PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

[Pr] PAROXETINE – 10
[Pr] PAROXETINE – 20
[Pr] PAROXETINE – 30

Paroxetine Tablets

Tablets, 10 mg, 20 mg and 30 mg paroxetine (as paroxetine hydrochloride), Oral

Manufacturer Standard

Selective Serotonin Reuptake Inhibitor

PRO DOC LTÉE
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Laval, Quebec
H7L 3W9

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, Cardiovascular	01/2023
7 WARNINGS AND PRECAUTIONS, Hematologic	01/2023
7 WARNINGS AND PRECAUTIONS, Immune	01/2023
7 WARNINGS AND PRECAUTIONS, Neurologic	01/2023
7 WARNINGS AND PRECAUTIONS, Psychiatric	01/2023
7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential	01/2023
7 WARNINGS AND PRECAUTIONS, 7.1.1 Pregnant Women	01/2023

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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

PAROXETINE (paroxetine hydrochloride) is indicated in adults for the symptomatic treatment of:

- **Major Depressive Disorder (MDD)**
- **Obsessive-Compulsive Disorder (OCD)**
- **Panic Disorder (with or without agoraphobia)**
- **Social Phobia (Social Anxiety Disorder)**
- **Generalized Anxiety Disorder (GAD)**
- **Posttraumatic Stress Disorder (PTSD)**

Long-Term Use of PAROXETINE

Clinical trials have provided evidence that continuation treatment with paroxetine in patients with moderate to moderately severe depressive disorder is effective for at least 6 months (see 14.1 Trial Design by indication, Major Depressive Disorder).

The effectiveness of paroxetine in long-term use (i.e. more than 8 weeks for GAD and 12 weeks for other indications) has not yet been established in controlled trials for OCD, panic disorder, social phobia (social anxiety disorder), generalized anxiety disorder and posttraumatic stress disorder. Therefore, the health professional who elects to use PAROXETINE for extended periods in these indications should periodically re-evaluate the long-term usefulness of the drug for individual patients (see 4.1 Dosing Considerations).

1.1 Pediatrics

Pediatrics (< 18 years of age): Health Canada has not authorized an indication for pediatric use (see 7 WARNINGS AND PRECAUTIONS, GENERAL, Potential Association with Behavioral 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 indicates that there are differences in the pharmacokinetic profile of paroxetine in the geriatric population relative to younger adults, which may be associated with differences in safety or effectiveness. A brief discussion can be found in the appropriate sections (see 7.14 Geriatrics;10 CLINICAL PHARMACOLOGY; 4 DOSAGE AND ADMINISTRATION).

2 CONTRAINDICATIONS

PAROXETINE (paroxetine hydrochloride) is contraindicated:

- **Hypersensitivity:** 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:** In combination with a monoamine oxidase inhibitor (MAOI) or within a minimum of 2 weeks of terminating or starting treatment with a MAOI (see 7 WARNINGS AND PRECAUTIONS, Serotonin Toxicity/Neuroleptic Malignant Syndrome; 9.1 Serious Drug Interactions; 9.4 Drug-Drug Interactions).
- **Thioridazine:** In combination with thioridazine or within a minimum of 2 weeks of terminating treatment with thioridazine (see 9.1 Serious Drug Interactions; 9.4 Drug-Drug Interactions).
- **Pimozide:** In combination with pimozide or within a minimum of 2 weeks of terminating treatment with pimozide. (see 9.1 Serious Drug Interactions; 9.4 Drug-Drug Interactions).

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

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

General

- PAROXETINE is not indicated for use in children under the age of 18.
- Paroxetine should only be used during pregnancy if the benefits outweigh the risks, particularly during the third trimester as there are implications for neonatal health (see 4.2 Recommended Dose and Dosage Adjustment and 7.1.1 Pregnant Women).
- Due to the potential for life-threatening serotonin toxicity:
  - Concurrent use with MAOIs is contraindicated.
  - Washout periods are necessary if switching between paroxetine and MAOIs.
  - Use with other serotonergic agents is not recommended (see 7 WARNINGS AND PRECAUTIONS, Serotonin Toxicity /Neuroleptic Malignant Syndrome).
  - Dose tapering is recommended when switching between antidepressants, including paroxetine.

- Dosing:
  - Reduced doses may be needed for the elderly, and those with renal impairment.
  - All dose changes should be gradual, including discontinuation.
  - Monitor for discontinuation symptoms when decreasing or stopping treatment.
- Periodically reassess the need for ongoing therapy.

Monitor for agitation, suicidal tendencies

Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages, especially when initiating therapy or during any change in dose or dosage regimen. This includes monitoring for agitation-type emotional and behavioural changes (see 7 WARNINGS AND PRECAUTIONS, Potential Association with Behavioural and Emotional Changes, Including Self-Harm).

4.2 Recommended Dose and Dosage Adjustment

Depression

- **Usual Adult Dose:** The administration of PAROXETINE should be initiated at 20 mg daily. For most patients, 20 mg daily will also be the optimum dose. The therapeutic response may be delayed until the third or fourth week of treatment.
- **Dose Range:** For those patients who do not respond adequately to the 20 mg daily dose, a gradual increase in dosage up to 40 mg daily may be considered. The maximum recommended daily dose is 50 mg.

Obsessive-Compulsive Disorder

- **Usual Adult Dose:** The administration of PAROXETINE should be initiated at 20 mg/day. The recommended dose of PAROXETINE in the treatment of OCD is 40 mg daily.
- **Dose Range:** For those patients who do not respond adequately to the 40 mg daily dose, a gradual increase in dosage may be considered. The maximum recommended daily dose is 60 mg.

Panic Disorder

- **Usual Adult Dose:** The recommended starting dose of PAROXETINE in the treatment of panic disorder is 10 mg/day. The recommended dose of PAROXETINE in the treatment of panic disorder is 40 mg daily.
- **Dose Range:** For those patients who do not respond adequately to the 40 mg daily dose, a gradual increase in dosage may be considered. The maximum recommended daily dose is 60 mg.

Social Phobia (Social Anxiety Disorder)

- **Usual Adult Dose:** The recommended initial dosage is 20 mg/day. No clear dose-relationship has been demonstrated over a 20 to 60 mg/day dose range.
- **Dose Range**: Some patients not responding adequately to a 20 mg dosage may benefit from gradual dosage increases, in 10 mg/day increments, up to a maximum of 50 mg/day.

Generalized Anxiety Disorder

- **Usual Adult Dose:** The recommended initial dosage is 20 mg/day.
- **Dose Range:** Some patients not responding adequately to a 20 mg dosage may benefit from gradual dosage increases, in 10 mg/day increments, up to a maximum of 50 mg/day.

Posttraumatic Stress Disorder

- **Usual Adult Dose:** The recommended starting dosage is 20 mg/day.
- **Dose Range:** Some patients not responding adequately to a 20 mg/day dosage may benefit from gradual dosage increases, in 10 mg/day increments, up to a maximum of 50 mg/day.

Dose Adjustments
Based on pharmacokinetic parameters, steady-state paroxetine plasma levels are achieved over a 7 to 14 day interval. Hence, dosage adjustments in 10 mg increments should be made at 1 to 2 week intervals or according to clinician judgment.

Maintenance
During long-term therapy for any indication, the dosage should be maintained at the lowest effective level.

There is no body of evidence available to answer the question of how long a patient should continue to be treated with PAROXETINE. It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacologic therapy. Whether the dose of an antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Systematic evaluation of the efficacy of paroxetine hydrochloride has shown that efficacy is maintained for at least 6 months with doses that averaged about 30 mg (see 14.1 Clinical Trials by Indication, Major Depressive Disorder).

Discontinuation of Treatment
Symptoms associated with the discontinuation of paroxetine have been reported in clinical trials and post marketing. Patients should be monitored for these and other symptoms when discontinuing treatment, regardless of the indication for which PAROXETINE is being prescribed (see 7 WARNINGS AND PRECAUTIONS, Discontinuation of treatment with PAROXETINE and 8 ADVERSE REACTIONS, Adverse Reactions following Discontinuation of Treatment (or Dose

Reduction)).

A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response (see 8 ADVERSE REACTIONS).

Special Patient Populations

For any indication:

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

- **Geriatrics (> 65 years):** Administration of PAROXETINE to the elderly is associated with increased plasma levels and prolongation of the elimination half life relative to younger adults (see 10 CLINICAL PHARMACOLOGY). The recommended initial dose is 10 mg/day for elderly and/or debilitated patients. The dose may be increased, if indicated, up to a maximum of 40 mg daily.

- **Renal/Hepatic Insufficiency:** PAROXETINE should be used with caution in patients with renal or hepatic impairment. The recommended initial dose is 10 mg/day in patients with clinically significant renal or hepatic impairment. A maximum dose of 40 mg should not be exceeded (See 7 WARNINGS AND PRECAUTIONS and 10 CLINICAL PHARMACOLOGY).

- **Pregnant Women:** Epidemiological studies of pregnancy outcomes following maternal exposure to antidepressants in the first trimester have reported an increase in the risk of congenital malformations, particularly cardiovascular (e.g. ventricular and atrial septal defects), associated with the use of paroxetine. If a patient becomes pregnant while taking PAROXETINE, she should be informed of the current estimate of risk to the fetus (see 7.1 Special Populations) and consideration should be given to switching to other treatment options. Treatment with PAROXETINE should only be continued for an individual patient, if the potential benefits outweigh the potential risks. For women who intend to become pregnant, or are in their first trimester of pregnancy, initiation of paroxetine should be considered only after other treatment options have been evaluated (see 7.1 Special Populations).

Post-marketing reports indicate that some neonates exposed to paroxetine, SSRIs, or other newer antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see 7.1 Special Populations). When treating pregnant women with PAROXETINE during the third trimester, the health professional should carefully consider the potential risks and benefits of treatment. The health professional may consider tapering PAROXETINE in the third trimester.

4.4 Administration

PAROXETINE should be administered once daily in the morning and may be taken with or without food. The tablet should be swallowed rather than chewed.

4.5 Missed Dose

If a dose of PAROXETINE is missed at its usual time, it should be taken as soon as possible, unless it is too close to the time of the next dose. The missed dose should be skipped if it is almost time for the next regular dose. Two doses should not be taken at the same time.

5 OVERDOSAGE

The largest known ingestion from which a patient has recovered is 2000 mg. The smallest known dose of paroxetine alone associated with a fatal outcome is approximately 400 mg.

Symptoms

The most commonly reported adverse events subsequent to paroxetine-only overdose include: somnolence, nausea, tremor, dizziness, vomiting, diarrhea, agitation, aggression, anxiety, confused state, headache, fatigue, insomnia, tachychardia, hyperhydrosis, mydriasis, convulsion, parasthesia, serotonin syndrome, fever, blood pressure changes, involuntary muscle contraction and loss of consciousness. It should be noted that in some cases, patients may have consumed alcohol in addition to taking an overdose of paroxetine. **Some of these symptoms may also be seen with clinical use**.

Events such as coma and ECG changes have also been reported.

Treatment

The health professional should consider contacting a poison control centre for additional information on the treatment of any overdose.

No specific antidote is known. Treatment should consist of those general measures employed in the management of overdose with any antidepressant. Establish and maintain an airway; ensure adequate oxygenation and ventilation.

Induction of emesis is not recommended. Due to the large volume of distribution of paroxetine, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit.

Supportive care with frequent monitoring of vital signs and careful observation is indicated. An ECG should be taken and monitoring of cardiac function instituted if there is any evidence of abnormality. Patient management should be as clinically indicated, or as recommended by the national poisons centre, where available.

In managing overdosage, consider the possibility of multiple drug involvement.

A specific caution involves patients taking or recently having taken PAROXETINE who might ingest, by accident or intent, excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and its active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation.

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 and Composition

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	Tablet 10 mg, 20 mg, 30 mg	Anhydrous lactose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, sodium starch glycolate, titanium dioxide, and the following colouring agents all extended on an aluminum substrate: D&C yellow #10 and FD&C yellow #6 (10 mg tablets only), D&C red #30 (20 mg tablets only), and FD&C blue #2 (30 mg tablets only)

PAROXETINE 10 mg: Each bright yellow, oval, biconvex, film-coated tablet engraved "APO" on one side, and "10" on the other, contains paroxetine hydrochloride equivalent to 10 mg of paroxetine. Available in HDPE bottles of 30,100 and 250.

PAROXETINE 20 mg: Each pink, oval, biconvex, film-coated tablet engraved "APO" on one side, and scored and engraved "20" on the other, contains paroxetine hydrochloride equivalent to 20 mg of paroxetine. Available in HDPE bottles of 100 and 500, unit dose blisters of 30 and 60.

PAROXETINE 30 mg: Each blue, oval, biconvex, film-coated tablet engraved "APO" on one side, and "30" on the other, contains paroxetine hydrochloride equivalent to 30 mg of paroxetine. Available in HDPE bottles of 100, unit dose blisters of 30.

7 WARNINGS AND PRECAUTIONS

General

- **Discontinuation of treatment with PAROXETINE**

Discontinuation Symptoms: Patients currently taking PAROXETINE 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, regardless of the indication for which PAROXETINE is being prescribed, patients should be monitored for symptoms which may be associated with discontinuation (e.g. dizziness, sleep disturbances including abnormal dreams, sensory disturbances (including paresthesias, electric shock sensations and tinnitus), agitation, anxiety, headache, tremor, confusion, diarrhea, nausea, vomiting and sweating) or other symptoms which may be of clinical significance [see 8 ADVERSE REACTIONS, Adverse Events following Discontinuation of Treatment (or Dose Reduction)]. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response (see 8 ADVERSE REACTIONS and 4 DOSAGE AND ADMINISTRATION).

- **Potential for reduced efficacy of Tamoxifen with concomitant SSRI use, including PAROXETINE**

The antitumor agent tamoxifen is a pro-drug requiring metabolic activation by CYP2D6. Inhibition of CYP2D6 can lead to reduced plasma concentrations of a primary active metabolite (endoxifen). Chronic use of CYP2D6 inhibitors, including certain SSRIs, together with tamoxifen can lead to persistent reduction in levels of endoxifen (see also 9 DRUG INTERACTIONS, Tamoxifen). Some studies have shown that the efficacy of tamoxifen, as measured by the risk of breast cancer relapse/mortality, may be reduced when coprescribed with paroxetine as a result of paroxetine's irreversible inhibition of CYP2D6. This risk may increase with longer duration of coadministration. When tamoxifen is used for the treatment of breast cancer, prescribers should consider using an alternative antidepressant with little or no CYP2D6 inhibition.

- **Concomitant Illnesses**

Clinical experience with paroxetine in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using PAROXETINE in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Carcinogenesis and Mutagenesis

See 16 NON-CLINICAL TOXICOLOGY for animal data.

Cardiovascular

PAROXETINE has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. The usual precautions should be observed in patients with cardiac conditions.

- **QT Prolongation**

Cases of QT interval prolongation (with or without ventricular tachycardia) have been reported during post-market use of paroxetine, although causality with paroxetine has not been established.

PAROXETINE should be used with caution in patients with a history of QT interval prolongation, patients taking anti-arrhythmic or other medications that may potentially prolong QT interval, or those with relevant pre-existing cardiac disease (see 2 CONTRAINDICATIONS, 9.1 Serious Drug Interactions and 9.4 Drug-Drug Interactions).

Dependence/Tolerance

PAROXETINE has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. Health professionals should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of PAROXETINE.

Driving and Operating Machinery

Although paroxetine did not cause sedation or interfere with psychomotor performance in placebo- controlled studies in normal subjects, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that PAROXETINE does not affect them adversely.

Endocrine and Metabolism

- **Serum Cholesterol Elevation**

Several public domain studies have shown increased LDL-cholesterol levels of ~10% in volunteers and patients taking paroxetine for 8 to 12 weeks, which generally normalized after paroxetine discontinuation. In addition, of the patients in placebo-controlled clinical trials for whom baseline and on-treatment measurements were taken, total serum levels of cholesterol showed a mean increase of ~ 1.5 mg/dL in paroxetine-treated patients (n =

653), compared to a mean decrease of ~ 5.0 mg/dL in placebo-treated patients (n = 379). Increases from baseline of 45 mg/dL or greater were recorded in 6.6% of paroxetine-treated patients compared to 2.6% of placebo-treated patients (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Serum Cholesterol Elevation).

These data should be taken into consideration when treating patients with underlying cardiac risk factors.

Hematologic

- **Abnormal Bleeding**

SSRIs and serotonin / norepinephrine reuptake inhibitors (SNRIs) including PAROXETINE, 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 the risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding or gynecological hemorrhage. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening haemorrhages. Gastrointestinal and gynaecological bleeding have also been reported following treatment with paroxetine. SSRIs/SNRIs, including PAROXETINE, may increase the risk of postpartum hemorrhage (7.1.1 Pregnant Women, Complications following late third trimester exposure to SSRIs).

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

Hepatic/Biliary/Pancreatic

- **Hepatic Impairment**

Pharmacokinetic studies of paroxetine in subjects with clinically significant hepatic impairment suggest that prolongation of the elimination half-life and increased plasma levels can be expected in this patient group. PAROXETINE should be used with caution and dosages restricted to the lower end of the range in patients with clinically significant hepatic impairment (see 4.2 Recommended Dose and Dosage Adjustment, Special Patient Populations and 10.3 Pharmacokinetics, Hepatic Insufficiency).

Immune

- **Hypersensitivity**

  The 10 mg tablet coating contains an azo dye (FD&C Yellow No. 6 aluminium lake) which may cause allergic reactions.

Monitoring and Laboratory Tests

- **Serum Cholesterol Elevation**

  Of the patients in placebo-controlled clinical trials for whom baseline and on-treatment measurements were taken, increases from baseline of 45 mg/dL or greater were recorded in 6.6% of paroxetine-treated patients compared to 2.6% of placebo-treated patients (see 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data, Laboratory Changes-Cholesterol and 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

  These data should be taken into consideration when treating patients with underlying cardiac risk factors.

Musculoskeletal

- **Bone Fracture Risk**

  Epidemiological studies show an increased risk of bone fractures following exposure to some antidepressants, including SSRIs. 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 PAROXETINE. Elderly patients 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. Preliminary data from observational studies show association of SSRIs 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, including PAROXETINE, cannot be excluded, and may be a potential concern for patients with osteoporosis or major risk factors for bone fractures.

Neurologic

- **Epilepsy**

  As with other antidepressants, PAROXETINE should be used with caution in patients with epilepsy.

- **Seizures**

  During clinical trials, the overall incidence of seizures was 0.15% in patients treated with paroxetine. However, patients with a history of convulsive disorders were excluded from

these studies. Caution is recommended when the drug is administered to patients with a history of seizures. The drug should be discontinued in any patient who develops seizures.

- **Serotonin Toxicity /Neuroleptic Malignant Syndrome**

  On rare occasions, serotonin toxicity, also known as serotonin syndrome, has been reported with paroxetine, particularly during combined use with other serotonergic drugs (see 9.4 Drug-Drug Interactions).

  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 or 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 paroxetine, 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 PAROXETINE with monoamine oxidase inhibitors, including linezolid and methylthioninium chloride (methylene blue), is contraindicated (see 2 CONTRAINDICATIONS). PAROXETINE should be used with caution in patients receiving other serotonergic drugs or antipsychotics/neuroleptics. If concomitant treatment with PAROXETINE 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 PAROXETINE should be considered.

Ophthalmologic

- **Angle-Closure Glaucoma**

As with other antidepressants, PAROXETINE can cause mydriasis, which may trigger an angle-closure attack in a patient with anatomically narrow ocular angles. Caution should be used when PAROXETINE is prescribed for patients with untreated narrow angles. Open-angle glaucoma is not a risk factor for angle-closure glaucoma.

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 SSRIs and other newer antidepressants suggests that use of these drugs in patients under the age of 18 may be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour over that of placebo.

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

  Adult 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 events include: akathisia, agitation, disinhibition, emotional lability, hostility, aggression, and depersonalization. In some cases, the events occurred within several weeks of starting treatment.

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

  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 behaviour with antidepressant compared to placebo.

- **Suicide Risk**

  The possibility of a suicide attempt is inherent in depression and may persist until remission occurs. Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications. Notwithstanding, high risk patients should be closely supervised throughout therapy with appropriate consideration to the possible need for hospitalization. Health professionals should encourage patients of all ages, their families, and their caregivers to be alert to the emergence of any new or worsened distressing thoughts or feelings occurring at any time, and especially when initiating therapy or during any change in dose or dosage regimen. In order to minimize the opportunity for overdosage, prescriptions

for PAROXETINE should be written for the smallest quantity of drug consistent with good patient management.

Because of the well established comorbidity between depression and other psychiatric disorders, the same precautions observed when treating patients with depression should be observed when treating patients with other psychiatric disorders (see 7 Warnings And Precautions, General, Potential Association With Behavioural And Emotional Changes, Including Self-Harm).

- **Activation of Mania/Hypomania**

  During clinical testing in a patient population comprised primarily of unipolar depressed patients, approximately 1% of paroxetine-treated patients experienced manic reactions. When bipolar patients were considered as a sub-group the incidence of mania was 2%. As with all drugs effective in the treatment of depression, PAROXETINE should be used with caution in patients with a history of mania.

  A major depressive episode may be the initial presentation of bipolar disorder. Patients with bipolar disorder may be at an increased risk of experiencing manic episodes when treated with antidepressants alone. Therefore, the decision to initiate symptomatic treatment of depression should only be made after patients have been adequately assessed to determine if they are at risk for bipolar disorder.

- **Electroconvulsive Therapy (ECT)**

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

Renal

- **Hyponatremia**

  Several cases of hyponatremia have been reported. The hyponatremia appeared to be reversible when paroxetine was discontinued. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted.

- **Renal Impairment**

  Since paroxetine is extensively metabolized by the liver, excretion of unchanged drug in urine is a minor route of elimination. However, single dose pharmacokinetic studies in subjects with clinically significant renal impairment suggest that plasma levels of paroxetine are elevated in such subjects. PAROXETINE should therefore be used with caution and the dosage restricted to the lower end of the range in patients with clinically significant renal impairment (see 4.2 Recommended Dose and Dosage Adjustment and 10.3 Pharmacokinetics, Renal Insufficiency).

Reproductive Health: Female and Male Potential

- **Fertility**

  Some clinical studies have shown that SSRIs (including paroxetine) may affect sperm quality. This effect appears to be reversible following discontinuation of treatment. Changes in sperm quality may affect fertility in some men (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

- **Function**

  SSRIs may cause symptoms of sexual dysfunction (see 8 ADVERSE REACTIONS, Male and Female Sexual Dysfunction with SSRIs). Patients should be informed that there have been reports of long- lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs.

7.1 Special Populations

7.1.1 Pregnant Women

Risk of Cardiovascular Malformations following first trimester exposure to SSRIs

Epidemiological studies of pregnancy outcomes following maternal exposure to antidepressants in the first trimester have reported an increase in the risk of congenital malformations, particularly cardiovascular (e.g. ventricular and atrial septal defects), associated with the use of paroxetine. The data suggest that the risk of having an infant with a cardiovascular defect following maternal paroxetine exposure is approximately 1/50 (2%), compared with an expected rate for such defects of approximately 1/100 (1%) infants in the general population. In general, septal defects range from those that are symptomatic and may require surgery, to those that are asymptomatic and may resolve spontaneously. Information about the severity of the septal defects reported in the studies is not available.

While on PAROXETINE: Pregnancy, or intent to become pregnant

If a patient becomes pregnant while taking PAROXETINE, or intends to become pregnant, she should be informed of the current estimate of increased risk to the fetus with PAROXETINE over other antidepressants. Examinations of additional databases, as well as updated analyses, may result in changes to the current risk estimates. Consideration should be given to switching to other treatment options, including another antidepressant or non-pharmaceutical treatment such as cognitive behavioural therapy.

Treatment with PAROXETINE should only be continued for an individual patient, if the potential benefits outweigh the potential risks.

Due to the potential for discontinuation symptoms, if a decision is taken to discontinue PAROXETINE treatment, a gradual reduction in the dose rather than an abrupt cessation is

recommended (see 7 WARNINGS AND PRECAUTIONS, Discontinuation of treatment with PAROXETINE; 8 ADVERSE REACTIONS, Adverse Reactions following Discontinuation of Treatment (or Dose Reduction) and 4.1 Dosing Considerations).

Initiation of PAROXETINE: For women who intend to become pregnant, or are in their first trimester of pregnancy, initiation of PAROXETINE should be considered only after other treatment options have been evaluated.

Complications following late third trimester exposure to SSRIs

Post-marketing reports indicate that some neonates exposed to paroxetine, SSRIs, or other newer antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, 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, Serotonin Toxicity/Neuroleptic Malignant Syndrome).

There have been post-marketing reports of premature birth in pregnant women exposed to paroxetine or other SSRIs. The casual relationship between paroxetine and the emergence of these events has not been established.

Observational data have provided evidence of an increased risk (less than two-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see 7 WARNINGS AND PRECAUTIONS, Hematologic).

When treating a pregnant woman with PAROXETINE 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, Special Patient Population).

Risk of Persistent Pulmonary Hypertension of the Newborn (PPHN) and exposure to SSRIs (including paroxetine)

Epidemiological studies on PPHN have shown that the use of SSRIs (including paroxetine) in pregnancy, particularly use in late pregnancy, was associated with an increased risk of PPHN. PPHN occurs in 1 to 2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy (Odds Ratio 6.1, 95% CI 2.2-16.8). A study using data from

the Swedish Medical Birth Register for 831,324 infants born between 1997 and 2005 found an increased risk of PPHN of approximately 2-fold associated with patient-reported maternal use of SSRIs in the first trimester of pregnancy (Risk Ratio 2.4, 95% CI 1.2-4.3), and an increased risk of PPHN of approximately 4-fold associated with a combination of patient-reported maternal use of SSRIs in the first trimester and an antenatal SSRI prescription in later pregnancy (Risk Ratio 3.6, 95% CI 1.2-8.3).

7.1.2 Breast-feeding

The concentrations of paroxetine detected in the breast milk of lactating women are similar to those in the mother's plasma. Lactating women should not nurse their infants while receiving paroxetine unless in the opinion of the treating health professional, breast feeding is necessary, in which case the infant should be closely monitored.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): Health Canada has not authorized an indication for pediatric use (see 7 WARNINGS AND PRECAUTIONS, Potential Association with Behavioral and Emotional Changes, Including Self-Harm). (See also 1.1 Pediatrics and 4.2 Recommended Dose and Dosage Adjustment, Pediatrics).

Controlled clinical studies in depression failed to demonstrate efficacy and do not support the use of paroxetine in the treatment of children under the age of 18 years with depression. Moreover, a higher incidence of adverse events related to behavioural and emotional changes, including self harm, was reported with paroxetine treatment compared to placebo during controlled clinical trials in depression, OCD and social anxiety disorder (see 8.2.1 Clinical Trial Adverse Drug Reactions-Pediatrics).

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Administration of paroxetine to the elderly is associated with increased plasma levels and prolongation of the elimination half life relative to younger adults (see 10 CLINICAL PHARMACOLOGY). Elderly patients should be initiated and maintained at the lowest daily dose of paroxetine which is associated with clinical efficacy (see 4 DOSAGE AND ADMINISTRATION).

Evaluation of approximately 800 elderly patients (≥ 65 years) treated with paroxetine (10 to 40 mg daily) in worldwide premarketing clinical trials revealed no unusual pattern of adverse events relative to the clinical experience in younger patients. However, it is not possible to rule out potential age-related differences in safety and effectiveness during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Commonly Observed Adverse Events

The most commonly observed adverse experiences associated with the use of paroxetine in clinical trials and not seen at an equivalent incidence among placebo-treated patients were: nausea, somnolence, sweating, tremor, asthenia, dizziness, dry mouth, insomnia, constipation, diarrhea, decreased appetite and male sexual dysfunction (see Table 2 and Table 3).

Adverse Events Leading to Discontinuation of Treatment

Twenty-one percent of over 4000 patients who received paroxetine in worldwide clinical trials in depression discontinued treatment due to an adverse experience. In obsessive-compulsive disorder, panic disorder, social phobia (social anxiety disorder), generalized anxiety disorder and posttraumatic stress disorder studies, 11.8% (64/542), 9.4% (44/469), 16.1% (84/522), 10.7% (79/735) and 11.7% (79/676), respectively, of patients treated with paroxetine discontinued treatment because of adverse events. The most common events leading to discontinuation (reported by 1% or more of subjects) included: asthenia, headache, nausea, somnolence, insomnia, agitation, tremor, dizziness, constipation, impotence, abnormal ejaculation, sweating and diarrhea.

Adverse Events following Discontinuation of Treatment (or Dose Reduction)

- **Clinical Trials**

The following adverse events have been reported at an incidence of 2% or greater for paroxetine and were at least twice that reported for placebo: abnormal dreams (2.3 vs 0.5%), paresthesias (2.0 vs 0.4%), and dizziness (7.1 vs 1.5%).

The majority of these events were mild to moderate, self-limiting and did not require medical intervention. These adverse events were noted in GAD and PTSD clinical trials employing a taper phase regimen for discontinuation of treatment. This regimen involved an incremental decrease in the daily dose by 10 mg/day at weekly intervals. When a daily dose of 20 mg/day was reached, patients were continued on this dose for 1 week before treatment was stopped.

- **Post-Marketing**

There have been spontaneous reports of adverse events upon the discontinuation of paroxetine (particularly when abrupt), including but not limited to the following: dizziness, sensory disturbances (including paresthesias, electric shock sensations and tinnitus), agitation/restlessness, anxiety, nausea, tremor, confusion, diarrhea, vomiting, sweating, headache, and sleep disturbances (abnormal dreams). Generally, these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally, these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2 to 3 months or more). Symptoms associated with discontinuation have been reported for other selective serotonin reuptake inhibitors.

Patients should be monitored for these or any other symptoms when discontinuing treatment,

regardless of the indication for which PAROXETINE is being prescribed. 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 and 4 DOSAGE AND ADMINISTRATION).

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.

Incidence in Controlled Clinical Trials
Multiple doses of paroxetine were administered to 4126 subjects in clinical trials for depression, 542 subjects in clinical trials for OCD, 469 subjects in clinical trials for panic disorder, 522 subjects in clinical trials for social phobia (social anxiety disorder), 735 subjects in clinical trials for generalized anxiety disorder and 676 subjects in clinical trials for posttraumatic stress disorder. Untoward experiences associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing.

Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse experiences without first grouping similar types of untoward experiences into a limited (i.e. reduced) number of standardized experience categories.

Table 2 lists adverse experiences that occurred at an incidence of 1% or higher in short term (6-week) flexible dose (20 to 50 mg/day) placebo-controlled trials in depression. (An additional 460 patients participated in a fixed-dose, placebo-controlled study).

Table 3 enumerates adverse events that occurred at a frequency of 2% or more among patients on paroxetine who participated in placebo-controlled OCD trials of 12-weeks duration in which patients were dosed in the range of 20 to 60 mg/day, in placebo-controlled panic disorder trials of 10 to 12 weeks duration in which patients were dosed in the range of 10 to 60 mg/day, in placebo-controlled social phobia (social anxiety disorder) trials of 12 weeks duration in which patients were dosed in a range of 20 to 50 mg/day, in placebo-controlled generalized anxiety disorder trials of 8 weeks in which patients were dosed in a range from 10 to 50 mg/day and in placebo-controlled posttraumatic stress disorder trials of 12 weeks in which patients were dosed in a range from 20 to 50 mg/day.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly the cited incidences cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited frequencies do however provide the prescribing health professional with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied. Reported adverse experiences were classified using a COSTART-based dictionary terminology for the depression trials and an ADECS (a modified COSTART dictionary) for OCD and panic disorder trials.

Table 2 Treatment-Emergent Adverse Events in Short Term Flexible Dose Placebo-Controlled Clinical Trials in Depression[1]

Body System	Preferred Term	Paroxetine (n=421)	Placebo (n=421)
Body as a Whole	Headache	17.6%	17.3%
	Asthenia	15.0%	5.9%
	Abdominal Pain	3.1%	4.0%
	Fever	1.7%	1.7%
	Chest Pain	1.4%	2.1%
	Trauma	1.4%	0.5%
	Back Pain	1.2%	2.4%
Cardiovascular	Palpitation	2.9%	1.4%
	Vasodilation	2.6%	0.7%
	Postural Hypotension	1.2%	0.5%
Dermatological	Sweating	11.2%	2.4%
	Rash	1.7%	0.7%
Gastrointestinal	Nausea	25.7%	9.3%
	Dry Mouth	18.1%	12.1%
	Constipation	13.8%	8.6%
	Diarrhea	11.6%	7.6%
	Decreased Appetite	6.4%	1.9%
	Flatulence	4.0%	1.7%
	Vomiting	2.4%	1.7%
	Oropharynx Disorder[2]	2.1%	0.0%
	Dyspepsia	1.9%	1.0%
	Increased Appetite	1.4%	0.5%
Musculoskeletal	Myopathy	2.4%	1.4%
	Myalgia	1.7%	0.7%
	Myasthenia	1.4%	0.2%
Nervous System	Somnolence	23.3%	9.0%
	Dizziness	13.3%	5.5%
	Insomnia	13.3%	6.2%

Body System	Preferred Term	Paroxetine (n=421)	Placebo (n=421)
	Tremor	8.3%	1.9%
	Nervousness	5.2%	2.6%
	Anxiety	5.0%	2.9%
	Paraesthesia	3.8%	1.7%
	Libido Decreased	3.3%	0.0%
	Agitation	2.1%	1.9%
	Drugged Feeling	1.7%	0.7%
	Myoclonus	1.4%	0.7%
	CNS Stimulation	1.2%	3.6%
	Confusion	1.2%	0.2%
Respiration	Respiratory Disorder[3]	5.9%	6.4%
	Yawn	3.8%	0.0%
	Pharyngitis	2.1%	2.9%
Special Senses	Blurred Vision	3.6%	1.4%
	Taste Perversion	2.4%	0.2%
Urogenital System	*Abnormal Ejaculation+	12.9%	0.0%
	*Male Genital Disorders[4]	8.0%	0.0%
	Urinary Frequency	3.1%	0.7%
	Urination Impaired[5]	2.9%	0.2%
	*Impotence	2.5%	0.5%
	*Female Genital Disorders[6]	1.8%	0.0%

[1] Events reported by at least 1% of patients treated with paroxetine are included.

* Percentage corrected for gender Placebo: male, n=206 female, n=215 Paroxetine: male, n=201 female, n=220

+ Primarily ejaculatory delay. In a trial of fixed doses of paroxetine, the incidence of ejaculatory disturbance in males with 20 mg per day of paroxetine was 6.5% (3/46) versus 0% (0/23) in the placebo group.

[2] Includes mostly lump in throat and tightness in throat

[3] Includes mostly cold symptoms or URI

[4] Includes anorgasmia, erectile difficulties, delayed ejaculation/orgasm, sexual dysfunction and impotence

[5] Includes difficulty with micturition and urinary hesitancy

[6] Includes anorgasmia and difficulty reaching climax/orgasm

Table 3 Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Obsessive-Compulsive Disorder, Panic Disorder, Social Phobia (Social Anxiety Disorder), Generalized Anxiety Disorder and Posttraumatic Stress Disorder.[1]

Body System	Preferred Term	Obsessive-Compulsive Disorder		Panic Disorder		Social Phobia (Social Anxiety Disorder)		Generalized Anxiety Disorder		Posttraumatic Stress Disorder	
		Paroxetine (n=542)	Placebo (n=265)	Paroxetine (n=469)	Placebo (n=324)	Paroxetine (n=425)	Placebo (n=339)	Paroxetine (n=735)	Placebo (n=529)	Paroxetine (n=676)	Placebo (n=504)
Body as a Whole	Headache	25.3%	29.1%	25.4%	25.3%	22.4%	21.8%	16.9%	14.0%	18.9%	19.2%
	Asthenia	21.8%	13.6%	13.6%	4.6%	22.4%	13.6%	14.3%	6.4%	11.8%	4.2%
	Infection	5.4%	4.9%	5.3%	6.8%	3.8%	5.9%	5.6%	3.4%	4.9%	3.8%
	Abdominal Pain	4.8%	4.9%	4.3%	3.1%	2.1%	4.7%	4.5%	3.6%	4.3%	3.2%
	Chest Pain	2.8%	1.9%	2.3%	3.1%	0.7%	0.3%	1.0%	0.6%	1.2%	0.8%
	Back Pain	2.4%	4.9%	3.2%	2.2%	1.6%	4.1%	2.3%	3.6%	3.4%	3.4%
	Chills	2.0%	0.8%	2.3%	0.6%	0.2%	0.3%	1.0%	0.0%	0.1%	0.4%
	Trauma	3.1%	3.8%	3.6%	3.7%	2.6%	0.9%	2.6%	3.4%	5.8%	5.2%
Cardiovascular	Vasodilation	3.9%	1.1%	2.1%	2.8%	1.4%	0.6%	2.7%	0.8%	2.2%	1.2%
	Palpitation	2.0%	0.4%	2.3%	2.5%	1.2%	1.8%	1.1%	1.1%	1.0%	0.8%
Dermatologic	Sweating	8.9%	3.0%	14.3%	5.9%	9.2%	2.1%	6.3%	1.5%	4.6%	1.4%
	Rash	3.1%	1.9%	2.3%	1.5%	0.7%	0.3%	1.5%	0.9%	1.5%	2.0%
Gastrointestinal	Nausea	23.2%	9.8%	22.8%	17.3%	24.7%	6.5%	20.1%	5.3%	19.2%	8.3%
	Dry Mouth	18.1%	8.7%	18.1%	10.8%	8.9%	2.9%	10.9%	4.7%	10.1%	4.8%
	Constipation	15.7%	6.4%	7.9%	5.2%	5.4%	1.8%	10.5%	1.7%	5.5%	3.4%
	Diarrhea	10.3%	9.8%	11.7%	6.5%	8.5%	5.9%	9.1%	6.6%	10.5%	5.4%
	Decreased Appetite	9.0%	3.4%	7.0%	2.8%	7.8%	1.5%	5.2%	1.1%	5.9%	2.6%
	Dyspepsia	3.9%	6.8%	3.8%	6.8%	4.0%	2.4%	4.5%	4.9%	4.6%	3.4%
	Flatulence	3.0%	4.2%	1.7%	2.8%	4.0%	2.4%	1.4%	2.1%	1.0%	1.0%
	Increased Appetite	4.2%	3.0%	2.1%	0.6%	1.2%	1.8%	0.4%	1.1%	1.5%	1.0%
	Vomiting	2.2%	3.4%	1.9%	1.5%	2.4%	0.6%	2.7%	2.5%	3.0%	2.0%
Musculo-skeletal	Myalgia	3.1%	3.8%	2.3%	3.4%	4.0%	2.7%	2.9%	2.6%	1.8%	1.8%
Nervous System	Somnolence	24.4%	7.2%	18.8%	10.8%	21.6%	5.3%	15.4%	4.5%	16.0%	4.6%
	Insomnia	23.8%	13.2%	17.9%	10.2%	20.9%	15.9%	10.7%	7.9%	11.8%	11.3%
	Dizziness	12.4%	6.0%	14.1%	9.9%	11.3%	7.1%	6.1%	4.5%	6.1%	4.6%
	Tremor	10.5%	1.1%	8.5%	1.2%	8.7%	1.2%	4.6%	0.8%	4.3%	1.4%
	Nervousness	8.5%	8.3%	7.9%	8.3%	7.5%	6.5%	3.9%	2.8%	3.0%	4.4%
	Libido Decreased	7.2%	3.8%	8.5%	1.2%	11.5%	0.9%	9.4%	1.5%	5.2%	1.8%
	Anxiety	4.1%	6.8%	4.5%	4.0%	4.7%	4.1%	1.6%	0.9%	3.8%	4.0%

Body System	Preferred Term	Obsessive-Compulsive Disorder		Panic Disorder		Social Phobia (Social Anxiety Disorder)		Generalized Anxiety Disorder		Posttraumatic Stress Disorder	
		Paroxetine (n=542)	Placebo (n=265)	Paroxetine (n=469)	Placebo (n=324)	Paroxetine (n=425)	Placebo (n=339)	Paroxetine (n=735)	Placebo (n=529)	Paroxetine (n=676)	Placebo (n=504)
	Abnormal Dreams	3.9%	1.1%	2.8%	3.4%	1.9%	1.5%	0.5%	1.1%	2.5%	1.6%
	Myoclonus	3.3%	0.4%	3.2%	1.5%	2.1%	0.9%	1.6%	0.6%	1.0%	0.6%
	Concentration Impaired	2.8%	1.5%	1.1%	0.9%	3.5%	0.6%	1.1%	0.6%	1.5%	1.0%
	Depersonalization	2.6%	0.4%	1.7%	2.2%	0.7%	0.9%	0.7%	0.0%	0.9%	0.2%
	Amnesia	2.2%	1.1%	0.6%	0.0%	0.5%	0.3%	0.4%	0.6%	1.3%	1.0%
	Hyperkinesia	2.2%	1.5%	0.9%	0.9%	1.2%	0.0%	0.8%	0.0%	1.3%	0.2%
	Agitation	1.7%	2.3%	4.7%	3.7%	2.6%	0.9%	1.8%	1.1%	1.9%	3.2%
Respiratory System	Pharyngitis	3.7%	4.9%	3.2%	3.1%	3.8%	2.1%	2.3%	2.1%	2.4%	2.2%
	Rhinitis	1.5%	3.4%	2.6%	0.3%	1.2%	3.2%	1.5%	1.1%	1.0%	2.0%
	Sinusitis	1.5%	4.9%	5.8%	4.6%	2.1%	2.4%	3.5%	3.4%	3.8%	4.4%
	Yawn	1.7%	0.4%	1.9%	0.0%	4.9%	0.3%	4.2%	0.2%	2.1%	0.2%
	Cough Increased	1.1%	1.9%	2.3%	1.5%	0.7%	0.9%	0.8%	0.8%	1.2%	0.6%
	Respiratory Disorder[1]	-	-	-	-	-	-	6.8%	5.1%	3.3%	1.0%
Special Senses	Abnormal Vision	3.7%	2.3%	3.0%	2.8%	4.0%	0.3%	2.2%	0.6%	0.3%	0.0%
	Taste Perversion	2.0%	0.0%	1.1%	0.6%	0.7%	0.6%	0.7%	0.8%	0.7%	0.8%
Urogenital System	Abnormal Ejaculation[2]	23.3%	1.3%	20.5%	0.9%	27.6%	1.1%	24.7%	2.0%	12.6%	1.6%
	Dysmenorrhea[2]	1.4%	1.9%	2.0%	2.3%	4.6%	4.4%	1.3%	1.2%	1.6%	1.3%
	Impotence[2]	8.2%	1.3%	5.4%	0.0%	5.3%	1.1%	4.2%	3.0%	9.2%	0.5%
	Female Genital Disorder[2,3]	3.3%	0.0%	8.9%	0.5%	8.6%	0.6%	4.4%	0.6%	4.8%	0.6%
	Urinary Frequency	3.3%	1.1%	2.1%	0.3%	1.6%	1.8%	1.0%	0.6%	1.0%	0.2%
	Urination Impaired	3.3%	0.4%	0.4%	0.3%	1.9%	0.0%	1.0%	0.0%	0.6%	0.0%
	Urinary Tract Infection	1.5%	1.1%	2.1%	1.2%	0.2%	1.2%	1.2%	1.1%	0.6%	0.8%

1. Events reported by at least 2% of either OCD, Panic Disorder, Social Phobia (Social Anxiety Disorder), Generalized Anxiety Disorder or Posttraumatic Stress Disorder paroxetine-treated patients are included, except the following events which had an incidence on placebo ≥ paroxetine: [OCD]: depression, paraesthesia, and respiratory disorder. [Panic Disorder]: flu syndrome, depression, paraesthesia, respiratory disorder. [Social Phobia (Social Anxiety Disorder)]: depression, respiratory disorder. [Generalized Anxiety Disorder]: not applicable, [Posttraumatic Stress Disorder]: depression, respiratory disorder

2. Incidence is gender-corrected.

OCD:	Placebo: male, n=158; female, n=107 Paroxetine: male, n=330; female, n=212
PANIC:	Placebo: male, n=111; female, n=213 Paroxetine: male, n=166; female, n=303
SOCIAL PHOBIA: (SOCIAL ANXIETY DISORDER)	Placebo: male, n=180; female, n=159 Paroxetine: male, n=228; female, n=197
GENERALIZED ANXIETY DISORDER:	Placebo: male, n=197; female, n=332 Paroxetine: male, n=283; female, n=452
POSTTRAUMATIC STRESS DISORDER:	Placebo: male, n=190; female, n=314 Paroxetine: male, n=238; female, n=438

3. Includes anorgasmia and difficulty reaching climax/orgasm

Male and Female Sexual Dysfunction with SSRIs

Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Furthermore, there have been reports of long-lasting sexual dysfunction where these symptoms have continued despite discontinuation of SSRIs.

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

- Incidence of Sexual Adverse Events in Pooled Data

In placebo-controlled clinical trials involving more than 3,200 patients, the ranges for the reported incidence of sexual side effects in males and females with major depressive disorder, OCD, panic disorder, social anxiety disorder, GAD and PTSD are displayed in Table 4 below.

Table 4 Incidence of Sexual Adverse Events in Controlled Clinical Trials

	Paroxetine	Placebo
n (males)	**1446**	**1042**
Decreased Libido	6-15%	0-5%
Ejaculatory Disturbance	13-28%	0-2%
Impotence	2-9%	0-3 %
n (females)	**1822**	**1340**
Decreased Libido	0-9%	0-2%
Orgasmic Disturbance	2-9%	0-1%

There are no adequate and well-controlled studies examining sexual dysfunction with paroxetine treatment.

Paroxetine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, and health professionals should routinely inquire about such possible side effects.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

In placebo-controlled clinical trials conducted with pediatric patients aged 7 to 18 years with depression, OCD and Social Anxiety Disorder (involving 633 patients treated with paroxetine and 542 patients treated with placebo), the following adverse events were reported in at least 2% of pediatric patients treated with paroxetine and occurred at a rate at least twice that for pediatric patients receiving placebo: emotional lability (including self-harm, suicidal thoughts, attempted suicide, crying, and mood fluctuations), hostility, (predominantly aggression, oppositional behaviour and anger) decreased appetite, tremor, sweating, hyperkinesia, and agitation (see 7 WARNINGS AND PRECAUTIONS, Potential Association with Behavioral and Emotional Changes, Including Self-Harm).

In the pediatric clinical trials in depression, OCD and Social Anxiety Disorder that included a taper phase regimen (307 patients aged 7 to 18 years treated with paroxetine and 291 patients treated with placebo), events reported upon discontinuation of treatment, which occurred in at least 2% of patients who received paroxetine and which occurred at a rate at least twice that of placebo, were: emotional lability (including suicidal ideation, suicide attempt, mood changes, and tearfulness), nervousness, dizziness, nausea, and abdominal pain (see 7 WARNINGS AND PRECAUTIONS, Discontinuation of treatment With PAROXETINE).

8.3 Less Common Clinical Trial Adverse Reactions

Other Events Observed During the Clinical Development of Paroxetine

In the tabulations which follow, a COSTART or modified COSTART-based dictionary terminology has been used to classify reported adverse experiences. The frequencies presented therefore represent the portion of the 4126, 542, 469, 522, 735 and 676 paroxetine-exposed individuals in depression, OCD, panic, social phobia (social anxiety disorder), generalized anxiety disorder and posttraumatic stress disorder trials, respectively, who experienced an event of the type cited on at least one occasion while receiving paroxetine. Experiences are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent experiences are defined as those occurring on one or more occasion in at least 1/100 patients; infrequent adverse experiences are those occurring in less than 1/100 but at least 1/1000 patients; rare experiences are those occurring in less than 1/1000 patients.

All adverse experiences are included except those already listed in Table 2 and Table 3, those reported in terms so general as to be uninformative and those experiences for which the drug cause was remote. It is important to emphasize that although the experiences reported did occur during treatment with paroxetine, they were not necessarily caused by it.

Body as a Whole

- **Frequent:** Malaise, pain.
- **Infrequent:** Allergic reaction, chills, face edema, infection, moniliasis, neck pain, overdose.
- **Rare:** Abnormal laboratory value, abscess, adrenergic syndrome, cellulitis, chills and fever, cyst, hernia, intentional overdose, neck rigidity, pelvic pain, peritonitis, substernal chest pain, sepsis, ulcer.

Cardiovascular System

- **Frequent:** Hypertension, syncope, tachycardia.
- **Infrequent:** Bradycardia, conduction abnormalities, electrocardiogram abnormal, hypotension, migraine, ventricular extrasystoles.
- **Rare:** Angina pectoris, arrhythmia, atrial arrhythmia, atrial fibrillation, bundle branch block, cardiac disorder, cerebral ischemia, cerebrovascular accident, cerebrovascular disorder, congestive heart failure, extrasystoles, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombosis, varicose vein, vascular disorder, vascular headache.

Dermatological

- **Frequent:** Pruritus.
- **Infrequent:** Acne, alopecia, dry skin, ecchymosis, eczema, furunculosis, herpes simplex, urticaria.
- **Rare:** Angioedema, contact dermatitis, erythema nodosum, exfoliative dermatitis, herpes zoster, maculopapular rash, photosensitivity, skin discolouration, skin ulcer, skin hypertrophy, sweating decreased.
- **Very rare**: Severe cutaneous adverse reactions (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis).

Endocrine

- **Rare***:* Diabetes mellitus, fertility decreased female, goiter, hyperthyroidism, hypothyroidism, thyroiditis.

Gastrointestinal

- **Frequent:** Nausea and vomiting.
- **Infrequent:** Bruxism, buccal cavity disorders, dysphagia, eructation, gastroenteritis, gastrointestinal flu, glossitis, increased salivation, liver function tests abnormal, mouth ulceration, vomiting and diarrhea, rectal hemorrhage.
- **Rare:** Aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, colitis, duodenitis, esophagitis, fecal impaction, fecal incontinence, gastritis, gingivitis, hematemesis, hepatitis, ileitis, ileus, jaundice, melena, peptic ulcer, salivary gland enlargement, sialadenitis, stomach ulcer, stomatitis, tongue edema, tooth caries.

Hematologic and Lymphatic

- **Infrequent:** Anemia, leukopenia, lymphadenopathy, purpura, WBC abnormality.
- **Rare:** Abnormal bleeding, predominately of the skin and mucous membranes, bleeding time increased, eosinophilia, iron deficiency anemia, leukocytosis, lymphedema, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia, thrombocytopenia.

Immune System Disorders:

- **Very rare:** Severe allergic reactions (including anaphylactoid reactions and angioedema).

Metabolic and Nutritional

- **Frequent:** Weight gain, weight loss, increases in cholesterol levels.
- **Infrequent:** Edema, hyperglycemia, peripheral edema, thirst.
- **Rare:** Alkaline phosphatase increased, bilirubinemia, cachexia, dehydration, gout,

hypocalcemia, hypoglycemia, hypokalemia, hyponatremia (predominantly in the elderly) which is sometimes due to syndrome of inappropriate anti-diuretic hormone secretion (SIADH), non-protein nitrogen (NPN) increased, obesity, SGOT increased, SGPT increased.

Musculoskeletal

- **Infrequent:** Arthralgia, arthritis, traumatic fracture.
- **Rare:** Arthrosis, bone disorder, bursitis, cartilage disorder, myositis, osteoporosis, tetany.

Nervous System

- **Frequent:** CNS stimulation, concentration impaired, depression, emotional lability, vertigo.
- **Infrequent:** Akinesia, alcohol abuse, amnesia, ataxia, convulsion, depersonalization, hallucinations, hyperkinesia, hypertonia, incoordination, lack of emotion, manic reaction, paranoid reaction, thinking abnormal, hypesthesia.
- **Rare:** Abnormal electroencephalogram, abnormal gait, antisocial reaction, brain edema, choreoathetosis, circumoral paraesthesia, confusion, delirium, delusions, diplopia, drug dependence, dysarthria, dyskinesia, dystonia, euphoria, fasciculations, grand mal convulsion, hostility, hyperalgesia, hypokinesia, hysteria, libido increased, manic depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, psychosis, psychotic depression, reflexes increased, stupor, torticollis, withdrawal syndrome.

Respiratory System

- **Frequent:** Cough increased, rhinitis.
- **Infrequent:** Asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu, sinusitis.
- **Rare:** Hiccup, lung fibrosis, sputum increased, stridor, trachea disorder, voice alteration.

Special Senses

- **Infrequent:** Abnormality of accommodation, conjunctivitis, ear pain, eye pain, mydriasis, otitis media, tinnitus.
- **Rare:** Amblyopia, cataract specified, conjunctival edema, corneal lesion, corneal ulcer, exophthalmos, eye hemorrhage, acute glaucoma, hyperacusis, otitis externa, photophobia, retinal hemorrhage, taste loss, anisocoria, deafness, keratoconjunctivitis.

Urogenital system

- **Infrequent:** Abortion*, amenorrhea*, breast pain*, cystitis, dysmenorrhea*, dysuria, menorrhagia*, nocturia, polyuria, urinary incontinence, urinary retention, urinary tract infection, urinary urgency, vaginitis*.
- **Rare:** Breast atrophy*, cervix disorder*, endometrial disorder*, female lactation*, hematuria, kidney calculus, kidney function abnormal, kidney pain, mastitis*, nephritis,

oliguria, salpingitis*, spermatogenesis arrest* urethritis, urinary casts, urine abnormality, uterine neoplasm*, vaginal moniliasis*.

* Incidence corrected for gender.

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

Laboratory Changes - Cholesterol

Clinically and statistically relevant increases in cholesterol levels have been noted in studies using paroxetine (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

Of the patients in placebo-controlled clinical trials for whom baseline and on-treatment measurements were taken, total serum levels of cholesterol showed a mean increase of ~ 1.5 mg/dL in paroxetine- treated patients (n = 653), compared to a mean decrease of ~ 5.0 mg/dL in placebo-treated patients (n = 379). Increases from baseline of 45 mg/dL or greater were recorded in 6.6% of paroxetine-treated patients compared to 2.6% of placebo-treated patients.

8.5 Post-Market Adverse Reactions

Adverse events not listed above which have been reported since market introduction in patients taking paroxetine include: acute pancreatitis, hepatic events such as elevation of hepatic enzymes, and hepatitis, sometimes associated with jaundice, and/or liver failure (in very rare circumstances, with fatal outcomes), Guillain-Barré syndrome, priapism, thrombocytopenia, aggravated hypertension, syndrome of inappropriate ADH secretion, symptoms suggestive of hyperprolactinemia and galactorrhea, menstrual disorders (including menorrhagia, metrorrhagia and amenorrhea), blurred vision; extrapyramidal symptoms which have included akathisia, (characterized by an inner sense of restlessness and psychomotor agitation such as an inability to sit or stand still usually associated with subjective distress), bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide, tremor and trismus, abnormal dreams (including nightmares), restless legs syndrome (RLS), neuroleptic malignant syndrome-like events and serotonin syndrome (see 7 WARNINGS AND PRECAUTIONS, Serotonin Toxicity/Neuroleptic Malignant Syndrome), persistent pulmonary hypertension (see also 7.1.1 Pregnant Women, Risk of PPHN and exposure to SSRIs). There has been a case report of an elevated phenytoin level after 4 weeks of paroxetine and phenytoin co-administration.

There has been a case report of severe hypotension when paroxetine was added to chronic metoprolol treatment. The causal relationship between paroxetine and the emergence of these events has not been established.

There have been spontaneous reports of adverse events upon the discontinuation of paroxetine and other selective serotonin reuptake inhibitors (particularly when abrupt) (see 7 WARNINGS AND PRECAUTIONS, Discontinuation of treatment with PAROXETINE and 8 ADVERSE REACTIONS, Adverse Events following Discontinuation of Treatment (or Dose Reduction)).

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

PAROXETINE is contraindicated with:

- **Monoamine Oxidase Inhibitors:** Combined use of PAROXETINE and monoamine oxidase inhibitors (MAOIs) [including linezolid, an antibiotic which is a reversible non-selective MAOI and methylthioninium chloride (methylene blue)] is contraindicated due to the potential for serious reactions with features resembling serotonin syndrome or neuroleptic malignant syndrome.
- **Thioridazine:** Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsade de pointes-type arrhythmias, and sudden death. This effect appears to be dose-related and paroxetine has been shown to increase plasma thioridazine levels.
- **Pimozide:** Paroxetine 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 2 CONTRAINDICATIONS and 9.4 Drug-Drug Interactions

9.2 Drug Interactions Overview

Like some other selective serotonin re-uptake inhibitors, paroxetine inhibits the specific hepatic cytochrome P450 isozyme CYP2D6 which is responsible for the metabolism of debrisoquine and sparteine. Poor metabolizers of debrisoquine/sparteine represent approximately 5 to 10% of Caucasians. The median C_{min} (ss) for paroxetine (20 mg daily) at steady state in poor metabolizers (n=8) was almost triple that reported for extensive metabolizers (n=9). Although the full clinical significance of this effect has not been established, inhibition of CYP2D6 can lead to elevated plasma levels of co-administered drugs which are metabolized by this isozyme. Consideration should be given to decreasing the dose of the CYP2D6 metabolized drug or paroxetine and/or monitoring of drug plasma levels, especially when paroxetine is co-administered with drugs with a narrow therapeutic index.

Paroxetine co-administration has been associated with elevated levels of the anti-cholinergic procyclidine, certain neuroleptics/antipsychotics (e.g. perphenazine, risperidone), tricyclic antidepressants (e.g. desipramine), atomoxetine, type 1C antiarrhythmics (e.g. propafenone), and theophylline.

Co-administration of phenobarbitol or phenytoin with paroxetine has been associated with decreased levels of paroxetine. When co-administered with cimetidine, paroxetine levels were elevated.

9.3 Drug-Behavioural Interactions

Alcohol: The concomitant use of paroxetine and alcohol has not been studied and is not recommended. Patients should be advised to avoid alcohol while taking PAROXETINE.

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 5 – Established or Potential Drug-Drug Interactions

Paroxetine Hydrochloride	Source of Evidence	Effect	Clinical comment
MAOIs including linezolid and methylthioninium chloride (methylene blue)	C	Reports include serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Some cases showed features of serotonin syndrome or neuroleptic malignant syndrome (see 7 WARNINGS AND PRECAUTIONS, Serotonin Toxicity/Neuroleptic Malignant Syndrome).	Concurrent use of MAOIs and PAROXETINE is contraindicated (see 2 CONTRAINDICATIONS, 9.1 Serious Drug Interactions). PAROXETINE should not be used in combination with MAOIs or within a minimum of 2 weeks of terminating treatment with MAOIs. Treatment with PAROXETINE should then be initiated cautiously and dosage increased gradually until optimal response is reached. MAOIs should not be introduced within 2 weeks of cessation of therapy with PAROXETINE.
Thiordazine	T	Possible increase in thioridazine plasma levels due to PK interaction via CYP2D6 based on *in vivo* studies. Therefore, possible increased risk of QT prolongation, which is associated with serious	PAROXETINE should not be used in combination with thioridazine or within a minimum of 2 weeks of terminating treatment with paroxetine (see 2 CONTRAINDICATIONS, 9.1 Serious Drug Interactions).

Paroxetine Hydrochloride	Source of Evidence	Effect	Clinical comment
		ventricular arrhythmias, such as torsade de pointes-type arrhythmias, and sudden death.	
Pimozide	CT	Increased systemic exposure to pimozide due to PK interaction likely via CYP2D6. Therefore, possible increased risk of QT prolongation, which is associated with serious ventricular arrhythmias, such as torsade de pointes-type arrhythmias, and sudden death.	In an open label study of healthy volunteers, co-administration of a single dose of 2 mg pimozide, under steady state conditions of paroxetine (titrated to 60 mg daily) was associated with mean increases in pimozide AUC of 151% and C_{max} of 62%, compared to pimozide administered alone. Concomitant use of PAROXETINE and pimozide is contraindicated and paroxetine should not be started until a minimum of 2 weeks after pimozide has been discontinued (see 2 CONTRAINDICATIONS, 9.1 Serious Drug Interactions).
Antipsychotic drugs	C	Possible increased risk of neuroleptic malignant syndrome (see 7 WARNINGS AND PRECAUTIONS, Serotonin Toxicity/Neuroleptic Malignant Syndrome).	PAROXETINE should be used with caution in patients already receiving antipsychotics/ neuroleptics.
Serotonergic drugs such as tryptophan, triptans, serotonin reuptake inhibitors, lithium, fentanyl and its anologues, dextromethorphan, tramadol, tapentadol, meperidine, methadone and pentazocine or St. John's Wort	T	Potential increased risk of serotonin syndrome and neuroleptic malignant syndrome (see 7 WARNINGS AND PRECAUTIONS, Serotonin Toxicity/Neuroleptic Malignant Syndrome).	Caution is advised. Based on the mechanism of action of paroxetine and the potential for serotonin syndrome.
Drugs affecting platelet function	E	Serotonin release by platelets plays an important role in	Based on case-control and epidemiological cohort studies.

Paroxetine Hydrochloride	Source of Evidence	Effect	Clinical comment
(e.g. NSAIDs, ASA and other anticoagulants)		hemostasis. Interference with serotonin reuptake and the occurrence of upper gastrointestinal bleeding may be potentiated by the use of NSAIDs, ASAs or other anticoagulants. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs are co-administered with warfarin.	Patients receiving warfarin therapy should be carefully monitored when paroxetine is initiated or discontinued (see 7 WARNINGS AND PRECAUTIONS, Abnormal Bleeding).
Lithium	T	Potential increased risk of serotonin syndrome.	In a clinical study, no pharmacokinetic interaction between paroxetine and lithium was observed. However, due to the potential for serotonin syndrome, caution is advised when paroxetine is coadministered with lithium.
Triptans	C	Weakness, hyperreflexia, incoordination seen after use of SSRI and triptan (see 7 WARNINGS AND PRECAUTIONS, Serotonin Toxicity/Neuroleptic Malignant Syndrome).	Based on rare postmarketing reports. If concomitant treatment with triptan and an SSRI (e.g. fluoxetine, fluvoxamine, paroxetine, sertraline) is clinically warranted, appropriate observation of the patient is advised.
Tryptophan	T	Use of PAROXETINE and tryptophan may result in headache, nausea, sweating and dizziness, as well as serotonin syndrome (see 7 WARNINGS AND PRECAUTIONS, Serotonin Toxicity/Neuroleptic Malignant Syndrome).	Tryptophan may be metabolised to serotonin. Concomitant use of PAROXETINE and tryptophan is not recommended.
Tamoxifen	CT	Reduced plasma concentrations and possible efficacy of endoxifen, the active metabolite of tamoxifen (see 7 WARNINGS	Tamoxifen is metabolised into endoxifen via CYP2D6. Paroxetine inhibits CYP2D6

Paroxetine Hydrochloride	Source of Evidence	Effect	Clinical comment
		AND PRECAUTIONS, Potential for reduced efficacy of Tamoxifen with concomitant SSRI use, including PAROXETINE).	thereby reducing endoxifen plasma levels.
Drugs metabolised by CYP2D6	CT	Possible altered systemic exposure of CYP2D6-metabolised drugs due to inhibition of CYP2D6 by paroxetine.	In two studies, daily dosing of paroxetine (20 mg qd) under steady state conditions increased the following mean pharmacokinetic parameters for a single (100 mg) dose of desipramine in extensive metabolizers: C_{max} (2 fold), AUC (6 fold), and T½ (3-5 fold). Concomitant steady-state paroxetine treatment did not result in any further impairment of desipramine elimination in poor metabolizers. Insufficient information is available to provide recommendations on the necessary dosage adjustments for tricyclic antidepressants or paroxetine, if these drugs are to be used in combination. Plasma tricyclic antidepressant concentrations may need to be monitored in such instances. Concomitant use of paroxetine with other drugs metabolized by CYP2D6 has not been formally studied but may require lower doses than usually prescribed for either paroxetine or the other drug. Drugs metabolized by CYP2D6 include certain tricyclic antidepressants (e.g. nortriptyline, amitriptyline, imipramine and desipramine), selective serotonin reuptake inhibitors (e.g. fluoxetine),

Paroxetine Hydrochloride	Source of Evidence	Effect	Clinical comment
			phenothiazine neuroleptics (e.g. perphenazine), risperidone, atomoxetine, Type IC antiarrhythmics (e.g. propafenone and flecainide), and metoprolol.
Drugs metabolised by CYP3A4	T	No expected effect of paroxetine on CYP3A4-metabolised drugs.	An *in vivo* interaction study involving the co-administration under steady state conditions of paroxetine and terfenadine, a substrate for CYP3A4, revealed no effect of paroxetine on terfenadine pharmacokinetics. In addition, *in vitro* studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several substrates for this enzyme, including terfenadine, astemizole, cisapride, triazolam and cyclosporin. Based on the assumption that the relationship between paroxetine's *in vitro* Ki and its lack of effect on terfenadine's *in vivo* clearance predicts its effect on other CYP3A4 substrates, paroxetine's extent of inhibition of CYP3A4 activity would not be expected to be of clinical significance.
Neuromuscular blockers	C	Some antidepressants including paroxetine may reduce plasma cholinesterase activity resulting in a prolongation of the neuromuscular blocking action of succinylcholine.	Based on *in vitro* studies as well as a small number of clinical reports
Microsomal enzyme inhibition/induction	T	Altered systemic exposure to paroxetine.	The metabolism and pharmacokinetics of PAROXETINE may be affected by

Paroxetine Hydrochloride	Source of Evidence	Effect	Clinical comment
			the induction or inhibition of drug metabolizing enzymes.
Drugs highly bound to plasma protein	T	Administration of PAROXETINE to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events. Conversely, adverse effects could result from displacement of paroxetine by other highly bound drugs.	Paroxetine is highly bound to plasma protein.
Anti-cholinergic drugs	CT	PAROXETINE has been reported to increase significantly the systemic bioavailability of procyclidine. Steady state plasma levels of procyclidine (5 mg daily) were elevated by about 40% when 30 mg paroxetine was co-administered to steady-state.	If anti-cholinergic effects are seen, the dose of procyclidine should be reduced.
Antiretroviral	CT	Co-administration of fosamprenavir/ritonavir with paroxetine significantly decreased plasma levels of paroxetine (by ~ 60% in one study).	Any dose adjustment should be guided by clinical effect (tolerability and efficacy).
Phenobarbital	CT	Chronic daily dosing with phenobarbital (100 mg qid for 14 days) decreased the systemic availability of a single 30 mg dose of paroxetine in some subjects. The AUC and T½ of Paroxetine were reduced by an average of 25 and 38% respectively compared to PAROXETINE administered alone. The effect of paroxetine on phenobarbital	No initial PAROXETINE dosage adjustment is considered necessary when co-administered with phenobarbital; any subsequent adjustment should be guided by clinical effect.

Paroxetine Hydrochloride	Source of Evidence	Effect	Clinical comment
		pharmacokinetics was not studied.	
Anti-convulsants	CT	The co-administration of Paroxetine (30 mg/day for 10 days) had no significant effect on the plasma concentrations of patients with epilepsy on long-term treatment with carbamazepine (600-900 mg/day) n=6, phenytoin (250-400 mg/day) n=6 and sodium valproate (300-2500 mg/day) n=8. In healthy volunteers, co-administration of paroxetine with phenytoin has been associated with decreased plasma levels of paroxetine and an increased incidence of adverse experiences. Co-administration of PAROXETINE with anticonvulsants may be associated with an increased incidence of adverse experiences.	No initial dosage adjustment of Paroxetine is considered necessary when the drug is to be co-administered with known drug metabolizing enzyme inducers (e.g. carbamazepine, phenytoin, sodium valproate) and any subsequent dosage adjustment should be guided by clinical effect.
CNS drugs	CT	Experience in a limited number of healthy subjects has shown that paroxetine does not increase the sedation and drowsiness associated with haloperidol, amylbarbitone or oxazepam, when given in combination.	Since the effects of concomitant administration of paroxetine with neuroleptics have not been studied, the use of PAROXETINE with these drugs should be approached with caution.
Diazepam	CT	A multiple dose study of the interaction between paroxetine and diazepam showed no alteration in the pharmacokinetics of paroxetine that would warrant changes in the dose of paroxetine for	

Paroxetine Hydrochloride	Source of Evidence	Effect	Clinical comment
		patients receiving both drugs. The effects of paroxetine on the pharmacokinetics of diazepam were not evaluated.	
Cardiovascular drugs	CT	Multiple dose treatment with paroxetine 30 mg/day has little or no effect on the steady-state pharmacokinetics of digoxin (0.25 mg qd) or propanolol (80 mg bid).	
Theophylline	C	Reports of elevated theophylline levels associated with Paroxetine treatment have been reported.	While this interaction has not been formally studied, it is recommended that theophylline levels be monitored when these drugs are concurrently administered.
Cimetidine	CT	Steady state levels of Paroxetine (30 mg daily) were elevated by about 50% when cimetidine (300 mg tid), a known drug metabolizing enzyme inhibitor, was co-administered to steady-state.	Consideration should be given to using doses of PAROXETINE towards the lower end of the range when co-administered with known drug metabolizing enzyme inhibitors.

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

9.5 Drug-Food Interactions

The absorption and pharmacokinetics of paroxetine are not affected by food or antacids.

9.6 Drug-Herb Interactions

St. John's Wort: In common with other SSRIs, pharmacodynamic interactions between paroxetine 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

Paroxetine is a potent and selective serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitor (SSRI). This activity of the drug on brain neurons is thought to be responsible for its antidepressant and anxiolytic action in the treatment of depression, obsessive-compulsive disorder (OCD), panic disorder, social phobia (social anxiety disorder), generalized anxiety disorder (GAD) and posttraumatic stress disorder (PTSD).

Paroxetine is a phenylpiperidine derivative which is chemically unrelated to the tricyclic or tetracyclic antidepressants. In receptor binding studies, paroxetine did not exhibit significant affinity for the adrenergic (α1, α2, β), dopaminergic, serotonergic (5HT1, 5HT2), or histaminergic receptors of rat brain membrane. A weak affinity for the muscarinic acetylcholine receptor was evident. The predominant metabolites of paroxetine are essentially inactive as 5-HT reuptake inhibitors.

10.2 Pharmacodynamics

Paroxetine 30 mg administered in single doses to healthy non-depressed volunteers did not impair psychomotor function which was measured by psychomotor tasks such as Morse tapping and motor manipulation, assessment of subjective perception and general assessment of arousal.
Paroxetine at doses of up to 40 mg daily produces no clinically significant changes in blood pressure, heart rate or ECG after administration to healthy subjects.

10.3 Pharmacokinetics

No clear dose relationship has been demonstrated for the antidepressant effects of paroxetine at doses above 20 mg/day. The results of fixed-dose studies comparing paroxetine and placebo in the treatment of depression, panic disorder, generalized anxiety disorder and posttraumatic stress disorder revealed a dose dependency for some adverse events.

Absorption

Paroxetine is well absorbed after oral administration. In healthy volunteers, the absorption of a single 30 mg oral dose of paroxetine was not appreciably affected by the presence or absence of food.

Both the rate of absorption and the terminal elimination half-life appear to be independent of dose. Steady-state plasma concentrations of paroxetine are generally achieved in 7 to 14 days. No correlation has been established between paroxetine plasma concentrations and therapeutic efficacy or the incidence of adverse reactions.

In healthy young volunteers receiving a 20 mg daily dose of paroxetine for 15 days, the mean maximal plasma concentration was 41 ng/mL at steady state (see Table 6). Peak plasma levels generally occurred within 3 to 7 hours.

Distribution

Owing to the extensive distribution of paroxetine into the tissues, less than 1% of the total drug in the body is believed to reside in the systemic circulation.

At therapeutic concentrations, the plasma protein binding of paroxetine is approximately 95%.

Metabolism

Paroxetine is subject to a biphasic process of metabolic elimination which involves presystemic (first-pass) and systemic pathways. First-pass metabolism is extensive, but may be partially saturable, accounting for the increased bioavailability observed with multiple dosing. The metabolism of paroxetine is accomplished in part by cytochrome P450 ($2D_6$). Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. The role of this enzyme in paroxetine metabolism also suggests potential drug-drug interactions (see 9 DRUG INTERACTIONS). The majority of the dose appears to be oxidized to a catechol intermediate which is converted to highly polar glucuronide and sulphate metabolites through methylation and conjugation reactions. The glucuronide and sulphate conjugates of paroxetine are about >10,000 and 3,000 times less potent, respectively, than the parent compound as inhibitors of 5-HT reuptake in rat brain synaptosomes.

Elimination

Following the single or multiple dose administration of paroxetine at doses of 20 to 50 mg, the mean elimination half-life value for healthy subjects appears to be about 24 hours, although a range of 3 to 65 hours has been reported.

Approximately 64% of an administered dose of paroxetine is eliminated by the kidneys and 36% in the feces. Less than 2% of the dose is recovered in the form of the parent compound.

Special Populations and Conditions

- **Geriatrics:** In elderly subjects, increased steady-state plasma concentrations and prolongation of the elimination half life were observed relative to younger adult controls (Table 6). Elderly patients should, therefore, be initiated and maintained at the lowest daily dosage of paroxetine which is associated with clinical efficacy (see 4.2 Recommended Dose and Dosage Adjustment).

- **Hepatic Insufficiency:** The results from a multiple dose pharmacokinetic study in

subjects with severe hepatic dysfunction suggest that the clearance of paroxetine is markedly reduced in this patient group (see Table 6). As the elimination of paroxetine is dependent upon extensive hepatic metabolism, its use in patients with hepatic impairment should be undertaken with caution (see 4.2 Recommended Dose and Dosage Adjustment).

- **Renal Insufficiency:** In a single dose pharmacokinetic study in patients with mild to severe renal impairment, plasma levels of paroxetine tended to increase with deteriorating renal function (see Table 7). As multiple-dose pharmacokinetic studies have not been performed in patients with renal disease, paroxetine should be used with caution in such patients (see 4.2 Recommended Dose and Dosage Adjustment).

Table 6 Steady state pharmacokinetics of paroxetine after doses of 20 mg daily (mean and range)

	Young Healthy Subjects [n=22]	Elderly Healthy Subjects [n=22]	Hepatically* Impaired Subjects [n=10]
C_{max} (ss) (ng/mL)	41 (12-90)	87 (18-154)	87 (11-147)
T_{max} (ss) (hours)	5.0 (3-7)	5.0 (1-10)	6.4 (2-11)
C_{min} (ss) (ng/mL)	21 (4-51)	58 (9-127)	66 (7-128)
AUC (ss) (ng·h/mL)	660 (179-1436)	1580 (221-3286)	1720 (194-3283)
$T_{½}$ (hour)	19 (8-43)	31 (13-92)	66 (17-152)

*Galactose elimination capacity 30-70% of normal.

A wide range of interindividual variation is observed for the pharmacokinetic parameters.

Table 7 Pharmacokinetics of paroxetine after a single 30 mg dose in normal subjects and those with renal impairment

	[a]Renally Impaired Subjects Severe [n=6]	[b]Renally Impaired Subjects Moderate [n=6]	[c]Healthy young subjects [n=6]
C_{max} (ng/mL)	46.2 (35.9-56.7)	36 (3.6-59. 4)	19.8 (1.4-54.8)
T_{max} (hour)	6.5 (4.0-11.0)	4.8 (1.5-9.0)	4.3 (1-7)

AUC_4 (ng·h/mL)	2046 (605-3695)	1053 (48-2087)	574 (21-2196)
$T_{½}$ (hour)	29.7 (10.9-54.8)	18.3 (11.2-32.0)	17.3 (9.6-25.1)

[a] Creatinine clearance = 13-27 mL/min
[b] Creatinine clearance = 32-46 mL/min
[c] Creatinine clearance > 100 mL/min
Abbreviations:
C_{max} = maximum plasma concentration; T_{max} = time to reach C_{max}
AUC_4 = Area under the plasma concentration time curve at infinity
$T_{½}$ = terminal elimination half-life

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature 15°-30°C. Protect from moisture.

12 SPECIAL HANDLING INSTRUCTIONS

No Special Handling Instructions are required for this drug product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Paroxetine hydrochloride

Chemical name: (-)-trans-4R-(4'-fluorophenyl)-3S-(3',4'-methylene-dioxyphenoxymethyl)-piperidine hydrochloride hemihydrate.

Or

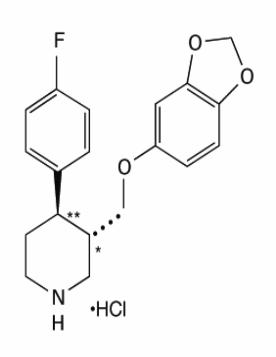
(-)-trans-4R-(4'-fluorophenyl)-3S-(3',4'-methylene-dioxyphenoxymethyl)-piperidine hydrochloride anhydrate.

Molecular formula and molecular mass: $C_{19}H_{20}NO_3F \bullet HCl$

374.8 g/mol (as hemihydrate salt)

329.4 g/mol (as free base)

Structural formula:



Physicochemical properties:

Description: a white to off-white solid

Melting point: 120-138°C

pKa and pH Values: It is not possible to measure directly the pKa of paroxetine in water owing to the aliphatic nature of the piperidine ring system and the low solubility of paroxetine base.

Measurements in 50% aqueous dimethyl sulphoxide indicate an aqueous pKa of 9.90 compared to a calculated value of 9.84.

The pH of a saturated solution of paroxetine hydrochloride is 5.7 and a solution containing 2 mg/mL of paroxetine hydrochloride is 6.3.

Oil-Water Coefficient of Partition:

The apparent partition coefficient of paroxetine hydrochloride in the octanol-water system (Poct/water) is 3.38 (log P=0.53).

The partition coefficient of paroxetine base between octanol-water determined using a solution of paroxetine hydrochloride in octanol and an aqueous phase of sodium hydroxide solution (1M) is 222 (log P=2.35).

Paroxetine hydrochloride is slightly soluble in water (4.9 mg pure free base/mL).

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Major Depressive Disorder

The efficacy of paroxetine hydrochloride as a treatment for depression has been established in six placebo-controlled clinical trials of 6 weeks in duration performed in patients with depression (ages 18 to 73).

In these 6 studies, paroxetine was shown to be significantly more effective than placebo in treating depression according to the following measures: Hamilton Depression Rating Scale (HDRS), the Hamilton depressed mood item, and the Clinical Global Impression (CGI) – Severity of Illness.

A study of outpatients with recurrent major depressive disorder who had responded to paroxetine (HDRS total score < 8) during an initial 8-week open-treatment phase and were then randomized to continuation on paroxetine or placebo for 1 year demonstrated that a significantly lower proportion of patients treated with paroxetine (15%) compared to placebo (39%) met criteria for partial relapse[1]. Criteria for full relapse[2] were met by a significantly lower percentage of paroxetine treated patients (12%) compared to placebo treated patients (28%). Effectiveness was similar for male and female patients.

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[1]Partial relapse was characterized by requirement for additional antidepressant medication and fulfillment of DSM IIIR criteria for major depressive episode

[2]Full relapse was characterized by requirement for additional antidepressant treatment, fulfillment of DSM IIIR criteria for major depressive episode, deterioration in depressive symptoms for at least 1 week, increase in CGI-Severity of Illness score by ≥ 2 points and CGI-Severity of Illness score of ≥4 (least moderately ill).

Obsessive-Compulsive Disorder

Three double-blind, placebo-controlled clinical trials of 12 weeks in duration have been performed to investigate the efficacy of paroxetine in obsessive-compulsive disorder: two flexible dose studies (20 to 60 mg/day) and one fixed dose study (20, 40, & 60 mg/day). Results for the fixed dose study and one of the flexible dose studies showed statistically significant differences from placebo in favour of paroxetine 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. In the fixed dose study, the proportion of patients who were considered to be much or very much improved at endpoint according to a Clinical Global Impression of Improvement was 15% (13/88) in the placebo group, 20% (17/85) in the 20 mg/day group, 36% (30/83) in the 40 mg/day group, and 37% (31/83) in the 60 mg/day group. In the two flexible dose studies, placebo response rates according to this criterion were 28% (28/99) and 25% (19/75), while paroxetine response rates were 45% (89/198) and 35% (28/79), respectively.

Panic Disorder (with or without agoraphobia)

One fixed dose and three flexible dose placebo-controlled clinical trials of 10 to 12 weeks in duration have been performed to investigate the efficacy of paroxetine in panic disorder.

The fixed dose study and two of the three flexible dose studies were supportive of differences from placebo in favour of paroxetine for measures of panic attack frequency. At endpoint, in the fixed dose study, the proportion of patients who were free of panic attacks was 44% (29/66) for the placebo group, 56% (33/59) for the 10 mg/day paroxetine group, 57% (35/61) for the 20 mg/day paroxetine group, and 76% (47/62) for the 40 mg/day paroxetine group.

Social Phobia (Social Anxiety Disorder)

One fixed dose and two flexible dose placebo-controlled clinical trials of 12 weeks in duration have been performed to investigate the efficacy of paroxetine in social phobia (social anxiety disorder).

These studies showed statistically significant differences from placebo in favour of paroxetine in terms of mean change from baseline to endpoint on the Liebowitz Social Anxiety Scale and the percentage of therapeutic responders according to the Clinical Global Impression of Improvement. In the fixed dose study, the proportion of patients who were considered to be much or very much improved at week 12 of treatment according to the Clinical Global Impression of Improvement was 28.3% (26/92) in the placebo group, 44.9% (40/89) in the 20

mg/day group, 46.6% (41/88) in the 40 mg/day group, and 42.9% (39/91) in the 60 mg/day group. In the two flexible dose (20 to 50 mg/day) studies, placebo response rates according to this criterion were 23.9% (22/92) and 32.4% (47/145), while paroxetine response rates were 54.9% (50/91) and 65.7% (90/137), respectively.

Generalized Anxiety Disorder (GAD)

The effectiveness of paroxetine in the treatment of Generalized Anxiety Disorder (GAD) (DSM IV) was demonstrated in two 8-week, multicentre, placebo-controlled studies. One trial was a flexible dose (20 to 50 mg/day) study while the other was a multiple fixed dose (20 or 40 mg/day) study.

In both studies paroxetine demonstrated statistically significant superiority over placebo on the primary outcome measure - the Hamilton Rating Scale for Anxiety (HAM-A) total score, and on a number of secondary outcomes including the HAM-A anxiety and tension items, the Clinical Global Impression (CGI) responder criterion and the Sheehan Disability Scale (SDS). An additional 8-week flexible dose study did not demonstrate a significant difference between paroxetine (20 to 50 mg/day), and placebo on the primary outcome measure. However, paroxetine (20 to 50 mg/day) was more effective than placebo on many secondary study outcomes.

Posttraumatic Stress Disorder (PTSD)

The efficacy of paroxetine in the treatment of Posttraumatic Stress Disorder (PTSD) was demonstrated in two 12 week, multicentre placebo controlled studies (Study 1 and Study 2) in adult patients who met the DSM-IV criteria for PTSD. Study outcome was assessed by (i) the Clinician Administered PTSD Scale Part (CAPS-2) score and (ii) the Clinical Global Impression Global Improvement Item (CGI-I). The CAPS-2 is a multi-item instrument that measures the three PTSD diagnostic symptom clusters of: reexperiencing/intrusion, avoidance/numbing and hyperarousal.

Study 1 was a 12 week study comparing fixed paroxetine doses of 20 or 40 mg/day to placebo.

Study 2 was a 12-week flexible-dose study comparing paroxetine (20 to 50 mg daily) to placebo.

The two primary outcomes for each trial were (i) change from baseline to endpoint on the CAPS-2 total score (17 items), and (ii) proportion of responders on the CGI-I, where responders were defined as patients having a score of 1 (very much improved) or 2 (much improved).

In study 1, Paroxetine 20 mg and 40 mg were demonstrated to be significantly superior to placebo for the CAPS-2 total score, and on proportion of responders on the CGI-I.

In study 2, Paroxetine was demonstrated to be significantly superior to placebo for the CAPS-2 total scorer, and on proportion of responders on the CGI-I.

The majority (66 - 68%) of patients in these trials were women. Subgroup analyses did not indicate differences in treatment outcomes as a function of gender. There were an insufficient number of patients who were 65 years or older or were non-Caucasian to conduct subgroup analyses on the basis of age or race, respectively.

14.3 Comparative Bioavailability Studies

A randomized, two-treatment, two-period, two-sequence, single oral dose (1 x 30 mg), crossover comparative bioavailability study of PAROXETINE tablets 30 mg (Pro Doc Ltée) and PAXIL® tablets 30 mg (SmithKline Beecham Pharma), was conducted in healthy, adult male subjects under fasting conditions. Comparative bioavailability data from 33 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Paroxetine (1 x 30 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	181 323 (114)	178 313 (114)	101.7	89.1 – 116.1
AUC_I (ng.h/mL)	209 391 (149)	202 385 (163)	102.3	89.5 – 117.5
C_{max} (ng/mL)	11.5 15.6 (72)	11.6 15.7 (69)	99.1	86.5 – 113.6
T_{max}[3] (h)	6.0 (3.0 – 8.0)	7.0 (3.0 – 10.0)		
$T_{½}$[4] (h)	14.0 (67)	13.4 (74)		

[1] PAROXETINE (paroxetine as paroxetine hydrochloride) tablets, 30 mg (Pro Doc Ltée)
[2] PAXIL® (paroxetine as paroxetine hydrochloride) tablets, 30 mg (SmithKline Beecham Pharma, Canada)
[3] Expressed as the median (range) only
[4] Expressed as the arithmetic mean (CV %) only

A randomized, double blinded, two-treatment, two-period, two-sequence, single oral dose (1 x 30 mg), crossover comparative bioavailability study of PAROXETINE tablets 30 mg (Pro Doc Ltée) and PAXIL® tablets 30 mg (SmithKline Beecham Pharma), was conducted in healthy, adult male subjects under fed conditions. Comparative bioavailability data from 34 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Paroxetine (1 x 30 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	139 209 (81)	144 210 (77)	96.2	90.5 – 102.2
AUC_I (ng.h/mL)	146 224 (87)	151 224 (83)	96.4	90.7 – 102.4
C_{max} (ng/mL)	7.70 9.91 (61)	7.56 9.20 (54)	101.8	94.6 – 109.5
T_{max}[3] (h)	5.5 (3.0 – 9.0)	7.0 (2.0 – 10.0)		
$T_{½}$[3] (h)	13.5 (37)	13.2 (34)		

[1] PAROXETINE (paroxetine as paroxetine hydrochloride) tablets, 30 mg (Pro Doc Ltée)
[2] PAXIL® (paroxetine as paroxetine hydrochloride) tablets, 30 mg (SmithKline Beecham Pharma, Canada)
[3] Expressed as the median (range) only
[4] Expressed as the arithmetic mean (CV %) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Animal Pharmacology

***In vitro*:** Paroxetine showed a high potency for the inhibition of 5-HT reuptake in rat hypothalamic synaptosomes (K_i=1.1nM), but exerted relatively weak effects upon noradrenaline reuptake (K_i=350nM). The predominant metabolites of paroxetine, a sulphate and a glucuronide conjugate, were essentially inactive as 5-HT reuptake inhibitors. Paroxetine has a low affinity for muscarinic cholinergic receptors (K_i of 89 nM for displacement of [^{3}H]quinuclidinyl benzilate). Animal studies have indicated only weak anticholinergic properties.

Radioligand binding techniques in rat brain, *in vitro*, have indicated that paroxetine has little affinity for α_1, α_2 and β-adrenoceptors, dopamine (D_2), 5-HT_1-like, 5-HT_2 and histamine (H_1) receptors at concentrations below 1 µM. This lack of interaction with post-synaptic receptors *in vitro* is substantiated by *in vivo* studies which demonstrate a lack of CNS depressant and hypotensive properties.

***In vivo*:** In mice, paroxetine (ED_{50}=0.4 mg/kg p.o.) was associated with potent and prolonged potentiation of the hypermotility induced by the 5-HT precursor, 5-hydroxytryptophan. Similarly, the anticonvulsant effects of 5-hydroxytryptophan in a mouse electroshock model were potentiated by paroxetine (ED_{50}=0.4 mg/kg p.o.). In rats, paroxetine (ED_{50}=0.8 mg/kg p.o.) inhibited the hypermotility induced by p-chloroamphetamine, an agent which depletes neuronal 5-HT stores. Paroxetine, 1 mg/kg i.p., in conscious rats with chronically implanted cortical electrodes, produced essentially no changes in the power spectrum and frequency analysis of the EEG.

Electrophysiological measures have demonstrated that paroxetine has a vigilance-increasing activity in animals. Oral doses of paroxetine 0.32 to 18 mg/kg to rats lengthened the waking period and shortened the slow-wave and paradoxical sleep periods in a dose-dependent fashion. As with other selective 5-HT uptake inhibitors, paroxetine, at a dose of 5 mg/kg i.p., causes symptoms of excessive 5-HT receptor stimulation when administered to rats previously given monoamine oxidase (MAO) inhibitors such as tranylcypromine or phenelzine, or the 5-HT precursor L-tryptophan.

Behavioural and EEG studies indicate that paroxetine is weakly activating at doses above those generally required to inhibit 5-HT reuptake. The activating properties are not "amphetamine-like" in nature. In rats trained to discriminate d-amphetamine, 1 mg/kg i.p., from saline, no generalization to amphetamine was observed after administration of paroxetine (0.3, 1, 3 or 10 mg/kg i.p.). Paroxetine caused seizures in mice at a lethal dose of 300 mg/kg p.o. At a dose of 50 mg/kg p.o., paroxetine lowered the threshold for electroshock-induced seizures in mice.

Animal studies indicate that paroxetine is well tolerated by the cardiovascular system. When the cardiovascular effects of paroxetine and amitriptyline were compared in the conscious rabbit and anaesthetized cat, intravenous doses of paroxetine approximately 2 to 4 times higher (on a mg/kg basis) than those of amitriptyline were required to produce significant changes in blood pressure, heart rate and electrocardiographic parameters. Similarly, in the pentobarbital anaesthetized dog, i.v. imipramine, amitriptyline and clomipramine (in doses of 10 mg/kg) caused severe atrioventricular block and ventricular arrhythmia's, while equivalent doses of paroxetine resulted in only slight prolongation of the PQ interval. In addition, low doses (0.3 to 1 mg/kg) of the tricyclic antidepressants caused marked tachycardia, whereas paroxetine in doses up to 10 mg/kg had no effect on heart rate.

Studies in the spontaneous hypertensive rat indicate that, in contrast to antidepressants which inhibit the uptake of noradrenaline, paroxetine at 5 mg/kg i.v. has a much reduced propensity to inhibit the antihypertensive effects of guanethidine.

5-HT is transported into blood platelets and central neurons by a similar active uptake transporter mechanism in the cell membrane. Thus, in common with other selective 5-HT reuptake inhibitors, administration of paroxetine results in depletion of 5-HT from platelets. This has been reported after repeated daily administration of paroxetine at doses of 0.1, 1 and 10 mg/kg i.p. in mice and rats, 1 to 7.5 mg/kg p.o. in monkeys and 10-50 mg orally to healthy human volunteers. Similarly, whole blood 5-HT levels were shown to be depleted in depressed patients after paroxetine administration.

General Toxicology

General toxicity studies have been conducted in rhesus monkeys and rats, in both of which the metabolic pathway for paroxetine is the same as in man.

- **Acute Toxicity:** In relation to the clinical dose, the acute LD50 of paroxetine is very high in both mice and rats (approximately 350 mg/kg).

- **Long-Term Toxicity**: The no-toxic effect levels in the rhesus monkeys and rats were 4 to 10 times and 6 to 15 times the recommended range of clinical doses respectively. At higher doses (40 mg/kg for 3 months and 25 mg/kg for 12 months), lipidosis was observed in several tissues of rats (lungs, mesenteric lymph nodes, epididymides, retinal tissues - the latter by electron microscopy only). As paroxetine is a lipophilic amine with both hydrophobic and hydrophilic moieties, it may accumulate in lysosomes leading to an impairment of lipid catabolism and, hence, the accumulation of lipids within the lysosomes. It should be noted that the slight degree of lipidosis seen in the rat was restricted to doses and plasma levels much higher than those observed in man. In a clinical study investigating lamellated inclusion bodies in peripheral white blood cells during long-term therapy, no difference between placebo and paroxetine could be detected.

Carcinogenicity

No carcinogenic potential was detected in rat (dose levels of 1, 5 and 20 mg/kg/day) and mouse (dose levels of 1, 5 and 25 mg/kg/day) life-span studies. A non dose-related increase in malignant liver cell tumours occurred in male mice at 1 and 5 mg/kg/day which was statistically significant at 5 mg/kg/day. There was no increase at 25 mg/kg/day or in female mice and the incidence was within the historical control range.

Reproductive and Developmental Toxicology

5-Hydroxytryptamine and compounds modulating this amine are known to affect reproductive function in animals and at high dose levels cause marked overt toxicity. Paroxetine at 15 and 50 mg/kg (hydrochloride salt) has been shown to impair reproductive function in rats.

In male rats, chronic administration of a 50 mg/kg dose has been associated with granulomatous reactions in the epididymides accompanied by atrophy and degeneration of the seminiferous tubules. There were no biologically significant effects on fertility of female rats but corpora lutea count was slightly reduced and preimplantation loss slightly increased at 50 mg/kg in association with marked maternal toxicity.

Reproduction studies were performed in rats and rabbits at doses up to 42 and 5 times the maximum recommended daily human dose (60 mg) on a mg/kg basis. These are 8.3 (rat) and 1.7 (rabbit) times the maximum recommended human dose on a mg/m^2 basis. These studies have revealed no evidence of teratogenic effects or of selective toxicity to the embryo.

Special Toxicology

- **Immunotoxicity**

Specific studies have demonstrated that paroxetine is unlikely to possess the potential for immunotoxicity.

Serum samples were obtained from depressed patients who had received 30 mg of paroxetine daily for between six and twelve months, from groups of rats on a repeat dose toxicity study in which daily doses of 1, 5 and 25 mg/kg of paroxetine were administered for 52 weeks, from guinea pigs epicutaneously exposed (topically under an occlusive patch) to paroxetine and from New Zealand White (NZW) rabbits parenterally (i.m. and s.c.) injected with paroxetine in Freund's adjuvant. In addition, as a positive control, sera were obtained from NZW rabbits which had been immunized by i.m. and s.c. injections of Freund's adjuvant emulsions containing paroxetine chemically conjugated to bovine gamma globulin (BGG).

Serum antibody levels were assessed by enzyme- or radio-immunoassays (ELISA or RIA). No anti-paroxetine antibody activity was detected in serum samples from patients, from rats in the toxicity study, from guinea pigs epicutaneously exposed to paroxetine, or from rabbits parenterally injected with paroxetine. Serum anti-paroxetine antibody was detected in rabbits immunized with Freund's adjuvant emulsions containing paroxetine coupled with BGG, verifying that the RIA system employed was capable of detecting antibodies directed against paroxetine.

Paroxetine also did not induce contact sensitivity reactions in guinea pigs following epicutaneous exposure.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PAXIL® (Tablets, 10 mg, 20 mg and 30 mg), submission control 263621, Product Monograph, GlaxoSmithKline Inc, SEP 22, 2022.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrPAROXETINE -10
PrPAROXETINE -20
PrPAROXETINE -30

Paroxetine Tablets

Read this carefully before you start taking **PAROXETINE** 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 **PAROXETINE**.

Serious Warnings and Precautions

New and worsened emotional or behaviour problems:

- When you first start taking PAROXETINE 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 PAROXETINE, 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 PAROXETINE.
- You may find it helpful to tell a relative or close friend that you are 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 PAROXETINE to work.

Self-harm or suicide:

- Antidepressants, such as PAROXETINE, may 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 PAROXETINE used for?

PAROXETINE is used in adults (18 years of age and older) to relieve symptoms of:

- **Major Depressive Disorder** (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 (with or without agoraphobia)** (panic attacks).
- **Social Phobia (social anxiety disorder)** (avoidance and/or fear of social situations).
- **Generalized Anxiety Disorder** (anxiety or nervousness).
- **Post-Traumatic Stress Disorder** (anxiety following a traumatic event, for example a car crash, physical assault, natural disaster such as an earthquake).

PAROXETINE is not for use in children under 18 years of age.

How does PAROXETINE work?

PAROXETINE belongs to a group of medicines called selective serotonin reuptake inhibitors (SSRIs). PAROXETINE is thought to work by increasing the levels of a chemical in the brain called serotonin (5- hydroxytryptamine). This helps to relieve your symptoms of depression, obsessive compulsive disorder, panic disorder, social phobia, generalized anxiety disorder or post-traumatic stress disorder. PAROXETINE may take a number of weeks to work.

What are the ingredients in PAROXETINE?

Medicinal ingredient: Paroxetine hydrochloride.

Non-medicinal ingredients: anydrous lactose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, sodium starch glycolate, titanium dioxide, and the following colouring agents all extended on an aluminum substrate: D&C yellow #10 and FD&C yellow #6 (10 mg tablets only), D&C red #30 (20 mg tablets only), and FD&C blue #2 (30 mg tablets only).

PAROXETINE comes in the following dosage forms:

- PAROXETINE is available as tablets containing 10 mg (yellow), 20 mg (pink) and a 30 mg (blue) paroxetine (as paroxetine hydrochloride).

Do not use PAROXETINE if:

- you are allergic to paroxetine hydrochloride or to any of the non-medicinal ingredients in PAROXETINE (see "What are the ingredients in PAROXETINE").
- you are currently taking or have recently taken in the last 14 days medicines called monoamine oxidase inhibitors (MAOI) including linezolid (an antibiotic) or methylene blue (a dye injected into a vein during surgery, x-rays or other imaging procedures).
- you are taking or have recently taken thioridazine or pimozide. These medicines are used to treat mental health problems.

Ask your healthcare provider or pharmacist if you are not sure if you take a MAOI or one of these medicines, including the antibiotic linezolid or intravenous methylene blue. Do not start taking a MAOI or thioridazine or pimozide for at least 14 days after you stop treatment with PAROXETINE.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PAROXETINE. Talk about any health conditions or problems you may have, including if you:

- have epilepsy or a history of seizures.
- have a history of liver or kidney problems.
- have heart problems.
- have a history or family history of mania/hypomania or bipolar disorder.
- have depression or other mental health disorders.
- have high cholesterol.
- have low levels of sodium in your blood.
- have had a recent bone fracture or were told you have osteoporosis or risk factors for osteoporosis.
- have a bleeding disorder or have been told that you have low platelets.
- are pregnant or thinking about becoming pregnant, or are breast feeding.
- have a history of alcohol or drug abuse.
- have ever had any allergic reaction to medications, food, etc.
- are allergic to azo dye (FD&C Yellow No. 6 aluminium lake). The 10 mg tablet contains an azo dye component.
- have an eye condition known as narrow angles (the iris and cornea of the eye are closer than normal).

Other warnings you should know about:

Pregnancy: Only take PAROXETINE during pregnancy if you and your **healthcare professional** have discussed the risks and have decided that you should. If you take PAROXETINE near the end of your pregnancy, you are at a higher risk of heavy vaginal bleeding shortly after birth. If you become pregnant while taking PAROXETINE, tell your healthcare professional **right away**.

Effects on newborns: In some cases, babies born to a mother taking PAROXETINE 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 PAROXETINE:

- During early pregnancy, there is a possible slight increased risk that your newborn may have birth defects, particularly 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.

Fertility and sexual function: Taking medicines like PAROXETINE may increase your risk of having sexual problems. This may continue after PAROXETINE has been discontinued, including for months or years afterwards in some cases. Tell your healthcare professional if you experience symptoms such as a decrease in sexual desire, performance or satisfaction. Medicines like PAROXETINE may affect sperm quality. Fertility in some men may be reduced while taking PAROXETINE.

Falls and fractures: PAROXETINE can cause you to feel dizzy or lightheaded and can affect your balance. This increases your risk of falling. In addition PAROXETINE may increase your risk of breaking a bone if you are:

- elderly,
- have osteoporosis, or
- have other major risk factors for breaking a bone.

You should take extra care to avoid falls especially if you get dizzy or have low blood pressure.

Driving and Using Machines: PAROXETINE may make you feel sleepy. Avoid driving a vehicle or using machinery until you know how it affects you.

Angle-closure glaucoma: PAROXETINE can cause an acute attack of glaucoma. Having your eyes examined before you take PAROXETINE could help identify if you are at risk of having angle-closure glaucoma. Seek immediate medical attention if you experience:

- eye pain,
- changes in vision,
- swelling or redness in or around the eye.

Cholesterol and blood tests: PAROXETINE can cause abnormal blood test results, including elevated levels of cholesterol. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Do NOT stop taking PAROXETINE without talking to your healthcare professional first. If stopped abruptly, PAROXETINE may cause unwanted side effects such as:

- light-headedness,
- nausea and vomiting,
- agitation/restlessness,
- anxiety,
- sweating,
- headache,
- sleep disturbance,
- electric shock sensations,
- tinnitus (buzzing, hissing, whistling, ringing or other persistent noise in the ears).

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 PAROXETINE if you are taking or have recently taken any of the following drugs as you may have serious side effects:

- monoamine oxidase inhibitors (MAOIs) such as the antibiotic linezolid and the intravenous dye methylene blue.
- thioridazine (typically used to treat schizophrenia and psychosis).
- pimozide (typically used to manage Tourette's syndrome).

Wait **14 days** after you stop taking a MAOI, or thioridazine, or pimozide before starting PAROXETINE. If you are unsure, ask your healthcare professional.

The following may also interact with PAROXETINE:

- other antidepressants, such as SSRIs, SNRIs, and certain tricyclics.
- other drugs that affect serotonin such as, lithium (used to treat bipolar depression), linezolid (antibiotic), tramadol (used to treat pain), tryptophan (used to treat anxiety or used as a sleep aid), and triptans (used to treat migraines).
- drugs used to prevent fits or treat epilepsy (anticonvulsants), such as carbamazepine, phenytoin, sodium valproate.
- drugs used to treat pain, such as fentanyl (used in anaesthesia or to treat chronic pain), tramadol, tapentadol, meperidine, methadone, and pentazocine.
- drugs used to treat breast cancer or fertility problems, such as tamoxifen.
- drugs used to treat patients with irregular heart beats (arrhythmias).
- drugs used to treat schizophrenia.
- drugs used to treat Human Immunodeficiency Virus (HIV) infection, such as a combination of fosamprenavir and ritonavir.
- drugs used to treat Parkinson's Disease or other movement disorders, such as procyclidine.
- drugs used to treat high blood pressure and angina, such as metoprolol.
- drugs which may affect blood clotting and increase bleeding, such as oral anti-coagulants (e.g. warfarin, dabigatran), acetylsalicylic acid (e.g. aspirin) and other non-steroidal anti- inflammatory drugs (e.g. ibuprofen).
- drugs that affect the central nervous system, such as haloperidol, amylbarbitone, and oxazepam.
- drugs used to treat cough, such as dextromethorphan.
- drug to treat heartburn, such as cimetidine.
- drugs to treat respiratory diseases (chronic obstructive pulmonary disease (COPD) and asthma), such as theophylline.
- any natural or herbal products (e.g. St. John's Wort).
- alcohol.

How to take PAROXETINE:

- It is very important that you take PAROXETINE exactly as your healthcare professional has instructed.
- Take your tablets in the morning, with or without food.
- Swallow the tablet(s) whole with water. Do not chew tablet(s).
- You should continue to take your medicine even if you do not feel better, as it may take a number of weeks for your medicine to work.
- Keep taking your tablets, as instructed, until the healthcare professional tells you to stop.
- Talk to your healthcare professional before you stop taking your medication on your own.

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

Usual dose:

The starting dose of PAROXETINE depends on your illness and current health. It is usually 10 mg or 20 mg once a day in the morning. Your healthcare professional may gradually increase your dose to help control your symptoms, up to a maximum of 50 mg to 60 mg once a day.

Overdose:

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

Missed Dose:

If you forget to take your tablet in the morning, take it as soon as possible, unless it is too close to the time of the next dose. Take your next dose at the normal time the next morning, then carry on as before. Do not try to make up for a missed dose by taking a double dose the next time.

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

Side effects may include:

- blurred vision
- constipation
- diarrhea
- dizziness

- drowsiness
- dry mouth
- feeling agitated
- headache
- loss of appetite
- nausea/vomiting
- nervousness
- sexual problems (decreases in sexual desire, performance and satisfaction, and may also lead to further decreases, which may continue after the drug is stopped)
- skin rash or hives alone
- sleep disturbances (abnormal dreams including nightmares)
- sweating
- tremor (shaking)
- weakness
- weight gain.

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**	
UNCOMMON			
Dilated pupils		✓	
Hallucinations: seeing and hearing things that are not really there		✓	
Hypotension (low blood pressure): dizziness, light-headedness or fainting when standing up from a sitting down or lying position.		✓	
Mania: elevated or irritable mood, decreased need for sleep, racing thoughts, overactive behaviour and thoughts.		✓	
Oedema: swelling of hands, ankles or feet.		✓	
Seizures (fits): uncontrollable shaking with or without loss of consciousness.			✓
Urinary incontinence (involuntary loss of urine)		✓	
Urinary retention (inability to pass urine or to empty the bladder): pain		✓	

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**	
RARE			
Akathisia (a type of movement disorder)**:** feeling restless, unable to sit or stand still.		✓	
Angle-closure glaucoma (eye condition that can cause damage to the optic nerve): increased pressure in your eyes, sudden eye pain, 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 or passing black, tarry stool, blood in the stool.			✓
Hyponatremia (low sodium in blood)**:** tiredness, weakness, muscle twitching, confusion combined with achy, stiff or uncoordinated muscles.		✓	
Liver disorder: nausea, vomiting, loss of appetite combined with itching, yellowing of the skin or eyes, dark urine.		✓	
Photosensitivity (sensitivity to sunlight): itchy, red skin when exposed to sunlight.	✓		
Thrombocytopenia (low platelets): bruising or unusual bleeding from the skin or other areas, bleeding for longer than usual if you hurt yourself, fatigue and weakness.		✓	
VERY RARE			

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**	
Severe allergic reactions: red and lumpy skin rash, hives, itching. swelling of the lips, face, tongue, throat, trouble breathing, wheezing, shortness of breath, skin rashes, collapse or loss of consciousness.			✓
Severe skin reactions (**Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme):** any combination of itchy skin rash, redness, blistering and peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or swollen glands, joint pain, yellowing of the skin or eyes, dark urine.			✓
UNKNOWN FREQUENCY			
Changes in feelings or behaviour: anger, anxiety or violent thoughts		✓	
Increase in the hormone prolactin: In women: breast discomfort, leakage of milk from the breasts, missed periods, or other problems with your menstrual cycle In men: decreased body and facial hair, breast swelling, leakage of milk from the breasts, difficulty in getting or maintaining erections, or other sexual dysfunction.		✓	
Menstrual period disorders: heavy periods, bleeding between periods and absence of periods.		✓	
Restless legs syndrome: irresistible urge to move the legs.		✓	

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**	
Serotonin toxicity (also known as serotonin syndrome) and Neuroleptic Malignant Syndrome (NMS): a combination of most or all of the following: confusion, restlessness, sweating, shaking, shivering, high fever, hallucinations, sudden jerking of the muscles, muscle stiffness, feeling very agitated or irritable, fast heartbeat. The severity can increase, leading to loss of consciousness.			✓
Thoughts or actions about hurting or killing yourself.			✓
Uncontrollable movements of the body or face.		✓	

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

Storage:

- Store at room temperature 15° to 30°C. Protect from moisture.
- Keep container tightly closed.
- If your healthcare professional tells you to stop taking PAROXETINE, please return any leftover medicine to your pharmacist.

- You may need to read this package insert again. Please do not throw it away until you have finished your medicine.
- Keep out of reach and sight of children.

If you want more information about PAROXETINE:

- 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 or by contacting Pro Doc Ltée at: https://www.prodoc.qc.ca, medinfo@prodoc.qc.ca or 1 800 361-8559.

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