PRODUCT MONOGRAPH

[Pr]CITALOPRAM - 10

(Citalopram Hydrobromide Tablets)

10 mg

ANTIDEPRESSANT

PRODOC LTÉE
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Laval, Quebec
H7L 3W9

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	tablet 10 mg	None. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

CITALOPRAM - 10 (citalopram hydrobromide) is indicated for the symptomatic relief of depressive illness.

The relapse rate was significantly lower in citalopram-treated patients than in placebo-treated patients in two placebo-controlled studies, that were conducted over a 24-week period in patients who responded to 6 or 8 weeks of acute treatment with citalopram (see Clinical Trials under ACTION AND CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use citalopram for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

Geriatrics (> 65 years of age): Lower doses and lower maximum doses are recommended for elderly patients (see Warnings and Precautions).

Pediatrics (0 to 18 years of age): No data is available.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **Dosage Forms, Composition and Packaging** section of the product monograph.
- Patients should not take citalopram in combination with a monoamine oxidase inhibitor (MAOI) or within 14 days of discontinuing treatment with a MAOI. Similarly, at least 14 days should elapse after discontinuing citalopram treatment before starting a MAOI (see DRUG-DRUG INTERACTIONS).
- Citalopram should not be used in combination with the anti-psychotic drug pimozide, as results from a

controlled study with racemic citalopram indicate that concomitant use is associated with an increased risk of Qtc prolongation compared to pimozide alone. This apparent pharmacodynamic interaction occurred in the absence of a clinically significant pharmacokinetic interaction; the mechanism is unknown (see PRECAUTIONS, Drug Interactions).

WARNINGS AND PRECAUTIONS

POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM.

- **Pediatrics: Placebo-Controlled Clinical Trial Data**
  Recent analyses of placebo-controlled clinical trial safety databases from SSRIs and other newer anti-depressants suggest that use of these drugs in patients under the age of 18 may be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour over that of placebo.

- **The small denominators in the clinical trial database, as well as the variability in placebo rates, preclude reliable conclusions on the relative safety profiles among these drugs.**

Adults and Pediatrics: Additional data

- **There are clinical trial and post-marketing reports with SSRIs and other newer anti-depressants, in both pediatrics and adults, of severe agitation-type adverse events coupled with self-harm or harm to others. The agitation-type events include: akathisia, agitation, disinhibition, emotional lability, hostility, aggression, depersonalization. In some cases, the events occurred within several weeks of starting treatment.**

Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring for agitation-type emotional and behavioural changes.

Discontinuation Symptoms
Patients currently taking CITALOPRAM - 10 should NOT be discontinued abruptly, due to risk of discontinuation symptoms. At the time that a medical decision is made to discontinue an SSRI or other newer antidepressant drug, a gradual reduction in the dose rather than an abrupt cessation is recommended.

Cardiovascular

Use in Patients with Cardiac Disease
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 trials during the drug's premarketing assessment. However, the electrocardiograms of patients, who received citalopram in clinical trials, indicate that citalopram was not associated with the development of clinically significant ECG abnormalities.

In clinical trials, citalopram caused small but statistically significant decreases in heart rate (see ECG under ADVERSE REACTIONS). Consequently, caution should be observed when citalopram is initiated in patients with pre-existing slow heart rate.

Dependence/Tolerance

Discontinuation of treatment with citalopram

When discontinuing treatment, patients should be monitored for symptoms which may be associated with discontinuation (e.g. dizziness, abnormal dreams, sensory disturbances [including paresthesias and electric shock sensations], agitation, anxiety, emotional indifference, impaired concentration, headache, migraine, tremor, nausea, vomiting and sweating or other symptoms which may be of clinical significance. (See ADVERSE REACTIONS). A gradual reduction in the dosage over several weeks, rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response. (See ADVERSE REACTIONS and DOSAGE and ADMINISTRATION).

Endocrine and Metabolism

Use in Diabetic Patients

Citalopram has not been systematically evaluated in diabetic patients since diabetes constituted an exclusion criterion. Although 13 patients did receive insulin during the studies, this number is too small to determine whether citalopram affects the response to insulin. Rare events of hypoglycemia were reported. Citalopram should be used with caution in diabetic patients on insulin or other antidiabetic drugs.

Hyponatremia

Hyponatremia and SIADH (syndrome of inappropriate antidiuretic hormone secretion) have been reported as a rare adverse event with use of citalopram as with other SSRIs. Elderly female patients in particular seem to be a group at risk.

Hematologic

Bleeding Disorders

There have been reports of cutaneous bleeding abnormalities such as ecchymosis and purpura with SSRIs. Caution is advised in patients taking SSRIs, particularly in concomitant use with drugs known to affect platelet function (e.g., atypical antipsychotics and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid, and non-steroidal anti-inflammatory drugs (NSAIDS)) as well as in patients with a history of bleeding disorders.

Hepatic/biliary/Pancreatic

Hepatic Impairment

In subjects with hepatic impairment, citalopram clearance was significantly decreased and plasma concentrations, as well as elimination half-life significantly increased (see PHARMACOKINETICS). Consequently, the use of citalopram in hepatically impaired patients should be approached with caution and a lower maximum dosage is recommended (see DOSAGE AND ADMINISTRATION).

Neurologic

Interference with Cognitive and Motor Performance

In studies in normal volunteers, citalopram in doses of 40 mg/day did not impair cognitive function or psychomotor performance. However, psychotropic medications may impair judgement, thinking or motor skills. Consequently, patients should be cautioned against driving a car or operating hazardous machinery until they are reasonably certain that citalopram does not affect them adversely.

Electroconvulsive Therapy (ECT)

The safety and efficacy of the concurrent use of citalopram and ECT have not been studied.

Serotonin Syndrome
Rarely, the occurrence of serotonin syndrome has been reported in patients receiving SSRIs. A combination of symptoms, possibly including agitation, confusion, tremor, myoclonus and hyperthermia, may indicate the development of this condition.

Seizures
Citalopram has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the premarketing testing of citalopram. In clinical trials, seizures occurred in 0.25% of patients treated with citalopram and in 0.23% patients treated with placebo. Like other antidepressants, citalopram should be used with caution in patients with a history of seizure disorder. The drug should be discontinued in any patient who develops seizures.

Psychiatric

Activation of Mania/Hypomania
In placebo-controlled trials with citalopram, some of which included patients with bipolar disorder, mania/hypomania was reported in 0.1% of 1027 patients treated with citalopram versus none of the 426 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. If a patient enters a manic phase, citalopram should be discontinued.

PRECAUTIONS

Suicide
The possibility of a suicide attempt is inherent in depression and may persist until remission occurs. Therefore, high risk patients should be closely supervised throughout therapy with citalopram and consideration should be given to the possible need for hospitalization. In order to minimize the opportunity for overdosage, prescription for citalopram should be written for the smallest quantity of drug consistent with good patient management (see **WARNINGS AND PRECAUTIONS: POTENTIAL ASSOCIATION WITH BEHAVIORAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM**).

Renal

Renal Impairment
No dosage adjustment is needed in patients with mild to moderate renal impairment. Since, no information is available on the pharmacokinetic or pharmacodynamic effects of citalopram in patients with severely reduced renal function (creatinine clearance <20 mL/min), citalopram should be used with caution in these patients.

Special Population

Pregnant Women
The safety of citalopram during pregnancy and has not been established. Therefore, citalopram should not be used during pregnancy, unless, in the opinion of the physician, the expected benefits to the patient markedly outweigh the possible hazards to the fetus.

Post-marketing reports indicate that some neonates exposed to SSRIs such as CITALOPRAM and other newer antidepressants 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, hyperreflexia, tremor jitteriness, irritability and constant crying. These features are consistent with either a direct toxic effect of SSRIs and other newer antidepressants, or possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS AND PRECAUTIONS, Neurologic, Serotonin Syndrome). When treating a pregnant woman with CITALOPRAM during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. (See DOSAGE AND ADMINISTRATION).

Nursing Women
The safety of citalopram during lactation has not been established. Citalopram is excreted in human milk.Therefore, citalopram should not be administered to nursing mothers unless, in the opinion of the treating physician, the expected benefits to the patient markedly outweigh the possible hazards to the fetus.

Pediatrics
Safety and effectiveness in patients below the age of 18 have not been established.

Geriatrics
In premarketing clinical trials, 800 elderly patients (≥65 years of age) have been treated with citalopram. Of these patients 298 were ≥75 years old. In a pharmacokinetic study (N=11, age 73 to 90 years), clearance was substantially decreased and half-life prolonged (see PHARMACOKINETICS). In a 6-week placebo-controlled study, approximately equal numbers of patients received citalopram at 20 or 30 mg per day, as the final dose. In about 5% of patients, the final dose was 10 mg per day (see CLINICAL TRIALS under ACTION AND CLINICAL PHARMACOLOGY). Consequently, elderly patients should be administered lower doses and a lower maximum dose (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

During the premarketing clinical development, 3652 patients received citalopram hydrobromide for the treatment of depression. Of these patients, 66% were females and 34% were males. The mean age of the patients was 50 years, with 70% being <60 years old (30% <40 years old, 40% 40 to 59 years old) and 30% being ≥60 years old.

Adverse events observed with citalopram are in general mild and transient. They usually attenuate during the first one or two weeks of treatment.

Most Frequent Adverse Events
Adverse events that occurred in citalopram -treated patients in the course of the short-term, placebo-controlled trials with an incidence greater than, or equal to, 10% were: nausea, dry mouth, somnolence, and increased sweating (Table 1).

CLINICAL TRIAL ADVERSE DRUG REACTIONS

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Findings Observed in Short-term, Placebo-controlled Trials

Adverse Reactions Associated with Discontinuation of Treatment

From the short-term (4 to 6 weeks) placebo-controlled, Phase III clinical trials, 15.9% (163/1027) of the citalopram -treated patients discontinued treatment due to an adverse event. The discontinuation rate in the placebo-treated patients was 7.7% (33/426).

The events associated with discontinuation of citalopram in 1% or more of patients at a rate of at least twice that of placebo, were as follows:

Nausea (4.1% *versus* 0.0%), insomnia (2.4% *versus* 1.2%), somnolence (2.4% *versus* 1.2%), dizziness (2.3% *versus* 0.7%), vomiting (1.3% *versus* 0.0%), agitation (1.2% *versus* 0.0%), asthenia (1.1% *versus* 0.5%), and dry mouth (1.1% *versus* 0.2%).

Incidence of Adverse Events in Placebo-controlled Studies

Table 1 enumerates the incidence of treatment emergent adverse events that occurred in 1027 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. Reported adverse events were classified using the standard World Health Organization (WHO)-based dictionary terminology.

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.

TABLE 1
Common Side Effects (≥1%)
TREATMENT-EMERGENT ADVERSE EVENTS*
INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

Body System/Adverse Event	Percentage of Patients Reporting	
	Citalopram (N = 1027)	**Placebo (N = 426)**
Autonomic Nervous System		
Dry mouth[1]	19.4	12.2
Sweating increased	10.5	8.0
Body as a Whole		
Fatigue	5.2	3.1
Fever[1]	2.4	0.2

Body System/Adverse Event	Percentage of Patients Reporting	
	Citalopram (N = 1027)	Placebo (N = 426)
Central and Peripheral Nervous System		
Tremor	8,4	6,3
Gastrointestinal System		
Nausea[1]	20.6	13.4
Diarrhea	8.1	5.4
Dyspepsia	4.3	3.5
Vomiting	3.9	2.6
Abdominal pain	3.1	2.1
Psychiatric		
Somnolence[1]	17.3	9.9
Anorexia[1]	4.2	1.6
Nervousness	3.6	3.5
Anxiety	3.3	2.1
Agitation[1]	2.4	0.7
Libido decreased[1]	2.2	0.2
Yawning[1]	2.1	0
Reproductive, Female[2]		
Dysmenorrhea (<50 years)	2,7	1,6
Reproductive, Male[3]		
Ejaculation disorder[1]	6.2	1.1
Impotence[3]	3.2	0.6
Respiratory System		
Upper respir. tract infection	5.1	4.7
Rhinitis	4.9	3.3
Pharyngitis	3.4	2.8
Sinusitis[1]	2.4	0.2
Urinary System		
Micturition disorder	2,3	2,1

[*]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.
[1]Statistically significantly higher incidence in the citalopram group ($p < 0.05$).
[2]Denominator used was for females only (N=623 for citalopram; N=245 for Placebo).
[3]Denominator used was for males only (N=404 for citalopram; N=181 for Placebo).

The following events had an incidence on placebo ≥ citalopram: asthenia, back pain, headache, dizziness, constipation, palpitation, insomnia, abnormal vision.

Dose Dependency of Adverse Events

The potential relationship between the dose of citalopram and the incidence of an adverse event was examined in a fixed dose short-term, placebo-controlled study in which patients received citalopram at doses of 10, 20, 40 or 60 mg per day. The incidence of diarrhea, dry mouth, fatigue insomnia, increased sweating, nausea and somnolence was dose-related.

Cardiovascular

ECG

Retrospective analyses of electrocardiograms in citalopram -treated (N=779 <60 years and N=313 ≥60 years) and placebo-treated (N=74 <60 years and N=43 ≥60 years) patients indicated that citalopram decreases heart rate. In patients <60 years old, the mean decrease was approximately 5 bpm, while in patients ≥60 years old, mean decreases ranged between 5 to 10 bpm. Following the initial drop, heart rate remained decreased but stable over prolonged periods of time (up to one year in over 100 younger and over 50 elderly patients). The effect was reversible within approximately a week after stopping treatment.

In the 6-week, fixed dose, dose-response study, the mean decreases in heart rate ranged between 2-6 bpm in the 20-60 mg/day dose range, but the effect did not seem to be dose-related and was independent of gender. In placebo-treated patients heart rates remained unaffected. The differences in heart rates between citalopram- and placebo-treated patients were statistically significant.

ECG parameters, including QT interval, remained unaffected.

Endocrine and Metabolism

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.

Sexual Function

Male and Female Sexual Dysfunction with SSRIs

While sexual dysfunction is often part of depression and other psychiatric disorders, there is increasing evidence that treatment with selective serotonin reuptake inhibitors (SSRIs) may induce sexual side effects. This is a difficult area to study because patients may not spontaneously report symptoms of this nature, and therefore, it is thought that sexual side effects with SSRIs may be underestimated.

In placebo-controlled, short-term clinical trials, the reported incidence of decreased libido, ejaculation disorders (primarily ejaculation delay and ejaculation failure), and impotence in male depressed patients receiving citalopram (N=404) was 3.7%, 6.2%, and 3.2%, respectively. In female depressed patients receiving citalopram (N=623), the reported incidence of decreased libido and anorgasmia was 1.3% and 1.1%, respectively. The reported incidence of each of these adverse events was ≤1% among male and female depressed patients receiving placebo.

Adverse Reactions following Discontinuation of Treatment (or Dose Reduction)

There have been reports of adverse reactions upon the discontinuation of citalopram (particularly when abrupt), including but not limited to the following: dizziness, abnormal dreams, sensory disturbances (including paresthesias and electric shock sensations), agitation, anxiety, emotional indifference, impaired concentration, headache, migraine, tremor, nausea, vomiting and sweating or other symptoms which may be of clinical significance, (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Patients should be monitored for these or any other symptoms. A gradual reduction in the dosage over several weeks, rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response. These events are generally self-limiting. Symptoms associated with discontinuation have been reported for other selective serotonin re-uptake inhibitors. (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Frequent Clinical Trial Adverse Drug Reactions (≥1%)

Body as a Whole - General Disorders*:* Influenza-like symptoms, non-pathological trauma, pain.
Cardiovascular Disorders: Postural hypotension, tachycardia.
Central and Peripheral Nervous System Disorders: Migraine, paraesthesia.
Gastrointestinal System Disorders*:* Flatulence.
Metabolic and Nutritional Disorders: Appetite decreased, Weight decrease, weight increase.
Psychiatric Disorders: Abnormal dreaming, aggravated depression, amnesia, apathy, confusion, depression, impaired concentration, increased appetite, sleep disorder, suicide attempt.
Reproductive Disorders, Female: Abnormal orgasm.
Skin and Appendage Disorders: Pruritus, rash.
Special Senses, Vision, Hearing and Vestibular Disorders*:* Abnormal accommodation.
Urinary System Disorders*:* Polyuria

Additional adverse events observed during the premarketing evaluation of Citalopram

The events listed below include all adverse events that were reported in the overall development program of citalopram (N=3652). All reported events are included except those already listed in Table 1 and those events which occurred 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. The events are enumerated using the following criteria: adverse events that occurred on one or more occasions in at least 1/100 patients; *infrequent:* adverse events that occurred in less than 1/100 patients but at least in 1/1000 patients; *rare:* adverse events that occurred in fewer than 1/1000 patients.

Body as a Whole - General Disorders
Infrequent: Alcohol intolerance, allergic reaction, allergy, chest pain, edema, hot flushes, leg pain, malaise, rigors, syncope. *Rare:* Peripheral edema, sudden death, traumatic injury.

Cardiovascular Disorders
Infrequent: Angina pectoris, arrhythmia, bradycardia, cardiac failure, cerebrovascular disorders, edema dependent, extrasystoles, flushing, hypertension, hypotension, myocardial infarction, myocardial ischemia, peripheral ischemia. *Rare:* Aggravated hypertension, bundle branch block, cardiac arrest, coronary artery disorder, ECG abnormal, heart disorder, phlebitis, supraventricular extrasystoles.

Central and Peripheral Nervous System Disorders
Infrequent: Abnormal gait, ataxia, convulsions, dysphonia, dystonia, extrapyramidal disorder, hyperkinesia, hypertonia, hypoesthesia, hypokinesia, involuntary muscle contractions, leg cramps, neuralgia, speech disorder, vertigo. *Rare:* Abnormal coordination, convulsions grand mal, hyperesthesia, ptosis, sensory disturbance, stupor.

Collagen Disorders
Rare: Rheumatoid arthritis.

Endocrine Disorders
Rare: Goiter, gynecomastia, hypothyroidism.

Gastrointestinal System Disorders
Infrequent: Colitis, dental abscess, dysphagia, eructation, gastritis, gastroenteritis, gastrointestinal disorder (not specified), hemorrhoids, increased saliva, teeth-grinding, toothache. *Rare:* Appendicitis, esophagitis, gastric ulcer, gastroesophageal reflux, gingivitis, stomatitis, tooth disorder, ulcerative stomatitis.

Hematopoietic and Lymphatic Disorders
Infrequent: Anemia, epistaxis, leukocytosis, purpura. *Rare:* Coagulation disorder, gingival bleeding, granulocytopenia, hematoma, leukopenia, lymphadenopathy, lymphocytosis, pulmonary embolism.

Liver and Biliary System Disorders
Infrequent: Cholecystitis, cholelithiasis, increased gamma-GT, increased SGPT. *Rare:* Bilirubinemia, increased SGOT, jaundice.

Metabolic and Nutritional Disorders
Infrequent: Leg edema, xerophthalmia. *Rare:* Dehydration, edema, hypoglycemia, hypokalemia, increased alkaline phosphatase, obesity, thirst.

Musculo-Skeletal System Disorders
Infrequent: Arthralgia, arthritis, arthrosis, dystonia, muscle weakness, myalgia. *Rare:* Bone disorder, bursitis, osteoporosis, tendon disorder.

Neoplasm
Rare: Breast neoplasm malignant female.

Psychiatric Disorders
Infrequent: Abnormal thinking, aggressive reaction, delusion, depersonalization, drug abuse, drug dependence, emotional lability, euphoria, hallucination, increased libido, manic reaction, neurosis, paranoid reaction, paroniria, psychosis, psychotic depression. *Rare:* Catatonic reaction, hysteria, personality disorder.

Reproductive Disorders, Female
Infrequent: Amenorrhea, breast pain, lactation nonpuerperal, menorrhagia, menstrual disorder, premenstrual syndrome, salpingitis, unintended pregnancy, vaginal dryness, vaginitis. *Rare:* Breast enlargement, vaginal hemorrhage.

Reproductive Disorders, Male
Infrequent: Penis disorder, prostatic disorder, testis disorder.

Resistance Mechanism Disorders
Infrequent: Abscess, fungal infection, herpes simplex infection, otitis media, viral infection. *Rare:* Bacterial infection, moniliasis, sepsis.

Respiratory System Disorders
Infrequent: Bronchitis, coughing, dyspnea, pneumonia. *Rare:* Asthma, bronchospasm, increased sputum, laryngitis, pneumonitis, respiratory disorder.

Skin and Appendage Disorders
Infrequent: Acne, alopecia, dermatitis, dry skin, eczema, photosensitivity reaction, psoriasis, rash erythematous, rash maculo-papular, skin discoloration, urticaria. *Rare:* Cellulitis, decreased sweating, hypertrichosis, melanosis, pruritus ani.

Special Senses, Vision, Hearing and Vestibular Disorders
Infrequent: Conjunctivitis, earache, eye pain, mydriasis, taste perversion, tinnitus. *Rare:* Eye abnormality, keratitis, photophobia.

Urinary System Disorders
Infrequent: Abnormal urine, cystitis, hematuria, micturition frequency, urinary incontinence, urinary retention, urinary tract infection. *Rare:* Dysuria, facial edema, oliguria, renal calculus, renal pain.

Events observed during the post-marketing evaluation of CITALOPRAM - 10

Adverse events which have been reported to be temporally (but not necessarily) associated with citalopram treatment in at least 3 patients since its market introduction include:

Abnormal hepatic function, acute renal failure, aggravated condition, aggravated migraine, akathisia, anaphylaxis, angioedema, asthma, choreoathetosis, convulsion NOS, decreased drug level, decreased prothrombin time, delirium, dyskinesia, ecchymosis, eosinophilia, epidermal necrolysis, erythema multiforme, gastrointestinal hemorrhage, gynecological problems, hemolytic anemia, hepatitis, hypersensitivity NOS, hyperprolactinemia, hypomania, hyponatremia, increased drug level, increased prothrombin time, menometrorrhagia, myoclonic jerks, neuroleptic malignant syndrome, neuropathy, nystagmus, pancreatitis, pancytopenia, purpura NOS, rhabdomyolysis, serotonin syndrome, SIADH, spontaneous abortion/fetal death, suicide ideation, thrombocytopenia, vasodilatation, ventricular arrhythmia, Torsades de pointes, withdrawal syndrome.

SERIOUS DRUG-DRUG INTERACTIONS

MONOAMINE OXIDASE INHIBITORS (MAOI)

In patients, receiving selective serotonin reuptake inhibitors (SSRIs) 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, including 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 serotonin syndrome.

Therefore, 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 elapse after discontinuing citalopram treatment before starting a MAOI. (see CONTRAINDICATIONS)

DRUG INTERACTIONS

Drug-Drug Interactions

Monoamine Oxidase Inhibitors (MAOI)

For interactions between CITALOPRAM - 10 and MAOI, see CONTRAINDICATIONS

General
The studies described in this section were carried out in young, healthy, mostly male volunteers. In addition, some of the studies, namely interactions with metoprolol, warfarin, digoxin, imipramine, and levomepromazine, utilized only single doses of these drugs, although citalopram was given repeatedly to attain steady state. Thus, data are not available in patients who would be receiving these drugs on an ongoing basis at therapeutic doses.

Carbamazepine
Carbamazepine, titrated to 400 mg/day, was given for 21 days alone and then in combination with citalopram (40 mg/day) for an additional 14 days. Citalopram did not affect the plasma levels of either carbamazepine,

a CYP3A4 substrate, or its metabolite, carbamazepine-epoxide. However, since carbamazepine is a microsomal enzyme inducer, the possibility that carbamazepine may increase the clearance of citalopram should be considered if the two drugs are given concomitantly.

Cimetidine
Citalopram 40 mg/day was administered for 29 days. During the last 8 days of treatment, cimetidine (400 mg bid) was added to the treatment regimen. In the presence of cimetidine, a potent inhibitor of hepatic cytochrome P450 enzymes, the C_{max} and AUC of citalopram was increased by 39% and 41%, respectively. Thus, caution should be exercised at the upper end of the dose range of citalopram when it is used concomitantly with high doses of cimetidine.

Cytochrome P450 Isozymes
Using *in vitro* models of human liver microsomes, the biotransformation of citalopram to its demethyl metabolites was shown to depend on both CYP 2C19 and CYP 3A4, with a small contribution from CYP 2D6. Studies have also indicated that citalopram is a weak inhibitor of CYP 2D6 and CYP 2C19 and a weak or negligible inhibitor of CYP 3A4 and CYP 1A2.

One *in vitro* study using human liver microsomes has shown that ketoconazole and omeprazole reduced the rate of formation of the demethylcitalopram metabolite of citalopram to 45-60% and 75-85% of control, respectively. As data are not available from clinical pharmacokinetic studies, the possibility that the clearance of citalopram will be decreased when citalopram is administered with a potent inhibitor of CYP 3A4 (e.g., ketoconazole, itraconazole, fluconazole or erythromycin), or a potent inhibitor of CYP 2C19 (e.g., omeprazole), should be considered.

Digoxin
Administration of citalopram (40 mg/day for 21 days) did not affect the pharmacokinetics of digoxin (single dose of 1 mg), although the serum levels of citalopram were slightly lower in the presence of digoxin.

Imipramine
Coadministration of citalopram (40 mg/day for 10 days) and the tricyclic antidepressant, imipramine (single dose of 100 mg), did not affect the pharmacokinetics of either drug. However, in the presence of citalopram, the concentration of desipramine, the metabolite of imipramine, increased by approximately 50% and its half-life was prolonged. The results indicate that citalopram does not interfere with the demethylation of imipramine to desipramine but does inhibit the metabolism of desipramine to its 2-hydroxy metabolite. Consequently, concomitant treatment with citalopram and imipramine/desipramine should be undertaken with caution.

Levomepromazine
Coadministration of citalopram (40 mg/day for 10 days) and levomepromazine (single dose of 50 mg), did not affect the pharmacokinetics of either drug.

Lithium
Coadministration of citalopram (40 mg/day for 10 days) and lithium (30 mmol/day for 5 days), did not affect the pharmacokinetics of either drug. However, since lithium may increase serotonergic neurotransmission, concomitant treatment with these two drugs should be undertaken with caution.

Metoprolol
Coadministration of citalopram (40 mg/day for 22 days) and the β-adrenergic blocking agent metoprolol (single dose of 150 mg), resulted in a twofold increase in the plasma levels of metoprolol. However, the effect of metoprolol on blood pressure and heart rate was not affected.

Pimozide

Citalopram should not be used in combination with the anti-psychotic drug pimozide, as results from a controlled study with racemic citalopram indicate that concomitant use is associated with an increased risk of Qtc prolongation compared to pimozide alone. This apparent pharmacodynamic interaction occurred in the absence of a clinically significant pharmacokinetic interaction; the mechanism is unknown (see PRECAUTIONS, Drug Interactions)

Other Drugs
No pharmacodynamic interactions have been noted in clinical trials where citalopram has been given concomitantly with benzodiazepines (anxiolytics/hypnotics), analgesics (NSAIDs, non-NSAIDs), antihistamines, antihypertensives or other cardiovascular drugs. Pharmacokinetic interactions between citalopram and these drugs were not specifically studied.

Serotonergic drugs
There have been rare postmarketing reports describing patients with weakness, hyperreflexia and incoordination, following the concomitant use of a SSRI and the antimigraine drug sumatriptan, a 5-HT_1 agonist. Such interaction should be considered if citalopram is to be used in combination with a 5-HT_1 agonist.

Warfarin
Administration of citalopram (40 mg/day for 21 days), did not affect either the pharmacokinetics or the pharmacodynamics (prothrombin time) of a single, 25 mg dose of warfarin.

Drug-Lifestyle Interactions

Alcohol
Although citalopram did not potentiate the cognitive and psychomotor effects of alcohol in volunteers, the concomitant use of alcohol and citalopram should be avoided.

Various scientific publications have acknowledged that the main components in grapefruit juice may act as a CYP3A4 inhibitor. Citalopram is also metabolized by other isoenzymes not affected by grapefruit juice, namely CYP2C19 and CYP2D6. Although there is a theoretical possibility of pharmacokinetic drug interactions resulting from co-administration of citalopram with grapefruit juice, the onset of an interaction is considered unlikely.

Drug-Herb Interactions

St. John's Wort: In common with other SSRI's, pharmacodynamic interactions between citalopram and the herbal remedy St. John's Wort may occur and may result in undesirable effects.

Drug-Laboratory Test Interactions
There are no known interactions of citalopram with commonly used laboratory tests.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Adult patients
- Elderly patients
- Hepatic impairment
- Renal impairment
- Maintenance treatment
- Switching patients to or from a monoamine oxidase inhibitor
- Discontinuation of CITALOPRAM - 10 treatment
- Children

CITALOPRAM - 10 (citalopram) is an Adult dosage and is not indicated for use in children under 18 years of age (see WARNINGS AND PRECAUTIONS: POTENTIAL ASSOCIATION WITH BEHAVIORAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM).

Switching Patients To or From a Monoamine Oxidase Inhibitor (MAOI)
At least 14 days should elapse between discontinuation of a MAOI and initiation of therapy with CITALOPRAM - 10. Similarly, at least 14 days should be allowed after stopping CITALOPRAM - 10 before starting a MAOI (see CONTRAINDICATIONS).

Recommended Dose and Dosage Adjustment

CITALOPRAM - 10 (citalopram hydrobromide) should be administered once daily, in the morning or evening, with or without food.

Adults

CITALOPRAM - 10 should be administered as a single oral dose of 20 mg/day. In patients who do not respond adequately, an increase of dosage to 40 mg/day should be considered. Certain patients may require 60 mg/day. However, in a dose-response study, the 60 mg/day dose did not demonstrate an advantage regarding effectiveness over the 40 mg/day dose.
Dose increases should usually occur in increments of 20 mg, at intervals of no less than one week.

Treatment of Pregnant Women During Third Trimester
Post-marketing reports indicate that some neonates exposed to SSRIs such as CITALOPRAM and other newer antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see WARNINGS AND PRECAUTIONS). When treating a pregnant woman with CITALOPRAM during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering CITALOPRAM in the third trimester.

Elderly Patients

A single oral dose of 20 mg/day is the recommended dose for most elderly patients. Some patients may respond to a 10 mg/day dose (see Clinical Trials under ACTION AND CLINICAL PHARMACOLOGY). The dose may be titrated to a maximum of 40 mg/day if needed and tolerated. As with other SSRIs, caution should be exercised in treating elderly female patients who may be more susceptible to adverse events such as hyponatremia and SIADH (syndrome of inappropriate antidiuretic hormone secretion). (See PRECAUTIONS).

Hepatic Impairment

Patients with reduced hepatic function should receive dosages of no more than 30 mg/day.

Renal Impairment

No dosage adjustment is necessary for patients with mild to moderate renal impairment. Since there is no information available on the pharmacokinetic or pharmacodynamic effects of citalopram in patients with severe renal impairment, citalopram should be used with caution in these patients.

Maintenance Treatment

Evaluation of citalopram in two placebo-controlled studies has shown that its antidepressant efficacy was maintained for periods of up to 24 weeks, following 6 or 8 weeks of initial treatment (total of 32 weeks) (See Clinical Trials under ACTION AND CLINICAL PHARMACOLOGY). In the flexible dose study, the great majority of patients were receiving 20 or 40 mg/day doses both at 12 and 24 weeks. During maintenance therapy, the dosage should be kept at the lowest effective level and patients should be periodically reassessed to determine the need for continued treatment.

Discontinuation of CITALOPRAM - 10 Treatment

Symptoms associated with the discontinuation or dosage reduction of CITALOPRAM - 10 have been reported. Patients should be monitored for these and other symptoms when discontinuing treatment or during dosage reduction (See PRECAUTIONS and ADVERSE REACTIONS).

A gradual reduction in the dose over several weeks rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response. (See PRECAUTIONS and ADVERSE REACTIONS).

CHILDREN

See Potential Association with Behavioral and Emotional Changes, Including Self-Harm under WARNINGS.

OVERDOSAGE

Citalopram hydrobromide has a wide margin of safety in overdose. Cases of overdoses involved the ingestion of citalopram either alone or in combination with other drugs and/or alcohol. Cases of overdoses of citalopram ranging from 180 mg to 2000 mg have been reported during the premarketing clinical development. All patients recovered. One patient, ingesting over 1500 mg citalopram, had reversible ECG abnormalities, the most important of which was prolongation of QTc.

Citalopram is given to patients at potential risk of suicide and reports of attempted suicide have been received after its market introduction. Post-marketing reports of drug overdoses involving citalopram have included fatalities with citalopram alone as well as non-fatal overdoses of up to 5200 mg. In many cases, details regarding the precise dose of citalopram or combination with other drugs and/or alcohol are often lacking. Although most patients recovered without sequelae, fatalities have been reported at doses of citalopram up to 3920 mg.

Fatal cases of serotonin syndrome have been reported in patients who took overdoses of moclobemide (Manerix) and citalopram . The plasma concentrations of moclobemide were between 16 and 90 mg/L (therapeutic range: 1 to 3 mg/L) and those of citalopram between 0.3 and 1.7 mg (therapeutic concentration: 0.3 mg/L). This indicates that a relatively low dose of citalopram, given with an overdose of moclobemide represents a serious risk for the patient.

Symptoms most often accompanying citalopram overdose included dizziness, sweating, nausea, vomiting, tremor, and somnolence. In more rare cases, observed symptoms included confusion, loss of consciousness, convulsions, coma, sinus tachycardia, cyanosis, hyperventilation and rhabdomyolysis.

Management of Overdose

Establish and maintain an airway to ensure adequate ventilation and oxygenation. Gastric lavage and use of activated charcoal should be considered. Cardiac and vital sign monitoring are recommended, along with general symptomatic and supportive measures. There are no specific antidotes for citalopram.
Due to the large volume of distribution of citalopram, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit.

In managing overdosage, the possibility of multiple drug involvement must be considered.

ACTION AND CLINICAL PHARMACOLOGY

Citalopram hydrobromide is a highly selective and potent serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitor with minimal effects on the neuronal reuptake of norepinephrine (NE) and dopamine (DA). The ability of Citalopram to potentiate serotonergic activity in the central nervous system *via* inhibition of the neuronal reuptake of serotonin is thought to be responsible for its antidepressant action. Tolerance to the inhibition of serotonin reuptake is not induced by long-term (14 days) treatment of rats with Citalopram.

Citalopram has no or very low affinity for a series of receptors including serotonin 5-HT_{1A}, 5-HT_2, dopamine D_1 and D_2, α_1-, α_2-, β-adrenergic, histamine H_1, muscarinic cholinergic, benzodiazepine, gamma aminobutyric acid (GABA) and opioid receptors.

Pharmacokinetics

Absorption

Following the administration of a single oral dose of citalopram (40 mg) to healthy male volunteers, peak blood levels occurred at about 4 hours (range 1 to 6 hours). The absolute bioavailability of citalopram was about 80% (range 52 to 93%) relative to an intravenous dose. Absorption was not affected by food.

Distribution

After intravenous infusion in healthy male volunteers, the apparent volume of distribution $(V_d)\beta$ was about 12 L/kg (range 9-17 L/kg), indicating a pronounced tissue distribution; $(V_d)\beta$ oral was about 17 L/kg (range 14-21 L/kg). The binding of citalopram and its demethylated metabolites to human plasma proteins is about 80%.

Steady-state

The single- and multiple-dose pharmacokinetics of citalopram are linear and dose-proportional in a dose range of 10 to 60 mg/day. Steady-state plasma levels are achieved in patients in 1-2 weeks. At a daily dose of 40 mg, the average plasma concentration is about 83 ng/mL (n=114) with a range from 30 to 200 ng/mL. Citalopram does not accumulate during long-term treatment. A clear relationship between citalopram plasma levels and therapeutic response or side effects has not been established.

Metabolism

Citalopram is metabolized in the liver to demethylcitalopram (DCT), didemethylcitalopram (DDCT), citalopram-N-oxide, and a deaminated propionic acid derivative. *In vitro* studies show that DCT, DDCT and citalopram-N-oxide also inhibit the neuronal reuptake of serotonin but are less selective and less potent than the parent compound and are of minor clinical importance. Unchanged citalopram is the predominant compound in plasma.

In vitro studies indicated that the biotransformation of citalopram to its demethyl metabolites depends on both CYP2C19 and CYP3A4, with a small contribution from CYP2D6.

Elimination

The elimination half-life of citalopram ($t_{½\beta}$) is approximately 37 hours (range: 30-42 hours) which allows recommendation of once-daily dosing. The systemic citalopram plasma clearance (Cl_S) is 0.33 L/min.

Citalopram is eliminated primarily via the liver (85%) and the remainder via the kidneys; approximately 12% (range 6-21%) of the daily dose is excreted in urine as unchanged citalopram.

Special Populations and Conditions

Elderly Patients
Elderly patients (4 males and 7 females aged 73-90 years), received a 20 mg/day dose of citalopram for 3-4 weeks. In the elderly, steady state plasma levels were elevated (106 ng/mL), half-life prolonged (1.5-3.75 days) and clearance decreased (0.08-0.3 L/min). Elevation of citalopram plasma levels occurred at an earlier age in females than in males. In this population, lower doses and a lower maximum dose of citalopram are recommended (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Reduced Hepatic Function
The pharmacokinetics of citalopram were compared in patients with reduced hepatic function (3 female and 6 male patients aged 41-60 years) to those seen in 12 healthy male volunteers (aged 21-43 years). In patients with reduced hepatic function the half-life of citalopram was approximately doubled (83 hours *versus* 37 hours), steady state citalopram concentrations increased by 61% and oral clearance decreased by 37%. Consequently the use of citalopram in patients with reduced hepatic function should be approached with caution and lower maximal doses should be prescribed (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Reduced Renal Function
In patients with mild to moderate reduction of the renal function (4 female and 3 male patients aged 30-55 years), citalopram was being eliminated more slowly than in 12 healthy male volunteers (aged 21-43 years); half-lives being 49 hours *versus* 37 hours. However, mild to moderate renal impairment had no major influence on the kinetics of citalopram. At present, no information is available for chronic treatment of patients with severely reduced renal function (creatinine clearance <20 mL/min). (See PRECAUTIONS.)

STORAGE AND STABILITY

CITALOPRAM - 10 tablets should be stored in a dry place at room temperature between 15º and 30ºC.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability of Dosage Forms

CITALOPRAM - 10 (citalopram hydrobromide) is available as film-coated, white tablets. Tablets are supplied as:

10 mg tablets: Each White, oval, coated tablet debossed with "10" on one side and plain on the other side. contains 10 mg citalopram (as citalopram hydrobromide). HDPE bottles of 100 tablets.

Composition

CITALOPRAM - 10 tablets contain citalopram hydrobromide corresponding to 10mg citalopram, and the following non-medicinal ingredients: Colloidal Silicon Dioxide, Lactose Monohydrate, Magnesium Stearate, Microcrystalline Cellulose, Hydroxypropyl Methylcellulose, Hydroxypropyl Cellulose, Titanium Dioxide, Polyethylene Glycol and Sodium Starch Glycolate.

Product Monograph available upon request.

PRODOC LTÉE
Laval, Quebec H7L 3W9

PART II: SCIENTIFIC INFORMATION

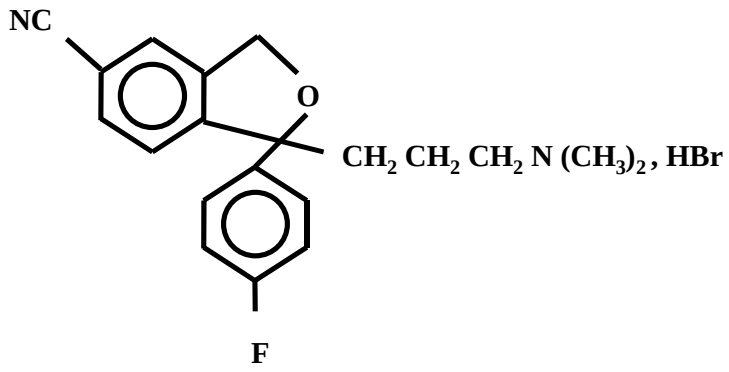
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Citalopram hydrobromide

Chemical Name: (R-S)-1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl) -5-phthalancarbonitrile hydrobromide

Structural formula:



Molecular Formula: $C_{20}H_{22}BrFN_2O$

Molecular mass: 405.35

Description: White to off-white, crystalline material having no more than a slight odour.

Melting point: 185˚ - 188˚ C

pH: 5.5 - 6.5 (0.5% w/v in water)

pKa: 9.5 (microtitration)

Solubility: Water (sparingly soluble)
Ethanol (soluble)
Chloroform (freely soluble)
Diethylether (very slightly soluble)

Partition Coefficient: Log P (octanol/phosphate buffer pH 7.4) - 1.57

Composition: CITALOPRAM - 10 tablets contain citalopram hydrobromide corresponding to 10 mg citalopram, and the following non-medicinal ingredients: cornstarch, lactose monohydrate, microcrystalline cellulose, copolyvidone glycerin, croscarmellose sodium, magnesium stearate, methylhydroxypropyl cellulose, polyethylene glycol 400, and titanium dioxide.

Stability and Storage: CITALOPRAM - 10 tablets should be stored in a dry place at room temperature between 15o and 30oC.

CLINICAL TRIALS

Clinical Trials

The efficacy of citalopram in the treatment of depression was established in five placebo-controlled studies in patients who met the DSM-III or DSM-III-R criteria for major depression. Response to treatment was evaluated by the Hamilton Depression Rating Scale (HAMD) and/or the Montgomery Asberg Depression Rating Scale (MADRS), as well as the Clinical Global Impression (CGI) Severity Scale. On the HAMD and MADRS, total scores, selected single items, and percentage of responders (defined as patients whose HAMD/MADRS total score decreased by at least 50% *versus* baseline) were assessed.

In a 6-week fixed-dose, dose-response study, patients received citalopram, at doses of 10, 20, 40, or 60 mg/day or placebo (n=129 to 131 per group). The 40 and 60 mg/day doses were titrated, with patients reaching these designated doses within 4 and 8 days, respectively. The study showed that the 40 and 60 mg/day doses were significantly more effective than placebo, although the 60 mg/day dose was not more effective than the 40 mg/day dose. The lower doses did not show statistically significant superiority over placebo, except on the MADRS; on this scale the percent of 'responders' was significantly higher in all the citalopram-treated groups than in the placebo-treated group.

The second study was a 4-week flexible-dose study in which 85% of the depressed patients met the criteria for melancholia. At entry, 89 and 91 patients were randomized to the citalopram and placebo groups, respectively. This was the only study in which more male than female patients participated (64% *versus* 36%). The initial dose of citalopram, 20 mg/day, could be titrated to the maximal tolerated dose or a maximum dose of 80 mg/day. Patients treated with citalopram showed significantly greater improvement than patients treated with placebo. At week 4, the average daily dose was 63 mg, with 52% of patients receiving the 80 mg/day dose.

In a 6-week fixed-dose study, patients received citalopram, 20 or 40 mg/day, or placebo (n=64 to 70 per group). Patients treated with citalopram, 40 mg/day, showed significantly greater improvement than placebo-treated patients. The difference between the lower dose of citalopram and placebo was not significant.

In another 6-week fixed-dose study, patients received citalopram, 20 or 40 mg/day or placebo (n=88 to 97 per group). Although citalopram-treated patients improved to a somewhat greater degree than the placebo-treated patients, the differences between drug and control groups did not reach statistical significance due to a high placebo response, i.e., substantial improvement in the placebo group.

A 6-week, flexible-dose study was conducted in elderly, depressed patients (the mean age of male and female patients was 75 and 77 years, respectively) to determine the antidepressant effect and safety of citalopram in this subpopulation. The number of patients who received citalopram and placebo was 98 and 51, respectively. The study allowed patients to enter with lower baseline HAMD scores than are usually acceptable ($\geq$18 in clinical trials). However, only a small percentage of patients had HAMD scores of less than 18 at entry. The dose of citalopram was titrated from a starting dose of 10 mg/day to a maximum dose of 30 mg/day. Patients treated with citalopram showed significantly greater improvement than patients treated with placebo. The final dose of citalopram was 10, 20 and 30 mg/day in 5%, 51% and 44% of patients, respectively.

The effectiveness of citalopram in preventing relapse was assessed in two long-term studies. Depressed patients who 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 20-60 mg/day in the second study) were randomized to continue on citalopram or receive placebo. The number of patients who received citalopram and placebo was 257 and 116, respectively. In both studies, patients who continued on citalopram experienced significantly lower relapse rates over the subsequent 6 months compared to those receiving placebo. In the fixed-dose study, the relapse rates were similar at the 20 and 40 mg/day doses, namely 10% and 12%, respectively. Of the placebo-treated patients, 31% experienced relapse. In the flexible-dose study, the relapse rates were 14% and 24% in the citalopram- and placebo-treated patients, respectively. While the majority of patients (76%) were maintained on 20 or 40 mg/day of citalopram during most of the study, some patients received 60 mg/day, while a few patients were maintained on less than 20 mg/day.

Comparative Bioavailability Studies

A blind, randomized, 2-way crossover, bioequivalence study between Pharmascience's CITALOPRAM - 10 40 mg tablets was performed *versus* Lundbeck's Celexa®, administered as 1x 40 mg tablets in 22 healthy male volunteers under fasting conditions. Pharmacokinetic and bioavailability data are presented in the following table.:

SUMMARY TABLE OF COMPARATIVE BIOAVAILABILITY DATA
Citalopram
(A single 40 mg dose- 1 X 40 mg in the fasting state)
From measured data (analytes-citalopram)
uncorrected for potency
Geometric Mean
Arithmetic Mean (CV %)

PARAMETER	CITALOPRAM - 10	CELEXA †	% RATIO OF GEOMETRIC MEANS
AUC_{0-72} (**ng.h/mL**)	1201.10 1231.28 (23.3)	1206.48 1235.22 (22.7)	99.55
AUC_I (**ng.h/mL**)	1575.69 1646.51 (33.1)	1595.44 1656.87 (30.4)	98.76
C_{MAX} (**ng/mL**)	37.78 38.91 (25.0)	38.71 39.81 (24.4)	97.6
T_{MAX} ** (h)	4.77 (33.2)	5.02 (35.9)	---
$T_{½}$ ** (h)	34.97 (25.3)	36.21 (23.9)	---

† CELEXA ™ Tablets, manufactured by Lundbeck Canada Inc., purchased in Canada.
** Expressed as the arithmetic mean (CV%) only

DETAILED PHARMACOLOGY

Citalopram is a racemic mixture with the S (+) enantiomer mediating the pharmacological effects. The R (-) enantiomer contributes little to the activity of citalopram.

***In vitro* Experiments**

(a) Neuronal reuptake of serotonin, norepinephrine and dopamine

The primary pharmacological effect of citalopram is inhibition of the 5-HT reuptake mechanism. Citalopram was shown to inhibit 5-HT uptake in rabbit blood platelets, with an IC_{50} of 14 nM. Similarly, the drug inhibits 5-HT uptake in rat brain synaptosomal preparations.

Uptake of ^{3}H Amines into Rat Brain Synaptosomes
IC_{50} nM

	5-HT	NE	DA	NE/5-HT
citalopram	1.8	8800	41 000	4889
demethylcitalopram	7.4	780	26 000	105
didemethylcitalopram	24	1500	12 000	63
citalopram-N-oxide	56	3200	>100 000	57

The data indicate that citalopram is a potent and specific 5-HT uptake inhibitor with no activity on the neuronal reuptake of norepinephrine (NE) or dopamine (DA). The metabolites of citalopram are also specific inhibitors of 5-HT reuptake, albeit less active than the parent drug.
The ratio between the concentrations inhibiting the *in vitro* uptake of NE and 5-HT determine the selectivity of a SSRI. According to this criterion citalopram is a highly selective SSRI.

(b) Effect on neurotransmitter receptors

Citalopram has no or very low affinity for a series of receptors including 5-HT_{1A}, 5-HT_2, dopamine D_1 and D_2 receptors, α_1-, α_2-, β-adrenoreceptors, histamine H_1, muscarinic cholinergic, benzodiazepine, and opioid receptors.

A series of functional *in vitro* tests in isolated organs as well as functional *in vivo* tests have confirmed the lack of receptor affinity.

Behavioral Effects

In a 'behavioral despair paradigm', mice, trained to swim in a glass jar, eventually exhibit immobility. This behavior was dose-dependently reversed by citalopram.

The 5-HT precursors, tryptophan and 5-HTP, induce in mice and rats the 5-HT syndrome, characterized by tremor, hyperactivity, abnormal gait, lordosis, and abduction of the hind limbs. Citalopram potentiated these behavioral manifestations. The demethyl, didemethyl, and N-oxide metabolites were less potent than the parent drug.

The characteristic head twitches, induced by a combined treatment with a MAOI and 5-HTP, were potentiated by citalopram. However, head twitches induced by quipazine, a direct 5-HT mimetic, were not affected by citalopram, indicating that the drug has no anti-5-HT activity.

Although citalopram has no antinociceptive activity *per se*, it potentiated the antinociceptive effect of morphine.

In a food reinforcement paradigm, delivered under a multiple schedule, citalopram did not affect the responding in pigeons but potentiated the 5-HTP-induced decrease in responding.
In rats, citalopram did not facilitate self-stimulation, did not substitute for d-amphetamine, d-LSD, or 8-OHDPAT in a drug discrimination paradigm and did not increase ethanol consumption in an ethanol/water preference test. In the latter experiment, citalopram actually decreased ethanol consumption. These experiments indicate that citalopram would not be abused and would not cause dependence.

Citalopram had a slight protective effect against maximal electroshock-induced convulsions, isoniazide-induced convulsions and audiogenic seizure. However, in toxicity studies convulsions have been observed at very high plasma levels of citalopram (see TOXICOLOGY).

Cardiovascular Effects

In conscious dogs, single oral doses of 5 mg/kg of citalopram caused pronounced fluctuation of the blood pressure and heart rate. A 10 mg/kg dose caused tachycardia and elevated blood pressure. The ECG was unchanged.

In anaesthetized cats, single oral doses of 35 mg/kg decreased the following parameters: mean arterial blood pressure, left ventricular end diastolic pressure, contractility, cardiac performance, stroke volume, and cardiac output. Peripheral resistance was increased. ECG abnormalities included alterations in conduction, changes in rhythm and T-wave inversion in 2 of 6 cats.

Additional cardiovascular effects of citalopram and a metabolite are described under TOXICOLOGY.

PHARMACOKINETICS

Absorption

The kinetics of citalopram in mouse, rat, and dog are characterized by rapid absorption, with T_{max} ranging from 0.5 to 4 hours. In contrast to man, reduced systemic bioavailability due to extensive first-pass metabolism has been demonstrated in animals.

Distribution

Pharmacokinetic analysis of single dose i.v. data suggests two-compartment distribution characteristics. High levels of drug and demethylated metabolites were found in the lungs, liver, and kidneys, and lower levels in the heart and brain. Citalopram and the demethylated metabolites were shown to pass the placental barrier and were excreted in small amounts in milk.

The plasma protein binding of citalopram has been estimated to be 70-80%. The binding protein(s) has not been identified.

Both in mice and dogs, tissue concentrations of parent drug as well as those of the demethylated metabolites increased with increasing doses, although not necessarily in a dose-related manner. Levels of the didemethylated metabolites were higher in dogs than in mice in relation to the parent drug, resulting in smaller citalopram/didemethylcitalopram ratios in the dog, particularly in the heart and kidneys.

Metabolism

There are no major qualitative differences in the metabolism of citalopram between animals and man. Citalopram is metabolized to demethylcitalopram, didemethylcitalopram, citalopram-N-oxide, and the deaminated propionic acid.

Demethylcitalopram and didemethylcitalopram levels are more prominent in mouse, rat, and dog than in man.

Elimination

Elimination of citalopram after a single dose is rapid, the half-life ranging from 1.5-2 hours in the mouse to 3.5-8 hours in the dog. In the dog, the half-life is prolonged with increasing doses due to saturation of the first-pass metabolism.

Following the administration of ^{14}C-labelled citalopram to rats, at a dose of 20 mg/kg, approximately equal amounts of the dose were excreted in the urine and feces, with total recovery being about 80%.

Toxicokinetics

Plasma levels were determined in several long-term toxicity studies. The table below summarizes the results seen in some of these studies.

Species	Study	Dose mg/kg	CT[a] ng/mL	DCT[b] ng/mL	DDCT[c] ng/mL
Rat[d]	12-month tox po (diet)	32	male 330 female 334	474 391	246 204
		60	male 690 female 826	989 862	497 290
		120	male 1163 female 1286	1947 1655	758 577
Dog[e]	12-month tox po (in capsules)	1	19	22	95
		3	350	170	314
		8	1218	586	574
Man	multiple dose po 6 weeks	0.3	39	13	3.7
		0.6	83	28	5.2
		0.9	121	41	6.3

a: citalopram; b: demethylcitalopram; c: didemethylcitalopram; d: average value at Week 52;
e: 2 hours postdose - Week 52 (1 and 3 mg/kg dose groups), Week 57 (8 mg/kg dose group).

The data indicate that the plasma levels of citalopram, as well as those of the demethylated metabolites, are considerably higher in animals than in man. The approximate 0.9 mg/kg dose in man corresponds to the highest recommended dose (60 mg/day). The plasma levels of the parent drug, seen in rats and dogs at the highest doses, are approximately 10 times higher in animals than in man, while the levels of the didemethyl metabolites are almost 100 fold higher. In the rat, a NOEL could not be established in this study; at the low dose minimal vacuolization of hepatocytes with fatty infiltration, and foam cell accumulation in lungs were noted. The changes were reversible. In dogs, the NOEL was 3 mg/kg.

TOXICOLOGY

Acute toxicity

The LD_{50} values of citalopram ranged between 900-1700 mg/kg after oral administration and 38-74 mg/kg after intravenous administration. However, some mortality was also seen in the 400-600 mg/kg dose range, indicating a very flat dose-response curve regarding mortality. Signs of toxicity were sedation and tremor, while convulsions occurred at doses close to or above the LD_{50} values.

LD_{50} VALUES IN THE MOUSE AND RAT

(mg/kg body weight)

		Route of Administration				
Species	**Sex**	**i.v.**	**p.o.**	**i.p.**	**s.c.**	**i.m.**
Mouse	Male	72 ± 9	1140 ± 190	220 ± 9	534 ± 71	>400
	Female	74 ± 10	900 ± 120	207 ± 20	-	-
Rat	Male	40 ± 4	1710 ± 292	157 ± 27	1950 ± 364	>400
	Female	38 ± 7	1426 ± 554	133 ± 17	-	-

A number of single dose toxicity studies have been carried out in dogs to investigate the potential cardiovascular toxicity of citalopram. In these studies, cardiotoxicity was not observed, but tonic-clonic convulsions were seen after oral administration of 20-40 mg/kg, as well as after slow intravenous infusion of 20-24 mg/kg. The critical plasma concentration for convulsions was about 1950 ng/mL.

Long-term Toxicity

Toxicological studies, including daily dosing for periods up to 26 weeks in mice and 52 weeks in rats and dogs, have been carried out. Plasma drug monitoring in the long-term safety studies documented that animals have been exposed to average citalopram levels of up to about 1200 ng/mL (dogs and rats) and 2900 ng/mL (mice), as well as substantial levels of demethylcitalopram [up to about 1800 ng/mL (rats), 600 ng/mL (dogs), 1150 ng/mL (mice)] and didemethylcitalopram [up to about 650 ng/mL (rats), 600 ng/mL (dogs), 300 ng/mL (mice)].

Apart from behavioral and functional characteristics of exaggerated 5-HT stimulation (e.g., hyperactivity, tremor, tail rigidity, mydriasis, reduced food consumption, and reduced body weight gain), two treatment-related findings have been demonstrated in rodents, namely fatty infiltration of the liver and lipidosis (vacuolization of lymphocytes). Both of the findings were reversible. In addition, retinal degeneration and testicular atrophy were also observed in rats.

In dogs, two treatment-related effects were found. Firstly, convulsions and death when plasma citalopram levels exceeded 1950 ng/mL (p.o. or i.v.). Secondly, fatal ventricular arrhythmias at combined high levels of the didemethyl metabolite (about 300 ng/mL) and citalopram (about 1950 ng/mL) were seen following i.v. infusion.

Hepatic Fatty Infiltration in Rodents

Fatty infiltration in the liver was first observed in a 3-month gavage study in rats given 8-32 mg/kg/day of citalopram. This administration resulted in dose-related hepatic fatty infiltration in all male rats but not in female rats at any of the doses. The fatty infiltration in male rats was also observed in a 4-week study, however, only at considerably higher doses (>160 mg/kg). In female rats only minimal fatty infiltration was seen at a 200 mg/kg/day dose.

Lipidosis (phospholipids) in Rodents

Phospholipidosis, which has been seen in rodents, is an abnormal accumulation of phospholipids in phagocytic cells and cells which catabolize biomembranes, such as pulmonary alveolar macrophages and circulating leucocytes (especially lymphocytes).

Phospholipidosis developed in rats receiving citalopram at daily doses of 120 mg/kg and slight vacuolization of peripheral lymphocytes was observed in mice at daily doses of 100 mg/kg, in the 52-week and 26-week studies, respectively. Both conditions were reversible within 3-4 weeks.

Retinal Degeneration/Atrophy in Rats

In the rat carcinogenicity study, a slight, dose-related increase in lens opacity was seen, affecting males only. In addition, increased incidence/severity of retinal degeneration/atrophy was seen in the high-dose group (80 mg/kg/day). The incidence was higher in females, however, more female than male rats survived the study. It was concluded by an independent pathologist that the retinal changes were most likely related to drug-induced pupillary dilatation (mydriasis) which increased the risk of retinal damage in the already light-sensitive albino rat.

Testicular Atrophy in Rats

In the 52-week rat toxicity study, testicular atrophy was seen at the 60 and 120 mg/kg/day doses of citalopram.

Convulsions and Death in Dogs

Toxicity studies in dogs revealed that citalopram administration led to fatal ventricular arrhythmias. Consequently, studies were undertaken to elucidate the mechanism of this effect and to determine its relevance to humans.

The studies have shown that (1) i.v. infusion of citalopram, at a dose of 20 mg/kg, led to convulsions. The blood levels of citalopram were 1950 ng/mL at this dose. In the presence of diazepam, also infused intravenously, higher doses of citalopram could be infused, namely up to 70 mg/kg (6800 ng/mL). (2) Intravenous infusion of the didemethyl metabolite of citalopram caused QT prolongation in a dose range of 5 to 22 mg/kg. The blood levels of the metabolite were 300 ng/mL at the 5 mg/kg dose. The QT prolongation was dose-dependent. (3) When citalopram, 20 mg/kg, and didemethylcitalopram, 5 mg/kg, were infused concomitantly (in the presence of diazepam in order to prevent convulsions), 5 out of 9 dogs died due to ventricular fibrillation. At these doses, the plasma levels of citalopram and didemethylcitalopram were 1950 ng/mL and 300 ng/mL, respectively.

As shown in the table below, there is a substantial difference in the plasma levels of citalopram and its metabolite in dogs and in humans at the recommended therapeutic doses.

Treatment	**Dog** ventricular fibrillation	**Patients** at steady state after a 60 mg/day dose of citalopram
citalopram, 20 mg/kg **plus** didemethylcitalopram, 5 mg/kg	1950 ng/mL 300 ng/mL	121 ng/mL 6.3 ng/mL

Reproduction Studies

Citalopram did not affect the reproductive performance of rats at dosages up to 16 mg/kg/day (males) and 32 mg/kg/day (females).

In the teratology studies in rats, effects were observed in the conceptuses at dosages that were toxic to the dams. Minimal developmental toxicity was evident at 32 mg/kg/day: manifested as low incidences of resorptions, slightly reduced fetal and pup weights, and small reversible delays in ossification and postnatal development.

In rabbits, dosages of 4.8 mg/kg/day and above were toxic to the dams, and 16 mg/kg/day and above caused deaths. There were no effects on embryo-fetal development at the highest dose that could be assessed (16 mg/kg/day).

Mutagenic Potential

Citalopram did not have mutagenic activity in most of the *in vitro* tests (Ames Salmonella assay; chromosome aberration assay in cultured human lymphocytes; gene mutation assay in cultured mouse lymphoma L5178Y) and *in vivo* tests (micronucleus test; unscheduled DNA synthesis). However, citalopram was mutagenic in some *in vitro* studies (Ames Salmonella assay and Chinese hamster lung cell assay).

Carcinogenicity

Citalopram did not show any carcinogenic potential in mice at daily doses of 40-240 mg/kg (1.5 years) and in rats at 8-80 mg/kg (2 years). There was an increased incidence of small intestine carcinoma in rats treated with 8 and 24 mg/kg/day of citalopram but not in rats treated with an 80 mg/kg/day dose.

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IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

PrCITALOPRAM - 10
Citalopram Hydrobromide Tablets

This leaflet is part III of a three-part "Product Monograph" published when CITALOPRAM - 10 was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CITALOPRAM - 10. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
CITALOPRAM - 10 has been prescribed to you to relieve your symptoms of depression.

What it does:
CITALOPRAM - 10 belongs to the family of medicines called SSRIs (Selective Serotonin Reuptake Inhibitors). CITALOPRAM - 10 has been prescribed to you by your doctor to relieve your symptoms of depression. **Treatment with these types of medication is most safe and effective when you and your doctor have good communication about how you are feeling.**

When it should not be used:
You should not use CITALOPRAM - 10 if you:

- are hypersensitive to citalopram.
- are allergic to any of the other ingredients in the product, see What the important nonmedicinal ingredients are.
- are pregnant or breast-feeding.
- MAOI(monoamine oxidase inhibitors, a type of antidepressant) either at the same time or within 2 weeks of stopping.
- are taking pimozide.

Stop taking the drug and contact your doctor immediately if you experience an allergic reaction or any severe or unusual side effects.

What the medicinal ingredient is:
Citalopram as citalopram hydrobromide.

What the nonmedicinal ingredients are:
Colloidal Silicon Dioxide, Lactose Monohydrate, Magnesium Stearate, Microcrystalline Cellulose, Purified Water, Hydroxypropyl Methylcellulose, Hydroxypropyl Cellulose, Titanium Dioxide, Polyethylene Glycol and Sodium Starch Glycolate.

What dosage forms it comes in:
Tablets: 10 mg

WARNINGS AND PRECAUTIONS

POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM.

- **Particularly in the first few weeks or when doses are adjusted, a small number of patients taking drugs of this type may feel worse instead of better; for example, they may experience unusual feelings of agitation, hostility or anxiety, or have impulsive or disturbing thoughts such as thoughts of self-harm or harm to others. Should this happen to you, or to those in your care if you are a caregiver or guardian, consult your doctor immediately; do not discontinue your medication on your own.**

- **Contact your doctor before stopping or reducing your dosage of CITALOPRAM - 10. Symptoms such as dizziness, abnormal dreams, electric shock sensations, agitation, anxiety, emotional indifference, difficulty concentrating, headache, migraine, tremor (shakiness), nausea, vomiting, sweating or other symptoms may occur after stopping or reducing the dosage of CITALOPRAM - 10. Such symptoms may also occur if a dose is missed. These symptoms usually disappear without needing treatment. Tell your doctor immediately if you have these or any other symptoms. Your doctor may adjust the dosage of CITALOPRAM - 10 to reduce the symptoms.**

- **Use of SSRIs and other newer anti-depressants in patients under the age of 18 may be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour.**

Before you use CITALOPRAM - 10, talk to your doctor or pharmacist:

- About all your medical conditions, including heart problems, history of seizures, liver or kidney disease, diabetes, bleeding disorders.

- About any medications (prescription or non-prescription) which you are taking or have taken within the last 14 days, especially a monoamine oxidase inhibitor (e.g., phenelzine, tranylcypromine, moclobemide or selegiline), or any other antidepressant, lithium, tryptophan, or cimetidine, as well as any herbal product such as St. John's Wort, which may interact with citalopram.

-

If you ever had an allergic reaction to any medication.

- If you are pregnant or thinking of becoming pregnant, or if you are breast feeding.
- About your habits of alcohol consumption.

Other precautions:

- Usually CITALOPRAM - 10 does not affect patients' ability to carry out normal daily activities. However, you should not drive a car or operate machinery until you are reasonably certain that CITALOPRAM - 10 does not affect you adversely.

- Post-marketing reports indicate that some newborns whose mother took an SSRI (Selective Serotonin Reuptake Inhibitors) such as CITALOPRAM or other newer antidepressants during pregnancy have developed complications at birth requiring prolonged hospitalization, breathing support, and tube feeding. Reported symptoms include: feeding and/or breathing difficulties, seizures, tense or overly relaxed muscles, jitteriness and constant crying. In most cases, the newer antidepressant was taken during the third trimester of pregnancy. These symptoms are consistent with either a direct adverse effect of the antidepressant on the baby, or possibly a discontinuation syndrome caused by sudden withdrawal from the drug. These symptoms normally resolve over time. However, if your baby experiences any of these symptoms, contact your doctor as soon as you can.

  If you are pregnant and taking an SSRI, or other newer antidepressant, you should discuss the risks and benefits of the various treatment options with your doctor. It is very important that you do NOT stop taking these medications without first consulting your doctor.

INTERACTIONS WITH THIS MEDICATION

The following products in particular have been shown to have an interaction with CITALOPRAM - 10: monoamine oxidase inhibitors (MAOIs); metoprolol; imipramine; carbamazapine; cimetidine **(not available in Canada)**; pimozide; St. John's Wort; lithium and Cytochrome P450 isozymes.

- Avoid drinking alcohol while taking CITALOPRAM - 10.

PROPER USE OF THIS MEDICATION

- CITALOPRAM - 10 is an Adult dosage.

- It is important that you take CITALOPRAM - 10 exactly as your doctor has instructed.

- Usually your doctor will prescribe 20 mg per day, which you will take as a single dose either in the morning or in the evening. This dose may be increased. Never change the dose of CITALOPRAM - 10 you are taking, or that someone in your care is taking, unless your doctor tells you to.

- You should continue to take CITALOPRAM - 10 even if you do not feel better, as it may take several weeks for your medication to work. Improvement may be gradual.

- Continue to take CITALOPRAM - 10 for as long as your doctor recommends it. Do not stop taking your tablets even if you begin to feel better, unless you are told to do so by your doctor. Your doctor may tell you to continue to take CITALOPRAM - 10 for several months. Continue to follow your doctor's instructions.

- Swallow the tablets whole with a drink of water. Do not chew them. CITALOPRAM - 10 can be taken with or without food.

Overdose:
If you have accidentally taken too much CITALOPRAM - 10 contact your doctor or nearest hospital emergency department immediately, even if you do not feel sick. If you go to the doctor or the hospital, take the CITALOPRAM - 10 container with you.

Missed dose:
If you miss a dose, do not worry. Do not take the missed tablet(s) - just take the next dose when it is due.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

CITALOPRAM - 10 may cause unwanted effects (side-effects). You may experience some side effects such as tremor, diarrhea, sleep disturbance, drowsiness, sexual problems, nausea, dry mouth and increased sweating. You may experience other side effects such as fever, loss of appetite, vomiting, dizziness, weight loss, irregular or lack of menstruation, loss of strength, nervousness, anxiety, heartburn, stomach pain, runny nose, upper respiratory tract infections (e.g. colds, bronchitis...), problems urinating, difficulty concentrating, headache, migraine, sweating. Consult your doctor if you experience these or other side effects, as the dose may have to be adjusted.

Side-effects are often mild and may disappear after a few days. If they are troublesome or persistent, or if you develop any other unusual side-effects while taking CITALOPRAM - 10, please consult your doctor.

Please see **Warnings and Precautions, Other Precautions** for side effects of an SSRI (such as citalopram) on pregnant women.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Serotonin syndrome (symptoms include agitation, confusion, tremors, shivering)		✓	
Seizures		✓	
Decreased heart rate (symptoms include difficulty breathing, weakness, lightheadedness)		✓	

This is not a complete list of side effects. If you have any unexpected effects while taking this drug, contact your doctor or pharmacist.

HOW TO STORE IT

- As with all medicines, keep CITALOPRAM - 10 out of the reach of children. Store your tablets at room temperature (15º-30ºC) in a dry place.
- Keep the container tightly closed.
- If your doctor tells you to stop taking your medicine you should return any left-over tablets to the pharmacist, unless the doctor tells you to keep them at home.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting

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