PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]pms-SERTRALINE

Sertraline Hydrochloride Capsules

Capsules, 25 mg, 50 mg and 100 mg sertraline (as sertraline hydrochloride), Oral

Antidepressant / Antipanic / Antiobsessional Agent

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS	04/2022
7.1.1 Pregnant Women	04/2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

pms-SERTRALINE (sertraline hydrochloride capsules) is indicated for:

Adults

- **Depression**
  pms-SERTRALINE (sertraline hydrochloride) is indicated for the symptomatic relief of depressive illness. However, the antidepressant action of sertraline hydrochloride in hospitalized depressed patients has not been adequately studied.

  A placebo-controlled European study carried out over 44 weeks, in patients who were responders to sertraline hydrochloride has indicated that sertraline hydrochloride may be useful in continuation treatment, suppressing reemergence of depressive symptoms.

  However, because of methodological limitations, these findings on continuation treatment have to be considered tentative at this time.

- **Panic Disorder**
  pms-SERTRALINE is indicated for the symptomatic relief of panic disorder, with or without agoraphobia. The efficacy of sertraline hydrochloride was established in 10-week and 12-week controlled trials of patients with panic disorder as defined according to DSM-III-R criteria.

  The effectiveness of sertraline hydrochloride in long-term use for the symptomatic relief of panic disorder (i.e., for more than 12 weeks) has not been systematically evaluated in placebo-controlled trials. Therefore, the health professional who elects to use pms-SERTRALINE for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

- **Obsessive-Compulsive Disorder**
  pms-SERTRALINE is indicated for the symptomatic relief of obsessive-compulsive disorder (OCD). The obsessions or compulsions must be experienced as intrusive, markedly distressing, time-consuming, or significantly interfering with the person's social or occupational functioning.

  The effectiveness of sertraline hydrochloride in long-term use for the symptomatic relief of OCD (i.e., for more than 12 weeks) has not been systematically evaluated in placebo-controlled trials. Therefore, the health professional who elects to use pms-SERTRALINE for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

1.1 Pediatrics

Pediatrics (< 18 years of age): pms-SERTRALINE is not indicated for use in children under 18 years of age (see 7 WARNINGS AND PRECAUTIONS, Psychiatric, Potential Association with Behavioural and Emotional Changes, Including Self-Harm; 8.2.1 Clinical Trial Adverse Reactions – Pediatrics).

1.2 Geriatrics

Geriatrics (>65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

- pms-SERTRALINE is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- **Monoamine Oxidase Inhibitors**
  Cases of serious, sometimes fatal, reactions have been reported in patients receiving sertraline hydrochloride in combination with a monoamine oxidase inhibitor (MAOI), including the selective MAOI, selegiline and the reversible MAOI (reversible inhibitor of monoamine oxidase - RIMA), moclobemide and linezolid, an antibiotic which is a reversible non-selective MAOI and methylthioninium chloride (methylene blue), which is a MAOI. Some cases presented with features resembling the serotonin syndrome. Similar cases have been reported with other antidepressants during combined treatment with an MAOI and in patients who have recently discontinued an antidepressant and have been started on an MAOI. Symptoms of a drug interaction between an SSRI and an MAOI include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability, and extreme agitation progressing to delirium and coma. Therefore, pms-SERTRALINE 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 elapse after discontinuing pms-SERTRALINE treatment before starting an MAOI.

- **Pimozide**
  The concomitant use of pms-SERTRALINE and pimozide is contraindicated as sertraline hydrochloride has been shown to increase plasma pimozide levels. Elevation of pimozide blood concentration may result in QT interval prolongation and severe arrhythmias including *Torsade de Pointes* (see 7 WARNINGS AND PRECAUTIONS).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Increased risk of self-harm, harm to others, suicidal thinking and behavior with antidepressants use. Closely monitor all antidepressant-treated patients for clinical worsening and for emergence of agitation-type and/or suicidal thoughts and behaviors (see 7 WARNINGS AND PRECAUTIONS, Psychiatric, Potential Association with Behavioral and Emotional Changes, Including Self-Harm).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Switching Patients to or from a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with pms-SERTRALINE. In addition, at least 14 days should be allowed after stopping pms-SERTRALINE before starting an MAOI (see 2 CONTRAINDICATIONS).

4.2 Recommended Dose and Dosage Adjustment

Depression and Obsessive-Compulsive Disorder
As no clear dose-response relationship has been demonstrated over a range of 50-200 mg/day, a dose of 50 mg/day is recommended as the initial dose.

Panic Disorder
pms-SERTRALINE treatment should be initiated with a dose of 25 mg once daily. After one week, the dose should be increased to 50 mg once daily depending on tolerability and clinical response. No clear dose-response relationship has been demonstrated over a range of 50-200 mg/day.

Titration
In depression, OCD and panic disorder, a gradual increase in dosage may be considered if no clinical improvement is observed. Based on pharmacokinetic parameters, steady-state sertraline plasma levels are achieved after approximately 1 week of once daily dosing; accordingly, dose changes, if necessary, should be made at intervals of at least one week. Doses should not exceed a maximum of 200 mg/day.

The full therapeutic response may be delayed until 4 weeks of treatment or longer. Increasing the dosage rapidly does not normally shorten this latent period and may increase the incidence of side effects.

Maintenance
During long-term therapy for any indication, the dosage should be maintained at the lowest effective dose and patients should be periodically reassessed to determine the need for continued treatment.

Special Populations

- **Hepatic Impairment:** As with many other medications, pms-SERTRALINE should be used with caution in patients with hepatic impairment (see 7 WARNINGS AND PRECAUTIONS). The effects of sertraline hydrochloride in patients with moderate and severe hepatic impairment have not been studied.

- **Pediatrics (< 18 years):** Health Canada has not authorized an indication for pediatric use. (see 7 WARNINGS AND PRECAUTIONS, Psychiatric, Potential Association with Behavioral and Emotional Changes, Including Self-Harm).

- **Treatment of Pregnant Women During the Third Trimester:** Post-marketing reports indicate that some neonates exposed to sertraline hydrochloride, SSRIs, or other newer antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see 7.1.1 Pregnant Women). When treating a pregnant woman with sertraline hydrochloride during the third trimester, the health professional should carefully consider the potential risks and benefits of treatment. The health professional may consider tapering pms-SERTRALINE in the third trimester.

Discontinuation of pms-SERTRALINE Treatment
Symptoms associated with the discontinuation or dosage reduction of sertraline hydrochloride have been reported. Patients should be monitored for these and other symptoms when discontinuing treatment or during dosage reduction.

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 7 WARNINGS AND PRECAUTIONS, General, Discontinuation Symptoms; 8.5 Post-Market Adverse Reactions).

4.4 Administration

pms-SERTRALINE should be administered with food once daily preferably with the evening meal, or, if administration in the morning is desired, with breakfast.

5 OVERDOSAGE

Of 2,288 cases of overdose involving sertraline hydrochloride worldwide (circa 2012), alone or with other drugs, there were 244 cases with fatal outcome.

Deaths have been reported involving overdoses of sertraline, alone or in combination with other drugs and/or alcohol. Therefore, any overdosage should be treated aggressively.

The largest reported overdose of sertraline alone from which a patient recovered is 13.5 g. The lowest reported fatal case of overdose involving sertraline alone is 750 mg.

Symptoms
Symptoms of overdose include serotonin-mediated side effects such as somnolence, gastrointestinal disturbance (such as nausea, vomiting, diarrhea), tachycardia, tremor, agitation and dizziness, anxiety, dilated pupils, and ECG changes including QT-interval prolongation and *Torsade de Pointes*. Less frequently reported was coma.

Other important adverse events reported with sertraline hydrochloride overdose (single or multiple drugs) include alopecia, decreased libido, ejaculation disorder, fatigue, insomnia, bradycardia, bundle branch block, coma, convulsions, delirium, hallucinations, hypertension, hypotension, manic reaction, pancreatitis, serotonin syndrome, stupor and syncope.

Treatment
Establish and maintain an airway, and ensure adequate oxygenation and ventilation, if necessary. Activated charcoal, which may be used with sorbitol, may be as or more effective than lavage, and should be considered in treating overdose. Induction of emesis is not recommended.

Treatment was primary supportive and included monitoring and use of activated charcoal, gastric lavage or cathartics and hydration.

Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Monitoring of cardiac rhythm and vital signs is recommended along with general symptomatic and supportive measures. There are no specific antidotes for sertraline hydrochloride.

Due to the large volume of distribution of sertraline hydrochloride, 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. The health professional should consider contacting a poison control centre for additional information on the treatment of any overdose.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength /Composition	Non-medicinal Ingredients
Oral	Capsule / 25 mg, 50 mg, 100 mg	Corn Starch, Lactose, Magnesium Stearate and Sodium Lauryl Sulfate. In addition, the capsule shells contain the following additional ingredients: *The 25 mg capsules:* D&C Yellow #10, FD&C Yellow #6, Gelatin, Titanium Dioxide. *The 50 mg capsules:* D&C Yellow #10, FD&C Yellow #6, Gelatin, Titanium Dioxide. *The 100 mg capsules:* D&C Yellow #10, FD&C Red #40, Gelatin, Titanium Dioxide.

pms-SERTRALINE contains sertraline hydrochloride equivalent to 25 mg, 50 mg and 100 mg of sertraline.

Packaging
pms-SERTRALINE capsules are packaged in white high-density polyethylene bottles of:
25 mg: 100 and 1450 capsules
50 mg: 100, 250 and 1450 capsules
100 mg: 100 and 800 capsules

7 WARNINGS AND PRECAUTIONS

General

Discontinuation Symptoms: Patients currently taking pms-SERTRALINE 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.

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, fatigue, confusion, headache, tremor, nausea, vomiting and sweating or other symptoms which may be of clinical significance (see 8.5 Post-Market 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 4.2 Recommended Dose and Dosage Adjustment; 8.5 Post-Market Adverse Reactions).

Monoamine Oxidase Inhibitors: See 2 CONTRAINDICATIONS.

Use in Patients with Concomitant Illness: Clinical experience with sertraline hydrochloride in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using pms-SERTRALINE in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Carcinogenesis
In carcinogenicity studies in CD-1 mice, sertraline at doses up to 40 mg/kg produces a dose related increase in the incidence of liver adenomas in male mice. Liver adenomas have a very variable rate of spontaneous occurrence in the CD-1 mouse. The clinical significance of these findings is unknown (see 16 NON-CLINICAL TOXICOLOGY).

Cardiovascular
Sertraline hydrochloride has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. However, the electrocardiograms of 1,006 patients who received sertraline hydrochloride in double-blind trials were evaluated and the data indicate that sertraline hydrochloride is not associated with the development of clinically significant ECG abnormalities.

In placebo-controlled trials, the frequency of clinically noticeable changes (±15-20 mmHg) in blood pressure was similar in patients treated with either sertraline hydrochloride or placebo.

QTc Prolongation/*Torsade de Pointes*: Sertraline has been demonstrated to cause a concentration-dependent prolongation of the QTc interval (see 8.4 Abnormal Laboratory

Findings: Hematologic, Clinical Chemistry and Other Quantitative Data). Cases of QTc prolongation and *Torsade de Pointes* have been reported during post-marketing use of sertraline, including at therapeutic doses.

Torsade de Pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of *torsade de pointes* increases with the magnitude of QTc prolongation produced by the drug. *Torsade de Pointes* may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, t*orsade de pointes* can progress to ventricular fibrillation and sudden cardiac death.

The majority of reports occurred in patients with other risk factors such as concomitant illness, concomitant medications known to cause electrolyte imbalance or increase QT interval, and overdose.

Caution should be exercised when sertraline is prescribed in patients with an increased risk of QT prolongation including but not limited to those who are suspected to be at an increased risk of experiencing *torsade de pointes* during treatment with a QTc-prolonging drug, or in patients with cardiovascular disease or family history of QT prolongation, or in patients taking medicines known to increase QT interval, especially for patients with increased risk of QT prolongation (see 5 OVERDOSAGE; 9.4 Drug-Drug Interactions).

Risk factors for *torsade de pointes* in the general population include, but are not limited to, the following: female gender; age 65 years or older; baseline prolongation of the QT/QTc interval; presence of genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes; family history of sudden cardiac death at < 50 years; cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, left ventricular hypertrophy, cardiomyopathy, conduction system disease); history of arrhythmias (especially ventricular arrhythmias, atrial fibrillation, or recent conversion from atrial fibrillation); electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia) or conditions that can lead to electrolyte disturbances (e.g., eating disorders); bradycardia (< 50 beats per minute); acute neurological events (e.g., intracranial or subarachnoid hemorrhage, stroke, intracranial trauma); diabetes mellitus; autonomic neuropathy.

When drugs that prolong the QTc interval are prescribed, healthcare professionals should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug.

Dependence/Tolerance

Physical and Psychological Dependence: In a placebo-controlled, double-blind, randomized study of the comparative abuse liability of sertraline hydrochloride, alprazolam, and d-amphetamine in humans, sertraline hydrochloride did not produce the positive subjective

effects indicative of abuse potential, such as euphoria or drug liking, that were observed with the other two drugs. Premarketing clinical experience with sertraline hydrochloride did not reveal any drug-seeking behavior. In animal studies, sertraline hydrochloride does not demonstrate stimulant or barbiturate-like (depressant) abuse potential. As with any CNS active drug, however, health professionals should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of pms-SERTRALINE misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

Driving and Operating Machinery

Any psychoactive drug may impair judgement, thinking, or motor skills, and patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that the drug treatment does not affect them adversely.

Endocrine and Metabolism

Diabetes/Loss of Glycemic Control: Cases of new onset diabetes mellitus have been reported in patients receiving SSRIs including sertraline hydrochloride. Loss of glycemic control including both hyperglycemia and hypoglycemia has also been reported in patients with and without pre-existing diabetes. Patients should therefore be monitored for signs and symptoms of glucose fluctuations. Diabetic patients especially should have their glycemic control carefully monitored since their dosage of insulin and/or concomitant oral hypoglycemic drug may need to be adjusted.

Hyponatremia: Hyponatremia may occur as a result of treatment with SSRIs or SNRIs including sertraline. In many cases, hyponatremia appears to be the result of a syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases of serum sodium levels 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 7.1.4 Geriatrics). Several cases of hyponatremia have been reported and appeared to be reversible when sertraline was discontinued. Discontinuation of sertraline 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.

Microsomal Enzyme Induction: Sertraline hydrochloride was shown to induce hepatic enzymes as determined by the decrease of the antipyrine half-life. This degree of induction reflects a clinically insignificant change in hepatic metabolism.

Hematologic

Abnormal Bleeding: SSRIs and SNRIs, including sertraline hydrochloride, may increase the risk of bleeding events by causing abnormal platelet aggregation. Concomitant use of acetylsalicylic acid (ASA), nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages. SSRIs/SNRIs, including sertraline hydrochloride, may increase the risk of postpartum hemorrhage (7.1.1 Pregnant Women).

Caution is advised in patients with a history of bleeding disorder or predisposing conditions (e.g., thrombocytopenia). Patients should be cautioned about the risk of bleeding associated with the concomitant use of sertraline hydrochloride and NSAIDs, ASA or other drugs that affect coagulation (see 9.4 Drug-Drug Interactions, Drugs Affecting Platelet Function).

Platelet Function: There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking sertraline hydrochloride. While there have been reports of abnormal bleeding or purpura in several patients taking sertraline hydrochloride, it is unclear whether sertraline hydrochloride had a causative role (see 7 WARNINGS AND PRECAUTIONS, Hematologic, Abnormal Bleeding).

Hepatic/Biliary/Pancreatic

Hepatic Dysfunction: Sertraline hydrochloride is extensively metabolized by the liver. A single dose pharmacokinetic study in subjects with mild, stable cirrhosis demonstrated a prolonged elimination half-life and increased AUC in comparison to normal subjects. The effects of sertraline hydrochloride in patients with moderate and severe hepatic impairment have not been studied. The use of pms-SERTRALINE in patients with hepatic disease must be approached with caution. If pms-SERTRALINE is administered to patients with hepatic impairment, a lower or less frequent dose should be considered (see 4.2 Recommended Dose and Dosage Adjustment, Special Populations; 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency; and Renal Insufficiency).

Musculoskeletal

Bone Fracture Risk: Elderly patients and patients with osteoporosis and patients with important risk factors for bone fractures should be advised of possible adverse events which increase the risk of falls, such as dizziness and orthostatic hypotension, especially at the early stages of treatment but also soon after withdrawal.

Epidemiological studies show an increased risk of bone fractures following exposure to some antidepressants, including SSRIs/SNRIs. The risks appear to be greater at the initial stages of

treatment, but significant increased risks were also observed at later stages of treatment. The possibility of fracture should be considered in the care of patients treated with pms-SERTRALINE. Preliminary data from observational studies show association of SSRIs/SNRIs and low bone mineral density in older men and women. Until further information becomes available, a possible effect on bone mineral density with long-term treatment with SSRIs/SNRIs, including sertraline hydrochloride, cannot be excluded.

Neurologic

Serotonin Toxicity/Neuroleptic Malignant Syndrome: Serotonin toxicity, also known as serotonin syndrome, is a potentially life-threatening condition and has been reported with SNRIs and SSRIs, including sertraline hydrochloride.

Serotonin toxicity is characterized by neuromuscular excitation, autonomic stimulation (e.g., tachycardia, flushing) and altered mental state (e.g., anxiety, agitation, hypomania). In accordance with the Hunter criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation and diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature > 38°C and ocular clonus or inducible clonus

Neuroleptic malignant syndrome has also been rarely reported with sertraline hydrochloride, particularly during combined use with neuroleptic/antipsychotic drugs. The clinical manifestations of neuroleptic malignant syndrome often overlap with those of serotonin toxicity, including hyperthermia, hypertonia, altered mental status, and autonomic instability. In contrast to serotonin toxicity, patients with neuroleptic malignant syndrome may present with "lead pipe" muscle rigidity as well as hyporeflexia.

The concomitant use of sertraline hydrochloride with monoamine oxidase inhibitors, including linezolid and methylthioninium chloride (methylene blue), or serotonergic precursors, L-tryptophan, oxitriptan is contraindicated (see 2 CONTRAINDICATIONS). pms-SERTRALINE should be used with caution in patients receiving other serotonergic drugs including amphetamines, triptans, opioids (e.g., fentanyl, tramadol) fenfluramine, lithium, St. John's Wort, most tricyclic antidepressants, other antidepressants, antipsychotics/neuroleptics. If concomitant treatment with pms-SERTRALINE and other serotonergic drugs and/or antipsychotics/neuroleptics is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see 9.4 Drug-Drug Interactions). Serotonin toxicity and neuroleptic malignant syndrome may result in potentially life-threatening conditions. If serotonin toxicity or neuroleptic malignant syndrome is suspected, discontinuation of pms-SERTRALINE should be considered.

Seizure: Sertraline hydrochloride has not been evaluated in patients with seizure disorders.

These patients were excluded from clinical studies during the product's premarket testing. No seizures were observed among approximately 3,000 patients treated with sertraline hydrochloride in the development program for depression. However, 4 patients out of approximately 1,800 (220 < 18 years of age) exposed during the development program for obsessive-compulsive disorder experienced seizures representing a crude incidence of 0.2%. Three of these patients were adolescents, two with a seizure disorder and one with a family history of seizure disorder, none of whom were receiving anticonvulsant medication. Accordingly, pms-SERTRALINE should be introduced with care in patients with a seizure disorder and should be avoided in patients with unstable epilepsy; patients with controlled epilepsy should be carefully monitored. pms-SERTRALINE should be discontinued in any patient who develops seizures.

Ophthalmologic

Angle-Closure Glaucoma: As with other antidepressants, pms-SERTRALINE can cause mydriasis, which may trigger an angle-closure attack in a patient with anatomically narrow ocular angles. Healthcare providers should inform patients to seek immediate medical assistance if they experience eye pain, changes in vision or swelling or redness in or around the eye.

Psychiatric

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

- Pediatrics: Placebo-Controlled Clinical Trial Data

Recent analyses of placebo-controlled clinical trial safety databases from SSRI and other newer antidepressants suggest that use of these drugs in patients under the age of 18 may be associated with behavioral and emotional changes, including an increased risk of suicidal ideation and behavior 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 antidepressants, in both pediatrics and adults, of severe agitation-type adverse events coupled with self-harm or harm to others. The agitation-type adverse 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 behavior is advised in patients of all ages. This includes monitoring for agitation-type emotional and behavioral changes.

An FDA meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients ages 18 to 24 years with psychiatric disorders showed an increased risk of suicidal behavior with antidepressants compared to placebo.

Families and caregivers of patients being treated with pms-SERTRALINE should be alerted about the need to monitor patients for the emergence of agitation, anxiety, panic attacks, hostility, irritability, hypomania or mania, unusual changes in behavior, and other symptoms, as well as the emergence of suicidality particularly within several weeks of starting treatment or changing the dose. Such symptoms should be reported immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers.

See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Suicide: The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Therefore, high risk patients should be closely supervised throughout therapy and consideration should be given to the possible need for hospitalization. It should be noted that a causal role for SSRIs and other newer anti-depressants in inducing self-harm or harm to others has not been established. In order to minimize the opportunity for overdosage, prescriptions for pms-SERTRALINE should be written for the smallest quantity of drug consistent with good patient management (see 7 WARNINGS AND PRECAUTIONS, Psychiatric, Potential Association with Behavioral and Emotional Changes, Including Self-Harm).

Because of the well-established co-morbidity between both obsessive-compulsive disorder and depression and panic disorder and depression, the same precautions should be observed when treating patients with obsessive-compulsive disorder and panic disorder.

Activation of Mania/Hypomania: During clinical testing in depressed patients, hypomania or mania occurred in approximately 0.6% of sertraline hydrochloride treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants.

Akathisia: The use of sertraline has been associated with the development of akathisia (psychomotor restlessness), characterized by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Electroconvulsive Therapy: There are no clinical studies with the combined use of electroconvulsive therapy (ECT) and sertraline hydrochloride.

Renal

Renal Dysfunction: Sertraline hydrochloride is extensively metabolized and excretion of

unchanged drug in the urine is a minor route of elimination. In patients with mild to moderate renal impairment (creatinine clearance 30-60 mL/min) or moderate to severe renal impairment (creatinine clearance 10-29 mL/min), multiple-dose pharmacokinetic parameters (AUC_{0-24} or C_{max}) were not significantly different compared with controls. Half-lives were similar and there were no differences in plasma protein binding in all groups studied. This study indicates that, as expected from the low renal excretion of sertraline, sertraline dosing does not have to be adjusted based on the degree of renal impairment.

Reproductive Health: Female and Male Potential

- **Fertility**

Male Fertility
Animal data have shown that some SSRIs may affect sperm quality. In human case reports, some reversible changes in sperm quality have been reported with some SSRIs. An impact on human fertility has not been observed. (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology)

- **Function**

Sexual Dysfunction
Selective serotonin reuptake inhibitors (SSRIs) may cause symptoms of sexual dysfunction. There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs. (see 8.2 Clinical Trial Adverse Reactions)

7.1 Special Populations

7.1.1 Pregnant Women

The safety of sertraline hydrochloride during pregnancy and lactation has not been established and therefore, it should not be used in women of childbearing potential or nursing mothers, unless, in the opinion of the health professional, the potential benefits to the patient outweigh the possible hazards to the fetus.

Observational studies have provided evidence of an increased risk (less than 2-fold) of postpartum hemorrhage following exposure to SSRIs, including sertraline, especially within the month prior to birth (see 7 WARNINGS AND PRECAUTIONS, Hematologic, Abnormal Bleeding).

Exposure during late pregnancy to SSRIs may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1-2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. 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. A study of 831,324 infants born in Sweden in 1997-2005 found a PPHN risk ratio of 2.4 (95% CI 1.2-4.3) associated with patient-reported maternal use of SSRIs "in early pregnancy" and a PPHN risk ratio of 3.6 (95% CI 1.2-8.3) associated with a combination of patient-reported maternal use of SSRIs "in early pregnancy" and an antenatal SSRI prescription "in later pregnancy."

Post-marketing reports indicate that some neonates exposed to sertraline hydrochloride, SSRIs (Selective Serotonin Reuptake Inhibitors), or 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, hypertonia, 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 7 WARNINGS AND PRECAUTIONS, General, Monoamine Oxidase Inhibitors). When treating a pregnant woman with pms-SERTRALINE during the third trimester, the health professional should carefully consider the potential risks and benefits of treatment (see 4.2 Recommended Dose and Dosage Adjustment).

Labor and Delivery: The effect of sertraline hydrochloride on labor and delivery in humans is unknown.

7.1.2 Breast-feeding

It is unknown if pms-SERTRALINE is excreted in human milk. Precaution should be exercised because many drugs can be excreted in human milk.

7.1.3 Pediatrics

Pediatrics (<18 years of age): The safety and effectiveness of sertraline hydrochloride in children below the age of 18 have not been established; therefore, Health Canada has not authorized an indication for pediatric use.

Only limited clinical evidence is available concerning long-term safety data in children and adolescents, including effects on growth, sexual maturation and cognitive and behavioural developments (see 16 NON-CLINICAL TOXICOLOGY, Chronic Toxicity/Oncogenicity – Rat (juvenile animal study).

7.1.4 Geriatrics

462 elderly patients (≥ 65 years) with depressive illness have participated in multiple dose therapeutic studies with sertraline hydrochloride. The pattern of adverse reactions in the elderly was comparable to that in younger patients.

SSRIS and SNRIs, including sertraline hydrochloride, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyponatremia).

8 ADVERSE REACTIONS

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Depression
In clinical development programs, sertraline hydrochloride has been evaluated in 1,902 subjects with depression. The most commonly observed adverse events associated with the use of sertraline hydrochloride were: gastrointestinal complaints; including nausea, diarrhea/loose stools and dyspepsia; male sexual dysfunction (primarily ejaculatory delay) (see 7 WARNINGS AND PRECAUTIONS); insomnia and somnolence; tremor; increased sweating and dry mouth; and dizziness. In the fixed dose placebo- controlled study, the overall incidence of side effects was dose related with a majority occurring in the patients treated with 200 mg dose.

The discontinuation rate due to adverse events was 15% in 2,710 subjects who received sertraline hydrochloride in premarketing multiple dose clinical trials. The more common events (reported by at least 1% of subjects) associated with discontinuation included agitation, insomnia, male sexual dysfunction (primarily ejaculatory delay), somnolence, dizziness, headache, tremor, anorexia, diarrhea/loose stools, nausea and fatigue. Table 2 enumerates adverse events that occurred at a frequency of 1% or more among sertraline hydrochloride patients who participated in controlled trials comparing titrated sertraline hydrochloride with placebo for depression in adults.

Table 2 : Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Depression in Adults*

ADVERSE EVENTS	Percent of Patients Reporting	
	Sertraline Hydrochloride (n = 861)	Placebo (n = 853)
Autonomic Nervous System Disorders		
Mouth Dry	16.3	9.3
Sweating Increased	8.4	2.9

ADVERSE EVENTS	Percent of Patients Reporting	
	Sertraline Hydrochloride (n = 861)	Placebo (n = 853)
Cardiovascular		
Palpitations	3.5	1.6
Chest Pain	1.0	1.6
Centr. & Periph. Nerv. System Disorders		
Headache	20.3	19.0
Dizziness	11.7	6.7
Tremor	10.7	2.7
Paresthesia	2.0	1.8
Hypoesthesia	1.7	0.6
Twitching	1.4	0.1
Hypertonia	1.3	0.4
Disorders of Skin and Appendages		
Rash	2.1	1.5
Gastro-Intestinal Disorders		
Nausea	26.1	11.8
Diarrhea/Loose Stools	17.7	9.3
Constipation	8.4	6.3
Dyspepsia	6.0	2.8
Vomiting	3.8	1.8
Flatulence	3.3	2.5
Anorexia	2.8	1.6
Abdominal Pain	2.4	2.2
Appetite Increased	1.3	0.9
General		
Fatigue	10.6	8.1
Hot Flushes	2.2	0.5
Fever	1.6	0.6
Back Pain	1.5	0.9
Metabolic and Nutritional Disorders		
Thirst	1.4	0.9
Musculo-Skeletal System Disorders		
Myalgia	1.7	1.5
Psychiatric Disorders		
Insomnia	16.4	8.8
Sexual Dysfunction - Male [(1)]	15.5	2.2
Somnolence	13.4	5.9
Agitation	5.6	4.0
Nervousness	3.4	1.9
Anxiety	2.6	1.3
Yawning	1.9	0.2
Sexual Dysfunction - Female [(2)]	1.7	0.2
Concentration Impaired	1.3	0.5
Reproduction		

ADVERSE EVENTS	Percent of Patients Reporting	
	Sertraline Hydrochloride (n = 861)	Placebo (n = 853)
Menstrual Disorder [2]	1.0	0.5
Respiratory System Disorders		
Rhinitis	2.0	1.5
Pharyngitis	1.2	0.9
Special Senses		
Vision Abnormal	4.2	2.1
Tinnitus	1.4	1.1
Taste Perversion	1.2	0.7
Urinary System Disorders		
Micturition Frequency	2.0	1.2
Micturition Disorder	1.4	0.5

* Events reported by at least 1% of patients treated with sertraline hydrochloride are included.

(1) %based on male patients only: 271 sertraline hydrochloride and 271 placebo patients. Male sexual dysfunction can be broken down into the categories of decreased libido, impotence and ejaculatory delay. In this data set, the percentages of males in the sertraline hydrochloride group with these complaints are 4.8%, 4.8% and 8.9%, respectively. It should be noted that since some sertraline hydrochloride patients reported more than one category of male sexual dysfunction, the incidence of each category of male sexual dysfunction combined is larger than the incidence for the general category of male sexual dysfunction, in which each patient is counted only once.

(2) % based on female patient only: 590 sertraline hydrochloride and 582 placebo patients.

Panic Disorder

In placebo-controlled clinical trials, 430 patients with panic disorder were treated with sertraline hydrochloride in doses of 25– 200 mg/day. During treatment, most patients received doses of 50 – 200 mg/day. Adverse events observed at an incidence of at least 5% for sertraline hydrochloride and at an incidence that was twice or more the incidence among placebo-treated patients included: diarrhea, ejaculation failure (primarily ejaculatory delay), anorexia, constipation, libido decreased, agitation, and tremor.

In the total safety data base for panic disorder, 14% of patients discontinued treatment due to an adverse event. The most common events leading to discontinuation were nausea (2.6%), insomnia (2.3%), somnolence (2.3%), and agitation (2.1%).

Obsessive-Compulsive Disorder

In placebo-controlled clinical trials for OCD, adverse events observed at an incidence of at least 5% for sertraline hydrochloride and at an incidence that was twice or more the incidence among placebo-treated patients included: nausea, insomnia, diarrhea, decreased libido, anorexia, dyspepsia, ejaculation failure (primarily ejaculatory delay), tremor, and increased sweating.

In placebo-controlled clinical trials for OCD, 10% of patients treated with sertraline hydrochloride discontinued treatment due to an adverse event. The most common events leading to discontinuation were nausea (2.8%), insomnia (2.6%), and diarrhea (2.1%).

Incidence in Controlled Clinical Trials for Panic and Obsessive-compulsive disorder in adults
Table 3 enumerates adverse events that occurred at a frequency of 2% or more among patients on sertraline hydrochloride who participated in controlled trials comparing sertraline hydrochloride with placebo in the treatment of panic disorder and obsessive-compulsive disorder. Only those adverse events which occurred at higher rate during sertraline hydrochloride treatment than during placebo treatment are included.

Table 3: Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled – Clinical Trials for Panic and Obsessive-Compulsive Disorder in Adults*

	(Percent of Patients Reporting)			
ADVERSE EVENTS	**PANIC DISORDER**		**OBSESSIVE COMPULSIVE DISORDER**	
	Sertraline hydrochloride (n = 430)	**Placebo (n = 275)**	**Sertraline hydrochloride (n = 533)**	**Placebo (n = 373)**
Autonomic Nervous System Disorders				
Mouth Dry	15	10	14	9
Sweating Increased	5	1	6	1
Cardiovascular				
Palpitations	-	-	3	2
Chest Pain	-	-	3	2
Centr. & Periph. Nerv. System Disorder				
Tremor	5	1	8	1
Paresthesia	4	3	3	1
Headache	-	-	30	24
Dizziness	-	-	17	9
Hypertonia	-	-	2	1
Disorders of Skin and Appendages				
Rash	4	3	2	1
Gastrointestinal Disorders				
Nausea	29	18	30	11
Diarrhea	20	9	24	10
Dyspepsia	10	8	10	4
Constipation	7	3	6	4
Anorexia	7	2	11	2
Vomiting	6	3	3	1
Flatulence	-	-	4	1
Appetite Increased	-	-	3	1
General				
Fatigue	11	6	14	10
Hot Flushes	3	1	2	1
Pain	-	-	3	1
Back Pain	-	-	2	1
Metabolic and Nutritional Disorders				

ADVERSE EVENTS	(Percent of Patients Reporting)			
	PANIC DISORDER		OBSESSIVE COMPULSIVE DISORDER	
	Sertraline hydrochloride (n = 430)	Placebo (n = 275)	Sertraline hydrochloride (n = 533)	Placebo (n = 373)
Weight Increase	-	-	3	0
Musculoskeletal System Disorders				
Arthralgia	2	1	-	-
Psychiatric Disorders				
Insomnia	25	18	28	12
Somnolence	15	9	15	8
Nervousness	9	5	7	6
Libido Decreased	7	1	11	2
Agitation	6	2	6	3
Anxiety	4	3	8	6
Concentration Impaired	3	0	-	-
Depersonalization	2	1	3	1
Paroniria	-	-	2	1
Respiratory System Disorders				
Pharyngitis	-	-	4	2
Special Senses				
Tinnitus	4	3	-	-
Vision Abnormal	-	-	4	2
Taste Perversion	-	-	3	1
Urogenital				
Ejaculation Failure (1)	19	1	17	2
Impotence (2)	2	1	5	1

* Events reported by at least 2% of patients treated with sertraline hydrochloride are included, except for the following events which had an incidence on placebo greater than or equal to sertraline hydrochloride [Panic Disorder]: headache, dizziness, malaise, abdominal pain, respiratory disorder, pharyngitis, flatulence, vision abnormal, pain, upper respiratory tract infection, and paroniria. [OCD]: abdominal pain, respiratory disorder, depression, and amnesia.

(1) Primarily ejaculatory delay; % based on male patients only: Panic Disorder: 216 sertraline hydrochloride and 134 placebo patients, OCD: 296 sertraline hydrochloride and 219 placebo patients.

(2) % based on male patients only: Panic Disorder: 216 sertraline hydrochloride and 134 placebo patients, OCD: 296 sertraline hydrochloride and 219 placebo patients.

Other events observed during the premarketing evaluation of sertraline hydrochloride

During its premarketing assessment, multiple doses of sertraline hydrochloride were administered to 2,710 subjects. The conditions and duration of exposure to sertraline hydrochloride varied greatly, and included (in overlapping categories) clinical pharmacology studies, open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and studies for indications other than depression. Untoward events associated with this exposure were 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 untoward events into a smaller number of standardized

event categories.

All events are included except those already listed in the previous table or in the 7 WARNINGS AND PRECAUTIONS section, and those reported in terms so general as to be uninformative.

It is important to emphasize that although the events reported occurred during treatment with sertraline hydrochloride, they were not necessarily caused by it.

Autonomic Nervous System Disorders - Infrequent: flushing, mydriasis, increased saliva, cold clammy skin; Rare: pallor.

Cardiovascular - Infrequent: postural dizziness, hypertension, hypotension, postural hypotension, edema, dependent edema, periorbital edema, peripheral edema, peripheral ischemia, syncope, tachycardia; Rare: precordial chest pain, substernal chest pain, aggravated hypertension, myocardial infarction, varicose veins.

Central and Peripheral Nervous System Disorders - Frequent: confusion; Infrequent: ataxia, abnormal coordination, abnormal gait, hyperesthesia, hyperkinesia, hypokinesia, migraine, nystagmus, vertigo; Rare: local anesthesia, coma, convulsions, dyskinesia, dysphonia, hyporeflexia, hypotonia, ptosis.

Disorders of Skin and Appendages - Infrequent: acne, alopecia, pruritus, erythematous rash, maculopapular rash, dry skin; Rare: bullous eruption, dermatitis, erythema multiforme, abnormal hair texture, hypertrichosis, photosensitivity reaction, follicular rash, skin discoloration, abnormal skin odor, urticaria.

Endocrine Disorders - Rare: exophthalmos, gynecomastia.

Gastro-Intestinal Disorders - Infrequent: dysphagia, eructation; Rare: diverticulitis, fecal incontinence, gastritis, gastroenteritis, glossitis, gum hyperplasia, hemorrhoids, hiccup, gastrointestinal bleeding, melena, hemorrhagic peptic ulcer, proctitis, stomatitis, ulcerative stomatitis, tenesmus, tongue edema, tongue ulceration.

General - Frequent: allergic reaction, allergy, asthenia; Infrequent: malaise, generalized edema, rigors, weight decrease, weight increase; Rare: enlarged abdomen, halitosis, otitis media, aphthous stomatitis.

Hematopoietic and Lymphatic - Infrequent: lymphadenopathy, purpura; Rare: anemia, anterior chamber eye hemorrhage.

Metabolic and Nutritional Disorders - Rare: dehydration, hypercholesterolemia, hypoglycemia.

Musculo-Skeletal System Disorders - Infrequent: arthralgia, arthrosis, dystonia, muscle cramps, muscle weakness; Rare: hernia.

Psychiatric Disorders - Infrequent: abnormal dreams, aggressive reaction, amnesia, apathy, delusion, depersonalization, depression, aggravated depression, emotional lability, euphoria, hallucination, neurosis, paranoid reaction, suicide attempt (including suicidal ideation), teeth-grinding, abnormal thinking; Rare: hysteria, somnambulism, withdrawal reactions.

Reproductive - Infrequent: dysmenorrhea (2), intermenstrual bleeding (2); Rare: amenorrhea (2), balanoposthitis (1), breast enlargement (2), female breast pain (2), leukorrhea (2), menorrhagia (2), atrophic vaginitis (2).

(1) - % based on male subjects only: 1,005
(2) - % based on female subjects only: 1,705

Respiratory System Disorders - Infrequent: bronchospasm, coughing, dyspnea, epistaxis; Rare: bradypnea, hyperventilation, sinusitis, stridor.

Special Senses - Infrequent: abnormal accommodation, conjunctivitis, diplopia, earache, eye pain, xerophthalmia; Rare: abnormal lacrimation, photophobia, visual field defect.

Urinary System Disorders - Infrequent: dysuria, face edema, nocturia, polyuria, urinary incontinence; Rare: enuresis, oliguria, renal pain, urinary retention.

Laboratory Tests – In man, asymptomatic elevations in serum hepatic transaminases (SGOT [or AST] and SGPT [or ALT]) to a value ≥ 3 times the upper limit of normal have been reported infrequently (approximately 0.6% and 1.1%, respectively) in association with sertraline hydrochloride administration. The proportion of patients having these elevations was greater in the sertraline hydrochloride group than in the placebo group. These hepatic enzyme elevations usually occurred within the first 1 to 9 weeks of drug treatment and promptly diminished upon drug discontinuation.

False-positive urine immunoassay screening tests for benzodiazepines have been reported in patients taking sertraline. This is due to lack of specificity of the screening tests. False positive test results may be expected for several days following discontinuation of sertraline therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish sertraline from benzodiazepines.

Sertraline hydrochloride therapy was associated with small mean increases in total cholesterol (approximately 3%) and triglycerides (approximately 5%).

Uricosuric Effect - sertraline hydrochloride is associated with a small mean decrease in serum uric acid (approximately 7%) of no apparent clinical importance.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Suicidality-related adverse events from clinical trials in major depressive disorder in the pediatric population

In the safety analysis from controlled clinical trials in children and adolescents with major depressive disorder aged 6 to 17 years, both the number and percentage of patients for whom suicide attempts were reported was the same for the sertraline arm (2/189, 1.1%) as for the placebo arm (2/184, 1.1%), while the corresponding event rates of suicide attempts were 1.1% (2 attempts in 2/189 patients) in sertraline-treated patients versus 1.6% in placebo-treated patients (3 attempts in 2/184 patients). For the additional category of "other events possibly related to self-harm", which includes suicidal ideation and self-injurious behaviors such as cutting, event rates were 2.1% (4 events in 189 patients) in sertraline-treated patients and 0% in placebo-treated patients.

Overall, the total reported event rates for both suicide attempts and other events possibly related to self-harm are as follows: 3.2% or 6 /189 for sertraline versus 1.6% or 3/184 for placebo (see 7 WARNINGS AND PRECAUTIONS, Psychiatric, Potential Association with Behavioral and Emotional Changes, Including Self-Harm).

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Cardiac Electrophysiology: In a randomised, three-way crossover, double-blind, placebo- and positive-controlled ECG assessment study, healthy subjects (N = 50) were upward titrated over 6 days to a target 200 mg BID dose of sertraline that was administered from days 7-13, with a single 200 mg dose on day 14. Serial ECG data collected over 24 h on day 14 showed QTcF ($QTcF=QT/RR^{0.33}$) prolongation averaging approximately 6-10 ms, with a maximum difference from placebo in the mean change from baseline QTcF of 9.7 ms (90% CI 7.6, 11.7) at the 4 h time point. Exposure-response analysis demonstrated a statistically significant positive relationship between the change from baseline QTcF and sertraline plasma concentrations. The observed mean C_{max} (234 ng/mL) at the supratherapeutic 200 mg BID dose in this study is slightly higher than the mean C_{max} of 190 ng/mL reported for the maximum recommended therapeutic dose of 200 mg following once-daily doses.

8.5 Post-Market Adverse Reactions

Adverse events not listed above which have been reported in temporal association with sertraline hydrochloride since market introduction include:

Blood and Lymphatic Disorders: agranulocytosis, aplastic anemia, pancytopenia, leukopenia, thrombocytopenia

Cardiovascular Disorders: bradycardia, AV block, atrial arrhythmias, ventricular tachycardia (including *torsade de pointes*-type arrhythmias)

Endocrine Disorders: hypothyroidism, syndrome of inappropriate ADH secretion, hyperprolactinemia

Eye Disorders: blindness, cataract, oculogyric crisis

Gastrointestinal Disorders: pancreatitis

Hepatobilary Disorders: liver events

Immune System Disorders: anaphylactoid reaction, serum sickness

Investigations: increased coagulation times, QT interval prolongation

Metabolism and Nutrition Disorders: diabetes mellitus, hyperglycemia, hypoglycemia

Musculoskeletal System Disorders: Muscle contractions involuntary, Lupus-like syndrome, trismus, bone fractures, rhabdomyolysis

Nervous System Disorders: cerebrovascular spasm (including reversible cerebral vasoconstriction syndrome and call-fleming syndrome), optic neuritis, neuroleptic malignant syndrome, extrapyramidal symptoms, serotonin syndrome

Psychiatric Disorders: psychosis

Reproductive System Disorders: priapism, galactorrhea

Respiratory Disorders: pulmonary hypertension

Skin Disorders: angioedema, severe skin reactions such as Stevens-Johnson syndrome, epidermal necrosis, photosensitivity, other severe cutaneous disorders

Urinary System Disorders: acute renal failure, hematuria

Vascular Disorders: vasculitis

The causal relationship between sertraline hydrochloride treatment and the emergence of these events has not been established. The clinical features of hepatic events (which in the majority of cases appeared to be reversible with discontinuation of sertraline hydrochloride) occurring in one or more patients include: elevated enzymes, increased bilirubin, hepatomegaly, hepatitis, jaundice, abdominal pain, vomiting, liver failure and death. There

have been spontaneous reports of symptoms such as dizziness, paresthesia, nausea, headache, anxiety, fatigue, and agitation following the discontinuation of sertraline hydrochloride treatment.

Adverse Reactions following Discontinuation of Treatment (or Dose Reduction)
There have been reports of adverse reactions upon the discontinuation of sertraline hydrochloride (particularly when abrupt), including but not limited to the following: dizziness, abnormal dreams, sensory disturbances (including paresthesias and electric shock sensations), agitation, anxiety, fatigue, confusion, headache, tremor, nausea, vomiting and sweating or other symptoms which may be of clinical significance (see 4.2 Recommended Dose and Dosage Adjustment; 7 WARNINGS AND PRECAUTIONS, General, Discontinuation Symptoms).

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 reuptake inhibitors (see 4.2 Recommended Dose and Dosage Adjustment; 7 WARNINGS AND PRECAUTIONS General, Discontinuation Symptoms).

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions
• Monoamine Oxidase Inhibitors: See 2 CONTRAINDICATIONS • Pimozide: See 2 CONTRAINDICATIONS

9.3 Drug-Behavioural Interactions

Alcohol

Although sertraline hydrochloride did not potentiate the cognitive and psychomotor effects of alcohol in experiments with normal subjects, the concomitant use of sertraline hydrochloride and alcohol in depressed, panic disorder or OCD patients has not been studied and is not recommended.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e.

those identified as contraindicated).

Table 4 – Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Beta Blockers	T	There is no experience with the use of sertraline hydrochloride in hypertensive patients controlled by beta-blockers. In a placebo-controlled crossover study in normal volunteers, the effect of sertraline hydrochloride on the β-adrenergic blocking activity of atenolol was assessed. The mean CD25's (the doses of isoproterenol required to increase heart rate by 25 bpm, the chronotropic dose 25 or CD25) and the average decreases in heart rate seen with atenolol during exercise test were not statistically different in the sertraline hydrochloride versus the placebo group.	Data suggests that sertraline hydrochloride does not alter the β-blocking action of atenolol; therefore, no dosage adjustment is required.
Cimetidine	CT	In a placebo-controlled crossover study in normal volunteers, the potential of cimetidine to alter the disposition of a single 100 mg dose of sertraline hydrochloride was assessed. The mean sertraline C_{max} and AUC were significantly higher in the cimetidine-treated	Data suggests that concomitant administration of cimetidine may inhibit the metabolism of sertraline and its metabolite, desmethylsertraline, and may result in a decrease in the clearance and first pass metabolism of sertraline, with a

		group, as were the mean desmethylsertraline T_{max} and AUC.	possible increase in drug-related side effects.
CNS Active Drugs	CT	Sertraline hydrochloride (200 mg daily) did not potentiate the effects of carbamazepine, haloperidol or phenytoin on cognitive and psychomotor performance in healthy subjects.	The risk of using sertraline hydrochloride in combination with other CNS active drugs has not been systematically evaluated. Caution is advised if the concomitant administration of sertraline hydrochloride and such drugs is required.
Diazepam	CT	In a normal volunteer, double-blind, placebo-controlled study comparing the disposition of intravenously administered diazepam before and after administration of sertraline (200 mg/day final dose) to steady state or placebo, there was a statistically significant 13% decrease relative to baseline in diazepam clearance for the sertraline group over that of the placebo group.	These changes in baseline diazepam clearance are of unknown clinical significance.
Digoxin	CT	In a parallel placebo-controlled trial in normal volunteers (10 subjects per group), the administration of sertraline hydrochloride for 17 days (dose of sertraline hydrochloride: 200 mg for the last 10 days) did not cause changes in	No dosage adjustment is required.

		the total plasma concentrations of digoxin except a decrease of T_{max} as compared to baseline.	
Drugs Affecting Platelet Function (e.g. warfarin, NSAIDS, ASA and other anticoagulants)	CT	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, ASA or other anticoagulants may potentiate the risk of bleeding. Altered anticoagulant effects, including increased bleeding, have also been reported when SSRIs or SNRIs are coadministered with warfarin. In a placebo-controlled study in healthy men comparing prothrombin time AUC (0-120 hr) following single dosing with warfarin (0.75 mg/kg) before and after dosing to steady state with either sertraline (200 mg/day final dose) or placebo, there was a statistically significant	The clinical significance of the increase in prothrombin time changes are unknown. Accordingly, prothrombin time should be carefully monitored when pms-SERTRALINE is initiated or discontinued in patients receiving warfarin (see 7 WARNINGS AND PRECAUTIONS, Hematologic, Abnormal Bleeding). Because sertraline is highly bound to plasma protein, the administration of pms-SERTRALINE to a patient taking another drug which is tightly bound to protein may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely adverse effects may result from displacement of protein bound sertraline by other tightly bound drugs.

		mean increase in prothrombin time of 8% relative to baseline for sertraline compared to a 1% decrease for placebo. The normalization of prothrombin time for the sertraline group was delayed compared to the placebo group.	
Drugs Metabolized by P450 2D6 (e.g. tricyclic antidepressants and type Ic antiarrhythmics such as propafenone and flecainide)		Many antidepressants, inhibit the biochemical activity of the drug metabolizing isozyme, cytochrome P450 2D6 (debrisoquin hydroxylase), and thus may increase the plasma concentration of co-administered drugs that are metabolized primarily by 2D6 and which have a narrow therapeutic index. There is variability among the antidepressants in the extent of clinically important P450 2D6 inhibition. In two drug interaction clinical trials using desipramine and the recommended starting SSRI doses in normal volunteers, the effect of sertraline hydrochloride was compared to two other SSRIs. In the first study, mean desipramine steady state AUC (24) increased by 23% and 380% during coadministration with sertraline hydrochloride and the	Concomitant use of a drug metabolized by P450 2D6 with sertraline hydrochloride may require lower doses than are usually prescribed for the other drug. Furthermore, whenever pms-SERTRALINE is withdrawn from co-therapy, an increased dose of the co-administered drug may be required.

		comparative SSRI, respectively. In a second study using a different comparative SSRI, mean desipramine steady state AUC (24) increased by 37% and 421% during coadministration with sertraline hydrochloride and the comparative SSRI, respectively. Trial results indicate that the effect of sertraline hydrochloride was significantly less pronounced than that of the two comparative SSRIs.	
Drugs Metabolized by P450 3A4	CT	In two separate *in vivo* interaction studies, sertraline was co-administered with cytochrome P450 3A4 substrates, terfenadine or carbamazepine, under steady-state conditions. The results of these studies demonstrated that sertraline co-administration did not increase plasma concentrations of terfenadine or carbamazepine.	The data suggests that sertraline's extent of inhibition of P450 3A4 activity is not likely to be of clinical significance.
Drugs that Affect Electrolytes (e.g. loop, thiazide, and related diuretics; laxatives and enemas; amphotericin B; high dose corticosteroids)	T		The concomitant use of pms-SERTRALINE with drugs that can disrupt electrolyte levels is discouraged. (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular)
Hypoglycemic Drugs	C	There are no controlled clinical trials with	Close monitoring of glycemia in patients

		sertraline hydrochloride in diabetic patients treated with insulin or oral hypoglycemic drugs. In a placebo-controlled trial in normal volunteers, the administration of sertraline hydrochloride for 22 days (dose of sertraline was 200 mg/day for the final 13 days), caused a statistically significant 16% decrease in the clearance of tolbutamide following an I.V. dose of 1000 mg. In a placebo-controlled study in normal volunteers, glibenclamide (5 mg) was given before and after administration of sertraline (200 mg/day final dose) to steady state or placebo. No significant changes were observed in the total plasma concentration of glibenclamide. Hypoglycemia requiring dextrose infusion was observed in one patient treated with sertraline hydrochloride, glibenclamide, haloperidol, bisacodyl, acetylsalicylic acid and flucloxacillin. The causal relationship to sertraline hydrochloride	treated with pms-SERTRALINE and oral hypoglycemic drugs or insulin is recommended since their dosage of insulin and/or concomitant oral hypoglycemia drug may need to be adjusted (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Diabetes/Loss of Glycemic Control).

		treatment was not firmly established.	
Monoamine Oxidase Inhibitors	C		See 2 CONTRAINDICATIONS.
Lithium	T	In placebo-controlled trials in normal volunteers, the co-administration of sertraline with lithium did not significantly alter lithium pharmacokinetics, but did result in an increase in tremor relative to placebo, indicating a possible pharmacodynamic interaction.	When co-administering sertraline with medications, such as lithium, which may act via serotonergic mechanisms, patients should be appropriately monitored.
Metamizole[1]		Metamizole may cause a reduction in plasma concentrations of sertraline when co-administered, with potential decrease in clinical efficacy.	Caution is advised. Healthcare professionals should monitor clinical response and/or sertraline plasma levels and consider dose adjustment, as appropriate.
Phenytoin	T	The pharmacokinetic and pharmacodynamic effects have not been adequately characterized.	It is recommended that plasma phenytoin concentrations be monitored following initiations of sertraline therapy, with appropriate adjustments to the phenytoin dose.
Pimozide	CT	In a controlled study of a single dose (2 mg) of pimozide, 200 mg sertraline (q.d.) co-administration to steady state was associated with a mean increase in pimozide	Although these increases were not identified in the trial as being associated with clinically important effects on QT intervals, the trial design was not optimal for the investigation of

[1] Currently not marketed in Canada for human use

		AUC and C_{max} of about 40%. For ethical considerations, a trial with higher doses could not be done. Since the highest recommended pimozide dose (12 mg) has not been evaluated in combination with sertraline, the effect on QT interval and PK parameters at doses higher than 2 mg at this time are not known.	pharmacodynamic effects in the clinical setting. While the mechanism of this interaction is unknown, due to the narrow therapeutic index of pimozide and due to the interaction noted at a low dose of pimozide, concomitant administration of pms-SERTRALINE and pimozide is contraindicated (see 2 CONTRAINDICATIONS).
QTc-Prolonging Drugs - Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide); - Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide, dronedarone); - Class IC antiarrhythmics (e.g., flecainide, propafenone); - antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone); - antidepressants (e.g. citalopram, fluoxetine, venlafaxine), tricyclic/tetracyclic antidepressants (e.g., amitriptyline, imipramine, maprotiline); - opioids (e.g., methadone);	T	Pharmacokinetic and pharmacodynamic studies of sertraline combined with other medicinal products that prolong the QT interval have not been performed. An additive effect of sertraline and these medicinal products cannot be excluded.	Co-administration of sertraline with medicinal products that have a clear QT interval prolonging effect is discouraged.

- macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, telithromycin, tacrolimus); - quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxacin); - antimalarials (e.g., quinine, chloroquine); - azole antifungals (e.g., ketoconazole, fluconazole, voriconazole); - domperidone; - 5-HT3 receptor antagonists (e.g., dolasetron, ondansetron); - tyrosine kinase inhibitors (e.g., vandetanib, sunitinib, nilotinib, lapatinib); - histone deacetylase inhibitors (e.g., vorinostat); - beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol).			
Serotonergic Drugs (e.g., almotriptan, sumatriptan, rizatriptan, naratriptan, zolmitriptan, amphetamines, dextromethorphan, opioids (including tramadol, fentanyl and its analogues, tapentadol, meperidine, methadone and pentazocine), fenfluramine and tryptophan)	C	There is limited controlled experience regarding the optimal timing of switching from other antidepressants and antipanic agents to sertraline. Co-administration with tryptophan, TCAs and other antidepressants may lead to a higher incidence of serotonin-associated side effects. Rare postmarketing reports describe	Care and prudent medical judgment should be exercised when switching, particularly from long-acting agents. The duration of washout period which should intervene before switching from one selective serotonin reuptake inhibitor (SSRI) or Tricyclic Antidepressants (TCAs) etc. to another has not been established.

		patients with weakness, hyperreflexia, and incoordination following the combined use of a selective serotonin reuptake inhibitor (SSRI) and 5-HT1 agonists (triptans).	If concomitant treatment with pms-SERTRALINE and a triptan, tricyclic antidepressants, or other drugs with serotonergic activity is clinically warranted, appropriate observation of the patient for acute and long-term adverse events is advised.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Food appears to increase the bioavailability by about 40%: it is recommended that pms-SERTRALINE be administered with meals (see 4.4 Administration).

9.6 Drug-Herb Interactions

St. John's Wort
In common with other SSRI's, pharmacodynamic interactions between pms-SERTRALINE and the herbal remedy St. John's Wort may occur and may result in an increase in undesirable effects.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The mechanism of action of sertraline is presumed to be linked to its ability to inhibit the neuronal reuptake of serotonin. It has only very weak effects on norepinephrine and dopamine neuronal reuptake. At clinical doses, sertraline blocks the uptake of serotonin into human platelets.

Like most clinically effective antidepressants, sertraline downregulates brain norepinephrine and serotonin receptors in animals. In receptor binding studies, sertraline has no significant affinity for adrenergic (*alpha1, alpha$_2$ & beta*), cholinergic, GABA, dopaminergic, histaminergic, serotonergic (5- HT1A, 5-HT1B, 5-HT2) or benzodiazepine binding sites.

In placebo-controlled studies in normal volunteers, sertraline hydrochloride did not cause sedation and did not interfere with psychomotor performance.

10.3 Pharmacokinetics

Absorption
Following multiple oral once-daily doses of 200 mg, the mean peak plasma concentration (C_{max}) of sertraline is 0.19 mcg/mL occurring between 6 to 8 hours post-dose. The area under the plasma concentration time curve is 2.8 mg hr/L. Food appears to increase the bioavailability by about 40%: it is recommended that pms-SERTRALINE be administered with meals. For desmethylsertraline, C_{max} is 0.14 mcg/mL, the half-life 65 hours and the area under the curve 2.3 mg hr/L. Following single or multiple oral once-daily doses of 50 to 400 mg/day the average terminal elimination half-life is approximately 26 hours. Linear dose proportionality has been demonstrated over the clinical dose range of 50 to 200 mg/day.

Distribution
Approximately 98% of sertraline is plasma protein bound. The interactions between sertraline and other highly protein bound drugs have not been fully evaluated (see 9.4 Drug-Drug Interactions).

Metabolism
Sertraline is extensively metabolized to N-desmethylsertraline, which shows negligible pharmacological activity. Both sertraline and N-desmethylsertraline undergo oxidative deamination and subsequent reduction, hydroxylation and glucuronide conjugation.

Elimination
Biliary excretion of metabolites is significant.

Special Populations and Conditions

- **Geriatrics**
  The pharmacokinetics of sertraline itself appears to be similar in young and elderly subjects. Plasma levels of N-desmethylsertraline show a 3-fold elevation in the elderly following multiple dosing, however, the clinical significance of this observation is not known.

- **Sex**
  Analyses for gender effects on outcome did not suggest any differential responsiveness on the basis of sex.

- **Hepatic Insufficiency**
  The pharmacokinetics of sertraline in patients with significant hepatic dysfunction has not been determined (see 4.2 Recommended Dose and Dosage Adjustment; 7

WARNINGS AND PRECAUTIONS Hepatic/Biliary/Pancreatic).

- **Renal Insufficiency**
  The pharmacokinetics of sertraline in patients with significant renal dysfunction has not been determined (see 4.2 Recommended Dose and Dosage Adjustment; 7 WARNINGS AND PRECAUTIONS, Renal).

11 STORAGE, STABILITY AND DISPOSAL

Store between 15°C and 30°C. Keep out of the reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

No special handling is necessary for this product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Sertraline Hydrochloride

Code Name: CP-51,974-01

Chemical Name: (1S, *cis*) -4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-l-naphthalenamine hydrochloride

Molecular Formula and molecular mass: $C_{17}H_{17}NCl_2 \cdot HCl$, 342.7 g / mol

Structural Formula:

Physicochemical Properties:

Description: Sertraline hydrochloride is a white to off-white crystalline powder

Solubility: Slightly soluble in water and isopropyl alcohol, very slightly soluble in 0.1N aqueous hydrochloric acid, practically insoluble in 0.1N aqueous sodium hydroxide, sparingly soluble in ethanol, and soluble in chloroform.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Panic Disorder

Summary of patient demographics for clinical trials in panic disorder: Four placebo-controlled clinical trials have been performed to investigate the efficacy of sertraline hydrochloride in panic disorder: two flexible dose studies and two fixed dose studies.

Results of studies in panic disorder: At the last week of treatment (week 10 or 12), both flexible dose studies and one of the fixed dose studies showed statistically significant differences from placebo in favour of sertraline hydrochloride in terms of mean change from baseline in the total number of full panic attacks (last observation carried forward analysis). As the flexible dose studies were of identical protocol, data for these investigations can be pooled. The mean number of full panic attacks at baseline was 6.2/week (n = 167) in the sertraline hydrochloride group and 5.4/week in the placebo group (n = 175). At week 10 (last observation carried forward analysis), the mean changes from baseline were -4.9/week and -2.5/week for the sertraline hydrochloride and placebo groups, respectively. The proportion of patients having no panic attacks at the final evaluation was 57% in the placebo group and 69% in the sertraline hydrochloride group. The mean daily dose administered at the last week of treatment was approximately 120 mg (range: 25-200 mg) in the flexible dose studies. No clear dose-dependency has been demonstrated over the 50 to 200 mg/day dose range investigated in the fixed dose studies.

Obsessive-Compulsive Disorder

Summary of patient demographics for clinical trials in obsessive-compulsive disorder: Five placebo-controlled clinical trials, in adults, of 8 to 16 weeks in duration have been performed to investigate the efficacy of sertraline hydrochloride in obsessive-compulsive disorder: four flexible dose studies (50-200 mg/day) and one fixed dose study (50, 100 & 200 mg/day).

Results of studies in obsessive-compulsive disorder: Results for three of the four flexible dose studies and the 50 and 200 mg dose groups of the fixed dose study were supportive of differences from placebo in favour of sertraline hydrochloride in terms of mean change from baseline to endpoint on the Yale-Brown Obsessive-Compulsive Scale and/or the National Institute of Mental Health Obsessive-Compulsive Scale (last observation carried forward analysis). No clear dose- dependency was demonstrated over the 50 to 200 mg/day dose range investigated in the fixed dose studies. In the flexible dose studies, the mean daily dose administered at the last week of treatment ranged from 124-180 mg.

14.3 Comparative Bioavailability Study

A comparative bioavailability study was performed in the fasting state to compare the pharmacokinetic parameters of pms-SERTRALINE 100 mg capsules (Pharmascience Inc.) versus ZOLOFT® 100 mg capsules (Pfizer Canada Inc.). The results of the study are shown in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Sertraline hydrochloride (1 x 100 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**Confidence Interval 90%**
AUC_{0-72} (ng•h/mL)	511.20 551.39 (42.88)	587.66 627.20 (39.57)	87	82 to 92
AUC_I (ng•h/mL)	593.78 646.44 (46.47)	685.34 740.75 (43.60)	87	81 to 92
C_{MAX} (ng/mL)	19.27 20.79 (41.30)	22.88 24.07 (33.21)	84	
T_{MAX}§ (h)	8.26 (12.76)	7.61 (16.69)		
$T_{½el}$§ (h)	24.21 (20.13)	24.88 (21.57)		

* pms-SERTRALINE 100 mg capsules, Pharmascience Inc.

† ZOLOFT® 100 mg capsules, Pfizer Canada Inc.

§ Expressed as the arithmetic mean (CV %) only.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Acute Toxicity: mice and rats

Table 5 – Acute Oral and Intraperitoneal Toxicity Studies in Mice and Rats

Species	Sex	LD50 (mg Sertraline base/kg)		Max Mortality (hr)	
		Oral	IP	Oral	IP
Mice	M	548 (495-612)	73 (66-79)	2 1/4	1
	F	419 (371-465)		1 3/4	
Rats	M	1591 (1348-1847)	79 (70-90)	24	24
	F	1327 (1071-1562)		4.5	

Signs of toxicity observed in both mice and rats dosed orally and by intraperitoneal administration included hyperactivity, convulsions, depression, weakness, decreased food consumption, and weight gain inhibition. Oral administration in both mice and rats produced exophthalmia, soft stools, and labored respiration. Orally dosed rats also showed marked salivation. Acute oral administration produced no gross pathological findings. Acute intraperitoneal administration, on the other hand, caused adhesion of the intestines or pancreas to the liver in 2 of 10 male mice and liver lobe adhesions which were dose-related in rats.

Sertraline was also given in single doses of 10, 20, 30, and 50 mg base/kg p.o. (in capsules) to two female beagle dogs at each dose. At the lowest level, dogs were mydriatic and anorectic but otherwise asymptomatic. At higher doses, increased salivation, tremors and twitches were observed, along with the mydriasis and anorexia. None of the dogs at any dose level exhibited motor stimulation, circling or stereotypy. The duration of the anorexia was 12 to 15 hr, but eating resumed late in the day after treatment and the dogs recovered uneventfully.

Chronic Toxicity/Oncogenicity: mice, rats and dogs

Table 6 – Chronic Toxicity/Oncogenicity

<table>
<tr><th>SPECIES</th><th>ROUTE</th><th>DOSE mg/kg/day</th><th>ANIMAL PER DOSE LEVEL</th><th>DURATION</th><th>FINDINGS</th></tr>
<tr><td colspan="6">36-Day Diet Study in Mice</td></tr>
<tr><td>CD-1 Mice</td><td>Diet</td><td>0
10
40
80</td><td>10/sex</td><td>36 Days</td><td>Drug and desmethyl metabolite serum levels drug related
Serum Concentration (ng/mL)
<table><tr><th></th><th colspan="2">Drug</th><th colspan="2">Metabolite</th></tr><tr><th>Dose (mg/kg/day)</th><th>Male</th><th>Female</th><th>Male</th><th>Female</th></tr><tr><td>10</td><td>22</td><td>17</td><td>40</td><td>23</td></tr><tr><td>40</td><td>52</td><td>16</td><td>181</td><td>< 10</td></tr><tr><td>80</td><td>142</td><td>63</td><td>307</td><td>169</td></tr></table>Some degree of alopecia occurred in three mid-dose animals and one high-dose animal. Fatty change occurred in the livers of 8/10 high-dose males compared to 3/10 control males. On the basis of these findings, daily doses of 10, 20 and 40 mg sertraline hydrochloride base/kg were proposed for the 2-year feeding study.</td></tr>
<tr><td colspan="6">2-Year Diet Study in Mice</td></tr>
<tr><td>CD-1 Mice</td><td>Diet</td><td>0
0
10
20
40</td><td>50/Sex</td><td>24 Months</td><td>Survival of drug treated females was slightly less than control. Bronchioalveolar adenomas occurred in 9/49, 1/50, and 12/50 low-, mid-, and high-dose females compared to 6/50 and 2/50 in females of the two control groups. Hepatocellular adenomas were observed in 8/50, 8/50 and 12/50 low-, mid-, and high-dose males compared to 3/50 and 4/50 males in the two control groups. These tumors were benign and the type usually occurring spontaneously in this strain of mouse. There were no treatment-related increases in tissue specific or total malignant tumors.</td></tr>
<tr><td colspan="6">16-Day P.O. Study in Rats</td></tr>
<tr><td>Sprague Dawley Rats</td><td>Gavage</td><td>0
40
80
160</td><td>5/sex</td><td>16 Days</td><td>Anorexia and transient body weight gain inhibition; latter effect was high in high-dose females. Dose-related increase in liver weights due to microsomal enzyme induction; centrilobular degeneration at all dose levels and slightly elevated SGPT and SGOT at 160 mg/kg only.</td></tr>
<tr><td colspan="6">6-Week Diet Study in Rats</td></tr>
<tr><td>Sprague Dawley Rats</td><td>Diet</td><td>0
10
40
80</td><td>10/sex</td><td>6 Weeks</td><td>Minimal effect on body weight gain of males and slight inhibition of body weight (< 10%) in mid- and high-dose females. Liver weight increase in mid- and high-dose males and females; hepatocellular hypertrophy and minimal midzonal fatty change in high-dose males and females and mid-dose males accompanied by slight elevations in serum SDH, GOT and 5'NT in some animals.
No adverse effect level: 10 mg/kg/day.</td></tr>
</table>

<table>
<tr><th>SPECIES</th><th>ROUTE</th><th>DOSE mg/kg/day</th><th>ANIMAL PER DOSE LEVEL</th><th>DURATION</th><th>FINDINGS</th></tr>
<tr><td colspan="6">3-Month P.O. Study in Rats</td></tr>
<tr><td>Sprague Dawley Rats</td><td>Gavage</td><td>0
10
40
80</td><td>15M
10F</td><td>3 Months</td><td>Dose-related plasma levels at 10 and 40 mg/kg.
Plasma Levels (mcg/mL) of Drug 2 hr Post-Dose on Days 1, 5 and 30
<table>
<tr><th>Dose (mg/kg/day)</th><th>Sex</th><th></th><th>Day 1</th><th>Day 5</th><th>Day 30</th></tr>
<tr><td>80</td><td>M</td><td>Mean</td><td>0.63</td><td>0.31</td><td>0.46</td></tr>
<tr><td></td><td></td><td>± SD</td><td>0.19</td><td>0.05</td><td>0.20</td></tr>
<tr><td></td><td>F</td><td>Mean</td><td>0.75</td><td>0.37</td><td>0.84</td></tr>
<tr><td></td><td></td><td>± SD</td><td>0.19</td><td>0.10</td><td>0.48</td></tr>
<tr><td>40</td><td>M</td><td>Mean</td><td>0.70</td><td>0.20</td><td>0.32</td></tr>
<tr><td></td><td></td><td>± SD</td><td>0.11</td><td>0.06</td><td>0.18</td></tr>
<tr><td></td><td>F</td><td>Mean</td><td>0.42</td><td>0.33</td><td>0.92</td></tr>
<tr><td></td><td></td><td>± SD</td><td>0.14</td><td>0.05</td><td>0.28</td></tr>
<tr><td>10</td><td>M</td><td>Mean</td><td>0.25</td><td>0.10</td><td>0.10</td></tr>
<tr><td></td><td></td><td>± SD</td><td>0.10</td><td>0.03</td><td>0.03</td></tr>
<tr><td></td><td>F</td><td>Mean</td><td>0.19</td><td>0.14</td><td>0.27</td></tr>
<tr><td></td><td></td><td>± SD</td><td>0.06</td><td>0.03</td><td>0.08</td></tr>
</table>
Dose-related increases in absolute and relative liver weights due to induction of microsomal enzymes; increases associated with centrilobular hepatocellular hypertrophy; mild midzonal fatty changes observed in 10/15 males and 1/10 females at 80 mg/kg.</td></tr>
<tr><td colspan="6">2-Year Diet Study in Rats</td></tr>
<tr><td>Long Evans Rats</td><td>Diet</td><td>0
10
20
40</td><td>65/sex</td><td>24 Months</td><td>Interim sacrifice (15/sex) at 6 months: Kidney/body weight was increased. Increase in mean absolute and relative liver weights in males and females at high-dose and in females at mid-dose.

2 years sacrifice: Deaths were dose-related; inhibition of weight gain was dose-related in males and present at high-dose only in females. Slight elevations of serum 5'nucleotidase (5'NT) activity in the high and mid-dose groups occurred throughout the study.

Increase of liver and kidney/body weight ratios. These effects are considered to be related to drug-metabolizing enzyme induction. Hepatocytes with large clear fat-containing vacuoles were observed; number of affected animals in groups was dose-related in females but distribution was more erratic in males. In no case was there evidence of necrosis or of an inflammatory response. There were no treatment related effects on the number of tumor-bearing animals, total malignant tumors or total benign tumors in either sex. Hence, there was no evidence of oncogenic potential.</td></tr>
</table>

SPECIES	ROUTE	DOSE mg/kg/day	ANIMAL PER DOSE LEVEL	DURATION	FINDINGS
Rat (Special Toxicology Study) IV					
Sprague Dawley Rats	IV	0 0.125 0.250 0.500	10/sex	15 days 16 days 17 days 18 days	Hemoglobinuria, identifiable only by reagent test strip as early as 5 minutes after injection, the only treatment related clinical pathology finding, was not dose-related. It is analogous to the *in vitro* hemolytic effects of sertraline hydrochloride in the concentrations utilized in this study, i.e., 0.125, 0.25, and 0.5 mg/mL. No hemolysis was detected *in vitro* when red cells were exposed to 0.005 mg/mL sertraline hydrochloride. *In vitro* studies have also demonstrated incompatibility (cloudiness) of plasma exposed to equal volumes of 0.25 and 0.5 mg sertraline hydrochloride/mL. These data suggest that intravenous sertraline hydrochloride solutions should be administered by drip rather than by bolus injections. A total of 3 high-dose and 12 control rats had perivascular hemorrhage and/or chronic perivasculitis at the injection site in the tail.
Rat (juvenile animal study) oral					
Sprague Dawley Rats	Gavage	0 10 40 80	30/sex	Postnatal day 21 through postnatal day 56 with non-dosing recovery phase up to postnatal day 196	The administration of 80 mg/kg of sertraline to males and females on post-natal Days 21 to 56 resulted in dehydration, chromorhinorrhea and reduced average body weight gain. In addition, rales, hunched posture, reduced food consumption and two early deaths (plus one early euthanization due to poor condition) also occurred in male rats given 80 mg/kg/day. Decreases in brain weight were seen in treated male animals around post-natal day 140. Delays in sexual maturation occurred in males (80 mg/kg/day) and females (≥10 mg/kg/day), but despite this finding there were no sertraline-related effects on other organ weights, mating and fertility, sperm motility or sperm concentration in males or female reproductive endpoints (estrous cycling, mating and fertility, or ovarian and uterine parameters). There were no sertraline-related effects on any behaviour parameter (learning and memory, auditory startle response, and locomotor activity) in males, while a decrease in auditory startle response occurred in females at 40 and 80 mg/kg/day. There were no sertraline-related effects on female brain weights, male or female femur lengths, gross necropsy or microscopic observations at any dose level. In juvenile males, the no-observed-adverse-effect level (NOAEL) for general toxicity was 40 mg/kg/day (correlating to a C_{max} of 262 ng/mL and an AUC_{0-t} to 3,170 ng·hr/mL on post-natal Day 56). In juvenile females, the NOAEL could not be established based on the delays in sexual maturation that occurred at ≥10 mg/kg. All of the aforementioned effects attributed to the administration of sertraline were reversed at some point during the non-dosing recovery phase of the study.

<table>
<tr><th>SPECIES</th><th>ROUTE</th><th>DOSE mg/kg/day</th><th>ANIMAL PER DOSE LEVEL</th><th>DURATION</th><th>FINDINGS</th></tr>
<tr><td colspan="6">7-Day Oral Study in Dogs</td></tr>
<tr><td rowspan="6">Beagle</td><td rowspan="6">Oral (Capsule)</td><td rowspan="6">0
15
45</td><td rowspan="6">2 Males</td><td rowspan="6">7 Days</td><td>Slight anorexia, body weight loss and hind limb weakness at high-dose. Plasma drug levels suggested good oral absorption.</td></tr>
<tr><td>Plasma Concentrations of Drug 3 hr Post-Dose on Days 1 and 7
<table><tr><td></td><td></td><td colspan="2">Plasma Concentration (mcg/mL)</td></tr><tr><td>Dose (mg/kg/day)</td><td>Dog No.</td><td>Day 1</td><td>Day 7</td></tr><tr><td>45</td><td>832255
832259</td><td>2.28
2.04</td><td>2.48
0.82</td></tr><tr><td>15</td><td>832258
832260</td><td>1.12
0.42</td><td>0.13
0.68</td></tr></table></td></tr>
<tr><td>Apparent losses of small lymphocytes from thymus was observed; lymphoid depletion in spleen, mesenteric lymph nodes and ileum were seen in one high-dose dog.</td></tr>
<tr><td colspan="6">14-Day Oral Study in Dogs</td></tr>
<tr><td>Beagle</td><td>Oral (Capsule)</td><td>0
40
80
160</td><td>1/sex</td><td>14 Days</td><td>Dose-related anorexia and body weight loss. Increase of serum alkaline phosphatase at high-dose and of SGPT in the high-dose females.
Depletion of small lymphocytes from spleen in the 80 mg male and from spleen and ileum in the high-dose male.</td></tr>
<tr><td colspan="6">3-Month Oral Study in Dogs</td></tr>
<tr><td>Beagle</td><td>Oral (Capsule)</td><td>0
10
40
80</td><td>3/sex</td><td>3 Months</td><td>Dose-related CNS stimulation during the first one or two weeks of treatment. One high-dose animal died of convulsions 5.5 hours after drug administration on the first day of treatment. Necropsy of this animal revealed generalized congestion and lymphoid depletion of the thymus, spleen and mesenteric lymph node consistent with the cause of death. Elevated alkaline phosphatase (ALP) values were measured in all dogs of the high-dose group and in 2 males and 2 females of the mid-dose group. The ALP elevation together with a trend toward increased liver weights reflect the ability of sertraline hydrochloride to induce drug metabolizing enzymes at 40 and 80 mg/kg.

Slight SGPT elevations in the high-dose animals were not associated with histopathological changes.</td></tr>
<tr><td colspan="6">6-Month Oral Study in Dogs</td></tr>
<tr><td>Beagle</td><td>Oral (Capsule)</td><td>0
10
30
90</td><td>4/sex</td><td>6 Months</td><td>Pronounced clinical signs of CNS stimulation were observed at high-dose; they diminished in intensity or completely disappeared after 1 to 2 weeks of dosing.

At the 90 mg/kg dose level increase in absolute and relative liver weights, proliferation of smooth endoplasmic reticulum and mild serum alkaline phosphatase elevations</td></tr>
</table>

<table>
<tr><th>SPECIES</th><th>ROUTE</th><th>DOSE mg/kg/day</th><th>ANIMAL PER DOSE LEVEL</th><th>DURATION</th><th>FINDINGS</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>were all consistent with sertraline hydrochloride being an enzyme inducer. This was demonstrated by a shortening of the plasma half-life of antipyrine at the high-dose level only (30 min compared to 54 min). A few dogs at 30 mg/kg had slight sporadic alkaline phosphatase elevations. Some dogs at the high-dose level only had SGPT elevations. The mild bile duct hyperplasia detected in two high-dose males could have been drug-related; however, this lesion sometimes is observed in control beagle dogs.</td></tr>
<tr><td colspan="6">1-Year Oral Study in Dogs</td></tr>
<tr><td>Beagle</td><td>Oral (Capsule)</td><td>0
10
30
90</td><td>4/sex</td><td>1 year</td><td>Dose-related incidences of central and autonomic nervous system clinical signs during the first few weeks of the study were observed.
Slight to moderate elevations in serum alkaline phosphatase activity occurred in 1/8, 4/8 and 7/8 low-, mid- and high-dose dogs, respectively. SGPT levels were increased in 2/8 high-dose animals. Liver/body weight ratios were increased in high-dose males (25%) and females (32%) and in mid-dose females (25%). Sertraline hydrochloride was previously shown to be an inducer of hepatic microsomal drug metabolizing enzymes, a phenomenon often associated with elevated liver weights and serum alkaline phosphatase activity in dogs. There were no gross or microscopic histologic changes in the liver or in other tissues. Plasma levels of sertraline hydrochloride and its desmethyl metabolite, CP-62,508, confirmed dose-related systemic exposure throughout the study:
<table>
<tr><td colspan="8">C_{max} of drug and 0-24 hour AUC of metabolite</td></tr>
<tr><td colspan="2">(mg/kg)</td><td colspan="3">C_{max} CP-51,974 (mcg/mL)</td><td colspan="3">AUC CP-62,508 (mg.hr/L)</td></tr>
<tr><td></td><td></td><td>Day 1</td><td>Day 99</td><td>Day 274</td><td>Day 1</td><td>Day 99</td><td>Day 274</td></tr>
<tr><td>10</td><td>Mean
S.D.</td><td>0.344
0.165</td><td>0.218
0.142</td><td>0.262
0.190</td><td>3.4
1.7</td><td>2.6
0.8</td><td>3.0
1.0</td></tr>
<tr><td>30</td><td>Mean
S.D.</td><td>0.723
0.454</td><td>0.643
0.299</td><td>1.26
0.90</td><td>4.9
2.3</td><td>8.8
4.4</td><td>11.6
5.0</td></tr>
<tr><td>90</td><td>Mean
S.D.</td><td>1.33
0.81</td><td>1.06
0.61</td><td>2.16
1.24</td><td>11.8
6.2</td><td>12.2
5.0</td><td>39.9
25.1</td></tr>
</table>
</td></tr>
</table>

Genotoxicity: Genotoxicity studies including Ames Salmonella and mouse lymphoma TK+/TK- assays for point mutations, tests for cytogenetic aberrations *in vivo* on mouse bone marrow and on human lymphocytes *in vitro* with and without metabolic activation were uniformly negative.

Sertraline did not induce mutations at the gene level in the Ames microbial assay with and

without metabolic activation against *Salmonella typhimurium* strains TA 1535, TA 1537, TA 98, and TA 100 nor at the chromosomal level in bone marrow of mice treated with 80 mg/kg p.o. (*in vivo* cytogenetic assay) or in human lymphocytes (*in vitro* cytogenetic assay) at 0.5 to 25 mg/mL in culture. Sertraline produced no significant increase in mutant frequency in L5178Y mouse lymphoma (TK+/-) cells either in the presence or absence of exogenous metabolic activation by normal rat liver S9 microsomes.

Reproductive and Developmental Toxicology

Table 7 – Fertility and Reproductive Performance

SPECIES	ROUTE	DOSE mg/kg/day	ANIMAL PER DOSE LEVEL	DURATION	FINDINGS
A Study of the Reproduction and Fertility of Rats. Segment I (Extended to produce F_2 litters)					
Rat	Oral (gavage)	0 10 40 80	F_0 = 30F/ dose F_0 = 15M/ dose		F_0 males were treated in the 64 days prior to mating and throughout mating. F_0 females were treated in the 14 days prior to mating and during mating and gestation. Offspring (F_1 generation) were raised for 3 months free of drug treatment and then mated to produce an F_2 generation which, together with F_1 dams were sacrificed 21-24 days post-partum. The F_0 treated dams showed decreased pregnancy rates, most marked at 80 mg/kg. The pregnancy rates were 47%, 83%, 92% and 100% respectively in the high, mid, low dose and control groups. Survival of F_1 pups to Day 4 post-partum was also depressed in a dose-related order. High-dose F_1 pups showed evidence of earlier behavioural development.
Fetotoxicity and Fertility Study (FDA Protocol, Segment I) in Rats by Oral Administration					
Rat	Oral (gavage)	0 10 20 80	20M 40F		Males were treated for 71 days before mating. Females were treated for 2 weeks before mating, during mating and throughout gestation. Four additional groups of 20 undosed females were mated with the same males to test their fertility. Drug treatment produced inhibition (approximately 20 g) during pregnancy in all treated females and reduced birth weights of pups at Day 1 post-partum (males: ≤ 0.15 g, females: ≤ 0.3 g). At Days 4 and 21 of age, the weights of the pups treated also led to a lower neonatal survival rate at the two

SPECIES	ROUTE	DOSE mg/kg/day	ANIMAL PER DOSE LEVEL	DURATION	FINDINGS
					highest doses (survival was 61% and 69% respectively at high- and mid-dose groups compared with a survival of 94% in the low-dose group and 98% in controls at 21 days). Some of this mortality was attributed to a higher incidence of hemoperitoneum in 18 high-dose and 12 mid-dose than in 6 low dose and 1 control F_1 neonates. Hemoperitoneum was not seen in newborn pups in any of the other studies. In behavioural tests, some early hyperactivity observed in pups of the treated groups was consistent with the pharmacology of the drug. No adverse effects were observed in the F_2 generation.

Table 8 – Teratology

SPECIES	ROUTE	DOSE mg/kg/day	ANIMAL PER DOSE LEVEL	DURATION	FINDINGS
Fetotoxicity Study (Segment II) in Rats by the Oral Route					
Rat	Oral (gavage)	0 10 20 80	20F		Drug administered to inseminated females at days 6-15 post-insemination. Treatment caused transient aggressiveness at the beginning of the treatment period and reduced body weight gain (an average of 26 g) of the high-dose dams. A slight delay in ossification of fetuses appears to be related to lower fetal weights in the mid- and high-dose groups which were probably functions of maternal toxicity (e.g., delay in ossification of metacarpus in 20 pups among 1,181 at 80 mg/kg and in 13 pups among 1,825 in the control group).
Fetotoxicity Study (FDA Segment II) in Rabbits by the Oral Route					
Rabbit	Oral (gavage)	0 5 20 40	20F		Sertraline hydrochloride administered to pregnant rabbits during organogenesis (days 7 to 18 post-insemination). At the highest dose level of 40 mg/kg, the compound induced severe maternal toxicity which in turn delayed the ossification processes of the fetuses (e.g., delay in ossification in hyoid bone: control = 20%, 40 mg/kg = 36%; in Talus bone: control = 27%, 40 mg/kg = 44%).

Table 9 – Peri- Post-Natal Studies

SPECIES	ROUTE	DOSE mg/kg/day	ANIMAL PER DOSE LEVEL	DURATION	FINDINGS
Peri- Post-Natal Study in Rats (Segment III) by the Oral Route					
Rat	Oral	0 10 20 80	20F		Sertraline hydrochloride was administered by gavage to inseminated rats from day 15 post-insemination until parturition and throughout the whole lactation period. The treatment produced some adverse effects in dams and pups at the two higher dose levels; a dose-related delay in body weight gain of the dams during gestation and lactation in mid- and high-dose groups was observed. In some animals in each of these groups, hyperactivity was observed during the first few days of treatment. Food and water consumption was also affected in these two dose groups. Statistically significant decreases in mean litter size were observed at the high-dose level on Day 1 post-partum, at the mid- and high-dose levels on Day 4 post-partum; this effect was dose- related on Day 21 post-partum. The mean body weights of pups were lower in both sexes at both of the higher dose level groups when compared to controls on Days 1 post-partum but there were no statistically significant differences between the groups on Day 21 post-partum. No external or visceral anomalies were observed in the pups that died during the lactation phase or were sacrificed at weaning. The post-natal development of pups was also affected by the treatment of dams: fewer pups showed positive responses on the last day when reflexes were tested and the appearance of the incisors was retarded. This was most evident at the high-dose, but also to some extent at the mid-dose. Post-weaning examination revealed no treatment related changes.

SPECIES	ROUTE	DOSE mg/kg/day	ANIMAL PER DOSE LEVEL	DURATION	FINDINGS
Experiment (Segment III) to Further Investigate the Effect of Sertraline on Neonates					
Rat	Oral (gavage)	80			A second Segment III Study was carried out to further investigate the effects of sertraline hydrochloride on the neonates. In this study, pups from dams treated at 80 mg base/kg were fostered by untreated dams and, vice versa, pups from untreated dams were fostered by drug treated dams. As observed in previous studies, sertraline hydrochloride affected the weight gain of the dams (body weight difference between control and high-dose group: at 20 days of pregnancy = 34 g, at 21 days post-partum = 19 g). The effects observed on the progeny can be separated into two categories: Those directly related to the *in utero* exposure of foetuses: perinatal mortality and pup weight impairment on Day 1; those related to the exposure during lactation: post-natal growth impairment and delay in development. Vision and hearing, evaluated after weaning, were not affected.
Experiment to Delineate the Prenatal Period of Fetal Vulnerability					
Rat	Oral (gavage)	0 80	20 20 x 4		Sertraline hydrochloride administered to pregnant rats throughout or during late gestation, has been shown to exert deleterious effects on neonatal growth and survival to Day 4 post-partum. Another experiment was done in which sertraline hydrochloride (80 mg base/kg/day) was administered in 0.1% methylcellulose by oral gavage to 4 groups of pregnant dams (20/group) from Day 0 to Days 5, 10, or 15 and throughout gestation, respectively, in order to delineate the prenatal period of fetal vulnerability. Pup survival was unaffected by sertraline hydrochloride treatment during the first 5, 10 or 15 days of gestation. Mortality of live-born pups in these groups during the first 4 days of life ranged from 0.8% to 3% compared with 2% for the controls whereas 56% of pups born alive to dams treated throughout the gestational period did not survive their first 4

SPECIES	ROUTE	DOSE mg/kg/day	ANIMAL PER DOSE LEVEL	DURATION	FINDINGS
					days of life. However, survival of pups from Day 4 to Day 21 (lactation index) was comparable in all treatment and control groups. Pups born to mothers dosed throughout gestation also weighed less than control on Days 1 and 4 post-partum, but body weights of pups were comparable to control by Day 14. This experiment demonstrates that the immediate prenatal period, gestation Days 16-21, is the period of vulnerability of the neonatal pup for survival from the *in utero* effects of a high-dose (80 mg/kg) of sertraline hydrochloride.

17 SUPPORTING PRODUCT MONOGRAPHS

PrZOLOFT® (capsules, 25 mg 50 mg and 100 mg), submission control number 265271, Product Monograph, Upjohn Canada ULC (October 19, 2022).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]pms-SERTRALINE

Sertraline (as Sertraline Hydrochloride) Capsules

Read this carefully before you start taking **pms-SERTRALINE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **pms-SERTRALINE**.

Serious Warnings and Precautions

New and worsened emotional or behaviour problems:

- When you first start taking pms-SERTRALINE or when your dose is adjusted, you may feel worse instead of better. You may feel new or worsened feelings of agitation, hostility, anxiety or impulsivity.
- During your treatment with pms-SERTRALINE, it is important that you and your healthcare professional talk regularly about how you are feeling. They will closely monitor you for signs of new or worsened emotions or behaviours while you are taking pms-SERTRALINE.
- You may find it helpful to tell a relative or close friend that you depressed. Ask them to read this leaflet. You might ask them to tell you if they:
  - think your depression is getting worse, or
  - are worried about changes in your behaviour.
- If your depression worsens or you experience changes in your behaviour, tell your healthcare professional right away. Do not stop taking your medicine as it takes time for pms-SERTRALINE to work.

Self-harm or suicide:

- Antidepressants, such as pms-SERTRALINE, can increase the risk of suicidal thoughts and actions.
- If you have thoughts of harming or killing yourself at any time, tell your healthcare professional or go to a hospital right away. Close observation by a healthcare professional is necessary in this situation.

What is pms-SERTRALINE used for?

pms-SERTRALINE is used in **adults** to relieve your symptoms of:

- **Depression** (feeling sad, a change in appetite or weight, difficulty concentrating or sleeping, feeling tired, headaches, unexplained aches and pain)

- **Obsessive-compulsive disorder** (recurrent and intrusive thoughts, feelings, ideas, or sensations; recurrent pattern of behaviour, or unwanted thoughts or actions)
- **Panic disorder** (repeated, unexpected panic attacks)

How does pms-SERTRALINE work?
pms-SERTRALINE belongs to a group of medicines known as antidepressants, more specifically to the family of medicines called SSRIs (**S**elective **S**erotonin **R**euptake **I**nhibitors).

pms-SERTRALINE is thought to work by increasing the levels of a chemical in the brain called serotonin. This helps to relieve your symptoms of depression, obsessive-compulsive disorder and/or panic disorder.

What are the ingredients in pms-SERTRALINE?
Medicinal ingredients: Sertraline Hydrochloride
Non-medicinal ingredients: Cornstarch, Lactose, Magnesium Stearate and Sodium Lauryl Sulfate. In addition, the capsule shells contain the following additional ingredients:
The 25 mg capsules: D&C Yellow #10, FD&C Yellow #6, Gelatin, Titanium Dioxide.
The 50 mg capsules: D&C Yellow #10, FD&C Yellow #6, Gelatin, Titanium Dioxide.
The 100 mg capsules: D&C Yellow #10, FD&C Red #40, Gelatin, Titanium Dioxide.

pms-SERTRALINE comes in the following dosage forms:
Capsules: 25 mg, 50 mg and 100 mg.

Do not use pms-SERTRALINE if:
- you are allergic to sertraline hydrochloride or to any of the non-medicinal ingredients in pms-SERTRALINE (see **What are the ingredients in pms-SERTRALINE**).
- you are currently taking or have recently taken any monoamine oxidase inhibitors (MAOIs), such as phenelzine sulphate, tranylcypromine sulphate, moclobemide. If you are unsure, ask your healthcare professional.
- you are currently taking pimozide

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take pms-SERTRALINE. Talk about any health conditions or problems you may have, including if you:
- have any diseases or conditions that affect your metabolism or heart function
- have or have a history of:
  - seizures
  - liver disease
  - high cholesterol
  - heart disease
  - heart rhythm problems
  - slow heartbeat
  - taking medications for your heart

- manic episodes
- have a family history of people younger than 50 years of age having a heart attack
- have levels of electrolytes in your body are either too high or too low or you have a condition (such as an eating disorder) that can affect your electrolyte levels
- have had a stroke
- are known to have heart problems or have been told you are at risk for heart problems
- have diabetes
- have or have a history of a bleeding disorder or have been told that you have low platelets
- have blood pressure problems
- are pregnant or thinking about becoming pregnant, or if you are breast feeding
- had a recent bone fracture or were told you have osteoporosis or risk factors for osteoporosis
- drink alcohol and/or use street drugs
- have ever had any allergic reaction to medications, food, etc.

Other warnings you should know about:

Do NOT stop taking pms-SERTRALINE without talking to your healthcare professional first, as it may cause unwanted side effects such as headache, insomnia, numbness, tingling, burning, or prickling, nervousness, anxiety, nausea, sweating, dizziness, jitteriness and weakness.

Pregnancy: Only take pms-SERTRALINE during pregnancy if you and your doctor have discussed the risks and have decided that you should. If you take pms-SERTRALINE near the end of your pregnancy, you may be at a higher risk of heavy vaginal bleeding shortly after birth. If you become pregnant while taking pms-SERTRALINE, tell your doctor right away.

Effects on newborns: In some cases, babies born to a mother taking pms-SERTRALINE during pregnancy may require hospitalization, breathing support and tube feeding. Be ready to seek medical help for your newborn if they:
have trouble breathing or feeding,
- have muscle stiffness, or floppy muscles (like a rag doll)
- have seizures (fits)
- are shaking (jitteriness)
- are constantly crying

If you take pms-SERTRALINE:
- During early pregnancy, there is a possible slight increased risk that your newborn may have a heart defect.
- During late pregnancy, your newborn may be at risk of having a serious lung condition called Persistent Pulmonary Hypertension of the Newborn (PPHN), which causes breathing problems.

Falls and fractures: pms-SERTRALINE can cause you to feel sleepy or dizzy and can affect your

balance. This increases your risk of falling, which can cause fractures or other fall related-injuries, especially if you:

- take sedatives
- consume alcohol
- are elderly
- have a condition that causes weakness or frailty

Serotonin toxicity (also known as Serotonin Syndrome): pms-SERTRALINE can cause serotonin toxicity, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop serotonin toxicity if you take pms-SERTRALINE with certain anti-depressants or migraine medications. Serotonin toxicity symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma

Driving and using machines: pms-SERTRALINE may make you feel sleepy. Give yourself time after taking pms-SERTRALINE to see how you feel before driving a vehicle or using machinery.

pms-SERTRALINE can cause serious side effects including:

- Angle-closure glaucoma (sudden eye pain or change in vision)
- Heart rhythm problems
- Sexual dysfunction

See the **Serious side effects and what to do about them** table below for more information on these and other serious side effects.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions
Do not take pms-SERTRALINE if you: • are taking or have recently taken (in the last 14 days) any MAOIs such as phenelzine, tranylcypromine, linezolid, methylene blue as you may have serious side effects • are taking pimozide, an antipsychotic medicine (used to manage psychosis)

The following may interact with pms-SERTRALINE:

- Other antidepressants, such as SSRIs and certain tricyclics
- Other drugs that affect serotonin such as, amphetamines, opioids, tryptophan, fenfluramine
- Certain medicines called “triptans” which are used to treat migraines, such as almotriptan,

sumatriptan, rizatriptan, naratriptan, zolmitriptan
- Certain medicines used to treat pain, such as fentanyl (used in anaesthesia or to treat chronic pain), tramadol, tapentadol, meperidine, methadone, pentazocine
- metamizole, used to treat fever or pain
- Certain medicines used to treat cough, such as dextromethorphan
- Certain medicines used to treat bipolar depression, such as lithium
- drugs that affect your electrolyte levels such as diuretics ("water pills"), laxatives and enemas, amphotericin B, high dose corticosteroids (drugs that reduce inflammation)
- Drugs that can affect how your blood clots such as warfarin, dabigatran, acetylsalicylic acid (Aspirin) and other non-steroidal anti-inflammatory drugs (NSAIDs)
- Certain medicines used to treat seizures such as phenytoin
- Cimetidine, a medicine used to treat heartburn
- Insulin or oral medicines used to treat diabetes
- An herbal medicine called St. John's Wort
- Alcohol, it is recommended to avoid drinking alcohol while taking pms-SERTRALINE

How to take pms-SERTRALINE:
- It is very important that you take pms-SERTRALINE exactly as your healthcare professional has instructed
- Keep taking pms-SERTRALINE unless your healthcare professional tells you to stop.
- Continue to take pms-SERTRALINE even if you do not feel better, as it may take several weeks for your medicine to start working.
- Take with food either in the morning or the evening.
- Swallow the capsules whole, do not divide, crush or chew them.

Remember, this medicine has been prescribed only for you. Do not give it to anybody else, as they may experience undesirable effects, which may serious.

Usual dose:

Depression: The usual starting dose is 50 mg once daily. Your healthcare professional may decide to slowly increase your dose. The maximum dose is 200 mg daily.

Obsessive-compulsive disorder: The usual starting dose is 50 mg once daily. Your healthcare professional may decide to slowly increase your dose. The maximum dose is 200 mg daily.

Panic disorder: The usual starting dose is 25 mg once daily. Your healthcare professional may decide to slowly increase your dose. The maximum dose is 200 mg daily.

Overdose:

If you think you, or a person you are caring for, have taken too much pms-SERTRALINE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed dose:
If you miss a dose, do not take the missed dose. Just take your next dose at the right time. Do not take a double dose to make up for a missed dose.

What are possible side effects from using pms-SERTRALINE?
These are not all the possible side effects you may have when taking pms-SERTRALINE. If you experience any side effects not listed here, tell your healthcare professional.

- headache
- nausea
- dry mouth
- diarrhea
- loss of appetite
- indigestion
- sleepiness
- dizziness
- insomnia
- nervousness
- agitation
- tremor
- increased sweating

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Sexual dysfunction: low sex drive, not being able to ejaculate, delayed ejaculation, erectile dysfunction		✓	
UNCOMMON			
Akathisia (a type of movement disorder)**:** feeling restless and unable to sit or stand still		✓	
Allergic reactions: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing, wheezing, feeling sick to your stomach and throwing up			✓
Bruising or unusual bleeding from the skin or other areas		✓	
Heart rhythm problems: dizziness, increased heart rate, fainting or seizures			✓
Liver Disorder: yellowing of the skin or eyes,		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
dark urine and pale stools, abdominal pain, nausea, vomiting, loss of appetite			
Low blood sugar: dizziness, lack of energy, drowsiness		✓	
Low sodium level in the blood: tiredness, weakness, confusion combined with achy, stiff or uncoordinated muscles		✓	
Mania: elevated or irritable mood, decreased need for sleep, racing thoughts		✓	
Uncontrollable movements of the body or face		✓	
RARE			
Angle-closure glaucoma (sudden eye pain): increased pressure in your eyes, eye and head pain, swelling or redness in or around the eye, hazy or blurred vision, sudden loss of sight			✓
Gastrointestinal bleeding (bleeding in the stomach or bowels): vomiting blood, black/tarry stool, blood in the stool		✓	
Seizures (fits): uncontrollable shaking with or without loss of consciousness			✓
Serotonin toxicity: a reaction which may cause feelings of agitation or restlessness, flushing, muscle twitching, involuntary eye movements, heavy sweating, high body temperature (> 38°C), or rigid muscles			✓
UNKNOWN			
Changes in feelings or behavior (anger, anxiety, suicidal or violent thoughts)		✓	
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue, weakness		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store between 15°C and 30°C.
- Keep container tightly closed.
- If your doctor tells you to stop taking pms-SERTRALINE, please return any leftover medicine to your pharmacist.

Keep out of reach and sight of children.

If you want more information about pms-SERTRALINE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html, or by contacting the sponsor Pharmascience Inc. at: 1-888-550-6060.

This leaflet was prepared by Pharmascience Inc.

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