PRODUCT MONOGRAPH

[Pr] BIO-PAROXETINE

Paroxetine Tablets USP

10 mg, 20 mg, 30 mg paroxetine (as paroxetine hydrochloride hemihydrate)

Antidepressant – Antiobsessional – Antipanic – Anxiolytic Agent –
Social Phobia (Social Anxiety Disorder) - Posttraumatic Stress Disorder Therapy

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Paroxetine Tablets USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablet 10 mg, 20 mg, 30 mg	Dibasic Calcium Phosphate Dehydrate, Hypromellose, Sodium Starch Glycolate, Magnesium Stearate, Hypromellose, Titanium Dioxide, Macrogol/PEG 400, Polysorbate 80, D&C Yellow No. 10 Aluminum Lake (10mg tablets only), FD&C Yellow No. 6/Sunset Yellow FCF Aluminum Lake (10mg tablets only), D&C Red No. 30 Helindon Pink Aluminum Lake(20mg tablets only), FD&C Blue No. 2-Indigo Carmine Aluminum Lake (30mg tablets only)

INDICATIONS AND CLINICAL USE

Adults

Depression
BIO-PAROXETINE (paroxetine hydrochloride) is indicated for symptomatic relief of Major Depressive Disorder (MDD).

Clinical trials have provided evidence that continuation treatment with paroxetine hydrochloride in patients with moderate to moderately severe depressive disorder is effective for at least 6 months (see Clinical Trials, Depression).

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

Panic Disorder
BIO-PAROXETINE is indicated for the symptomatic treatment of panic disorder, with or without agoraphobia.

Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, i.e., a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

Social Phobia (Social Anxiety Disorder)
BIO-PAROXETINE is indicated for the symptomatic relief of generalized social phobia (social anxiety disorder), a disorder characterized by marked and persistent fear, anxious anticipation, or avoidance of multiple social situations (e.g. interacting with strangers, attending social gatherings, dealing with authority figures) and/or performance situations (e.g. eating, writing, working while being observed, or public speaking). A diagnosis of social phobia/social anxiety disorder should not be made unless the fear, anxious anticipation, or avoidance of social and/or performance situations interferes significantly with the person's normal routine, occupational functioning, social life, or causes marked distress.

Generalized Anxiety Disorder
BIO-PAROXETINE is indicated for the symptomatic relief of anxiety causing significant distress in patients with Generalized Anxiety Disorder (GAD).

Posttraumatic Stress Disorder
BIO-PAROXETINE is indicated for the symptomatic treatment of posttraumatic stress disorder (PTSD).

PTSD as defined by DSM-IV requires exposure to a traumatic event that involved actual or threatened death or serious injury, or threat to the physical integrity of self or others, and a response which involves intense fear, helplessness, or horror. Symptoms that occur as a result of exposure to the traumatic event include reexperiencing of the event in the form of intrusive thoughts, flashbacks or dreams, and intense psychological distress and physiological reactivity on exposure to clues to the event; avoidance of situations reminiscent of the traumatic event, inability to recall details of the event, and/or numbing of general responsiveness manifested as diminished interest in significant activities, estrangement from others, restricted range of affect,

or sense of foreshortened future; and symptoms of autonomic arousal including hypervigilance, exaggerated startle response, sleep disturbance, impaired concentration, and irritability or outbursts of anger.

A diagnosis of PTSD requires that the symptoms are present for at least one month and that they cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Long-Term Use Of Paroxetine Hydrochloride
The effectiveness of paroxetine hydrochloride 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 physician who elects to use paroxetine hydrochloride for extended periods in these indications should periodically re-evaluate the long-term usefulness of the drug for individual patients (see DOSAGE AND ADMINISTRATION, Dosing Considerations).

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 WARNINGS AND PRECAUTIONS Special Populations-Geriatrics, ACTIONS AND CLINICAL PHARMACOLOGY; DOSAGE AND ADMINISTRATION).

Pediatrics (< 18 years of age)
BIO-PAROXETINE is not indicated for use in patients below the age of 18 years (see WARNINGS AND PRECAUTIONS, General, Potential Association With Behavioural and Emotional Changes, Including Self-Harm)

CONTRAINDICATIONS

Hypersensitivity: Paroxetine hydrochloride is contraindicated in patients who are known to be hypersensitive to the drug or any of its components. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

Monoamine Oxidase Inhibitors: In patients receiving serotonin reuptake inhibitors (SSRIs) in combination with a MAO inhibitor, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have begun treatment on a MAO inhibitor. Some cases presented with features resembling serotonin syndrome or neuroleptic malignant syndrome (see WARNINGS AND PRECAUTIONS; Serotonin Syndrome/Neuroleptic Malignant Syndrome). Therefore, paroxetine hydrochloride should not be used in combination with MAO inhibitors [including linezolid, an antibiotic which is a reversible non-selective MAO inhibitor and

methylthioninium chloride (methylene blue)] or within a minimum of 2 weeks of terminating treatment with MAO inhibitors. Treatment with paroxetine hydrochloride should then be initiated cautiously and dosage increased gradually until optimal response is reached. MAO inhibitors should not be introduced within 2 weeks of cessation of therapy with paroxetine hydrochloride.

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.
An *in vivo* study suggests that drugs which inhibit P450 2D6, including certain SSRIs such as paroxetine, fluoxetine and fluvoxamine, will elevate plasma levels of thioridazine. Therefore, paroxetine hydrochloride should not be used in combination with thioridazine or within a minimum of 2 weeks of terminating treatment with thioridazine. At least 2 weeks should be allowed after discontinuing paroxetine hydrochloride therapy before initiating treatment with thioridazine.

Pimozide: The concomitant use of paroxetine hydrochloride and pimozide is contraindicated as paroxetine hydrochloride has been shown to increase plasma pimozide levels. Elevation of pimozide blood concentration may result in QT interval prolongation and severe arrhythmias including torsade de pointes (see Drug Interactions).

WARNINGS AND PRECAUTIONS

General

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

Pediatrics: Placebo-Controlled Clinical Trial Data

- **Recent analyses of placebo-controlled clinical trial safety databases from SSRIs and other newer 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.

Discontinuation Symptoms: Patients currently taking paroxetine hydrochloride 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.

Discontinuation of Treatment with Paroxetine Hydrochloride
When discontinuing treatment, regardless of the indication for which paroxetine hydrochloride 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 ADVERSE REACTIONS, Adverse Events following Discontinuation of Treatment (or Dose Reduction)-Post-Marketing]. 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 ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

Paroxetine Hydrochloride Treatment During Pregnancy Effects on Newborns
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 hydrochloride, consideration should be given to switching to other treatment options. Treatment with paroxetine hydrochloride should only be continued for an individual pregnant patient, if the potential benefits outweigh the potential risks. Initiation of paroxetine, for women who intend to become pregnant, or are in their first trimester of pregnancy, should be considered only after other treatment options have been evaluated (see WARNINGS AND PRECAUTIONS, Special Populations).

Post-marketing reports indicate that some neonates exposed to paroxetine hydrochloride, SSRIs (Selective Serotonin Reuptake Inhibitors), 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. When treating a pregnant woman with paroxetine hydrochloride during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see WARNINGS AND PRECAUTIONS, Special Populations; DOSAGE AND ADMINISTRATION, Special Patient

Populations-Treatment of Pregnant Women During the Third Trimester).

Sexual Dysfunction
Selective serotonin reuptake inhibitors (SSRIs) may cause symptoms of sexual dysfunction (see 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.

Potential for reduced efficacy of Tamoxifen with concomitant SSRI use, including Paroxetine Hydrochloride
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 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 hydrochloride 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.

Psychomotor Impairment
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 hydrochloride does not affect them adversely.

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 hydrochloride. 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 hydrochloride, cannot be excluded, and may be a potential concern for patients with osteoporosis or major risk factors for bone fractures.

The following additional precautions are listed alphabetically.

<u>Carcinogenesis and Mutagenesis</u>
See TOXICOLOGY for animal data.

Cardiovascular
Paroxetine hydrochloride 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.

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

Dependence Liability
Paroxetine hydrochloride has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. Physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of paroxetine hydrochloride.

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 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 including paroxetine hydrochloride may increase the risk of bleeding events by causing abnormal platelet aggregation. Concomitant use of acetylsalicylic acid (ASA), nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin and other anticoagulants may add to 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. Bleeding events related to SSRIs 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 hydrochloride.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of paroxetine hydrochloride and NSAIDs, ASA, or other drugs that affect coagulation (see DRUG INTERACTIONS, Drugs Affecting Platelet Function). Caution is advised in patients with a

history of bleeding disorder or predisposing conditions (e.g. thrombocytopenia) (see ADVERSE REACTIONS).

Hepatic/Biliary/Pancreatic

Hepatic Impairment: Pharmacokinetic studies of paroxetine hydrochloride 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 hydrochloride should be used with caution and dosages restricted to the lower end of the range in patients with clinically significant hepatic impairment (see DOSAGE AND ADMINISTRATION, Special Patient Populations and ACTIONS AND CLINICAL PHARMACOLOGY, Hepatic Insufficiency).

Immune

Hypersensitivity: The 10 mg tablet coating contains an azo dye (FD&C Yellow No. 6/Sunset Yellow FCF Aluminum Lake) which may cause allergic reactions.

Neurologic

Epilepsy: As with other antidepressants, paroxetine hydrochloride 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 hydrochloride. 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 Syndrome/Neuroleptic Malignant Syndrome: On rare occasions serotonin syndrome or neuroleptic malignant syndrome-like events have occured in association with treatment of paroxetine hydrochloride, particularly when given in combination with other serotonergic and/or neuroleptic/antipsychotic drugs. As these syndromes may result in potentially life-threatening conditions, treatment with paroxetine hydrochloride should be discontinued if patients develop a combination of symptoms possibly including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma, and supportive symptomatic treatment should be initiated. Due to the risk of serotonergic syndrome or neuroleptic malignant syndrome paroxetine hydrochloride should not be used in combination with MAO inhibitors [including linezolid, an antibiotic which is a reversible non-selective MAO inhibitor and methylthioninium chloride (methylene blue)] or serotonin precursors (such as L-tryptophan, oxitriptan) and should be used with caution in patients receiving other serotonergic drugs (e.g., triptans, lithium, tramadol, St. John's Wort, most tricyclic antidepressants) or neuroleptics/antipsychotics (see CONTRAINDICATIONS and DRUG INTERACTIONS).

Ophthalmologic

Angle-Closure Glaucoma: As with other antidepressants, paroxetine hydrochloride can cause mydriasis which may trigger an angle-closure attack in a patient with anatomically narrow ocular angles. Caution should be used when paroxetine hydrochloride is prescribed for patients with

untreated narrow angles. Open-angle glaucoma is not a risk factor for angle-closure glaucoma. Patients should be informed to seek immediate medical assistance if they experience eye pain, changes in vision or swelling or redness in or around the eye.

Psychiatric

Suicide: 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. In order to minimize the opportunity for overdosage, prescriptions for paroxetine hydrochloride 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 WARNINGS AND PRECAUTIONS, 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 hydrochloride -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 hydrochloride 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 hydrochloride and ECT have not been studied.

Renal

Hyponatremia: Several cases of hyponatremia have been reported. The hyponatremia appeared to be reversible when paroxetine hydrochloride 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 hydrochloride 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 DOSAGE AND ADMINISTRATION; Special Patient Populations; ACTIONS AND CLINICAL PHARMACOLOGY, Renal Insufficiency).

Sexual Function/Reproduction

Sexual Dysfunction: See WARNING AND PRECAUTIONS, Sexual Dysfunction

Sperm Quality: Some clinical studies have shown that SSRIs (including paroxetine hydrochloride) 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 also Part II: TOXICOLOGY, Reproduction and Impairment of Fertility Studies).

Special Populations

Pregnant Women and Newborns:

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 Hydrochloride: Pregnancy, or intent to become pregnant:
If a patient becomes pregnant while taking paroxetine hydrochloride, or intends to become pregnant, she should be informed of the current estimate of increased risk to the fetus with paroxetine hydrochloride 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 hydrochloride 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 hydrochloride treatment, a gradual reduction in the dose rather than an abrupt cessation is recommended (see WARNINGS AND PRECAUTIONS, Discontinuation of Treatment with Paroxetine hydrochloride, ADVERSE REACTIONS, Adverse Reactions Following Discontinuation of Treatment, and DOSAGE AND ADMINISTRATION, Discontinuation of Treatment).

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 hydrochloride, SSRIs (Selective Serotonin Reuptake Inhibitors), 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 WARNINGS AND PRECAUTIONS, Neurologic-Serotonin Syndrome/Neuroleptic Malignant Syndrome). When treating a pregnant woman with paroxetine hydrochloride during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION, Special Patient Populations-Treatment of Pregnant Women During the Third Trimester).

Risk of PPHN and exposure to SSRIs (including paroxetine):
Epidemiological studies on persistent pulmonary hypertension of the newborn (PPHN) have shown that the use of SSRIs (including paroxetine hydrochloride) 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 in 1997-2005 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).

Nursing Women: 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 physician, breast feeding is necessary, in which case the infant should be closely monitored.

Pediatrics (< 18 years of age): Paroxetine hydrochloride is not indicated for use in patients below the age of 18 years (see WARNINGS AND PRECAUTIONS, Potential Association with Behavioural and Emotional Changes, Including Self Harm). (See also INDICATIONS, Pediatrics; DOSAGE AND ADMINISTRATION, Special Patient Populations-Children).

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 ADVERSE DRUG REACTIONS, Clinical Trial Adverse Drug Reactions-Pediatrics).

Geriatrics (≥ 65 years of age): Administration of paroxetine hydrochloride to the elderly is associated with increased plasma levels and prolongation of the elimination half life relative to younger adults (see ACTION AND CLINICAL PHARMACOLOGY). Elderly patients should be initiated and maintained at the lowest daily dose of paroxetine which is associated with clinical efficacy (see DOSAGE AND ADMINISTRATION). Evaluation of approximately 800 elderly patients (≥ 65 years) treated with paroxetine hydrochloride (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.

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 ADVERSE REACTIONS, Laboratory Changes-Cholesterol and WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Commonly Observed Adverse Events:

The most commonly observed adverse experiences associated with the use of paroxetine hydrochloride 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 Tables 1 and 2).

Adverse Events Leading to Discontinuation of Treatment:

Twenty-one percent of over 4000 patients who received paroxetine hydrochloride 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 hydrochloride 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 hydrochloride 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 hydrochloride (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 hydrochloride 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 WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Clinical Trial Adverse Drug Reactions

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

Incidence in Controlled Clinical Trials

Adults
Multiple doses of paroxetine hydrochloride 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 1 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 2 enumerates adverse events that occurred at a frequency of 2% or more among patients on paroxetine hydrochloride 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 – 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 physician 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 1 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%
	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 Hydrochloride 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 2 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]

		Obsessive-Compulsive Disorder		Panic Disorder		Social Phobia (Social Anxiety Disorder)		Generalized Anxiety Disorder		Posttraumatic Stress Disorder	
Body System	Preferred Term	Paroxetine Hydrochloride (n=542)	Placebo (n=265)	Paroxetine Hydrochloride (n=469)	Placebo (n=324)	Paroxetine Hydrochloride (n=425)	Placebo (n=339)	Paroxetine Hydrochloride (n=735)	Placebo (n=529)	Paroxetine Hydrochloride (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%
Musculoskeletal	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%
	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%

Table 2 (cont'd) 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]

		Obsessive-Compulsive Disorder		Panic Disorder		Social Phobia (Social Anxiety Disorder)		Generalized Anxiety Disorder		Posttraumatic Stress Disorder	
Body System	Preferred Term	Paroxetine Hydrochloride (n=542)	Placebo (n=265)	Paroxetine Hydrochloride (n=469)	Placebo (n=324)	Paroxetine Hydrochloride (n=425)	Placebo (n=339)	Paroxetine Hydrochloride (n=735)	Placebo (n=529)	Paroxetine Hydrochloride (n=676)	Placebo (n=504)
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 Hydrochloride -treated patients are included, except the following events which had an incidence on placebo ≥ Paroxetine Hydrochloride: [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 selective serotonin reuptake inhibitors (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 physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence.

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 3 below.

Table 3 Incidence of Sexual Adverse Events in Controlled Clinical Trials

	Paroxetine Hydrochloride	**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, physicians should routinely inquire about such possible side effects.

Laboratory Changes - Cholesterol

Clinically and statistically relevant increases in cholesterol levels have been noted in studies using paroxetine (see 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.

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 hydrochloride 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.

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 hydrochloride 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 WARNINGS AND PRECAUTIONS, Discontinuation of Treatment With Paroxetine Hydrochloride).

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 hydrochloride -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 hydrochloride. 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 1 and Table 2, 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 hydrochloride, 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.

Immune System Disorders: Very rare were severe allergic reactions (including anaphylactoid reactions and angioedema).

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.

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.

Post-Marketing Adverse Drug Reactions
Adverse events not listed above which have been reported since market introduction in patients taking paroxetine hydrochloride 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, WARNINGS AND PRECAUTIONS, Neurologic-Serotonin Syndrome/Neuroleptic Malignant Syndrome), persistent pulmonary hypertension (PPHN; see also WARNINGS AND PRECAUTIONS, Pregnant Women and Newborns, Risk of PPHN and exposure to SSRIs). There has been a case report of an elevated phenytoin level after 4 weeks of paroxetine hydrochloride and phenytoin co-administration.

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

There have been spontaneous reports of adverse events upon the discontinuation of paroxetine hydrochloride and other selective serotonin reuptake inhibitors (particularly when abrupt) (see, WARNINGS AND PRECAUTIONS, General-Discontinuation of Treatment with Paroxetine hydrochloride and ADVERSE REACTIONS, Adverse Events Following Discontinuation of treatment).

DRUG INTERACTIONS

Serious Drug Interactions

1. **Monoamine Oxidase Inhibitors: See CONTRAINDICATIONS**
2. **Thioridazine: See CONTRAINDICATIONS**
3. **Pimozide: See CONTRAINDICATIONS**

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 hydrochloride (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 hydrochloride is co-administered with drugs with a narrow therapeutic index.

Paroxetine hydrochloride 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 hydrochloride has been associated with decreased levels of paroxetine hydrochloride. When co-administered with cimetidine, paroxetine hydrochloride levels were elevated.

The concomitant use of paroxetine hydrochloride and alcohol has not been studied.

Drug-Drug Interactions

Monoamine Oxidase Inhibitors: Combined use of paroxetine hydrochloride and monoamine oxidase inhibitors [including linezolid, an antibiotic which is a reversible non-selective MAO inhibitor and methylthioninium chloride (methylene blue)] is contraindicated due to the potential for serious reactions with features resembling serotonin syndrome or neuroleptic malignant syndrome (see CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS, Serotonin Syndrome/Neuroleptic Malignant Syndrome).

Thioridazine: Combined use of paroxetine hydrochloride and thioridazine is contraindicated due to a potential for elevated thioridazine plasma levels. Thioridazine treatment alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsade de pointes-type arrhythmias, and sudden death (see CONTRAINDICATIONS).

Pimozide: In an open label study of healthy volunteers, co-administration of a single dose of 2 mg

pimozide, under steady state conditions of paroxetine hydrochloride (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. This is likely explained by the known CYP2D6 inhibitory properties of paroxetine. Due to the narrow therapeutic index of pimozide, and its known ability to prolong the QT interval, and produce severe cardiac arrhythmias including torsade de pointes, concomitant use of pimozide and paroxetine hydrochloride is contraindicated (see CONTRAINDICATIONS).

Neuromuscular Blockers: *In vitro* studies, as well as a small number of clinical reports suggest that some antidepressants including paroxetine may reduce plasma cholinesterase activity resulting in a prolongation of the neuromuscular blocking action of succinylcholine.

Drugs Metabolized by Cytochrome P450 (CYP2D6): In two studies, daily dosing of paroxetine hydrochloride (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 $T_{½}$ (3-5 fold). Concomitant steady-state paroxetine hydrochloride 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 hydrochloride, 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 hydrochloride with other drugs metabolized by CYP2D6 has not been formally studied but may require lower doses than usually prescribed for either paroxetine hydrochloride 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), phenothiazine neuroleptics (e.g. perphenazine), risperidone, atomoxetine, Type IC antiarrhythmics (e.g. propafenone and flecainide), and metoprolol. Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, paroxetine hydrochloride and thioridazine should not be co-administered (see CONTRAINDICATIONS).

Fosamprenavir/ritonavir: 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).

Tamoxifen: Tamoxifen has an important active metabolite, endoxifen, which is produced by CYP2D6 and contributes significantly to the efficacy of tamoxifen. Irreversible inhibition of CYP2D6 by paroxetine leads to reduced plasma concentrations of endoxifen (see WARNINGS AND PRECAUTIONS, Potential for reduced efficacy of Tamoxifen with concomitant SSRI use, including paroxetine hydrochloride).

Drugs Metabolized by Cytochrome P450 (CYP3A4): An *in vivo* interaction study involving the co-administration under steady state conditions of paroxetine hydrochloride and terfenadine, a substrate for CYP3A4, revealed no effect of paroxetine hydrochloride 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.

Microsomal Enzyme Inhibition/Induction: The metabolism and pharmacokinetics of paroxetine hydrochloride may be affected by the induction or inhibition of drug metabolizing enzymes.

Drugs Highly Bound to Plasma Protein: Paroxetine is highly bound to plasma protein, therefore administration of paroxetine hydrochloride 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.

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

Anti-cholinergic Drugs: Paroxetine hydrochloride 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: 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: 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 hydrochloride were reduced by an average of 25 and 38% respectively compared to paroxetine hydrochloride administered alone. The effect of paroxetine hydrochloride on phenobarbital pharmacokinetics was not studied. No initial paroxetine hydrochloride dosage adjustment is considered necessary when co-administered with phenobarbital; any subsequent adjustment should be guided by clinical effect.

Anticonvulsants: In a limited number of patients with epilepsy on long-term treatment with anticonvulsants (carbamazepine 600-900 mg/day, n=6; phenytoin 250-400 mg/day, n=6; sodium valproate 300-2500 mg/day, n=8) the co-administration of paroxetine hydrochloride (30 mg/day for 10 days) had no significant effect on the plasma concentrations of these anticonvulsants. 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. However, no initial dosage adjustment of paroxetine hydrochloride 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. Co-administration of paroxetine hydrochloride with anticonvulsants may be associated with an increased incidence of adverse experiences.

Antipsychotic Drugs/Neuroleptic Malignant Syndrome: As with other SSRIs, paroxetine

hydrochloride should be used with caution in patients already receiving antipsychotics/ neuroleptics, since symptoms suggestive of Neuroleptic Malignant Syndrome cases have been reported with this combination (see WARNINGS AND PRECAUTIONS, Serotonin Syndrome/Neuroleptic Malignant Syndrome).

Serotonergic Drugs: Based on the mechanism of action of paroxetine and the potential for serotonin syndrome, caution is advised when paroxetine hydrochloride is coadministered with other drugs or agents that may affect the serotonergic neurotransmitter systems, such as tryptophan, triptans, serotonin reuptake inhibitors, lithium, fentanyl and its anologues, dextromethorphan, tramadol, tapentadol, meperidine, methadone and pentazocine or St. John's Wort (see WARNINGS AND PRECAUTIONS, Serotonin Syndrome/Neuroleptic Malignant Syndrome). Concomitant use of paroxetine hydrochloride and MAO inhibitors (including linezolid, an antibiotic which is a reversible non-selective MAO inhibitor) is contraindicated (see CONTRAINDICATIONS).

Drugs Affecting Platelet Function (e.g. NSAIDs, ASA and other anticoagulants):
Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID, ASA or other anticoagulants may potentiate the risk of bleeding.

Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs are co-administered with warfarin. Patients receiving warfarin therapy should be carefully monitored when paroxetine hydrochloride is initiated or discontinued (see WARNINGS AND PRECAUTIONS, Hematologic, Abnormal Bleeding).

Lithium: In a study of depressed patients stabilized on lithium, no pharmacokinetic interaction between paroxetine and lithium was observed. However, due to the potential for serotonin syndrome, caution is advised when paroxetine hydrochloride is coadministered with lithium.

Triptans: There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and the 5HT1 agonist, sumatriptan. If concomitant treatment with triptan and an SSRI (e.g. fluoxetine, fluvoxamine, paroxetine, sertraline) is clinically warranted, appropriate observation of the patient is advised. The possibility of such interactions should also be considered if other 5HT1 agonists are to be used in combination with SSRIs (see WARNINGS AND PRECAUTIONS, Serotonin Syndrome/Neuroleptic Malignant Syndrome).

Tryptophan: Tryptophan can be metabolized to serotonin. As with other serotonin reuptake inhibitors, the use of paroxetine hydrochloride together with tryptophan may result in adverse reactions consisting primarily of headache, nausea, sweating and dizziness as well as serotonin syndrome. Consequently, concomitant use of paroxetine hydrochloride with tryptophan is not recommended (see WARNINGS AND PRECAUTIONS, Serotonin Syndrome/Neuroleptic Malignant Syndrome).

CNS Drugs: Experience in a limited number of healthy subjects has shown that paroxetine hydrochloride 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 hydrochloride with neuroleptics have not been studied, the use of paroxetine hydrochloride with these drugs should be approached with caution.

Diazepam: A multiple dose study of the interaction between paroxetine hydrochloride and diazepam showed no alteration in the pharmacokinetics of paroxetine hydrochloride that would warrant changes in the dose of paroxetine hydrochloride for patients receiving both drugs. The effects of paroxetine hydrochloride on the pharmacokinetics of diazepam were not evaluated.

Cardiovascular Drugs: Multiple dose treatment with paroxetine hydrochloride 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: Reports of elevated theophylline levels associated with paroxetine hydrochloride 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: Steady state levels of paroxetine hydrochloride (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 hydrochloride towards the lower end of the range when co-administered with known drug metabolizing enzyme inhibitors.

Drug-Food Interactions
The absorption and pharmacokinetics of paroxetine hydrochloride are not affected by food or antacids.

Drug-Herb Interactions
St. John's Wort: In common with other SSRI's, pharmakodynamic interactions between paroxetine and the herbal remedy St. John's Wort may occur and may result in an increase in undesirable effects.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

General
BIO-PAROXETINE is not indicated for use in children under 18 years of age (see WARNINGS AND PRECAUTIONS, Potential Association with Behavioural and Emotional Changes, Including Self-Harm).

Lower initial doses of BIO-PAROXETINE are recommended for elderly and debilitated patients, and patients with renal or hepatic impairment (see DOSAGE AND ADMINISTRATION, Special Patient Populations).

BIO-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.

Dose Adjustments: Based on pharmacokinetic parameters, steady-state paroxetine plasma levels are achieved over a 7-14 day interval. Hence, dosage adjustments in 10 mg increments should be made at 1-2 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 hydrochloride. 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 CLINICAL TRIALS, Depression).

Discontinuation of Treatment: Symptoms associated with the discontinuation of paroxetine hydrochloride 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 BIO-PAROXETINE is being prescribed. (see WARNINGS AND PRECAUTIONS, Discontinuation of Treatment With Paroxetine Hydrochloride and ADVERSE REACTIONS, Adverse Reactions Following Discontinuation of Treatment).

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

Adults

Depression
Usual Adult Dose: The administration of BIO-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 BIO-PAROXETINE should be initiated at 20 mg/day. The recommended dose of BIO-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 BIO-PAROXETINE in the treatment of panic disorder is 10 mg/day. The recommended dose of BIO-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.

Special Patient Populations
Treatment of 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 BIO-Paroxetine, she should be informed of the current estimate of risk to the fetus (see WARNINGS AND PRECAUTIONS, Special Populations) and consideration should be given to switching to other treatment options. Treatment with BIO-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 WARNINGS AND PRECAUTIONS, Special Populations for more details).

Post-marketing reports indicate that some neonates exposed to paroxetine hydrochloride, SSRIs, or other newer antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see WARNINGS AND PRECAUTIONS, Special Populations). When treating pregnant women with BIO-PAROXETINE during the third trimester, the

physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering BIO-PAROXETINE in the third trimester.

Geriatrics: *(> 65 years):* Administration of paroxetine hydrochloride to the elderly is associated with increased plasma levels and prolongation of the elimination half life relative to younger adults. (see ACTION AND 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.

Pediatrics: **BIO-PAROXETINE is not indicated for use in children under 18 years of age (see INDICATION and WARNINGS AND PRECAUTIONS, Potential Association with Behavioural and Emotional Changes, Including Self-Harm).**

Renal/Hepatic Impairment: Paroxetine hydrochloride 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 WARNINGS and PRECAUTIONS; ACTION AND CLINICAL PHARMACOLOGY).

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 of Overdosage

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, paraethesia, 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 of Overdosage

The physician 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 hydrochloride, 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 hydrochloride 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.

ACTION AND CLINICAL PHARMACOLOGY

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 (α_1, α_2, β), dopaminergic, serotonergic ($5HT_1$, $5HT_2$), 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.

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 4). 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 (2D6). 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 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 4). Elderly patients should, therefore, be initiated and maintained at the lowest daily dosage of paroxetine which is associated with clinical efficacy (See DOSAGE AND ADMINISTRATION).

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 4). As the elimination of paroxetine is dependent upon extensive hepatic metabolism, its use in patients with hepatic impairment should be undertaken with caution. (see DOSAGE AND ADMINISTRATION, Special Patient Populations).

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 5). As multiple-dose pharmacokinetic studies have not been performed in patients with renal disease, paroxetine should be used with caution in such patients (see DOSAGE AND ADMINISTRATION, Special Patient Populations).

TABLE 4 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 5 Pharmacokinetics of paroxetine after a single 30 mg dose in normal subjects and those with renal impairment

	[a]Renally Impaired Severe [n=6]	[b]Renally Impaired 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)
AUC4 (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

STORAGE AND STABILITY

Store at 15-30°C

DOSAGE FORMS, COMPOSITION AND PACKAGING

BIO-PAROXETINE is available as film coated, oval biconvex tablets containing paroxetine hydrochloride equivalent to 10 mg (yellow tablets), 20 mg (pink tablets), 30 mg (blue tablets), paroxetine free base. The tablets have the PA engraved on one side and strength engraved on the other side. The 10 and 20 mg tablets are bisected. BIO-PAROXETINE 10 mg and 30 mg tablets are available in bottles of 100's. BIO-PAROXETINE 20 mg available in bottles of 100's and 500's.

Composition

BIO-PAROXETINE tablets contain either 10 mg, 20 mg or 30 mg of paroxetine (as paroxetine

hydrochloride hemihydrate). The tablets also contain the following non-medicinal ingredients: Dibasic Calcium Phosphate Dehydrate, Hypromellose, Sodium Starch Glycolate, Magnesium Stearate, Hypromellose, Titanium Dioxide, Macrogol/PEG 400, Polysorbate 80, D&C Yellow No. 10 Aluminum Lake (10mg tablets only), FD&C Yellow No. 6 / Sunset Yellow FCF Aluminum Lake (10mg tablets only), D&C Red No. 30 Helindon Pink Aluminum Lake(20mg tablets only), FD&C Blue No. 2-Indigo Carmine Aluminum Lake (30mg tablets only).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

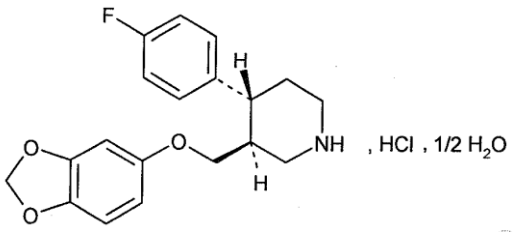
Proper Name: Paroxetine hydrochloride

Chemical Name: (3S-trans)-3-[(1,3-Benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine hydrochloride hemihydrate.

Molecular Formula: $C_{19}H_{21}ClFNO_3 \cdot \frac{1}{2} H_2O$.

Molecular Weight: 374.8 (as hemihydrate salt)

Structural Formula:



paroxetine hydrochloride hemihydrate

Physicochemical properties:

Description: a white to almost white crystalline powder

Melting point: 140°C – 147°C

pH: 5.0 to 6.0

Specific optical rotation: -86° to -91°

CLINICAL TRIALS

A double blind, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study of BIO-PAROXETINE (paroxetine hydrochlorides) 30mg tablets of Biomed Pharma, and PrPAXIL® (paroxetine hydrochloride) 30mg tablets of GlaxoSmithKline Inc. in 28 healthy, adult, Asian, male subjects under fasting conditions.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Paroxetine (1 x 30 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval
AUC_T‡ (ng*h/ml)	136.76 198.84 (87.375)	146.66 215.72 (88.36)	93.25	85.01 – 102.29
AUC_I (ng*h/ml)	153.63 243.88 (115.95)	162.32 249.58 (102.49)	94.64	86.76 – 103.25
C_{max} (ng /ml)	7.12 8.60 (60.00)	7.70 9.37 (57.13)	92.39	85.45 – 99.89
T_{max}§ (h)	6.00 (5.00-7.00)	6.33 (5.00-7.50)		
$T_{½}$€ (h)	17.05 (75.57)	15.44 (48.92)		

* BIO-PAROXETINE tablets by Biomed Pharma,
† Paxil tablets (manufactured by Glaxo Smithkline Inc), purchased in Canada.
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV%) only

Depression

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 studies, paroxetine hydrochloride 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 hydrochloride (HDRS total score < 8) during an initial 8-week open-treatment phase and were then randomized to continuation on paroxetine hydrochloride or placebo for 1 year demonstrated that a significantly lower proportion of patients treated with paroxetine hydrochloride (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 hydrochloride treated patients (12%) compared to placebo treated patients (28%). Effectiveness was similar for male and female patients.

Obsessive-Compulsive Disorder

Three double-blind, placebo -controlled clinical trials of 12 weeks in duration have been performed to investigate the efficacy of paroxetine hydrochloride 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 hydrochloride in terms of mean change from baseline to endpoint on the Yale-Brown Obsessive-Compulsive Scale and/or the National Institute of Mental Health Obsessive-Compulsive Scale. 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 hydrochloride response rates were 45% (89/198) and 35% (28/79), respectively.

Panic Disorder

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 hydrochloride 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 hydrochloride 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 hydrochloride group, 57% (35/61) for the 20 mg/day paroxetine hydrochloride group, and 76% (47/62) for the 40 mg/day paroxetine hydrochloride group.

[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).

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 hydrochloride in social phobia (social anxiety disorder). These studies showed statistically significant differences from placebo in favour of paroxetine hydrochloride 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 hydrochloride response rates were 54.9% (50/91) and 65.7% (90/137), respectively.

Generalized Anxiety Disorder

The effectiveness of paroxetine hydrochloride 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 hydrochloride 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 hydrochloride (20 to 50 mg/day), and placebo on the primary outcome measure. However, paroxetine hydrochloride (20 to 50 mg/day) was more effective than placebo on many secondary study outcomes.

Posttraumatic Stress Disorder

The efficacy of paroxetine hydrochloride 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. 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).

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

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

DETAILED PHARMACOLOGY

Animal Pharmacology

***In vitro*:** Paroxetine showed a high potency for the inhibition of 5-HT reuptake in rat hypothalamic synaptosomes (Ki=1.1nM), but exerted relatively weak effects upon noradrenaline reuptake (Ki=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 (Ki 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 α1, α2 and β-adrenoceptors, dopamine (D2), 5-HT1-like, 5-HT2 and histamine (H1) 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 (ED50=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 (ED50=0.4 mg/kg p.o.). In rats, paroxetine (ED50=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, 1-7.5 mg/kg p.o. in monkeys and 10 to 50 mg orally to healthy human volunteers. Similarly, whole blood 5-HT levels were shown to be depleted in depressed patients after paroxetine administration.

Human Pharmacology

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.

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.

Reproduction and Impairment of Fertility Studies

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.

Teratology Studies

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.

Immunotoxicity Studies

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.

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65. Paxil® Product Monograph, Submission Control No.: 237146, Date of Revision: June 18, 2020.

PART III: CONSUMER INFORMATION

Pr BIO-PAROXETINE
Paroxetine Tablets USP

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

Please read this information before you start to take your medication, even if you have taken this drug before. Keep this information with your medicine in case you need to read it again.

ABOUT THIS MEDICATION

What the medication is used for:
BIO-PAROXETINE has been prescribed to you by your doctor to relieve your symptoms of:

- depression (feeling sad, a change in appetite or weight, difficulty concentrating or sleeping, feeling tired, headaches, unexplained aches and pain)
- panic attacks
- social phobia (social anxiety disorder) - avoidance and/or fear of social situations
- generalized anxiety or nervousness
- obsessive compulsive disorder (recurrent and intrusive thought, feeling, idea or sensation; recurrent pattern of behaviour, or unwanted thoughts or actions), or
- posttraumatic stress disorder (anxiety following a traumatic event, for example a car crash, physical assault, natural disaster such as an earthquake)

What it does:
BIO-PAROXETINE belongs to the family of medicines called selective serotonin reuptake inhibitors. BIO-PAROXETINE is thought to work by increasing the levels of a chemical in the brain called serotonin (5-hydroxytryptamine).

When it should not be used:
Do not use BIO-PAROXETINE if you are:

- allergic to it or any of the components of its formulation (see list of components at the end of this section)
- currently taking or have recently taken monoamine oxidase (MAO) inhibitor antidepressants (e.g. phenelzine sulphate, moclobemide) or linezolid, a MAO inhibitor antibiotic
- currently taking or have recently taken thioridazine or pimozide

What the medicinal ingredient is:
Paroxetine hydrochloride

What the nonmedicinal ingredients are:
Dibasic Calcium Phosphate Dehydrate, Hypromellose, Sodium Starch Glycolate, Magnesium Stearate, Opadry Yellow, Opadry Pink and Opadry Blue.
Hypromellose, Titanium Dioxide, Macrogol/PEG 400, Polysorbate 80, D&C Yellow No. 10 Aluminum Lake (10mg tablets only), FD&C Yellow No. 6 Sunset Yellow FCF Aluminum Lake (10mg tablets only), D&C Red No. 30 Helindon Pink Aluminum Lake(20mg tablets only), FD&C Blue No. 2-Indigo Carmine Aluminum Lake (30mg tablets only)

What dosage forms it comes in:
BIO-PAROXETINE is available as tablets containing 10 mg (yellow), 20 mg (pink), or 30 mg (blue) paroxetine (as paroxetine hydrochloride).

WARNINGS AND PRECAUTIONS

During treatment with these types of medications it is important that you and your doctor have good ongoing communication about how you are feeling.

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

Changes in Feelings and Behaviour:
It is important that you have good communication with your doctor about how you feel. Discussing your feelings and treatment with a friend or relative who can tell you if they think you are getting worse is also useful.

Some patients may feel worse when first starting or changing the dose of drugs such as BIO-paroxetine. You may feel more anxious or may have thoughts of hurting yourself or others, especially if you have had thoughts of hurting yourself before. These changes in feelings can happen in patients treated with drugs like paroxetine for any condition, and at any age, although it may be more likely if you are aged 18 to 24 years old. **If this happens, see your doctor immediately.** Do not stop taking BIO-PAROXETINE on your own.

Taking medicines like BIO-PAROXETINE may increase your risk of experiencing sexual problems, which may continue after BIO-PAROXETINE has been discontinued, including for months or years afterwards in some cases. Tell your doctor if you experience symptoms such as a decrease in sexual desire, performance or satisfaction.

Taking BIO-PAROXETINE may increase your risk of breaking a bone if you are elderly or 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.

Medicines like BIO-PAROXETINE may affect your sperm. Fertility in some men may be reduced while taking BIO-PAROXETINE.

BEFORE you use BIO-PAROXETINE tell your doctor or pharmacist:

- all your medical conditions, including a history of seizures, liver or kidney disease, heart problems
- any medications (prescription or non prescription) which you are taking or have recently taken, especially monoamine oxidase inhibitor antidepressants (e.g. phenelzine sulphate, moclobemide) or any other antidepressants, thioridazine, pimozide, drugs used to prevent fits (anticonvulsants), drugs for Parkinson's disease, or drugs containing tryptophan
- if you are taking tamoxifen (used to treat breast cancer)
- if you have ever had any allergic reaction to medications, food, etc.
- any natural or herbal products you are taking (e.g. St. John's Wort)
- if you are pregnant or thinking about becoming pregnant, or if you are breast feeding
- your habits of alcohol and /or street drug consumption
- if you drive a vehicle or perform hazardous tasks during your work
- if you had a recent bone fracture or were told you have osteoporosis or risk factors for osteoporosis

□ if you have a bleeding disorder or have been told that you have low platelets

□ if you are allergic to a particular yellow dye known as FD&C Yellow No. 6/Sunset Yellow FCF Aluminum Lake

Effects on Pregnancy and Newborns:
As stated above, ask your doctor or pharmacist for advice before taking any medicine including BIO-PAROXETINE. **If you are already taking/using BIO-PAROXETINE and have just found out that you are pregnant, you should talk to your doctor immediately. You should also talk to your doctor if you are planning to become pregnant.**

Taking BIO-PAROXETINE in early stages of pregnancy:
Some studies have suggested an increased risk of birth defects particularly heart defects, in babies whose mothers received paroxetine hydrochloride in the first few months of pregnancy. These studies found that about 2 in 100 babies (2%) whose mothers received paroxetine in early pregnancy had a heart defect, compared with the normal rate of 1 in 100 babies (1%) seen in the general population. Also, in cases where paroxetine hydrochloride has been used, there have been reports of premature births although it is not known if these premature births are due to the use of paroxetine hydrochloride.

Taking BIO-PAROXETINE in later stages of pregnancy:
Possible complications at birth (from taking any newer antidepressant, including BIO-PAROXETINE):
Post-marketing reports indicate that some newborns whose mothers took an SSRI (selective serotonin reuptake inhibitor) or other newer antidepressant, during pregnancy have developed complications at birth requiring prolonged hospitalization, breathing support and tube feeding. Reported symptoms included feeding and/or breathing difficulties, seizures, tense or overly relaxed muscles, jitteriness and constant crying.

In most cases, the newer antidepressant was taken during the third trimester of pregnancy. These symptoms are consistent with either a direct adverse effect of the antidepressant on the baby, or possibly a discontinuation syndrome caused by sudden withdrawal from the drug. These symptoms normally resolve over time. However, if your baby experiences any of these symptoms, contact your doctor as soon as you can.

Persistent Pulmonary Hypertension (PPHN) and newer antidepressants, including BIO-PAROXETINE:
The use of BIO-PAROXETINE during pregnancy, particularly during late pregnancy, may increase the risk of a serious lung condition called persistent pulmonary hypertension of the newborn (PPHN) that causes breathing difficulties in newborns soon after birth. In the general population, PPHN is known to occur in about 1 or 2 per 1000 newborns but this may be increased 4 to 6 times in babies whose mothers used paroxetine hydrochloride during late pregnancy.

If you are pregnant and taking an SSRI, or other newer antidepressants, you should discuss the risks and benefits of the various treatment options with your doctor. It is very important that you do NOT stop taking these medications without first consulting your doctor. See SIDE EFFECTS AND WHAT TO DO ABOUT THEM section for more information.

Angle-closure Glaucoma:
BIO-PAROXETINE can cause an acute attack of glaucoma. Having your eyes examined before you take BIO-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

INTERACTIONS WITH THIS MEDICATION

Do not use BIO-PAROXETINE if you are taking or have recently taken (within the last 2 weeks) monoamine oxidase inhibitors, methylthioninium chloride (methylene blue), thioridazine, or pimozide .

You should tell your doctor if you are taking or have recently taken any medications (prescription, non-prescription or natural/herbal), especially:

- other antidepressants, such as SSRIs and certain tricyclics
- other drugs that affect serotonin such as, lithium, linezolid, tramadol, tryptophan, St. John's Wort, triptans used to treat migraines
- certain medicines used to treat pain, such as fentanyl (used in anaesthesia or to treat chronic pain), tramadol, tapentadol, meperidine, methadone, pentazocine
- tamoxifen, which is used to treat breast cancer or fertility problems
- certain medicines used to treat patients with irregular heart beats (arrhythmias)
- certain medicines used to treat schizophrenia
- certain medicines used to treat bipolar depression, such as lithium
- a combination of fosamprenavir and ritonavir, used to treat Human Immunodeficiency Virus (HIV) infection
- procyclidine, which is used to treat Parkinson's Disease or other movement disorders
- metoprolol, which is used to treat high blood pressure and angina
- certain medicines 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)
- certain medicines used to treat epilepsy
- in general, drinking alcoholic beverages should be kept to a minimum or avoided completely while taking BIO-PAROXETINE
- certain medicines used to treat cough, such as dextromethorphan

PROPER USE OF THIS MEDICATION

Usual dose:

- It is very important that you take BIO-PAROXETINE exactly as your doctor has instructed. Generally most people take between 20 mg to 40 mg of BIO-PAROXETINE per day for depression, obsessive-compulsive disorder, panic disorder, social phobia (social anxiety disorder), generalized anxiety disorder and posttraumatic stress disorder; although your doctor may start you at 10 mg per day for panic disorder
- Take your tablets in the morning, preferably with food. You should swallow the tablets whole with water. Do not chew them
- 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 doctor tells you to stop
- Talk to your doctor 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.

Missed Dose:

If you forget to take your tablet in the morning, take it as soon as you remember. 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.

Overdose:

If you have taken a large number of tablets all at once, contact your doctor or the nearest hospital emergency department immediately, even though you may not feel sick. Show the doctor your pack of tablets.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medications, BIO-PAROXETINE can cause some side effects. You may not experience any of them. For most patients these side effects are likely to be minor and temporary. However, some may be serious. Some of these side effects may be dose related. Consult your doctor if you experience these or other side effects, as the dose may have to be adjusted.

If you experience an allergic reaction (including skin rash, hives, swelling, trouble breathing) or any severe or unusual side effects, stop taking the drug and contact your doctor immediately.

The most common side effects of BIO-PAROXETINE are:

- nausea/vomiting
- dry mouth
- drowsiness
- weakness
- dizziness
- sweating
- tremor
- nervousness
- feeling agitated
- blurred vision

- sleep disturbances
- weight gain
- sexual problems
- Although psychiatric disorders are often associated with decreases in sexual desire, performance and satisfaction, treatment with this medication may lead to further decreases.

Other effects may include loss of appetite, constipation, diarrhea, abnormal dreams (including nightmares), headache and menstrual period disorders (including heavy periods, bleeding between periods and absence of periods).

Paroxetine hydrochloride does not usually affect people's normal activities. However, some people feel sleepy while taking it, in which case they should not drive or operate machinery.

BIO-PAROXETINE may raise cholesterol levels in some patients.

Discontinuation Symptoms

Contact your doctor before stopping or reducing your dosage of BIO-PAROXETINE. Symptoms such as dizziness, lightheadedness, nausea, vomiting, agitation/restlessness, anxiety, sweating, headache, sleep disturbance, electric shock sensations, tinnitus (buzzing, hissing, whistling, ringing or other persistent noise in the ears) and other symptoms have been reported after stopping treatment, reducing the dosage of paroxetine hydrochloride, or when a dose is missed. These symptoms usually disappear without needing treatment. Tell your doctor immediately if you have these or any other symptoms. Your doctor may adjust the dosage of BIO-PAROXETINE to alleviate the symptoms. See WARNINGS AND PRECAUTIONS section for more information.

Effects on Newborns

Some newborns whose mothers took an SSRI (Selective Serotonin Reuptake Inhibitor) or other newer antidepressant, such as BIO-PAROXETINE, during pregnancy have shown such symptoms as breathing and feeding difficulties, jitteriness and constant crying. If your baby experiences any of these symptoms, contact your doctor as soon as you can. See WARNINGS AND PRECAUTIONS section for more information.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist right away		Seek immediate emergency medical assistance
		Only if severe	In all cases	
Unc	Hallucinations [strange visions or sounds]		✓	
	Uncontrollable movements of the body or face		✓	
	Inability to urinate or loss of control of the bladder (*urinary incontinence*)		✓	
	Dilated pupils		✓	
	Low blood pressure (may cause dizziness, lightheadedness or fainting when standing up from a sitting down or lying position)		✓	
	Low Platelets [bruising or unusual bleeding from the skin or other areas]		✓	
Rare	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]			✓
	Allergic reactions (skin rash alone)		✓	
	Low sodium level in blood [symptoms of tiredness, weakness, confusion combined with achy, stiff or uncoordinated muscles]		✓	
	Akathisia [feeling restless and unable to sit or stand still]		✓	
	Mania [overactive behaviour and thoughts]		✓	
	Seizures [loss of consciousness with uncontrollable shaking ("fit")]			✓
	Restless Legs Syndrome (irresistible		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist right away		Seek immediate emergency medical assistance
		Only if severe	In all cases	
	urge to move the legs)			
	Angle-closure Glaucoma [eye pain, changes in vision and swelling or redness in or around the eye]			✓
	Abnormal secretion of breast milk in men and women		✓	
	Increased sensitivity of the skin to sunlight	✓		
	Swelling of hands, ankles or feet		✓	
	Menstrual period disorders (including heavy periods, bleeding between periods and absence of periods).		✓	
Very Rare	Serotonin syndrome and Neuroleptic Malignant Syndrome [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.			✓
	Gastrointestinal bleeding [vomiting blood or passing blood in stools]			✓
	Liver disorder [symptoms include nausea, vomiting, loss of appetite combined with itching, yellowing of the skin or eyes, dark urine]		✓	
	A severe wide spread rash with blisters and peeling skin, often with sores or pain in the mouth or eyes.			
	Skin rash, which may blister, and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) called erythema multiforme			✓
See Warnings & Precautions	- Changes in feelings or behaviour (anger, anxiety, suicidal or violent thoughts) - Thoughts of death or suicide		✓	✓

This is not a complete list of side effects. For any unexpected effects while taking BIO-PAROXETINE**,** *contact your doctor or pharmacist.*

HOW TO STORE IT

- Keep all medicines out of sight and reach of children.
- Store at room temperature (15-30°C) in a dry place
- Keep container tightly closed.
- If your doctor tells you to stop taking BIO-PAROXETINE please return any leftover medicine to your pharmacist.

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 (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

MORE INFORMATION

You may need to read this package insert again. Please do not throw it away until you have finished your medicine. This document plus the full product monograph, prepared for health professionals by contacting the sponsor.
Biomed Pharma at 1-888-731-6703 or info@biomed-pharma.ca.

This leaflet was prepared by:
Biomed Pharma

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