes of COVID-19 Hospitalizations

Victor M. Castro, M.S., et al.

A study of nearly 3,000 individuals hospitalized for COVID-19 infection found robust effects of mood disorder diagnosis on outcomes, including mortality and need for rehabilitation post-hospitalization.

548 The World Health Organization Risk Drinking Levels Measure of Alcohol Consumption: Prevalence and Health Correlates in Nationally Representative Surveys of U.S. Adults, 2001–2002 and 2012–2013

Dvora Shmulewitz, Ph.D., et al.

Two sets of nationally representative U.S. survey data show that problematic drinking levels have risen over time and that the World Health Organization's "risk drinking levels" may be useful in establishing drinking reduction treatment goals, as opposed to abstinence, which could engage more people in treatment.

560 Subjective Responses to Alcohol in the Development and Maintenance of Alcohol Use Disorder

Andrea King, Ph.D., et al. EDITORIAL • CME • VIDEO

Drinkers who are sensitive to alcohol's pleasurable effects are at heightened risk to develop alcohol use disorder 10 years later. These stimulating and rewarding effects increase as the addiction gets more severe. Long-held views that alcohol's pleasurable effects diminish among those who develop addictions are not substantiated.

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572 Comment on "Understanding the Clinical Effects and Mechanisms of Action of Neurosteroids"

David R. Rubinow, M.D., et al.

573 Comment on "Understanding the Clinical Effects and Mechanisms of Action of Neurosteroids": Response to Rubinow et al.

Robert A. Kleinman, M.D., Alan F. Schatzberg, M.D.

Cover: In an issue devoted to COVID-19 and stress-related disorders, He et al. (p. 530) report promising neuromarkers for early identification of individuals who are at risk for high anxiety induced by major stressful events such as COVID-19. Image taken from the authors' figure depicting how the functional connectome was used to predict an individual's anxiety score. (Image courtesy Li He et al.)

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Improving Suicide Prevention Through Evidence-Based Strategies: A Systematic Review

Suicide is the tenth leading cause of death in the United States, and the age-adjusted annual suicide rate has steadily risen 36.7% over two decades. A systematic review designed to identify promising suicide prevention strategies scalable to state and national levels suggests that the training of general practitioners might hold particular promise.

Association Between Benzodiazepine or Z-Drug Prescriptions and Drug-Related Poisonings Among Patients Receiving Buprenorphine Maintenance

A review of prescription claims and nonfatal drug-related poisoning data found that patients prescribed buprenorphine have double the odds of drug-related poisoning when co-prescribed benzodiazepines. Short-acting and high-dose benzodiazepines conferred additional risk, while buprenorphine remained protective against overdose.

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See the table below for the articles in this month's issue that are the subject of a CME quiz.

AJP Multimedia *Access audio and video for highlights of each issue*

In **AJP Audio** each month, Executive Editor Michael Roy speaks with the author(s) of an article about the results of their research. In addition, Deputy Editor Daniel S. Pine, M.D., summarizes one or two articles in an **Issue Highlights** video. The table below lists the articles included in this month's audio podcast and video.

In this issue	CME	Podcast	Video
Autoimmune Encephalitis Presenting With Malignant Catatonia in a 40-Year-Old Male Patient With COVID-19 (p. 485)	✓		
Functional Connectome Prediction of Anxiety Related to the COVID-19 Pandemic (p. 530)	✓		✓
Subjective Responses to Alcohol in the Development and Maintenance of Alcohol Use Disorder (p. 560)	✓		✓

History of Psychiatry *Revisit the field's rich history through the AJP Archive*

50 years ago this month: A New Day of Hope for Alcoholics

Morris E. Chafetz, M.D., Acting Director of the at-the-time newly established National Institute on Alcohol Abuse and Alcoholism, introduces a special section on alcoholism that also features the Michigan Alcoholism Screening Test, a diagnostic instrument still in use today.

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