

ATTENTION DISPENSER: ACCOMPANYING MEDICATION GUIDE MUST BE DISPENSED WITH THIS PRODUCT.

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CITALOPRAM Oral Solution USP, 10 mg/5 mL

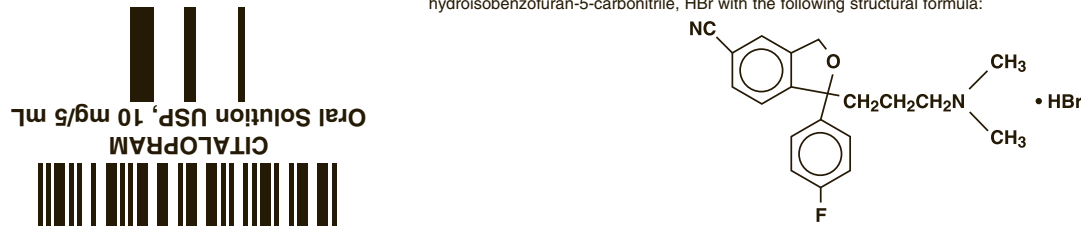
R_x only

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Citalopram Oral Solution USP or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Citalopram is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: information for use in pediatric patients.)

DESCRIPTION

Citalopram Oral Solution USP is an orally administered selective serotonin reuptake inhibitor (SSRI) with a chemical structure unrelated to that of other SSRIs or of tricyclic, tetracyclic, or other available antidepressant agents. Citalopram hydrobromide is a racemic bicyclic phthalane derivative designated (+)-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile. HBr with the following structural formula:



The molecular formula is C₂₀H₂₂BrFN₂O and its molecular weight is 405.35. Citalopram hydrobromide occurs as a fine, white to off-white powder. Citalopram hydrobromide is sparingly soluble in water and soluble in ethanol.

Citalopram is available as an oral solution. Citalopram Oral Solution USP contains citalopram hydrobromide USP equivalent to 2 mg/mL citalopram base. It also contains the following inactive ingredients: methylparaben, peppermint stick, propylene glycol, propylparaben, purified water, and sorbitol solution.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of citalopram as an antidepressant is presumed to be linked to potentiation of serotonergic activity in the central nervous system (CNS) resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT). *In vitro* and *in vivo* studies in animals suggest that citalopram is a highly selective serotonin reuptake inhibitor (SSRI) with minimal effects on norepinephrine (NE) and dopamine (DA) neuronal reuptake. Tolerance to the inhibition of 5-HT uptake is not induced by long-term (14-day) treatment of rats with citalopram. Citalopram is a racemic mixture (50/50), and the inhibition of 5-HT reuptake by citalopram is primarily due to the (S)-enantiomer. Citalopram has no or very low affinity for 5-HT_{1A}, 5-HT_{2A}, dopamine D₁ and D₂, α₁-, α₂-, and β-adrenergic, histamine H₁, gamma aminobutyric acid (GABA), muscarinic cholinergic, and benzodiazepine receptors. Antagonism of muscarinic, histaminergic, and adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects of other psychotropic drugs.

Pharmacokinetics

The single- and multiple-dose pharmacokinetics of citalopram are linear and dose-proportional in a dose range of 10 to 60 mg/day. Biotransformation of citalopram is mainly hepatic, with a mean terminal half-life of about 35 hours. With once daily dosing, steady state plasma concentrations are achieved within approximately one week. At steady state, the extent of accumulation of citalopram in plasma, based on the half-life, is expected to be 2.5 times the plasma concentrations observed after a single dose. The tablet and oral solution dosage forms of citalopram are bioequivalent.

Absorption and Distribution: Following a single oral dose of citalopram, peak blood levels occur at about 4 hours. The absolute bioavailability of citalopram was about 80% relative to an intravenous dose, and absorption is not affected by food. The volume of distribution of citalopram is about 12 L/kg and the binding of citalopram (CT), demethylcitalopram (DCT) and didemethylcitalopram (DDCT) to human plasma proteins is about 80%.

Metabolism and Elimination: Following intravenous administrations of citalopram, the fraction of drug recovered in the urine as citalopram and DCT was about 10% and 65%, respectively. The systemic clearance of citalopram was 330 mL/min, with approximately 20% of that due to renal clearance.

Citalopram is metabolized to demethylcitalopram (DCT), didemethylcitalopram (DDCT), citalopram-N-oxide, and a deaminated propionic acid derivative. In humans, unchanged citalopram is the predominant compound in plasma. At steady state, the concentrations of citalopram's metabolites, DCT and DDCT, in plasma are approximately one-half and one-tenth, respectively, that of the parent drug. *In vitro* studies show that citalopram is at least 8 times more potent than its metabolites in the inhibition of serotonin reuptake, suggesting that the metabolites evaluated do not likely contribute significantly to the antidepressant actions of citalopram.

In vitro studies using human liver microsomes indicated that CYP3A4 and CYP2C19 are the primary isozymes involved in the N-demethylation of citalopram.

Population Subgroups: Age: Citalopram pharmacokinetics in subjects >60 years of age were compared to younger subjects in two normal volunteer studies. In a single-dose study, citalopram AUC and half-life were increased in the subjects > 60 years old by 30% and 50%, respectively, whereas in a multiple-dose study they were increased by 29% and 30%, respectively. 20 mg/day is the maximum recommended dose for patients who are greater than 60 years of age (see WARNINGS and DOSAGE AND ADMINISTRATION), due to the risk of QT prolongation.

Gender: In three pharmacokinetic studies (total N=32), citalopram AUC in women was one and a half to two times that in men. This difference was not observed in five other pharmacokinetic studies (total N=114). In clinical studies, no differences in steady state serum citalopram levels were seen between men (N=237) and women (N=388). There were no gender differences in the pharmacokinetics of DCT and DDCT. No adjustment of dosage on the basis of gender is recommended.

Reduced hepatic function: Citalopram oral clearance was reduced by 37% and half-life was doubled in patients with reduced hepatic function compared to normal subjects. 20 mg/day is the maximum recommended dose for hepatically impaired patients (see WARNINGS and DOSAGE AND ADMINISTRATION), due to the risk of QT prolongation.

CYP2C19 poor metabolizers: In CYP2C19 poor metabolizers, citalopram steady state C_{max} and AUC was increased by 68% and 107%, respectively. Citalopram 20 mg/day is the maximum recommended dose in CYP2C19 poor metabolizers due to the risk of QT prolongation (see WARNINGS and DOSAGE AND ADMINISTRATION).

CYP2D6 poor metabolizers: Citalopram steady state levels were not significantly different in poor metabolizers and extensive metabolizers of CYP2D6.

Reduced renal function: In patients with mild to moderate renal function impairment, oral clearance of citalopram was reduced by 17% compared to normal subjects. No adjustment of dosage for such patients is recommended. No information is available about the pharmacokinetics of citalopram in patients with severely reduced renal function (creatinine clearance <20 mL/min).

Drug-Drug Interactions: *In vitro* enzyme inhibition data did not reveal an inhibitory effect of citalopram on CYP3A4, -2C9, or -2E1, but did suggest that it is a weak inhibitor of CYP1A2, -2D6, and -2C19. Citalopram would be expected to have little inhibitory effect on *in vivo* metabolism mediated by these enzymes. However, *in vivo* data to address this question are limited.

CYP3A4 and CYP2C19 inhibitors: Since CYP3A4 and CYP2C19 are the primary enzymes involved in the metabolism of citalopram, it is expected that potent inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, and macrolide antibiotics) and potent inhibitors of CYP2C19 (e.g., omeprazole) might decrease the clearance of citalopram. However, coadministration of citalopram and the potent CYP3A4 inhibitor ketoconazole did not significantly affect the pharmacokinetics of citalopram. Citalopram 20 mg/day is the maximum recommended dose in patients taking concomitant cimetidine or another CYP2C19 inhibitor, because of the risk of QT prolongation (see WARNINGS and DOSAGE AND ADMINISTRATION).

CYP2D6 Inhibitors: Coadministration of a drug that inhibits CYP2D6 with citalopram is unlikely to have clinically significant effects on citalopram metabolism, based on the study results in CYP2D6 poor metabolizers.

Clinical Efficacy Trials

The efficacy of citalopram as a treatment for depression was established in two placebo-controlled studies (of 4 to 6 weeks in duration) in adult outpatients (ages 18 to 66) meeting DSM-III or DSM-III-R criteria for major depression. Study 1, a 6-week trial in which patients received fixed citalopram doses of 10, 20, 40, and 60 mg/day, showed that citalopram at doses of 40 and 60 mg/day was effective as measured by the Hamilton Depression Rating Scale (HAM-D) total score, the HAM-D depressed mood item (Item 1), the Montgomery Asberg Depression Rating Scale, and the Clinical Global Impression (CGI) Severity scale. This study showed no clear effect of the 10 and 20 mg/day doses, and the 60 mg/day dose was not more effective than the 40 mg/day dose. In study 2, a 4-week, placebo-controlled trial in depressed patients, of whom 85% met criteria for melancholia, the initial dose was 20 mg/day, followed by titration to the maximum tolerated dose or a maximum dose of 60 mg/day. Patients treated with citalopram showed significantly greater improvement than placebo patients on the HAM-D total score, HAM-D item 1, and the CGI Severity score. In three additional placebo-controlled depression trials, the difference in response to treatment between patients receiving citalopram and patients receiving placebo was not statistically significant, possibly due to high spontaneous response rate, smaller sample size, or, in the case of one study, too low a dose.

In two long-term studies, depressed patients who had responded to citalopram during an initial 6 or 8 weeks of acute treatment (fixed doses of 20 or 40 mg/day in the study and flexible doses of 20 to 60 mg/day in the second study) were randomized to continue citalopram or placebo. In both studies, patients receiving continued citalopram treatment experienced significantly lower relapse rates over the subsequent 6 months compared to those receiving placebo. In the fixed-dose study, the decreased rate of depression relapse was similar in patients receiving 20 or 40 mg/day of citalopram.

Analyses of the relationship between treatment outcome and age, gender, and race did not suggest any differential responsiveness on the basis of these patient characteristics.

Comparison of Clinical Trial Results: Highly variable results have not been seen in the clinical development of all antidepressants in clinical trials. The maximum dose should be exposed in the same controlled study. The maximum dose should be limited to 20 mg/day in patients with hepatic impairment and in patients who are greater than 60 years of age because of expected higher exposures. Electrolyte and/or ECG monitoring is recommended in certain circumstances. Patients being considered for citalopram treatment who are at risk for significant electrolyte disturbances should have baseline serum potassium and magnesium measurements with periodic monitoring. Hypokalemia (and/or hypomagnesemia) may increase the risk of QTc prolongation and arrhythmia, and should be corrected prior to initiation of treatment and periodically monitored. ECG monitoring is recommended in patients for whom citalopram use is not recommended (see above), but nevertheless, considered to be essential. The following patients should be monitored for cardiac conditions noted above, and those taking other drugs that may prolong the QTc interval.

INDICATIONS AND USAGE

Citalopram Oral Solution USP is indicated for the treatment of depression. The efficacy of Citalopram Oral Solution USP in the treatment of depression was established in 4 to 6 week, controlled trials of outpatients whose diagnosis corresponded most closely to the DSM-III and DSM-III-R category of major depressive disorder.

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation. The antidepressant action of Citalopram Oral Solution USP in these patients should be noted that citalopram is not approved for use in treating bipolar depression.

The efficacy of Citalopram Oral Solution USP in maintaining an antidepressant response for up to 24 weeks following 6 to 8 weeks of acute treatment was demonstrated in two placebo-controlled trials (see CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use Citalopram Oral Solution USP for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

The use of MAOIs intended to treat psychiatric disorders with citalopram or within 14 days of stopping treatment with citalopram is contraindicated because of an increased risk of serotonin syndrome. The use of citalopram within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated (see WARNINGS and DOSAGE AND ADMINISTRATION).

Citalopram in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome (see WARNINGS and DOSAGE AND ADMINISTRATION). Concomitant use in patients taking pimozide is contraindicated (see PRECAUTIONS).

Citalopram is contraindicated in patients with a hypersensitivity to citalopram or any of the inactive ingredients in Citalopram Oral Solution USP.

WARNINGS

WARNINGS-Clinical Worsening and Suicide Risk
Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal thoughts and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analysis of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 256 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18 to 24	5 additional cases
	Decreases Compared to Placebo
25 to 64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive or other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION: Discontinuation of Treatment with Citalopram, for a description of the risks of discontinuation of citalopram).

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Citalopram should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

QT-Prolongation and Torsade de Pointes
Citalopram causes dose-dependent QTc prolongation, an ECG abnormality that has been associated with Torsade de Pointes (TdP), ventricular tachycardia, and sudden death, all of which have been observed in postmarketing reports for citalopram.

Individual corrected QTc (QTcNI) interval was evaluated in a randomized, placebo and active (moxifloxacin 400 mg) controlled cross-over, escalating multiple-dose study in 119 healthy subjects. The maximum mean (upper bound of the 95% one-sided confidence interval) difference from placebo were 8.5 (10.8) and 18.5 (21) msec or 20 mg and 60 mg citalopram, respectively. Based on the established exposure-response relationship, the predicted QTcNI change from placebo (upper bound of the 95% one-sided confidence interval) under the C_{max} for the dose of 40 mg is 12.6 (14.3) msec.

Because of the risk of QTc prolongation at higher citalopram doses, it is recommended that citalopram should not be given at doses above 40 mg/day.

It is recommended that citalopram should not be used in patients with congenital long QT syndrome, bradycardia, hypokalemia or hypomagnesemia, recent acute myocardial infarction, or uncompensated heart failure. Citalopram should also not be used in patients who are taking other drugs that prolong the QTc interval, such as Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine, antipsychotics (e.g., galofaxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval (e.g., pentamidine, levomethadyl acetate, methadone).

The citalopram dose should be limited in certain populations. The maximum dose should be limited to 20 mg/day in patients who are CYP2C19 poor metabolizers or those patients who may be taking concomitant cimetidine or another CYP2C19 inhibitor, since higher citalopram exposures would be expected. The maximum dose should also be limited to 20 mg/day in patients with hepatic impairment and in patients who are greater than 60 years of age because of expected higher exposures.

Electrolyte and/or ECG monitoring is recommended in certain circumstances. Patients being considered for citalopram treatment who are at risk for significant electrolyte disturbances should have baseline serum potassium and magnesium measurements with periodic monitoring. Hypokalemia (and/or hypomagnesemia) may increase the risk of QTc prolongation and arrhythmia, and should be corrected prior to initiation of treatment and periodically monitored. ECG monitoring is recommended in patients for whom citalopram use is not recommended (see above), but nevertheless, considered to be essential. The following patients should be monitored for cardiac conditions noted above, and those taking other drugs that may prolong the QTc interval.

Citalopram should be discontinued in patients who are found to have persistent QTc measurements >500 ms. If patients taking citalopram experience symptoms that could indicate the occurrence of cardiac arrhythmias, e.g., dizziness, palpitations, or syncope, the prescriber should initiate further evaluation, including cardiac monitoring.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that citalopram is not approved for use in treating bipolar depression.

Serotonin Syndrome: The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including citalopram, alone but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fenflurine, lithium, tramadol, tryptophan, buspirone, and St. John's Wort) and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Serotonin syndrome symptoms include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of citalopram with MAOIs intended to treat psychiatric disorders is contraindicated. Citalopram should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking citalopram. Citalopram should be discontinued before initiating treatment with the MAOI (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).

Concomitant use of citalopram with other serotonergic drugs including triptans, tricyclic antidepressants, fenflurine, lithium, tramadol, buspirone, tryptophan and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome particularly during treatment initiation and dose increases.

Treatment with citalopram and any concomitant serotonergic agents should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Angle-Closure Glaucoma: The pupillary dilation that can occur following use of many antidepressant drugs including citalopram may trigger a acute angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

PRECAUTIONS

General

Discontinuation of Treatment with Citalopram: During marketing of citalopram and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been reports of adverse events upon discontinuation of these drugs, particularly when abrupt, including: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with citalopram. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If adverse events occur upon discontinuation of these drugs, particularly when abrupt, including: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

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Abnormal Bleeding: SSRIs and SNRIs, including citalopram, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants may add to the risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of citalopram and NSAIDs, aspirin, or other drugs that affect coagulation.

Hypomania/Hypomania: Hypomania has been reported as a result of treatment with SSRIs and SNRIs, including citalopram. In many cases, this hypomania appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), and was reversible when citalopram was discontinued. Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk (see Geriatric Use). Discontinuation of citalopram should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

Activation of Mania/Hypomania: In placebo-controlled trials of citalopram, some of which included patients with bipolar disorder, activation of mania/hypomania was reported in 0.2% of 1063 patients treated with citalopram and in none of the 446 patients treated with placebo. Activation of mania/hypomania has also been reported in a small proportion of patients with the major affective disorders treated with other marketed antidepressants. As with all antidepressants, citalopram should be used cautiously in patients with a history of mania.

Interference with Cognitive and Motor Performance: In studies in normal volunteers, citalopram in doses of 40 mg/day did not produce impairment of intellectual function or psychomotor performance. Because any psychoactive drug may impair judgment, thinking, or motor skills, however, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that citalopram therapy does not affect their ability to engage in such activities.

Use in Patients with Concomitant Illness: Clinical experience with citalopram in mice receiving up to 240 mg/kg/day, which is equivalent to 20 times the maximum recommended dose (MRHD) of 60 mg on a surface area (mg/m²) basis. There was an increased incidence of small intestine carcinoma in rats receiving 8 or 24 mg/kg/day, doses which are approximately 1.3 and 4 times the MRHD, respectively, on a mg/m² basis. A no-effect dose for this finding was not established. The relevance of these findings to humans is unknown.

Mutagenesis: Citalopram was mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) in 2 of 5 bacterial

strains (see DOSAGE AND ADMINISTRATION).

Because citalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with citalopram, however, it should be used with caution in such patients (see DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe citalopram. Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of citalopram and triptans, tramadol or other serotonergic agents.

Although in controlled studies citalopram has not been shown to impair psychomotor performance, any psychoactive drug may impair judgment, thinking, or motor skills, so patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that citalopram therapy does not affect their ability to engage in such activities.

Patients should be told that, although citalopram has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of citalopram and alcohol in depressed patients is not advised.

Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, as there is a potential for interactions.

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Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with citalopram and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions" is available for citalopram. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to ask questions to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if they occur while taking citalopram. Patients should be advised that taking citalopram can cause mild pupillary dilation, which in susceptible individuals, can lead to an episode of angle-closure glaucoma. Pre-existing glaucoma is almost always open-angle glaucoma because angle-closure glaucoma, when diagnosed, is promptly treated. Pre-existing angle-closure glaucoma is a risk factor for angle closure glaucoma. Patients may wish to be examined to determine whether they are susceptible to angle closure, and have a prophylactic procedure (e.g., iridectomy), if they are susceptible.

Clinical Worsening and Suicide Risk: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment. Patients should be advised to seek medical attention if any of these symptoms occur. Patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

Serotonergic Drugs: See CONTRAINDICATIONS, WARNINGS, and DOSAGE AND ADMINISTRATION. Triptans: There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of citalopram with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see WARNINGS: Serotonin Syndrome). CNS Drugs: Given the primary CNS effects of citalopram, caution should be used when it is taken in combination with other centrally acting drugs.

Alcohol: Although citalopram did not potentiate the cognitive and motor effects of alcohol in a clinical trial, as with other psychotropic medications, the use of alcohol by depressed patients taking citalopram is not recommended.

Monoamine Oxidase Inhibitors (MAOIs): See CONTRAINDICATIONS, WARNINGS, and DOSAGE AND ADMINISTRATION.

Drugs That Interfere with Hemostasis (NSAIDs, Aspirin, Warfarin, etc.): Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate the risk of bleeding. After anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be closely monitored. If concomitant treatment with warfarin and citalopram is necessary, the primary CNS effects of citalopram, caution should be used when it is taken in combination with other centrally acting drugs.

Cimetidine: In subjects who had received 21 days of 40 mg/day citalopram, combined administration of 400 mg/day cimetidine for 8 days resulted in an increase in citalopram AUC and C_{max} of 43% and 39%, respectively.

Citalop

of these symptoms:

- high fever
- uncontrolled muscle spasms
- stiff muscles
- rapid changes in heart rate or blood pressure
- confusion
- loss of consciousness (pass out)
- take the antipsychotic medicine pimozide (Orap®)
- because this can cause serious heart problems.
- have a heart problem including congenital long QT syndrome.

What should I tell my healthcare provider before taking citalopram? Ask if you are not sure.

Before starting citalopram, tell your healthcare provider if you:

- Are taking certain drugs such as:
 - Medicines for heart problems
 - Medicines that lower your potassium or magnesium levels in your body
 - Cimetidine
 - Triptans used to treat migraine headache
- Medicines used to treat mood, anxiety, psychotic or thought disorders, including tricyclics, lithium, SSRIs, SNRIs, or antipsychotics
- Tramadol
- Over-the-counter supplements such as tryptophan or St. Johns Wort

• have liver problems

• have kidney problems

• have heart problems

• have or had seizures or convulsions

• have bipolar disorder or mania

• have low sodium levels in your blood

• have a history of a stroke

• have high blood pressure

• have or had bleeding problems

• are pregnant or plan to become pregnant. It is not known if citalopram will harm your unborn baby. Talk to your healthcare provider about the benefits and risks of treating depression during pregnancy

• are breast-feeding or plan to breastfeed. Some citalopram may pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby while taking citalopram.

Tell your healthcare provider about all the medicines that you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Citalopram and some medicines may interact with each other, may not work as well, or may cause serious side effects.

Your healthcare provider or pharmacist can tell you if it is safe to take citalopram with your other medicines. Do not start or stop any medicine while taking citalopram without talking to your healthcare provider first.

If you take citalopram, you should not take any other medicines that contain citalopram or escitalopram oxalate including: Lexapro.

How should I take citalopram?

• Take citalopram exactly as prescribed. Your healthcare provider may need to change the dose of citalopram until it is the right dose for you.

• Citalopram may be taken with or without food.

• If you miss a dose of citalopram, take the missed dose as soon as you remember. If it is almost time for the next dose, skip the missed dose and take your next dose at the regular time. Do not take two doses of citalopram at the same time.

• If you take too much citalopram, call your healthcare provider or poison control center right away, or get emergency treatment.

What should I avoid while taking citalopram?

Citalopram can cause sleepiness or may affect your ability to make decisions, think clearly, or react quickly. You should

not drive, operate heavy machinery, or do other dangerous activities until you know how citalopram affects you. Do not drink alcohol while using citalopram.

What are the possible side effects of citalopram?

Citalopram may cause serious side effects, including:

See “What is the most important information I should know about citalopram?”

Common possible side effects in people who take citalopram include:

- Nausea
- Sleepiness
- Weakness
- Dizziness
- Feeling anxious
- Trouble sleeping
- Sexual problems
- Sweating
- Shaking
- Not feeling hungry
- Dry mouth
- Constipation
- Diarrhea
- Respiratory infections
- Yawning

Other side effects in children and adolescents include:

- increased thirst
- abnormal increase in muscle movement or agitation
- nose bleed
- urinating more often
- heavy menstrual periods
- possible slowed growth rate and weight change. Your child’s height and weight should be monitored during treatment with citalopram.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of citalopram For more information, ask your healthcare provider or pharmacist.

The effect of citalopram on labor and delivery in humans is unknown.

CALL YOUR DOCTOR FOR MEDICAL ADVICE ABOUT SIDE EFFECTS. YOU MAY REPORT SIDE EFFECTS TO THE FDA AT 1-800-FDA-1088.

How should I store citalopram?

- Store citalopram at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature.]

- Keep citalopram bottle closed tightly.

Keep citalopram and all medicines out of the reach of children.

General information about citalopram

Medicines are sometimes prescribed for purposes other than those listed in the Medication Guide. Do not use citalopram for a condition for which it was not prescribed. Do not give citalopram to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about citalopram. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider or pharmacist for information about citalopram that is written for healthcare professionals.

For more information about citalopram call 1-800-962-8364 or go to www.Roxane.com.

What are the ingredients of citalopram?

Active ingredient: citalopram hydrobromide USP

Inactive ingredients: methylparaben, peppermint stick, propylene glycol, propylparaben, purified water, and sorbitol solution

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Roxane Laboratories, Inc.
Columbus, Ohio 43216

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strains (Salmonella TA98 and TA1537) in the absence of metabolic activation. It was clastogenic in the *in vitro* Chinese hamster lung cell assay for chromosomal aberrations in the presence and absence of metabolic activation. Citalopram was not mutagenic in the *in vitro* mammalian forward gene mutation assay (HPRT) in mouse lymphoma cells or in a coupled *in vitro/in vivo* mutagenicity DNA synthesis (UDS) assay in rat liver. It was not clastogenic in the *in vitro* chromosomal aberration assay in human lymphocytes or in *two in vivo* mouse micronucleus assays.

Impairment of Fertility: When citalopram was administered orally to 16 male and 24 female rats prior to and throughout mating and gestation at doses of 32, 48, and 72 mg/kg/day, mating was decreased at all doses, and fertility was decreased at doses >=32 mg/kg/day, approximately 5 times the MRHD of 60 mg/day on a body surface area (mg/m²) basis. Gestation duration was increased at 48 mg/kg/day, approximately 8 times the MRHD.

Pregnancy Category C: In animal reproduction studies, citalopram has been shown to have adverse effects on embryo/fetal and postnatal development, including teratogenic effects, when administered at doses greater than human therapeutic doses.

In two rat embryo/fetal development studies, oral administration of citalopram (32, 56, or 112 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased embryo/fetal growth and survival and an increased incidence of fetal abnormalities (including cardiovascular and skeletal defects) at the high dose, which is approximately 18 times the MRHD of 60 mg/kg/day on a body surface area (mg/m²) basis. This dose was also associated with increased maternal toxicity (clinical signs, decreased body weight gain). The developmental, no-effect dose of 56 mg/kg/day is approximately 9 times the MRHD on a mg/m² basis. In a rabbit study, no adverse effects on embryo/fetal development were observed at doses of up to 16 mg/kg/day, or approximately 5 times the MRHD on a mg/m² basis. Thus, teratogenic effects were observed at a maternally toxic dose in the rat and were not observed in the rabbit.

When female rats were treated with citalopram (4.8, 12.8, or 32 mg/kg/day) from late gestation through weaning, increased offspring mortality during the first 4 days after birth and persistent offspring growth retardation were observed at the highest dose, which is approximately 5 times the MRHD on a mg/m² basis. The no-effect dose of 12.8 mg/kg/day is approximately 2 times the MRHD on a mg/m² basis. Similar effects on offspring mortality and growth were seen when dams were treated throughout gestation and early lactation at doses >=24 mg/kg/day, approximately 4 times the MRHD on a mg/m² basis. A no-effect dose was not determined in that study.

There are no adequate and well-controlled studies in pregnant women; therefore, citalopram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy: Nonteratogenic Effects: Neonates exposed to citalopram and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotension, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a serotonin toxic and/or SSRI and SNRI or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see **WARNINGS: Serotonin Syndrome**).

Infants exposed to SSRIs in pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1- 2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. Several recent epidemiologic studies suggest a positive statistical association between SSRI use (including citalopram) in pregnancy and PPHN. Other studies do not show a significant statistical association.

Physicians should also note the results of a prospective longitudinal study of 201 pregnant women with a history of major depression, who were either on antidepressants or had received antidepressants less than 12 weeks prior to their last menstrual period, and were in remission. Women who discontinued antidepressant medication during pregnancy showed a significant increase in relapse of their major depression compared to those women who remained on antidepressant medication throughout pregnancy.

When treating a pregnant woman with citalopram, the physician should carefully consider both the potential risks of taking an SSRI along with the established benefits of treating depression with an antidepressant. This decision can only be made on a case by case basis (see **DOSEAGE AND ADMINISTRATION**).

Labor and Delivery

The effect of citalopram on labor and delivery in humans is unknown.

Nursing Mothers

As has been found to occur with many other drugs, citalopram is excreted in human breast milk. There have been two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with breastfeeding from a citalopram-treated mother; in one case, the infant was reported to recover completely upon discontinuation of citalopram by its mother, and in the second case, no follow-up information was available. The decision whether to continue or discontinue either nursing or citalopram therapy should take into account the risks of citalopram exposure for the infant and the benefits of citalopram treatment for the mother.

Feet: Safety and effectiveness in the pediatric population have not been established (see **BOX WARNING** and **WARNINGS: Clinical Worsening and Suicide Risk**). Two placebo-controlled trials in 407 pediatric patients with MDD have been conducted with citalopram, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of citalopram in a child or adolescent must balance the potential risks with the clinical need.

Decreased appetite and weight loss have been observed in association with the use of SSRIs. Consequently, regular monitoring of weight and growth should be performed in children and adolescents treated with citalopram.

Geriatric Use

Of 4422 patients in clinical studies of citalopram, 1357 were 60 and over, 1034 were 65 and over, and 457 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Most elderly patients treated with citalopram in clinical trials received daily doses between 20 and 40 mg (see **DOSEAGE AND ADMINISTRATION**).

SSRIs and SNRIs, including citalopram, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event (see **PRECAUTIONS: Hyponatremia**). In two pharmacokinetic studies, citalopram AUC was increased by 23% and 30%, respectively, in subjects > 60 years of age as compared to younger subjects, and its half-life was increased by 30% and 50%, respectively (see **CLINICAL PHARMACOLOGY**).

20 mg/day is the maximum recommended dose for patients who are greater than 60 years of age (see **WARNINGS and DOSEAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

The premarketing development program for citalopram included citalopram exposures in patients and/or normal subjects from 3 different groups of studies: 423 normal subjects in clinical pharmacology/pharmacokinetic studies; 4422 exposures from patients in controlled and uncontrolled clinical trials, corresponding to approximately 1370 patient-exposure years. There were, in addition, over 19,000 exposures from mostly open-label, European postmarketing studies. The conditions and duration of treatment with citalopram varied greatly and included (in overlapping categories) open-label and double-blind studies, inpatient and outpatient studies, fixed-dose and dose-titration studies, and short-term and long-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard World Health Organization (WHO) terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials

Adverse Events Associated with Discontinuation of Treatment: Among 1063 depressed patients who received citalopram at doses ranging from 10 to 80 mg/day in placebo-controlled trials of up to 8 weeks in duration, 16% discontinued treatment due to an adverse event, as compared to 8% of 446 patients receiving placebo. The adverse events associated with discontinuation and considered drug-related (i.e., associated with discontinuation in at least 1% of citalopram-treated patients at a rate at least twice that of placebo) are shown in **Table 2**. It should be noted that one patient can report more than one reason for discontinuation and be counted more than once in this table.

Body System/ Adverse Event	Percentage of Patients Discontinuing Due to Adverse Event	
	Citalopram (N=1063)	Placebo (N=446)
General		
Asthenia	1%	<1%
Gastrointestinal Disorders		
Nausea	4%	0%
Dry Mouth	1%	<1%
Vomiting	1%	0%

Central and Peripheral Nervous System Disorders		
Dizziness	2%	<1%
Psychiatric Disorders		
Insomnia	3%	1%
Somnolence	2%	1%
Agitation	1%	<1%

Adverse Events Occurring at an Incidence of 2% or More Among Citalopram-Treated Patients: **Table 3** enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 1063 depressed patients who received citalopram at doses ranging from 10 to 80 mg/day in placebo-controlled trials of up to 6 weeks in duration. Events included are those occurring in 2% or more of patients treated with citalopram and for which the incidence in patients treated with citalopram was greater than the incidence in placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

The only commonly observed adverse event that occurred in citalopram patients with an incidence of 5% or greater and at least twice the incidence in placebo patients was ejaculation disorder (primarily ejaculatory delay) in male patients (see **Table 3**).

Table 3: Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials*

Body System/ Adverse Event	(Percentage of Patients Reporting Event)	
	Citalopram (N=1063)	Placebo (N=446)
Autonomic Nervous System Disorders		
Dry Mouth	20%	14%
Sweating Increased	11%	9%
Central & Peripheral Nervous System Disorders		
Tremor	8%	6%
Gastrointestinal Disorders		
Nausea	21%	14%
Diarrhea	8%	5%
Dyspepsia	5%	4%
Vomiting	4%	3%
Abdominal Pain	3%	2%
General		
Fatigue	5%	3%
Fever	2%	<1%
Musculoskeletal System Disorders		
Arthralgia	2%	1%
Myalgia	2%	1%
Psychiatric Disorders		
Somnolence	18%	10%
Insomnia	15%	14%
Anxiety	4%	3%
Anorexia	4%	2%
Agitation	3%	1%
Dysmenorrhea ¹	3%	2%
Libido Decreased	2%	<1%
Yawning	2%	<1%
Respiratory System Disorders		
Upper Respiratory Tract Infection	5%	4%
Rhinitis	5%	3%
Sinusitis	3%	<1%
Urogenital		
Ejaculation Disorder ^{2,3}	6%	1%
Impotence ⁴	2%	<1%

¹ Events reported by at least 2% of patients treated with citalopram are reported, except for the following events which had an incidence on placebo > citalopram: headache, asthenia, dizziness, constipation, palpitation, vision abnormal, sleep disorder, nervousness, pharyngitis, micturition disorder, back pain.

² Denominator used was for females only (N=638 citalopram; N=252 placebo).

³ Primarily ejaculatory delay

⁴ Denominator used was for male males only (N=425 citalopram; N=194 placebo).

Dose Dependency of Adverse Events: The potential relationship between the dose of citalopram administered and the incidence of adverse events was examined in a fixed-dose study in depressed patients receiving placebo or citalopram 10, 20, 40, and 60 mg. Jonckheere’s trend test revealed a positive dose response (p<0.05) for the following adverse events: fatigue, impotence, insomnia, sweating increased, somnolence, and yawning.

Female-Specific Sexual Dysfunction with SSRIs: Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling, are likely to underestimate their actual incidence.

The table below displays the incidence of sexual side effects reported by at least 2% of patients taking citalopram in a pool of placebo-controlled clinical trials in patients with depression.

Treatment	Citalopram (425 males)	Placebo (194 males)
Abnormal Ejaculation (mostly ejaculatory delay)	6.1% (males only)	1% (males only)
Libido Decreased	3.8% (males only)	<1% (males only)
Impotence	2.8% (males only)	<1% (males only)

In female depressed patients receiving citalopram, the reported incidence of decreased libido and anorgasmia was 1.3% (N=638 females) and 1.1% (N=252 females), respectively.

There are no adequately designed studies examining sexual dysfunction with citalopram treatment.

Prisaprim has been reported with all SSRIs.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Vital Sign Changes: Citalopram and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with citalopram treatment. In addition, a comparison of supine and standing vital sign measures for citalopram and placebo treatments indicated that citalopram treatment is not associated with orthostatic changes. *Weight Changes:* Patients treated with citalopram in controlled trials experienced a weight loss of about 0.5 kg compared to no change for placebo patients.

Laboratory Changes: Citalopram and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with citalopram treatment.

ECG Changes: In a through QT study, citalopram was found to be associated with a dose-dependent increase in the QTc interval (see **WARNINGS: QT-Prolongation and Torsade de Pointes**).

Electrocardiograms from citalopram (N=802) and placebo (N=241) groups were compared with respect to outliers defined as subjects with QTc changes over 60 msec from baseline or absolute values over 500 msec post-dose, and subjects with heart rate increases to over 100 bpm or decreases to less than 50 bpm with a 25% change from baseline (tachycardia or

bradycardia outliers, respectively). In the citalopram group 1.9% of the patients had a change from baseline in QTcF >60 msec compared to 1.2% of the patients in the placebo group. None of the patients in the placebo group had a post-dose QTcF >500 msec compared to 0.5% of the patients in the citalopram group. The incidence of lachycardia outliers was 0.5% in the citalopram group and 0.4% in the placebo group. The incidence of bradycardia outliers was 0.9% in the citalopram group and 0.4% in the placebo group.

Other Events Observed During the Premarketing Evaluation of Citalopram

Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the **ADVERSE REACTIONS** section, reported by patients treated with citalopram at multiple doses in a range of 10 to 80 mg/day during any phase of a trial within the premarketing database of 4422 patients. All reported events are included except those already listed in **Table 3** or elsewhere in labeling, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and those occurring in only one patient. It is important to emphasize that, although the events reported occurred during treatment with citalopram, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients.

Cardiovascular – Frequent: tachycardia, postural hypotension, hypotension. *Infrequent:* hypertension, bradycardia, edema (extremities), angina pectoris, extrasystoles, cardiac failure, flushing, myocardial infarction, cerebrovascular accident, myocardial ischemia. *Rare:* transient ischemic attack, phlebitis, atrial fibrillation, cardiac arrest, bundle branch block.

Central and Peripheral Nervous System Disorders – Frequent: paresthesia, migraine. *Infrequent:* hyperkinesia, dystonia, vertigo, hypertonia, extrapyramidal disorder, leg cramps, involuntary muscle contractions, hypokinesia, neuroalgia, dyskinesia, abnormal gait, hyposthesia, ataxia. *Rare:* abnormal coordination, hyperesthesia, ptoxis, stupor.

Endocrine Disorders – Rare: hypothyroidism, goiter, gynecomastia.

Gastrointestinal Disorders – Frequent: saliva increased, flatulence. *Infrequent:* gastritis, gastroenteritis, stomatitis, eructation, hemorrhoids, dysphagia, teeth grinding, gingivitis, esophagitis. *Rare:* colitis, gastric ulcer, cholecystitis, cholelithiasis, duodenal ulcer, gastroesophageal reflux, glossitis, jaundice, diverticulitis, rectal hemorrhage, hiccups.

General – Infrequent: hot flashes, rigors, alcohol intolerance, syncope, influenza-like symptoms. *Rare:* hayfever.

Hemic and Lymphatic Disorders – Infrequent: purpura, ecchymosis, leukocytosis, leucopenia, myophadenopathy. *Rare:* pulmonary embolism, granulocytopenia, lymphocytosis, lymphopenia, hypochromic anemia, coagulation disorder, gingival bleeding.

Metabolic and Nutritional Disorders – Frequent: decreased weight, increased weight. *Infrequent:* increased hepatic enzymes, thirst, dry eyes, increased alkaline phosphatase, abnormal glucose tolerance. *Rare:* bilirubinemia, hypokalemia, obesity, hypoglycemia, hyperkalemia, dehydration.

Musculoskeletal System Disorders – Infrequent: arthritis, muscle weakness, skeletal pain. *Rare: bursitis, osteoporosis.*

Psychiatric Disorders – Frequent: impaired concentration, anhedonia, apathy, depression, increased appetite, aggravated depression, suicide attempt, confusion. *Infrequent:* increased libido, aggressive reaction, paranoia, drug dependence, depersonalization, hallucination, euphoria, psychotic depression, delusion, paranoid reaction, emotional lability, panic reaction, psychosis. *Rare:* catatonic reaction, melancholia.

Reproductive Disorders/Female* – Frequent: amenorrhea. *Infrequent:* galactorrhea, breast pain, breast enlargement, vaginal hemorrhage.

* % based on female subjects only: 2955

Respiratory System Disorders – Frequent: coughing. *Infrequent:* bronchitis, dyspnea, pneumonia. *Rare:* asthma, laryngitis, bronchospasm, pneumonitis, sputum increased.

Skin and Appendages Disorders – Fre