

PERRIGO CITALOPRAM- citalopram tablet
Contract Pharmacy Services-PA

CITALOPRAM TABLETS, 20 mg

Citalopram Tablets, USP

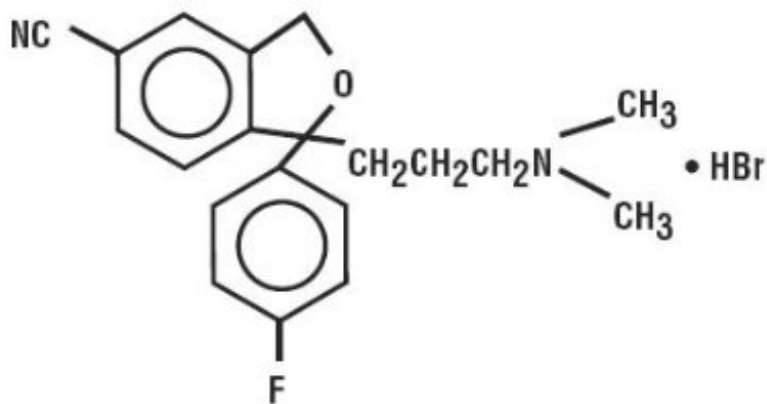
Rx only

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 HBr Tablets or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in the 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 HBr Tablets are not approved for use in pediatric patients. (See WARNINGS:CLINICAL WORSENING AND SUICIDE RISK, PRECAUTIONS:Information for Patients, and PRECAUTIONS: Pediatric Use)

DESCRIPTION

Citalopram HBr 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 HBr is a racemic bicyclic phthalane derivative designated (\pm)-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1, 3-dihydroisobenzofuran-5-carbonitrile, HBr with the following structural formula:



The molecular formula is C₂₀H₂₂BrFN₂O and its molecular weight is 405.35.

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

Citalopram Tablets, USP 10 mg are film coated, round tablets containing citalopram HBr in strength equivalent to 10 mg citalopram base. Citalopram Tablets, USP 20 mg and 40 mg tablets are film coated, round, scored tablets containing citalopram HBr in strengths equivalent to 20 mg or 40 mg citalopram base. The tablets also contain the following inactive ingredients: colloidal silicon dioxide, corn starch, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. Orange 40L13864 is used as a coloring agent in the beige (10 mg) tablets and contains: FD&C yellow #6, hypromellose 2910 3cP, 6cP, and 50cP, polydextrose, polyethylene glycol, titanium dioxide, and triacetin. Orange 40L13950 is used as a coloring agent in the pink (20 mg) tablets and contains: FD&C red #40, FD&C yellow #6, hypromellose 2910 3cP, 6cP, and 50cP, polydextrose, polyethylene glycol, titanium dioxide, and triacetin. White Y-22-7719 is used as a coloring agent in the white (40 mg) tablets and contains: hypromellose 2910 3cP, 6cP, and 50cP, polydextrose, polyethylene glycol, titanium dioxide, and triacetin.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of citalopram HBr as an antidepressant is presumed to be linked to potentiation of serotonergic activity in the central nervous system (CNS) resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT).

In vitro and *in vivo* studies in animals suggest that citalopram is a highly selective serotonin reuptake inhibitor (SSRI) with minimal effects on norepinephrine (NE) and dopamine (DA) neuronal reuptake. Tolerance to the inhibition of 5-HT uptake is not induced by long-term (14-day) treatment of rats with citalopram. Citalopram is a racemic mixture (50/50), and the inhibition of 5-HT reuptake by citalopram is primarily due to the (S)-enantiomer.

Citalopram has no or very low affinity for 5-HT_{1A}, 5-HT_{2A}, dopamine D₁ and D₂, α ₁-, α ₂-, and β -adrenergic, histamine H₁, gamma aminobutyric acid (GABA), muscarinic cholinergic, and benzodiazepine receptors. Antagonism of muscarinic, histaminergic and adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative and cardiovascular effects of other psychotropic drugs.

Pharmacokinetics

The single- and multiple-dose pharmacokinetics of citalopram are linear and dose-proportional in a dose range of 10-60 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.

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

Reduced hepatic function - Citalopram oral clearance was reduced by 37% and half-life was doubled in patients with reduced hepatic function compared to normal subjects. 20 mg 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 CYP1A2, -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, itraconazole, and macrolide antibiotics) and potent inhibitors of CYP2C19 (e.g., omeprazole) might decrease the clearance of citalopram. However, coadministration of citalopram and the potent 3A4 inhibitor ketaconazole 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 HBr Tablets, suggesting that coadministration, with Citalopram HBr Tablets, 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 HBr Tablets as a treatment for depression was established in two placebo-controlled studies (of 4 to 6 weeks in duration) in adult outpatients (ages 18-66) meeting DSM-III or DSM-III-R criteria for major depression. Study 1, a 6-week trial in which patients received fixed

Citalopram HBr Tablets doses of 10, 20, 40, and 60 mg/day, showed that Citalopram HBr Tablets 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 HBr Tablets 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 HBr Tablets 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 HBr Tablets 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 20-60 mg/day in the second study) were randomized to continuation of Citalopram HBr Tablets or to placebo. In both studies, patients receiving continued Citalopram HBr Tablet 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 HBr Tablets. 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 HBr Tablets are indicated for the treatment of depression.

The efficacy of Citalopram HBr Tablets in the treatment of depression was established in 4-6 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 HBr Tablets in hospitalized depressed patients has not been adequately studied. The efficacy of Citalopram HBr Tablets 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 HBr Tablets 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 (MAOIs) is contraindicated (see **WARNINGS**).

Concomitant use in patients taking pimozide is contraindicated (see **PRECAUTIONS**).

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

WARNINGS

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. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) 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 9 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 across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in **TABLE 1**.

TABLE 1

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

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

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

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

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive 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 **DOSAGE AND ADMINISTRATION - Discontinuation of Treatment with Citalopram HBr Tablets**, for a description of the risks of discontinuation of Citalopram HBr Tablets).

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 HBr Tablets 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 mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Citalopram HBr Tablets are not approved for use in treating bipolar depression.

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 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 HBr Tablets 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 HBr Tablets before starting an MAOI.

Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome may occur with SNRIs and SSRIs, including Citalopram HBr treatment, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin 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).

The concomitant use of Citalopram HBr with MAOIs intended to treat depression is contraindicated (see **CONTRAINDICATIONS and WARNINGS - Potential for Interaction with Monoamine Oxidase Inhibitors**.) If concomitant treatment of Citalopram HBr with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **PRECAUTIONS - Drug Interactions**). The concomitant use of Citalopram HBr with serotonin precursors (such as tryptophan) is not recommended (see **PRECAUTIONS- Drug Interactions**).

PRECAUTIONS

General

Discontinuation of Treatment with Citalopram HBr Tablets

During marketing of Citalopram HBr Tablets 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., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with Citalopram HBr Tablets. 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 **DOSAGE AND ADMINISTRATION**).

Abnormal Bleeding

Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (see **Drug Interactions**). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of Citalopram HBr Tablets with NSAIDs, aspirin, or other drugs that affect coagulation.

Hyponatremia

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including citalopram. In many

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

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

Activation of Mania/Hypomania

In placebo-controlled trials of Citalopram HBr Tablets, some of which included patients with bipolar disorder, activation of mania/hypomania was reported in 0.2% of 1063 patients treated with Citalopram HBr Tablets 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 HBr Tablets should be used cautiously in patients with a history of mania.

Seizures

Although anticonvulsant effects of citalopram have been observed in animal studies, Citalopram HBr Tablets have 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 HBr Tablets, seizures occurred in 0.3% of patients treated with Citalopram HBr Tablets (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 HBr Tablets 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 HBr Tablets 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 HBr Tablet therapy does not affect their ability to engage in such activities.

Use in Patients with Concomitant Illness

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

Citalopram HBr Tablets have 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 product's premarketing testing. However, the electrocardiograms of 1116 patients who received Citalopram HBr Tablets in clinical trials were evaluated and the data indicate that Citalopram HBr Tablets are 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 HBr Tablets 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 HBr Tablets, 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 HBr Tablets.

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

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

Patients should be told that, although Citalopram HBr Tablets have not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of Citalopram HBr Tablets 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 HBr Tablets and NSAIDs, aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin 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 HBr Tablet therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.

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

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Citalopram HBr Tablets.

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.

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 HBr, and the potential for serotonin syndrome, caution is advised when Citalopram HBr is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (see **WARNINGS - Serotonin Syndrome**). The concomitant use of Citalopram HBr 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 HBr 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 HBr Tablets 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 potentiated the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with Citalopram HBr Tablets.

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

Lithium - Coadministration of Citalopram HBr Tablets (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 HBr Tablets and lithium are coadministered.

Pimozide - In a controlled study, a single dose of pimozide 2 mg co-administered with citalopram 40 mg given once daily for 11 days was associated with a mean increase in QT_c values of approximately 10 msec compared to pimozide given alone. Citalopram did not alter the mean AUC or C_{max} of pimozide. The mechanism of this pharmacodynamic interaction is not known.

Theophylline - Combined administration of Citalopram HBr Tablets (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 an 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 HBr Tablets 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 HBr Tablets (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 HBr Tablets (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 - Combined administration of Citalopram HBr Tablets (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 HBr Tablets 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 HBr Tablets 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 HBr Tablets (40 mg/day for 10 days) with the TCA 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 TCAs with Citalopram HBr Tablets.

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

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/m²) basis. There was an increased incidence of small intestine carcinoma in rats receiving 8 or 24 mg/kg/day, doses which are approximately 1.3 and 4 times the MRHD, respectively, on a mg/m² basis. A no-effect dose for this finding was not established. The relevance of these findings to humans is unknown.

Mutagenesis

Citalopram was mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) in 2 of 5 bacterial strains (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 16 male and 24 female rats prior to and throughout mating and gestation at doses of 32, 48, and 72 mg/kg/day, mating was decreased at all doses, and fertility was decreased at doses \geq 32 mg/kg/day, approximately 5 times the MRHD of 60 mg/day on a body surface area (mg/m²) basis. Gestation duration was increased at 48 mg/kg/day, approximately 8 times the MRHD.

Pregnancy

Pregnancy Category C

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

In two rat embryo/fetal development studies, oral administration of citalopram (32, 56, or 112 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased embryo/fetal growth and survival and an increased incidence of fetal abnormalities (including cardiovascular and skeletal defects) at the high dose, which is approximately 18 times the MRHD of 60 mg/day on a body surface area (mg/m²) basis. This 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 embryo/fetal development were observed at doses of up to 16 mg/kg/day, or approximately 5 times the MRHD on a mg/m² basis. Thus, teratogenic effects were observed at a maternally toxic dose in the rat and were not observed in the rabbit.

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

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

Nonteratogenic Effects

Neonates exposed to Citalopram HBr Tablets and other SSRIs or SNRIs, late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, 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- 2 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 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to

SSRIs after the 20th 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 enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk.

When treating a pregnant woman with Citalopram HBr Tablets during the third trimester, the physician should carefully consider both; the potential risks and benefits of treatment (see **DOSAGE 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 HBr Tablets on labor and delivery in humans is unknown.

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in the pediatric population have not been established (see **BOX WARNING** and **WARNINGS - CLINICAL WORSENING AND SUICIDE RISK**). Two placebo-controlled trials in 407 pediatric patients with MDD have been conducted with Citalopram HBr Tablets, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of Citalopram HBr Tablets in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use

Of 4422 patients in clinical studies of Citalopram HBr Tablets, 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 HBr Tablets 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 PHARMACOLOGY**). 20 mg/day is the recommended dose for most elderly patients (see **DOSAGE AND ADMINISTRATION**). SSRIs and SNRIs, including citalopram, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event (see **PRECAUTIONS, Hyponatremia**).

ADVERSE REACTIONS

The premarketing development program for Citalopram HBr Tablets 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 patientexposure years. There were, in addition,

over 19,000 exposures from mostly open-label, European postmarketing studies.

The conditions and duration of treatment with Citalopram HBr Tablets 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 HBr Tablets 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 HBr Tablet-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 in Short-Term, Placebo Controlled, Depression Trials

TABLE 2

| Percentage of Patients Discontinuing Due to Adverse Event | | |
|--|---|---|
| <u>Body System/Adverse Event</u> | <u>Citalopram</u> (N=1063) | <u>Placebo</u> (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 HBr Tablet-Treated Patients

Table 3 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 1063 depressed patients who received Citalopram HBr Tablets 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 HBr Tablets and for which the incidence in patients treated with Citalopram HBr Tablets 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 HBr Tablet 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**).

Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials* (Percentage of Patients Reporting Event)

TABLE 3

| 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 HBr Tablets are reported, except for the following events which had an incidence on placebo \geq Citalopram HBr Tablets: 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 HBr Tablets; N=252 placebo).

² Primarily ejaculatory delay.

³ Denominator used was for males only (N=425 Citalopram HBr Tablets; N=194 placebo).

Dose Dependency of Adverse Events

The potential relationship between the dose of Citalopram HBr Tablets administered and the incidence of adverse events was examined in a fixed-dose study in depressed patients receiving placebo or Citalopram HBr Tablets 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 SSRIs can cause such untoward sexual experiences.

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

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

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

In female depressed patients receiving Citalopram HBr Tablets, 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 HBr Tablet 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 HBr Tablet treatment. In addition, a comparison of supine and standing vital sign measures for Citalopram HBr Tablet and placebo treatments indicated that Citalopram HBr Tablet treatment is not associated with orthostatic changes.

Weight Changes

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

Laboratory Changes

Citalopram HBr Tablet 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 HBr Tablet treatment.

ECG Changes

Electrocardiograms from Citalopram HBr Tablet (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 HBr Tablets 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 HBr Tablets

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 HBr Tablets 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 HBr Tablets, 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, hypoglycemia, 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, paroniria, 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 Postmarketing Evaluation of Citalopram HBr Tablets

It is estimated that over 30 million patients have been treated with Citalopram HBr Tablets since market introduction. Although no causal relationship to Citalopram HBr Tablet treatment has been found, the following adverse events have been reported to be temporally associated with Citalopram HBr Tablet treatment, and have not been described elsewhere in labeling: acute renal failure, akathisia, allergic reaction, anaphylaxis, angioedema, choreoathetosis, chest pain, delirium, dyskinesia, ecchymosis, epidermal necrolysis, erythema multiforme, gastrointestinal hemorrhage, glaucoma, grand mal

convulsions, hemolytic anemia, hepatic necrosis, myoclonus, neuroleptic malignant syndrome, nystagmus, pancreatitis, priapism, prolactinemia, prothrombin decreased, QT prolonged, rhabdomyolysis, serotonin syndrome, spontaneous abortion, thrombocytopenia, thrombosis, ventricular arrhythmia, torsades de pointes, and withdrawal syndrome.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Citalopram HBr Tablet is not a controlled substance.

Physical and Psychological Dependence

Animal studies suggest that the abuse liability of Citalopram HBr Tablets is low. Citalopram HBr Tablets have not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. The premarketing clinical experience with Citalopram HBr Tablets 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 HBr Tablet 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

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 HBr Tablet 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 rarely reported.

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 very rare cases of torsades 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 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 HBr Tablets.

In managing overdose, 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 HBr Tablets 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 HBr Tablets 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 HBr Tablets should be used with caution in patients with severe renal impairment.

Treatment of Pregnant Women During the Third Trimester

Neonates exposed to Citalopram HBr Tablets and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see **PRECAUTIONS**). When treating pregnant women with Citalopram HBr Tablets during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Citalopram HBr Tablets 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 HBr Tablets 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 HBr Tablets (20-60 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 HBr Tablets 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.

Discontinuation of Treatment with Citalopram HBr Tablets

Symptoms associated with discontinuation of Citalopram HBr Tablets 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 HBr Tablet therapy. Similarly, at least 14 days should be allowed after stopping Citalopram HBr Tablets before starting an MAOI (see **CONTRAINDICATIONS** and **WARNINGS**).

HOW SUPPLIED

Citalopram Tablets, USP

20 mg Blister of 30 NDC # 67046-111-30

Pink, round, bi-convex, scored, film coated tablets debossed "KALI" on one side and "281" on the scored side.

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

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 (39-155 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 dogs has not been directly examined because DCT is rapidly converted to DDCT in that species.

DISTRIBUTED BY

PERRIGO®

ALLEGAN, MI 49010

Made in India

Manufactured by:

Matrix Laboratories Limited

Secunderabad, India

: 06000 RC J3

Rev. 02/08

Repackaged by:

Contract Pharmacy Services-PA

125 Titus Ave Suite 200
Warrington, PA 18976 USA

Original--02/2010--NJW

Medication Guide

Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with your or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines.

Talk to your, or your family member's, healthcare provider about:

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.

2. Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions. These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.

3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?

- Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
- Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
- Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

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

Call your doctor for medical advice about side effects.

You may report side effects to FDA at 1-800-FDA-1088.


Principal Display Panel - 30 Tablet Label

Citalopram Tablets, USP

20 mg*

Rx Only

CITALOPRAM
20MG TAB #30



58180020100320
Rx Only

LOT# SAMPLE
ID: KALI 281
EXP: 12/11

PERRIGO

USUAL DOSAGE:
SEE INSERT


STORAGE
CONDITIONS: SEE
INSERT
(STORE AT
CONTROLLED ROOM
TEMPERATURE)

FILLED BY: _____

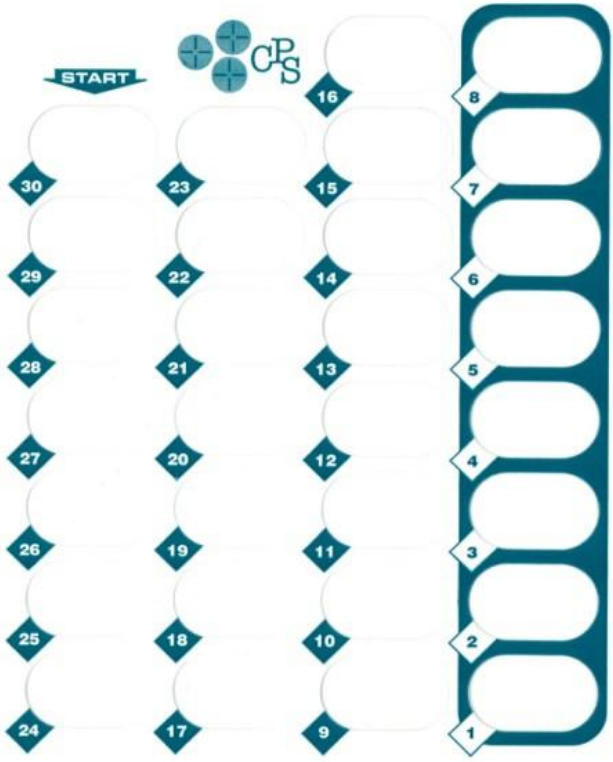
CHECKED BY: _____


Med. _____
STRENGTH _____
EXP. DATE _____
MFG. _____
LOT NO. _____

Contract Pharmacy Services-PA
125 Titus Avenue, Suite #200, Warrington, PA 18976



START





Contract Pharmacy Services

CAUTION: This package NOT CHILD RESISTANT. Store this and all medications out of reach of children.

PERRIGO CITALOPRAM

citalopram tablet

Product Information

| | | | |
|--------------------------------|-------------------------|---------------------------|------------------------------|
| Product Type | HUMAN PRESCRIPTION DRUG | Item Code (Source) | NDC:67046-111(NDC:45802-596) |
| Route of Administration | ORAL | | |

Active Ingredient/Active Moiety

| Ingredient Name | Basis of Strength | Strength |
|---|-------------------|----------|
| CITALOPRAM HYDROBROMIDE (UNII: IIE9D14F36) (CITALOPRAM - UNII:0DHU5B8D6V) | CITALOPRAM | 20 mg |

Product Characteristics

| | | | |
|-----------------|-------|---------------------|----------|
| Color | PINK | Score | 2 pieces |
| Shape | ROUND | Size | 9mm |
| Flavor | | Imprint Code | KALI;281 |
| Contains | | | |

Packaging

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|---|------------------|----------------------|----------------------|--------------------|
| 1 | NDC:67046-111-30 | 30 in 1 BLISTER PACK | | |

Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|--------------------|--|----------------------|--------------------|
| ANDA | ANDA077042 | 02/25/2010 | |

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Revised: 2/2010

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