

Citalopram Tablets, USP

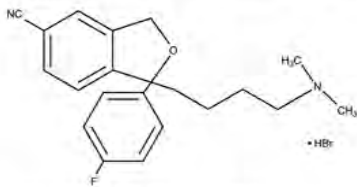
Rx Only

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 hydrobromide in 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 hydrobromide is not approved for use in pediatric patients. (See Warnings: Clinical Worsening and Suicide Risk, Precautions: Information for Patients, and Precautions: Pediatric Use.)

DESCRIPTION

Citalopram hydrobromide, 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, USP is a racemic bicyclic piperazine derivative designates (+)-1-(S)-dimethylaminoethylpiperazine-4-carboxylic acid hydrobromide with the following structural formula:



The molecular formula is $C_{17}H_{20}FNO_2$ and its molecular weight is 305.35.

Citalopram hydrobromide, USP occurs as a fine, white to off-white powder. Citalopram hydrobromide, USP is sparingly soluble in water and soluble in ethanol.

Citalopram hydrobromide, USP is available as tablets.

Citalopram hydrobromide, USP 10 mg tablets are film-coated, round tablets containing citalopram hydrobromide in strengths equivalent to 10 mg of citalopram. Citalopram hydrobromide, USP 20 mg and 40 mg tablets are film-coated, round, scored tablets containing citalopram hydrobromide in strengths equivalent to 20 mg or 40 mg of citalopram. The tablets also contain the following inactive ingredients: copovidone, croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose. Opacity color: HPMC 2910/hydroxypropyl methylcellulose K100 (pink to yellow and iron oxide red) and Opacity Pink (HPMC 2910/hydroxypropyl methylcellulose K100, hydroxypropyl methylcellulose K100, iron oxide red, and Opady white titanium dioxide, HPMC 2910/hydroxypropyl methylcellulose K100, Macrogol/Peg400 and Polyethylene Glycol) are used as coating agents in the beige (10 mg), pink (20 mg) and white (40 mg) tablets.

CLINICAL PHARMACOLOGY

Pharmacodynamics
The mechanism of action of citalopram hydrobromide 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 selective 5-HT_{2A} and 5-HT_{2C} antagonist. 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_{1B}, dopamine D₁ and D₂, α₁- and β₂-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

Citalopram has multiple-dose pharmacokinetics of citalopram are linear and dose-proportional in a dose range of 10–80 mg/day. Bioavailability 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 hydrobromide are bioequivalent.

Absorption and Distribution

Following a single oral dose (40 mg tablet), citalopram peak blood levels occur at about 4 hours. The absolute bioavailability of citalopram was about 20% 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 dimethylcitalopram (DDCT) to human plasma proteins is about 80%.

Metabolism and Elimination

Following intravenous administration of citalopram, the fraction of drug recovered in the urine as citalopram and DCT was about 10% and 5%, 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), dimethylcitalopram (DDCT), citalopram-N-oxide, and a demethylated propionic acid derivative. In humans, unchanged citalopram is the predominant component 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 serotonergic reuptake, suggesting that the metabolites would not likely contribute significantly to the antidepressant action of citalopram.

In vivo studies using human liver microsomes indicated that CYP3A4 and CYP2C19 are the primary enzymes 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 elderly subjects by 30% and 50%, respectively, whereas in a multiple-dose study they were increased by 23% and 20%, respectively. 20 mg is the recommended dose for most elderly patients (see **DOSEAGE AND ADMINISTRATION**).

Gender—In three pharmacokinetic studies (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=38). There were no gender differences in the pharmacokinetics of DCT and DDCT. No adjustment of doses 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 (Child-Pugh class 2). The recommended dose for most hepatically impaired patients (see **DOSEAGE AND ADMINISTRATION**).

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 on 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 CYP2A6, -2C6, and -2C19. Citalopram would be expected to have little inhibitory effect on *in vivo* metabolism mediated by these cytochromes. However, *in vivo* data to address this question are limited.

Since CYP3A4 and 2C19 are the primary enzymes involved in the metabolism of citalopram, it is expected that potent inhibitors of 3A4 (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 potent 3A4 and 2C19 inhibitors did not significantly affect the pharmacokinetics of citalopram. Because citalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease citalopram clearance. Citalopram steady state levels were not significantly different in poor metabolizers and extensive 2D6 metabolizers after multiple-dose administration of Citalopram hydrobromide, suggesting that coadministration with Citalopram hydrobromide of a drug that inhibits CYP2D6 is unlikely to have clinically significant effects on citalopram metabolism. See **Drug Interactions** under **PRECAUTIONS** for more detailed information on available drug interaction data.

Clinical Efficacy Trials

The efficacy of Citalopram hydrobromide as a treatment for depression was established in two placebo-controlled studies (4 to 5 weeks in duration) in adult outpatients (ages 18–66) meeting DSM-IV or DSM-IV-TR criteria for major depression. Study 1, a 6-week trial in which patients received fixed Citalopram hydrobromide doses of 10,

20, 40, and 60 mg/day, showed that Citalopram hydrobromide at doses of 40 and 60 mg/day were effective as measured by the Hamilton Depression Rating Scale (HAM-D) total score, the HAM-D depressed mood item (Item 1), the Montgomery-Åsberg 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 major depression, showed that Citalopram hydrobromide at the maximum tolerated dose (10 mg or a maximum dose of 80 mg/day). Patients treated with Citalopram hydrobromide scored significantly greater improvement than placebo patients on the HAM-D total score, HAM-D item 1, and the CGI Severity scale. In three additional placebo-controlled depression trials, the difference in response to treatment between patients receiving Citalopram hydrobromide 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 hydrobromide during an initial 6 or 8 weeks of acute treatment (fixed doses of 20 to 40 mg/day in one study and flexible doses of 20–60 mg/day in the second study) were randomized to continuation of Citalopram hydrobromide or to placebo. In both studies, patients receiving continued Citalopram hydrobromide 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 hydrobromide.

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.

Combination of Clinical Trial Results

Key variable results have been seen in the clinical development of all antidepressant drugs. Furthermore, in these circumstances when the drugs have not been studied in the same controlled clinical trials), comparisons among the results of studies evaluating the effectiveness of different antidepressant drug products are inherently unreliable. Because conditions of testing (e.g., patient samples, investigators, doses of the treatments administered, treatment duration, outcome measures, etc.) may vary among trials, it is vitally important to distinguish a difference in drug effect from a difference due to one of the confounding factors just enumerated.

INDICATIONS AND USAGE

Citalopram hydrobromide is indicated for the treatment of depression.

The efficacy of Citalopram hydrobromide in the treatment of depression was established in 4–6 week controlled trials of outpatients whose diagnosis corresponded most closely to the DSM-IV and DSM-IV-TR category of major depressive disorder (see **CLINICAL PHARMACOLOGY**).

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 hydrobromide in hospitalized depressed patients has not been adequately studied.

The efficacy of Citalopram hydrobromide 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 hydrobromide for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see **WARNINGS**). Concomitant use in patients taking pimozide is contraindicated (see **PRECAUTIONS**).

Citalopram hydrobromide tablets are contraindicated in patients with a hypersensitivity to citalopram or any of the inactive ingredients in Citalopram hydrobromide tablets.

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 ideation 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. Suicidality 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) in children, adolescents, and young adults (ages 18–24) with major depressive disorder (MDD) and 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 8 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 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 between citalopram and placebo in adults with the highest suicide risk (10%). The risk difference (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug vs. 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
18–24	5 additional cases
	Decreases Compared to placebo
25–64	1 fewer case
≥65	5 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 short-term 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 weeks 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 disorder as well as for 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 **DOSEAGE AND ADMINISTRATION**)—Discontinuation of Treatment with Citalopram hydrobromide, for a description of the risks of discontinuation of Citalopram hydrobromide.

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 hydrobromide should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

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 mania/mixed 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 hydrobromide is not approved for use in treating bipolar depression.

Potential for Interaction with Monoamine Oxidase Inhibitors

In patients receiving serotonergic reuptake inhibitor drugs in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Furthermore, limited animal data on the effects of combined use of SSRIs and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that Citalopram hydrobromide should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping Citalopram hydrobromide before starting an MAOI.

Serotonin Syndrome and Neuroleptic Malignant Syndrome (NMS)-like Reactions

The pharmacology of a potentially destabilizing serotonergic syndrome (Neuroleptic Malignant Syndrome (NMS)-like reactions) have been reported with SSRIs and SSRIs alone, including citalopram hydrobromide treatment, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs) or with anticholinergics or other dopamine antagonists. Serotonergic syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

The concomitant use of citalopram hydrobromide with MAOIs intended to treat depression is contraindicated.

If concomitant treatment with Citalopram hydrobromide with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

The concomitant use of citalopram hydrobromide with serotonergic precursors (such as tryptophan) is not recommended.

Treatment with citalopram hydrobromide and any concomitant serotonergic or anticholinergic agents, including anticholinergics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

PRECAUTIONS

General

Discontinuation of Treatment with Citalopram hydrobromide

During marketing of Citalopram hydrobromide and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paraesthesiae such as electric shock sensations), anxiety, confusion, headache, irritability, 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 hydrobromide. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see **DOSEAGE AND ADMINISTRATION**).

Abnormal Bleeding

SSRIs and SNRIs, including Citalopram hydrobromide, 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 epistaxis, hematomas, ecchymosis, and petechiae to life-threatening hemorrhages.

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

Hypertension

Hypertension may occur as a result of treatment with SSRIs and SNRIs, including Citalopram hydrobromide. In many cases, this hypertension appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), and was reversible when Citalopram hydrobromide was discontinued. Cases with serum sodium lower than 110 mEq/L have been reported. Elderly patients may be at greater risk of developing hypertension 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 hydrobromide should be considered in patients with symptomatic hypotension and appropriate medical intervention should be instituted.

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

Activation of HLA/Hypersensitivity

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

Seizures

Although anticonvulsant effects of citalopram have been observed in animal studies, Citalopram hydrobromide has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarketing testing. In clinical trials of Citalopram hydrobromide, seizures occurred in 0.3% of patients treated with Citalopram hydrobromide (4 mg or 10 mg per 98 hours of exposure) and 0.5% of patients treated with placebo (4 mg or 10 mg per 98 hours of exposure). Like other antidepressants, Citalopram hydrobromide should be introduced with care in patients with a history of seizure disorder.

Interference with Cognitive and Motor Performance

In studies in normal volunteers, Citalopram hydrobromide 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 hydrobromide therapy does not affect their ability to engage in such activities.

Use in Patients with Concomitant Illness

Clinical experience with Citalopram hydrobromide in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using Citalopram hydrobromide in patients with diseases or conditions that produce altered metabolism or hemodynamic responses.

Citalopram hydrobromide has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable angina. Patients with these conditions were generally excluded from clinical studies during the product's premarketing testing. However, the electrocardiogram of 1118 patients who received Citalopram hydrobromide in clinical trials were evaluated and the data indicate that Citalopram hydrobromide is not associated with the development of clinically significant ECG abnormalities.

In subjects with hepatic impairment, citalopram clearance was decreased and plasma concentrations were increased. The use of Citalopram hydrobromide in hepatically impaired patients should be approached with caution and a lower maximum dosage is recommended (see **DOSEAGE AND ADMINISTRATION**).

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

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe Citalopram hydrobromide.

Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of Citalopram hydrobromide and triptans, tramadol or other serotonergic agents.

Although in controlled studies Citalopram hydrobromide has not been shown to impair psychomotor performance, patients should be cautioned about driving or operating machinery until they are reasonably certain that Citalopram hydrobromide therapy does not affect their ability to engage in such activities.

Patients should be told that, although Citalopram hydrobromide has not been shown in experiments with normal subjects to increase the mental and motor skills impairments caused by alcohol, the concomitant use of Citalopram hydrobromide 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.

Patients should be cautioned about the concomitant use of Citalopram hydrobromide and NSAIDs, aspirin, or other drugs that affect coagulation since the combined use of Citalopram hydrobromide with serotonergic reuptake and these agents has been associated with an increased risk of bleeding.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised to notify their physician if they are breastfeeding an infant.

While patients may notice improvement with Citalopram hydrobromide therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.

Prescribers and other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Citalopram hydrobromide and should counsel them on 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 hydrobromide. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and to discuss it with the prescriber if they are using this medicine. Patients should be given the opportunity to discuss the contents of the Medication Guide and to ask questions if they have any. 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 these occur while taking Citalopram hydrobromide.

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 and when the dose is adjusted up or down. Families and caregivers of 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. Citalopram hydrobromide is not approved for use in pediatric patients.

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

Serotonergic Drugs: Based on the mechanism of action of SNRIs and SSRIs including Citalopram hydrobromide, and the potential for serotonin syndrome, caution is advised when Citalopram hydrobromide is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (the antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (see **WARNINGS—Serotonin Syndrome**). The concomitant use of Citalopram hydrobromide with other SSRIs, SNRIs or tryptophan is not recommended (see **PRECAUTIONS—Drug Interactions**).

Triptans: There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Citalopram hydrobromide 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 hydrobromide is not recommended.

Monoamine Oxidase Inhibitors (MAOIs) — See CONTRAINDICATIONS and WARNINGS.

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 potentially increases the risk of bleeding. Abnormal anticoagulation, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Citalopram hydrobromide is initiated or discontinued.

Cimetidine—In subjects who had received 21 days of 40 mg/day Citalopram hydrobromide, 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. The clinical significance of these findings is unknown.

Digoxin—In subjects who had received 21 days of 40 mg/day Citalopram hydrobromide, combined administration of Citalopram hydrobromide and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin.

Pregnancy
Pregnancy Category C
 In animal reproduction studies, citalopram has been shown to have adverse effects on embryonic 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 embryofetal 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/day on a body surface area (mg/m²) basis. The dose was also associated with 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 embryofetal 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.

Female rats were treated with citalopram (4.8, 12.8, or 32 mg/kg/day) from late gestation through weaning; increased off-spring mortality during the first 4 days after birth and persistent off-spring 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 through gestation and early lactation at doses of 2.4 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 hydrobromide and other SSRIs, late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support and labor feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see **WARNINGS**).

Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1–4 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective, case-control study of 377 women whose infants were born with PPHN and 838 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 26th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include women cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk.

When treating a pregnant woman with Citalopram hydrobromide during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see **DOSEAGE AND ADMINISTRATION**). Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

Labor and Delivery

The effect of Citalopram hydrobromide 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-lactated 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 hydrobromide therapy should take into account the risks of citalopram exposure for the infant and the benefits of Citalopram hydrobromide treatment for the mother.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established (see **BOX WARNING** and **WARNINGS**—Clinical Warnings and Suicide Risk). No over all 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 hydrobromide in clinical trials received daily doses between 20 and 40 mg (see **DOSEAGE AND ADMINISTRATION**).

SSRIs and SNRIs, including Citalopram hydrobromide, 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 elderly subjects as compared to younger subjects, and its half-life was increased by 30% and 50%, respectively (see **CLINICAL PHARMACOLOGY**).
ADVERSE REACTIONS
 The premarketing development program for Citalopram hydrobromide included citalopram exposures in patients and/or normal subjects from 3 different groups of studies: 429 normal subjects in clinical pharmacology/pharmacokinetic studies; 422 associates from patients in controlled and uncontrolled clinical trials, corresponding to approximately 1370 patient-exposure years. There were, in addition, over 15,000 exposures from mostly open-label, European postmarketing studies. The conditions and duration of treatment with Citalopram hydrobromide 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 hydrobromide at doses ranging from 10 to 80 mg/day in placebo-controlled trials of up to 8 weeks in duration, 15% 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 hydrobromide-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.

Adverse Events Associated with Discontinuation of Treatment Among 1063 depressed patients who received Citalopram hydrobromide at doses ranging from 10 to 80 mg/day in placebo-controlled trials of up to 8 weeks in duration, 15% 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 hydrobromide-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.

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 hydrobromide at doses ranging from 10 to 80 mg/day in placebo-controlled trials of up to 8 weeks in duration, 15% 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 hydrobromide-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.

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 hydrobromide at doses ranging from 10 to 80 mg/day in placebo-controlled trials of up to 8 weeks in duration, 15% 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 hydrobromide-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.

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 hydrobromide at doses ranging from 10 to 80 mg/day in placebo-controlled trials of up to 8 weeks in duration, 15% 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 hydrobromide-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.

Adverse Events Occurring at an Incidence of 2% or More Among Citalopram Hydrobromide-Treated Patients
 Table 3 summarizes the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 1063 depressed patients who received Citalopram hydrobromide at doses ranging from 10 to 80 mg/day in placebo-controlled trials of up to 8 weeks in duration. Events included are those occurring in 2% or more of patients treated with Citalopram hydrobromide and for which the incidence in patients treated with Citalopram hydrobromide 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 equal 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 hydrobromide 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).

Body System/Adverse Event	TABLE 3 Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials ^a	
	Citalopram Hydrobromide (N=1063)	Placebo (N=446)
Autonomic Nervous System Disorders		
Dry Mouth	20%	14%
Sweating Increased	11%	9%
Central and 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		
Artralgia	2%	1%
Myalgia	2%	1%
Psychiatric Disorders		
Somnolence	18%	10%
Insomnia	15%	14%
Anxiety	4%	2%
Apathy	4%	2%
Dysmenorrhea	3%	2%
Libido Decreased	2%	<1%
Yawning	2%	<1%
Respiratory System Disorders		
Upper Respiratory Tract Infection	5%	4%
Rhinitis	5%	2%
Sinusitis	3%	<1%
Urogenital		
Ejaculation Disorder ^b	8%	1%
Impotence	3%	<1%

^a Events reported by at least 2% of patients treated with Citalopram hydrobromide are reported, except for the following events which had an incidence on placebo >Citalopram hydrobromide: headache, asthma, dizziness, constipation, palpitation, vision abnormal, sleep disorder, nervousness, pruritus, irritation disorder, back pain.
^b Discontinuation used was for females only (N=638 Citalopram hydrobromide, N=252 placebo).
^c Primarily ejaculatory delay.
^d Denominator used was for males only (N=425 Citalopram hydrobromide, N=194 placebo).

Dose Dependency of Adverse Events
 The potential relationship between the dose of Citalopram hydrobromide administered and the incidence of adverse events was examined in a fixed-dose study in depressed patients receiving placebo or Citalopram hydrobromide 10, 20, 40, and 80 mg. Jonkhoff's trend test revealed a positive dose response (p<0.05) for the following adverse events: fatigue, impotence, insomnia, sweating increased, somnolence, and yawning.

Male and Female 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 experiences and performance effect in patients taking 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 hydrobromide in a pool of placebo-controlled clinical trials in patients with depression.

Treatment	Citalopram hydrobromide (425 males)	Placebo (194 males)
Abnormal Ejaculation (mostly ejaculatory delay)	6% (males only)	1% (males only)
Libido Decreased	3% (males only)	<1% (males only)
Impotence	2% (males only)	<1% (males only)

In female depressed patients among Citalopram hydrobromide, the reported incidence of decreased libido and impotence was 1.3% (N=838 females) and 1.1% (N=552 females), respectively.

There are no adequately designed studies examining sexual dysfunction with citalopram treatment. Pruritus 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 be aware of the potential for such possible side effects.

Vital Signs Changes
 Citalopram hydrobromide 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 hydrobromide treatment. In addition, a comparison of pulse and standing vital sign measures for Citalopram hydrobromide and placebo treatments indicated that Citalopram hydrobromide treatment is not associated with orthostatic changes.

Weight Changes
 Patients treated with Citalopram hydrobromide in controlled trials experienced a weight loss of about 0.5 kg compared to no change for placebo patients.

Laboratory Changes
 Citalopram hydrobromide 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. These analyses revealed no clinically important changes in laboratory test parameters associated with Citalopram hydrobromide treatment.

ECG Changes
 Electrocardiograms from Citalopram hydrobromide (N=802) and placebo (N=241) groups were compared with respect to (1) mean change from baseline in various ECG parameters, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. The only statistically significant drug-placebo difference observed was a decrease in heart rate for Citalopram hydrobromide of 1.7 bpm compared to no change in heart rate for placebo. There were no observed differences in QT or other ECG intervals.

Other Events Observed During the Premarketing Evaluation of Citalopram Hydrobromide
 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 hydrobromide 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 hydrobromide, 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 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Cardiovascular - *Frequent:* tachycardia, postural hypotension, hypotension, *Infrequent:* hypertension, bradycardia, atria, extraxial, atrial, junctional, supraventricular, ventricular, and sinus bradycardia, myocardial infarction, cerebrovascular accident, myocardial ischemia. *Rare:* transient ischemic attack, paresthesia, atherosclerosis, cardiac arrest, bundle branch block.

Central and Peripheral Nervous System Disorders - *Frequent:* paresthesia, migraine, *Infrequent:* hyperkinesia, hyperreflexia, hypertonia, extrapyramidal disorder, leg cramps, involuntary muscle contractions, hypokinesia, nystagmus, dystonia, abnormal gait, hypotonia, ataxia. *Rare:* abnormal coordination, hyperreflexia, paresthesia, stupor.

Endocrine Disorders - *Rare:* hypothyroidism, goiter, gynecomastia.

Gastrointestinal Disorders - *Frequent:* saliva increased, flatulence, *Infrequent:* gastritis, gastroenteritis, stomatitis, arthralgia, hemorrhoids, dysplasia, keth ingestion, gingivitis, esophagitis, *Rare:* colitis, gastric ulcer, cholecystitis, cholelithiasis, duodenal ulcer, gastroesophageal reflux, glossitis, jaundice, diverticulitis, rectal hemorrhage, fecal impaction, fecaloma.

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

Hemic and Lymphatic Disorders - *Infrequent:* purpura, anemia, apatosis, leukocytosis, leukopenia, lymphadenopathy. *Rare:* pulmonary embolism, granulocytopenia, thrombocytopenia, 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, ketonuria, dehydration.

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

Psychiatric Disorders - *Frequent:* impaired concentration, anorexia, 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:* cataplexy reaction, mania/delusion.

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

^a % 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 - *Frequent:* rash, pruritus, *Infrequent:* photosensitivity reaction, urticaria, acne, skin discoloration, acne, alopecia, dermatitis, skin dry, psoriasis. *Rare:* hyperreflexia, decreased sweating, melasma, keratitis, cellulitis, pruritus, etc.

Special Senses - *Frequent:* accommodation abnormal taste perversion. *Infrequent:* vertigo, conjunctivitis, eye pain. *Rare:* mydriasis, photophobia, diplopia, abnormal lacrimation, cataract, taste loss.

Urinary System Disorders - *Frequent:* urinary incontinence. *Infrequent:* nocturia, urinary incontinence, urinary retention, dysuria. *Rare:* facial edema, hematuria, oliguria, pyroinfection, renal calculus, renal pain.

Other Events Observed During the Postmarketing Evaluation of Citalopram Hydrobromide
 It is estimated that over 30 million patients have been treated with Citalopram hydrobromide since market introduction. Although no causal relationship to Citalopram hydrobromide treatment has been found, the following adverse events have been reported to be temporally associated with Citalopram hydrobromide treatment, and have not been described elsewhere in labeling: acute renal failure, akathisia, allergic reaction, angioedema, angiodema, cholelithiasis, chest pain, delirium, dyskinesia, ecchymosis, epidermal necrosis, erythema multiforme, gastrointestinal hemorrhage, grand mal convulsions, hemolytic anemia, hepatic necrosis, myxoma, nystagmus, pancreatitis, palpitation, prolactinemia, prothrombin decreased, QT prolonged, rhabdomyolysis, spontaneous abortion, thrombocytopenia, thrombocytopenic, ventricular arrhythmia, torsades de pointes, and withdrawal syndrome.

DRUG ABUSE AND DEPENDENCE
Controlled Substance Class
 Citalopram hydrobromide is not a controlled substance.

Physical and Psychological Dependence
 Animal studies suggest that the abuse liability of Citalopram hydrobromide is low. Citalopram hydrobromide has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. The pre-marketing clinical experience with Citalopram hydrobromide did not reveal any drug-seeking behavior. However, the above observations were not systematic and it is not possible to predict, on the basis of this limited experience, the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate Citalopram hydrobromide patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g., development of tolerance, increments of dose, drug-seeking behavior).

OVERDOSE
Human Experience
 In clinical trials of citalopram, there were reports of citalopram overdose, including overdoses of up to 2000 mg, with no associated fatalities. During the postmarketing evaluation of citalopram, Citalopram hydrobromide overdoses, including overdoses of up to 6000 mg, have been reported. As with other SSRIs, a fatal outcome in a patient who has taken an overdose of citalopram has been reported.

Symptoms most often accompanying citalopram overdose, alone or in combination with other drugs and/or alcohol, include: nausea, vomiting, tachycardia, tremor, somnolence, and sinus tachycardia. In more rare cases, observed symptoms included anorexia, confusion, coma, convulsions, hyperventilation, cyanosis, rhabdomyolysis, and ECG changes (including QTc prolongation, nodal rhythm, ventricular arrhythmia, very rare cases of torsade de pointes). Acute renal failure has been very rarely reported accompanying overdose.

Management of Overdose
 Establish and maintain an airway to ensure adequate ventilation and oxygenation. Gastric lavage (using large and low volumes of activated charcoal should be considered. Careful observation and cardiac and vital sign monitoring are recommended along with general symptomatic and supportive care. Due to the large volume of distribution of citalopram, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. There are no specific antidotes for Citalopram hydrobromide.

In managing over dosage, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

DOSEAGE AND ADMINISTRATION
Initial Treatment
 Citalopram should be administered at an initial dose of 20 mg once daily, generally with an increase to a dose of 40 mg/day. Dose increases should usually occur in increments of 20 mg at intervals of no less than one week. Although certain patients may require a dose of 60 mg/day, the only study pertinent to dose response for effectiveness did not demonstrate an advantage for the 80 mg/day dose over the 40 mg/day dose; doses above 40 mg are therefore not ordinarily recommended.

Citalopram should be administered once daily, in the morning or evening, with or without food.

Special Populations
 20 mg/day is the recommended dose for most elderly patients and patients with hepatic impairment, with titration by 40 mg/day only for non-responder patients.

No dosage adjustment is necessary for patients with mild or moderate renal impairment. Citalopram hydrobromide should be used with caution in patients with severe renal impairment.

Treatment of Pregnant Women During the Third Trimester
 Neonates exposed to Citalopram hydrobromide and other SSRIs or SNRIs late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support, and labor feeding (see **PRECAUTIONS**). When treating pregnant women with Citalopram hydrobromide during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Citalopram hydrobromide in the third trimester.

Maintenance Treatment
 It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacologic therapy. Systematic evaluation of Citalopram hydrobromide in two studies has shown that its antidepressant efficacy is maintained for periods of up to 24 weeks following 6 or 8 weeks of initial treatment (32 weeks total). In one study, patients were assigned randomly to placebo or to the same dose of Citalopram (20-80 mg/day) during maintenance treatment as they had received during the acute stabilization phase, while in the other study, patients were assigned randomly to continuation of Citalopram 20 or 40 mg/day, or placebo, for maintenance treatment. In the latter study, the rates of relapse to depression were similar for the two dose groups (see **Clinical Trials** under **CLINICAL PHARMACOLOGY**). Based on these limited data, it is not known whether the dose of citalopram needed to maintain euthymia is identical to the dose needed to initiate remission. If adverse reactions are bothersome, a decrease in dose to 20 mg/day can be considered.

Discontinuation of Treatment with Citalopram Hydrobromide
 Symptoms associated with discontinuation of Citalopram hydrobromide and other SSRIs and SNRIs have been reported (see **PRECAUTIONS**). Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

Switching Patients To or From a Monoamine Oxidase Inhibitor
 At least 14 days should elapse between discontinuation of an MAOI and initiation of Citalopram hydrobromide therapy. Similarly, at least 14 days should be allowed after stopping Citalopram hydrobromide before starting an MAOI (see **CONTRAINDICATIONS** and **WARNINGS**).

HOW SUPPLIED
 Citalopram Tablets, USP: They are supplied in Bottles of 30 NDC # 24658-141-30, Bottles of 100 NDC # 24658-140-01 and 1000 NDC # 24658-140-10, Beige, film coated round, bi-convex tablets de-bossed with **IG** on one side and **140** on the other.

20 mg: They are supplied in Bottles of 30 NDC # 24658-141-30, Bottles of 100 NDC # 24658-141-01 and 1000 NDC # 24658-141-10, Pink, film coated, round, bi-convex tablets de-bossed with **I** on the left side of bisect and **G** on right side of bisect on one side and **207** on the other.

40 mg: They are supplied in Bottles of 30 NDC # 24658-142-30, Bottles of 100 NDC # 24658-142-01 and 1000 NDC # 24658-142-10, White, film coated, round, bi-convex tablets de-bossed with **I** on the left side of bisect and **G** on right side of bisect on one side and **208** on the other.

Store at 20°C to 25°C (68° to 77° F) [see USP Controlled Room Temperature].

ANIMAL TOXICOLOGY
Reproductive Toxicology in Rats
 Pathologic changes (degenerative/atrophy) were observed in the retina of albino rats in the 2-year carcinogenicity study with citalopram. There was an increase in both incidence and severity of retinal pathology in both male and female rats receiving 80 mg/kg/day (13 times the maximum recommended daily human dose of 60 mg on a mg/m² basis). Similar findings were not present in rats receiving 24 mg/kg/day for two years, in mice treated for 18 months at doses up to 240 mg/kg/day, or in dogs treated for one year at doses up to 20 mg/kg/day (4, 20, and 10 times, respectively, the maximum recommended daily human dose on a mg/m^{2</}