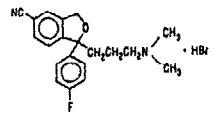
CITALOPRAM HYDROBROMIDE CAPSULES

℞ only

DESCRIPTION

Citalopram hydrobromide is an orally administered selective serotonin reuptake inhibitor (SSRI) with a chemical structure unrelated to that of other SSRI's 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 $C_{20}H_{21}BrFN_2O$ 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 hydrobromide 10 mg capsules have an ivory body and yellow cap and contain citalopram hydrobromide equivalent to 10 mg citalopram base. Citalopram hydrobromide 20 mg capsules have an ivory body and pink cap and contain citalopram hydrobromide equivalent to 20 mg citalopram base. Citalopram hydrobromide 40 mg capsules have an ivory body and green cap and contain citalopram hydrobromide equivalent to 40 mg citalopram base. The capsules also contain the following inactive ingredients: corn starch, crospovidone, edible inks, gelatin, lactose monohydrate, magnesium stearate, titanium dioxide, and yellow iron oxide. The following coloring agents are used in the yellow (10 mg) capsules: D&C Red No. 28, D&C Yellow No. 10, and FD&C Yellow No. 6. The following coloring agents are used in the pink (20 mg) capsules: D&C Red No. 28, D&C Yellow No. 10, FD&C Blue No. 1, and FD&C Red No. 40. The following coloring agents are used in the green (40 mg) capsules: D&C Yellow No. 10 and FD&C Blue No. 1.

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 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 D_1 and D_2, α_1-, α_2-, and β-adrenergic, histamine H_1, 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 hydrobromide are bioequivalent.

Absorption and Distribution

Following a single oral dose (40 mg tablet) 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 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), 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 elderly subjects by 30% and 50%, respectively, whereas in a multiple dose study they were increased by 23% and 30% respectively. 20 mg is the recommended dose for most elderly patients (see **DOSAGE AND ADMINISTRATION**).

Gender - In three pharmacokinetic studies (total N=92), 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 is the recommended dose for most hepatically impaired patients (see **DOSAGE 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 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 CYP-1A2, -2D6, 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, fluconazole, and macrolide antibiotics, and potent inhibitors of CYP2C19, e.g., omeprazole, might decrease the clearance of citalopram. Citalopram steady state levels were not significantly different in poor metabolizers and extensive 2D6 metabolizers after *multiple dose administration of citalopram*, suggesting that coadministration, with citalopram, 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 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 (HAMD) total score, the HAMD 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 80 mg/day. Patients treated with citalopram showed significantly greater improvement than placebo patients on the HAMD total score, HAMD 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 one study and flexible doses of 20 to 60 mg/day in the second study) were randomized to continuation of citalopram or to 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 been seen in the clinical development of all antidepressant drugs. Furthermore, in those circumstances when the drugs have not been studied in the same controlled clinical trial(s), 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 and compared, outcome measures, etc.) vary among trials, it is virtually impossible to distinguish a difference in drug effect from a difference due to one of the confounding factors just enumerated.

INDICATIONS AND USAGE

Citalopram is indicated for the treatment of depression.

The efficacy of citalopram 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 (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 in hospitalized depressed patients has not been adequately studied.

The efficacy of citalopram 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 for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Concomitant use in patients taking monoamine oxidase inhibitors (MAOI's) is contraindicated (see **WARNINGS**).

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

WARNINGS

Potential for Interaction with Monoamine Oxidase Inhibitors

In patients receiving serotonin 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 a MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Furthermore, limited animal data on the effects of combined use of SSRI's and MAOI's suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that citalopram should not be used in combination with a MAOI, or within 14 days of discontinuing treatment with a MAOI. Similarly, at least 14 days should be allowed after stopping citalopram before starting a MAOI.

PRECAUTIONS

General

Hyponatremia

Several cases of hyponatremia and SIADH (syndrome of inappropriate antidiuretic hormone secretion) have been reported in association with citalopram treatment. All patients with these events have recovered with discontinuation of citalopram and/or medical intervention.

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 major affective *disorders treated with other marketed antidepressants*. As with all antidepressants, citalopram should be used cautiously in patients with a history of mania.

Seizures

Although anticonvulsant effects of citalopram have been observed in animal studies, citalopram has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the products premarketing testing. In clinical trials of citalopram, seizures occurred in 0.3% of patients treated with citalopram (a rate of one patient per 98 years of exposure) and 0.5% of patients treated with placebo (a rate of one patient per 50 years of exposure). Like other antidepressants, citalopram should be introduced with care in patients with a history of seizure disorder.

Suicide

The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for citalopram should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

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

Citalopram has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the products premarketing testing. However, the electrocardiograms of 1116 patients who received citalopram in clinical trials were evaluated and the data indicate that citalopram 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 in hepatically impaired patients should be approached with caution and a lower maximum dosage is recommended (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:

Although in controlled studies citalopram has not been shown to impair psychomotor performance, any psychoactive drug may impair judgment, thinking or motor skills, and 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 skills* 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.

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 breast feeding an infant.

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

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

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 (MAOI's) - See **CONTRAINDICATIONS** and **WARNINGS**.

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. The clinical significance of these findings is unknown.

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

Lithium – Coadministration of citalopram (40 mg/day for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. Nevertheless, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of citalopram, caution should be exercised when citalopram and lithium are coadministered.

Theophylline – Combined administration of citalopram (40 mg/day for 21 days) and the CYP1A2 substrate theophylline (single dose of 300 mg) did not affect the pharmacokinetics of theophylline. The effect of theophylline on the pharmacokinetics of citalopram was not evaluated.

Sumatriptan – There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram) is clinically warranted, appropriate observation of the patient is advised.

Warfarin – Administration of 40 mg/day citalopram for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate. Prothrombin time was increased by 5%, the clinical significance of which is unknown.

Carbamazepine – Combined administration of citalopram (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/day for 35 days) did not *significantly affect the pharmacokinetics of carbamazepine*, a CYP3A4 substrate. Although trough citalopram plasma levels were unaffected, given the enzyme inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of citalopram should be considered if the two drugs are coadministered.

Triazolam – Combined administration of citalopram (titrated to 40 mg/day for 28 days) and the CYP3A4 substrate triazolam (single dose of 0.25 mg) did not significantly affect the pharmacokinetics of either citalopram or triazolam.

Ketoconazole – Coadministration of citalopram (40 mg) and ketoconazole (200 mg) decreased the C_{max} and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram.

CYP3A4 and 2C19 Inhibitors - *In vitro* studies indicated that CYP3A4 and 2C19 are the primary enzymes involved in the metabolism of citalopram. However, coadministration of citalopram (40 mg) and ketoconazole (200 mg), a potent inhibitor of CYP3A4, 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.

Metoprolol - Administration of 40 mg/day citalopram for 22 days resulted in a two-fold increase in the plasma levels of the beta-adrenergic blocker metoprolol. Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Coadministration of citalopram and metoprolol had no clinically significant effects on blood pressure or heart rate.

Imipramine and Other Tricyclic Antidepressants (TCAs) – *In vitro* studies suggest that citalopram is a relatively weak inhibitor of CYP2D6. Coadministration of citalopram (40 mg/day for 10 days) with the tricyclic antidepressant imipramine (single dose of 100 mg), a substrate for CYP2D6, did not significantly affect the plasma concentrations of imipramine or citalopram. However, the concentration of the imipramine metabolite desipramine was increased by approximately 50%. The clinical significance of the desipramine change is unknown. Nevertheless, caution is indicated in the coadministration of TCA's with citalopram.

Electroconvulsive Therapy (ECT) - There are no clinical studies of the combined use of electroconvulsive therapy (ECT) and citalopram.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Citalopram was administered in the diet to *NMRI/BOM strain mice and* COBS WI strain rats for 18 and 24 months, respectively. There was no evidence for carcinogenicity of citalopram in mice receiving up to 240 mg/kg/day, which is equivalent to 20 times the maximum recommended human daily dose (MRHD) of 60 mg on a surface area (mg/m^2) 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/m^2 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 (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* unscheduled 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 male and female rats prior to and throughout mating and gestation at doses of 16/24 (males/females), 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 maximum recommended human dose (MRHD) of 60 mg/day on a body surface area (mg/m^2) basis. Gestation duration was increased at 48 mg/kg/day, approximately 8 times the MRHD.

Pregnancy

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 10 times the maximum recommended human dose (MRHD) of 60 mg/day on a body surface area (mg/m^2) basis. This dose was also associated with maternal toxicity (clinical signs, decreased BW gain). The developmental no effect dose of 56 mg/kg/day is approximately 9 times the MRHD on a mg/m^2 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/m^2 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/m^2 basis. The no effect dose of 12.8 mg/kg/day is approximately 2 times the MRHD on a mg/m^2 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/m^2 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.

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 breast feeding 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.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

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 **DOSAGE AND ADMINISTRATION**).

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 PHARAMACOLOGY**).

20 mg/day is the recommended dose for most elderly patients (see **DOSAGE 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*: 429 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 6 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 1. It should be noted that one patient can report more than one reason for discontinuation and be counted more than once in this table.

TABLE 1

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Depression Trials		
	Percentage of Patients Discontinuing Due to Adverse Event	
Body System/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 2 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 2).

TABLE 2

Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials*		
	Percentage of Patients Reporting Event	
Body System/Adverse 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[3]	3%	<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.

[1]Denominator used was for females only (N=638 citalopram; N=252 placebo).
[2]Primarily ejaculatory delay.
[3]Denominator used was for 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.

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 selective serotonin reuptake inhibitors (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 the 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)
Decreased Libido	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.

Priapism 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

Electrocardiograms from citalopram (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 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

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 2 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 1/1000 patients; rare events are those occurring in fewer than 1/1000 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, vertigo, hypertonia, extrapyramidal disorder, leg cramps, involuntary muscle contractions, hypokinesia, neuralgia, dystonia, abnormal gait, hypesthesia, ataxia. *Rare:* abnormal coordination, hyperesthesia, ptosis, 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 flushes, rigors, alcohol intolerance, syncope, influenza-like symptoms. *Rare:* hayfever.

Hemic and Lymphatic Disorders – *Infrequent:* purpura, anemia, epistaxis, leukocytosis, leucopenia, lymphadenopathy. *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, hyperglycemia, hepatitis, dehydration.

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

Psychiatric Disorders – *Frequent:* impaired concentration, amnesia, 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 – *Frequent:* rash, pruritus. *Infrequent:* photosensitivity reaction, urticaria, acne, skin discoloration, eczema, alopecia, dermatitis, skin dry, psoriasis. *Rare:* hypertrichosis, decreased sweating, melanosis, keratitis, cellulitis, pruritus ani.

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

Urinary System Disorders – *Frequent:* polyuria. *Infrequent:* micturition frequency, urinary incontinence, urinary retention, dysuria. *Rare:* facial edema, hematuria, oliguria, pyelonephritis, renal calculus, renal pain.

Other Events Observed During the Non-US Postmarketing Evaluation of Citalopram

It is estimated that approximately 8 million patients have been treated with citalopram since market introduction. Although no causal relationship to citalopram treatment has been found, the following adverse events have been reported to be temporally associated with citalopram treatment in at least 3 patients (unless otherwise noted) and are not described elsewhere in labeling: angioedema, choreoathetosis, epidermal necrolysis (3 cases), erythema multiforme, hepatic necrosis (2 cases), neuroleptic malignant syndrome, pancreatitis, serotonin syndrome, spontaneous abortion, thrombocytopenia, ventricular arrhythmia, Torsades de pointes, priapism, 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 is low. Citalopram has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. The premarketing clinical experience with citalopram did not reveal any drug seeking behavior. However, these 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 patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g., development of tolerance, incrementations of dose, drug seeking behavior).

OVERDOSAGE

Human Experience

Although there were no reports of fatal citalopram overdose in clinical trials involving overdoses of up to 2000 mg, postmarketing reports of drug overdoses involving citalopram have included 12 fatalities, 10 in combination with other drugs and/or alcohol and 2 with citalopram alone (3920 mg and 2800 mg), as well as non-fatal overdoses of up to 6000 mg. Symptoms most often accompanying citalopram overdose, alone or in combination with other drugs and/or alcohol, included dizziness, sweating, nausea, vomiting, tremor, somnolence, and sinus tachycardia. In more rare cases, observed symptoms included amnesia, confusion, coma, convulsions, hyperventilation, cyanosis, rhabdomyolysis, and ECG changes (including QTc prolongation, nodal rhythm, ventricular arrhythmia, and one possible case of Torsades de pointes).

Management of Overdose

Establish and maintain an airway to ensure adequate ventilation and oxygenation. Gastric evacuation by lavage and use 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.

In managing overdosage, 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.

DOSAGE 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 60 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 to 40 mg/day only for nonresponding patients.

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

Maintenance Treatment

It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacologic therapy. Systematic evaluation of citalopram 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 to 60 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 Efficacy 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 induce remission if adverse reactions are bothersome, a decrease in dose to 20 mg/day can be considered.

Switching Patients To or From a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of citalopram therapy. Similarly, at least 14 days should be allowed after stopping citalopram before starting a MAOI (see **CONTRAINDICATIONS** and **WARNINGS**).

HOW SUPPLIED

Citalopram hydrobromide capsules are available as follows:

10 mg[†], ivory body, yellow cap printed in black with "CM10" and "G".

Bottles of 100 NDC 57315-084-01
Bottles of 1000 NDC 57315-084-03

20 mg[†], ivory body, pink cap printed in black with "CM20" and "G".

Bottles of 100 NDC 57315-085-01
Bottles of 1000 NDC 57315-085-03

40 mg[†], ivory body, green cap printed in black with "CM40" and "G".

Bottles of 100 NDC 57315-086-01
Bottles of 1000 NDC 57315-086-03

[†] Citalopram base equivalent.

Store at controlled room temperature 15° to 30°C (59° to 86°F)(see USP).

Dispense in a tight light-resistant container.

ANIMAL TOXICOLOGY

Retinal Changes in Rats

Pathologic changes (degeneration/atrophy) were observed in the retinas 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/m² basis).

Additional studies to investigate the mechanism for this pathology have not been performed, and the potential significance of this effect in humans has not been established.

Cardiovascular Changes in Dogs

In a one-year toxicology study, 5 of 10 beagle dogs receiving oral doses of 8 mg/kg/day (4 times the maximum recommended daily human dose of 60 mg on a mg/m² basis) died suddenly between weeks 17 and 31 following initiation of treatment. Although appropriate data from that study are not available to directly compare plasma levels of citalopram (CT) and its metabolites, demethylcitalopram (DCT) and didemethylcitalopram (DDCT), to levels that have been achieved in humans, pharmacokinetic data indicate that the relative dog to human exposure was greater for the metabolites than for citalopram. Sudden deaths were not observed in rats at doses up to 120 mg/kg/day, which produced plasma levels of CT, DCT and DDCT similar to those observed in dogs at doses of 8 mg/kg/day. A subsequent intravenous dosing study demonstrated that in beagle dogs, DDCT caused QT prolongation, a known risk factor for the observed outcome in dogs. This effect occurred in dogs at doses producing peak DDCT plasma levels of 810 to 3250 nM (39 to 155 times the mean steady state DDCT plasma level measured at the maximum recommended human daily dose of 60 mg). In dogs, peak DDCT plasma concentrations are approximately equal to peak CT plasma concentrations, whereas in humans, steady state DDCT plasma concentrations are less than 10% of steady state CT plasma concentrations. Assays of DDCT plasma concentrations in 2020 citalopram treated individuals demonstrated that DDCT levels rarely exceeded 70 nM; the highest measured level of DDCT in human overdose was 138 nM. While DDCT is ordinarily present in humans at lower levels than in dogs, it is unknown whether there are individuals who may achieve higher DDCT levels. The possibility that DCT, a principal metabolite in humans, may prolong the QT interval in the dog has not been directly examined because DCT is rapidly converted to DDCT in that species.

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