PRODUCT MONOGRAPH

[Pr] SANDOZ PAROXETINE

Paroxetine Hydrochloride

Tablets 10, 20 and 30 mg

Manufacturer's Standard

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

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Paroxetine Hydrochloride tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	Nonmedicinal Ingredients
Oral	Tablet / 10 mg, 20 mg, 30 mg	microcrystalline cellulose, mannitol, copovidone, sodium starch glycolate, silica colloidal anhydrous, magnesium stearate, hypermellose, talc, titanium dioxide, lemon yellow #10 (10mg only) sunset yellow # 6 (10mg only), allura red lake # 40 (20 and 30 mg), brilliant blue lake (20 and 30 mg), indigotine lake (20 and 30 mg)

INDICATIONS AND CLINICAL USE

Adults
Depression
Sandoz Paroxetine (paroxetine hydrochloride) is indicated for symptomatic relief of Major Depressive Disorder (MDD).

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

Obsessive-Compulsive Disorder
Sandoz 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
Sandoz 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)
Sandoz 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
Sandoz Paroxetine is indicated for the symptomatic relief of anxiety causing significant distress in patients with Generalized Anxiety Disorder (GAD).

Posttraumatic Stress Disorder
Sandoz 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 Sandoz Paroxetine
The effectiveness of paroxetine in long-term use (i.e. more than 8 weeks for GAD and 12 weeks for other indications) has not yet been established in controlled trials for OCD, panic disorder, social phobia (social anxiety disorder), generalized anxiety disorder and posttraumatic stress disorder. Therefore, the physician who elects to use Sandoz Paroxetine 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):
Sandoz Paroxetine is not indicated for use in patients below the age of 18 years (see WARNINGS AND PRECAUTIONS, General, Potential Association with Behavioral and Emotional Changes, Including Self-Harm)

CONTRAINDICATIONS

Hypersensitivity: Sandoz Paroxetine 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, Sandoz Paroxetine 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 Sandoz Paroxetine 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.

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, Sandoz Paroxetine 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 therapy before initiating treatment with thioridazine.

Pimozide: The concomitant use of Sandoz Paroxetine and pimozide is contraindicated as paroxetine has been shown to increase plasma pimozide levels. Elevation of pimozide blood concentration may result in QT interval prolongation and severe arrhythmias including torsade de pointes (see 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 behavioral and emotional changes, including an increased risk of suicidal ideation and behavior over that of placebo.**

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

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 behavior is advised in patients of all ages. This includes monitoring for agitation-type emotional and behavioral changes.

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

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

Discontinuation of Treatment with Sandoz Paroxetine
When discontinuing treatment, regardless of the indication for which Sandoz Paroxetine is being prescribed, patients should be monitored for symptoms which may be associated with discontinuation (e.g. dizziness, sleep disturbances including abnormal dreams, sensory disturbances (including paresthesias electric shock sensations and tinnitus), agitation, anxiety, headache, tremor, confusion, diarrhea, nausea, vomiting and sweating or other symptoms which may be of clinical significance [see 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).

Sandoz Paroxetine 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 Sandoz Paroxetine, consideration should be given to switching to other treatment options. Treatment with Sandoz Paroxetine should only be continued for an individual pregnant patient if the potential benefits outweigh the potential risks. Initiation of Sandoz 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, 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 Sandoz Paroxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see WARNINGS AND PRECAUTIONS, Special Populations and DOSAGE AND ADMINISTRATION, Special Patient Populations, Treatment of Pregnant Women during the Third Trimester).

Potential for reduced efficacy of Tamoxifen with concomitant SSRI use, including paroxetine
The antitumor agent tamoxifen is a pro-drug requiring metabolic activation by CYP2D6. Inhibition of CYP2D6 can lead to reduced plasma concentrations of a primary active metabolite (endoxifen). Chronic use of CYP2D6 inhibitors, including certain SSRIs, together with tamoxifen can lead to persistent reduction in levels of endoxifen (see also DRUG INTERACTIONS, Tamoxifen). Some studies have shown that the efficacy of tamoxifen, as measured by the risk of breast cancer relapse/mortality, may be reduced when coprescribed with paroxetine as a result of paroxetine's irreversible inhibition of CYP2D6. This risk may increase with longer duration of coadministration. When tamoxifen is used for

the treatment of breast cancer, prescribers should consider using an alternative antidepressant with little or no CYP2D6 inhibition.

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 Sandoz Paroxetine 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 Sandoz Paroxetine. Elderly patients and patients with important risk factors for bone fractures should be advised of possible adverse events which increase the risk of falls, such as dizziness and orthostatic hypotension, especially at the early stages of treatment but also soon after withdrawal. Preliminary data from observational studies show association of SSRIs and low bone mineral density in older men and women. Until further information becomes available, a possible effect on bone mineral density with long term treatment with SSRIs, including paroxetine, cannot be excluded, and may be a potential concern for patients with osteoporosis or major risk factors for bone fractures.

The following additional precautions are listed alphabetically.

Carcinogenesis and Mutagenesis
See TOXICOLOGY for animal data.

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

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

Dependence Liability
Paroxetine 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 Sandoz Paroxetine.

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 n=653 paroxetine-treated patients, 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 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 (casecontrol 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 Sandoz Paroxetine.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of Sandoz Paroxetine 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 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. Sandoz Paroxetine 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).

Neurologic

Epilepsy: As with other antidepressants, Sandoz Paroxetine should be used with caution in patients with epilepsy.

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

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

Serotonin Syndrome/Neuroleptic Malignant Syndrome: On rare occasions serotonin syndrome or neuroleptic malignant syndrome-like events have occurred in association with treatment of paroxetine, 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 Sandoz Paroxetine 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 Sandoz Paroxetine 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, Sandoz Paroxetine can cause mydriasis which may trigger an angle-closure attack in a patient with anatomically narrow ocular angles. Caution should be used when Sandoz Paroxetine 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 behaviors (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 Sandoz Paroxetine should be written for the smallest quantity of drug consistent with good patient management.

Because of the well established comorbidity between depression and other psychiatric disorders, the same precautions observed when treating patients with depression should be observed when treating patients with other psychiatric disorders (see WARNINGS AND PRECAUTIONS, Potential Association with Behavioral and Emotional Changes, Including Self-Harm).

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

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

Electroconvulsive Therapy (ECT): The efficacy and safety of the concurrent use of paroxetine and ECT have not been studied.

Renal

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

Renal Impairment: Since paroxetine is extensively metabolized by the liver, excretion of unchanged drug in urine is a minor route of elimination. However, single dose pharmacokinetic studies in subjects with clinically significant renal impairment suggest that plasma levels of paroxetine are elevated in such subjects. Paroxetine hydrochloride 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

Some clinical studies have shown that SSRIs (including paroxetine) may affect sperm quality. This effect appears to be reversible following discontinuation of treatment. Changes in sperm quality may affect fertility in some men (see 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: Pregnancy, or intent to become pregnant:
If a patient becomes pregnant while taking Sandoz Paroxetine, or intends to become pregnant, she should be informed of the current estimate of increased risk to the fetus with paroxetine over other antidepressants. Examinations of additional databases, as well as updated analyses, may result in changes to the current risk estimates. Consideration should be given to switching to other treatment options, including another antidepressant or non-pharmaceutical treatment such as cognitive behavioral therapy. Treatment with Sandoz Paroxetine should only be continued for an individual patient, if the potential benefits outweigh the potential risks.

Due to the potential for discontinuation symptoms, if a decision is taken to discontinue Sandoz Paroxetine treatment, a gradual reduction in the dose rather than an abrupt cessation is recommended (see WARNINGS AND PRECAUTIONS, Discontinuation of Treatment with Paroxetine, 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 Sandoz Paroxetine should be considered only after other treatment options have been evaluated.

Complications following late third trimester exposure to SSRIs:
Post-marketing reports indicate that some neonates exposed to paroxetine, SSRIs (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 Sandoz Paroxetine 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) 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 831324 infants born in 1997 to 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 Sandoz 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): Sandoz Paroxetine is not indicated for use in patients below the age of 18 years (see **WARNINGS AND PRECAUTIONS, Potential Association with Behavioral and Emotional Changes, Including Self Harm).** See also INDICATIONS, Pediatrics and 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 behavioral 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 pre-marketing 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 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 in worldwide clinical trials in depression discontinued treatment due to an adverse experience. In obsessive-compulsive disorder, panic disorder, social phobia (social anxiety disorder), generalized anxiety disorder and posttraumatic stress disorder studies, 11.8% (64/542), 9.4 % (44/469), 16.1% (84/522) 10.7% (79/735) and 11.7% (79/676), respectively, of patients treated with paroxetine discontinued treatment because of adverse events. The most common events leading to discontinuation (reported by 1% or more of subjects) included: asthenia, headache, nausea, somnolence, insomnia, agitation, tremor, dizziness, constipation, impotence, abnormal ejaculation, sweating and diarrhea.

Adverse Events following Discontinuation of Treatment (or Dose Reduction)

Clinical Trials:

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

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

Post-Marketing:

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

Patients should be monitored for these or any other symptoms when discontinuing treatment, regardless of the indication for which paroxetine is being prescribed. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response (see 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 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 (20-50 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 who participated in placebo-controlled OCD trials of 12-weeks duration in which patients were dosed in the range of 20 to 60 mg/day, in placebo-controlled panic disorder trials of 10 to 12-weeks duration in which patients were dosed in the range of 10 to 60 mg/day, in placebo-controlled social phobia (social anxiety disorder) trials of 12 weeks duration in which patients were dosed in a range of 20 to 50 mg/day, in placebo-controlled generalized anxiety disorder trials of 8 weeks in which patients were dosed in a range from 10 to 50 mg/day and in placebo-controlled posttraumatic stress disorder trials of 12 weeks in which patients were dosed in a range from 20 to 50 mg/day.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly the cited incidences cannot be compared with figures obtained from other clinical investigations involving

different treatments, uses and investigators. The cited frequencies do however provide the prescribing 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%
	Paresthesia	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%

Body System	Preferred Term	Paroxetine (n=421)	Placebo (n=421)
	Taste Perversion	2.4%	0.2%
Urogenital System	*Abnormal Ejaculation[+]	12.9%	0.0%
	*Male Genital Disorders[4]	8.0%	0.0%
	Urinary Frequency	3.1%	0.7%
	Urination Impaired[5]	2.9%	0.2%
	*Impotence	2.5%	0.5%
	*Female Genital Disorders[6]	1.8%	0.0%

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

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

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

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

[3] Includes mostly cold symptoms or URI.

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

[5] Includes difficulty with micturition and urinary hesitancy.

[6] Includes anorgasmia and difficulty reaching climax/orgasm.

Table 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 (n=542)	Placebo (n=265)	Paroxetine (n=469)	Placebo (n=324)	Paroxetine (n=425)	Placebo (n=339)	Paroxetine (n=735)	Placebo (n=529)	Paroxetine (n=676)	Placebo (n=504)
Body as a Whole	Headache	25.3%	29.1%	25.4%	25.3%	22.4%	21.8%	16.9%	14.0%	18.9%	19.2%
	Asthenia	21.8%	13.6%	13.6%	4.6%	22.4%	13.6%	14.3%	6.4%	11.8%	4.2%
	Infection	5.4%	4.9%	5.3%	6.8%	3.8%	5.9%	5.6%	3.4%	4.9%	3.8%
	Abdominal Pain	4.8%	4.9%	4.3%	3.1%	2.1%	4.7%	4.5%	3.6%	4.3%	3.2%
	Chest Pain	2.8%	1.9%	2.3%	3.1%	0.7%	0.3%	1.0%	0.6%	1.2%	0.8%
	Back Pain	2.4%	4.9%	3.2%	2.2%	1.6%	4.1%	2.3%	3.6%	3.4%	3.4%
	Chills	2.0%	0.8%	2.3%	0.6%	0.2%	0.3%	1.0%	0.0%	0.1%	0.4%
	Trauma	3.1%	3.8%	3.6%	3.7%	2.6%	0.9%	2.6%	3.4%	5.8%	5.2%
Cardiovascular	Vasodilation	3.9%	1.1%	2.1%	2.8%	1.4%	0.6%	2.7%	0.8%	2.2%	1.2%
	Palpitation	2.0%	0.4%	2.3%	2.5%	1.2%	1.8%	1.1%	1.1%	1.0%	0.8%
Dermatologic	Sweating	8.9%	3.0%	14.3%	5.9%	9.2%	2.1%	6.3%	1.5%	4.6%	1.4%
	Rash	3.1%	1.9%	2.3%	1.5%	0.7%	0.3%	1.5%	0.9%	1.5%	2.0%
Gastro-intestinal	Nausea	23.2%	9.8%	22.8%	17.3%	24.7%	6.5%	20.1%	5.3%	19.2%	8.3%
	Dry Mouth	18.1%	8.7%	18.1%	10.8%	8.9%	2.9%	10.9%	4.7%	10.1%	4.8%
	Constipation	15.7%	6.4%	7.9%	5.2%	5.4%	1.8%	10.5%	1.7%	5.5%	3.4%
	Diarrhea	10.3%	9.8%	11.7%	6.5%	8.5%	5.9%	9.1%	6.6%	10.5%	5.4%
	Decreased Appetite	9.0%	3.4%	7.0%	2.8%	7.8%	1.5%	5.2%	1.1%	5.9%	2.6%
	Dyspepsia	3.9%	6.8%	3.8%	6.8%	4.0%	2.4%	4.5%	4.9%	4.6%	3.4%
	Flatulence	3.0%	4.2%	1.7%	2.8%	4.0%	2.4%	1.4%	2.1%	1.0%	1.0%
	Increased Appetite	4.2%	3.0%	2.1%	0.6%	1.2%	1.8%	0.4%	1.1%	1.5%	1.0%
	Vomiting	2.2%	3.4%	1.9%	1.5%	2.4%	0.6%	2.7%	2.5%	3.0%	2.0%
Musculo-skeletal Nervous System	Myalgia	3.1%	3.8%	2.3%	3.4%	4.0%	2.7%	2.9%	2.6%	1.8%	1.8%
	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%

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

1. Events reported by at least 2% of either OCD, Panic Disorder, Social Phobia (Social Anxiety Disorder), Generalized Anxiety Disorder or Posttraumatic Stress Disorder paroxetine-treated patients are included, except the following events which had an incidence on placebo ≥paroxetine hydrochloride [OCD]: depression, paresthesia, and respiratory disorder. [Panic Disorder]: flu syndrome, depression, paresthesia, 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.

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.

In placebo-controlled clinical trials involving more than 3200 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	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 sequel.

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 n=653 paroxetine-treated patients, 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 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 behavior 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 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).

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

All adverse experiences are included except those already listed in Table 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, 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 discoloration, 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 antidiuretic 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 paresthesia, 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 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 and phenytoin co-administration.

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

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

DRUG INTERACTIONS

Serious Drug Interactions

- **Monoamine Oxidase Inhibitors: See CONTRAINDICATIONS**
- **Thioridazine: See CONTRAINDICATIONS**
- **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 (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 Sandoz Paroxetine and/or monitoring of drug plasma levels, especially when paroxetine is co-administered with drugs with a narrow therapeutic index.

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

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

The concomitant use of paroxetine 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 and WARNINGS AND PRECAUTIONS, Serotonin Syndrome/Neuroleptic Malignant Syndrome).

Thioridazine: Combined use of paroxetine 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 Sandoz Paroxetine 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 (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 treatment did not result in any further impairment of desipramine elimination in poor metabolizers. Insufficient information is available to provide recommendations on the necessary dosage adjustments for tricyclic antidepressants or paroxetine, if these drugs are to be used in combination. Plasma tricyclic antidepressant concentrations may need to be monitored in such instances.

Concomitant use of paroxetine with other drugs metabolized by CYP2D6 has not been formally studied but may require lower doses than usually prescribed for either paroxetine or the other drug. Drugs metabolized by CYP2D6 include certain tricyclic antidepressants (e.g. nortriptyline, amitriptyline, imipramine and desipramine), selective serotonin reuptake inhibitors (e.g. fluoxetine), 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, Sandoz Paroxetine 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).

Drugs Metabolized by Cytochrome P450 (CYP3A4): An *in vivo* interaction study involving the co-administration under steady-state conditions of paroxetine and terfenadine, a substrate for CYP3A4, revealed no effect of paroxetine on terfenadine pharmacokinetics. In addition, *in vitro* studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several substrates for this enzyme, including terfenadine, astemizole, cisapride, triazolam and cyclosporin. Based on the assumption that the relationship between paroxetine's *in vitro* Ki and its lack of effect on terfenadine's *in vivo* clearance predicts its effect on other CYP3A4 substrates, paroxetine's extent of inhibition of CYP3A4 activity would not be expected to be of clinical significance.

Microsomal Enzyme Inhibition/Induction: The metabolism and pharmacokinetics of paroxetine 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 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 and alcohol has not been studied and is not recommended. Patients should be advised to avoid alcohol while taking Sandoz Paroxetine.

Anti-cholinergic Drugs: Paroxetine has been reported to increase significantly the systemic bioavailability of procyclidine. Steady-state plasma levels of procyclidine (5 mg daily) were elevated by about 40% when 30 mg paroxetine was co-administered to steady state. If anti-cholinergic effects are seen, the dose of procyclidine should be reduced.

Antiretroviral: 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 $T_{½}$ of paroxetine were reduced by an average of 25% and 38% respectively compared to paroxetine administered alone. The effect of paroxetine on phenobarbital pharmacokinetics was not studied. No initial Sandoz Paroxetine 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 to 900 mg/day, n=6; phenytoin 250 to 400 mg/day, n=6; sodium valproate 300 to 2500 mg/day, n=8) the co-administration of paroxetine (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 Sandoz Paroxetine is considered necessary when the drug is to be co-administered with known drug metabolizing enzyme inducers (e.g. carbamazepine, phenytoin, sodium valproate) and any subsequent dosage adjustment should be guided by clinical effect. Co-administration of paroxetine with anticonvulsants may be associated with an increased incidence of adverse experiences.

Antipsychotic Drugs/Neuroleptic Malignant Syndrome: As with other SSRIs, paroxetine 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 Sandoz Paroxetine is co-administered 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 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 Sandoz Paroxetine 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 Sandoz Paroxetine is co-administered with lithium.

Triptans: There have been rare post-marketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and the $5HT_1$ 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 $5HT_1$ 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 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 Sandoz Paroxetine 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 does not increase the sedation and drowsiness associated with haloperidol, amylbarbitone or oxazepam, when given in combination. Since the effects of concomitant administration of paroxetine with neuroleptics have not been studied, the use of Sandoz Paroxetine with these drugs should be approached with caution.

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

Cardiovascular Drugs: Multiple dose treatment with paroxetine 30 mg/day has little or no effect on the steady-state pharmacokinetics of digoxin (0.25 mg qd) or propanolol (80 mg bid).

Theophylline: Reports of elevated theophylline levels associated with paroxetine treatment have been reported. While this interaction has not been formally studied, it is recommended that theophylline levels be monitored when these drugs are concurrently administered.

Cimetidine: Steady-state levels of paroxetine (30 mg daily) were elevated by about 50% when cimetidine (300 mg tid), a known drug metabolizing enzyme inhibitor, was co-administered to steady-state. Consideration should be given to using doses of Sandoz

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

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

Sandoz 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 to 14 day interval. Hence, dosage adjustments in 10 mg increments should be made at 1 to 2 week intervals or according to clinician judgment.

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

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

Systematic evaluation of the efficacy of paroxetine hydrochloride has shown that efficacy is maintained for at least 6 months with doses that averaged about 30 mg (see CLINICAL TRIALS, Depression).

Discontinuation of Treatment: Symptoms associated with the discontinuation of paroxetine have been reported in clinical trials and post-marketing. Patients should be monitored for these and other symptoms when discontinuing treatment, regardless of the indication for which Sandoz Paroxetine is being prescribed. (see WARNINGS AND PRECAUTIONS, Discontinuation of Treatment with Paroxetine 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 Sandoz 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 Sandoz Paroxetine should be initiated at 20 mg/day. The recommended dose of Sandoz 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 Sandoz Paroxetine in the treatment of panic disorder is 10 mg/day. The recommended dose of Sandoz 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 Sandoz 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 Sandoz 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, 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 Sandoz Paroxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering paroxetine in the third trimester.

Geriatrics: (>65 years): Administration of paroxetine to the elderly is associated with increased plasma levels and prolongation of the elimination half-life relative to younger adults. (see 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: Sandoz Paroxetine is not indicated for use in children under 18 years of age (see INDICATIONS and WARNINGS AND PRECAUTIONS, Potential Association with Behavioral and Emotional Changes, Including Self-Harm).

Renal/Hepatic Impairment: Sandoz Paroxetine should be used with caution in patients with renal or hepatic impairment. The recommended initial dose is 10 mg/day in patients with clinically significant renal or hepatic impairment. A maximum dose of 40 mg should not be exceeded (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY).

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit

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

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

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

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 ($2D_6$). Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. The role of this enzyme in paroxetine metabolism also suggests potential drug-drug

interactions (see 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 3000 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)
AUC_{∞} (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_{∞} = Area under the plasma concentration time curve at infinity
$T_{½}$ = terminal elimination half-life

STORAGE AND STABILITY

Store between 15 and 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Sandoz Paroxetine (paroxetine hydrochloride) is available as film-coated, tablets containing paroxetine hydrochloride equivalent to 10 mg (yellow tablets), 20 mg (pink tablets), 30 mg (blue tablets), paroxetine free base. The 10 mg tablets are engraved “10”on one side and “S” on the other side, the 20 mg tablets are engraved “20”on one side and “S” on the other side, and the 30 mg tablets are engraved “30”on one side. and “S” on the other side The 10 and 20mg tablets are scored. Available in package sizes of:

10 mg - Blisters of 30’s and Bottles of 100’s
20 mg - Blisters of 30’s and Bottles of 100’s
30 mg - Blisters of 30's and Bottles of 100’s

Composition

Paroxetine hydrochloride, microcrystalline cellulose, mannitol, copovidone, sodium starch glycolate, silica colloidal anhydrous, magnesium stearate, hypermellose, talc, titanium dioxide, lemon yellow #10 (10mg only) sunset yellow # 6 (10mg only), allura red lake # 40 (20 and 30 mg), brilliant blue lake (20 and 30 mg), indigotine lake (20 and 30 mg).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

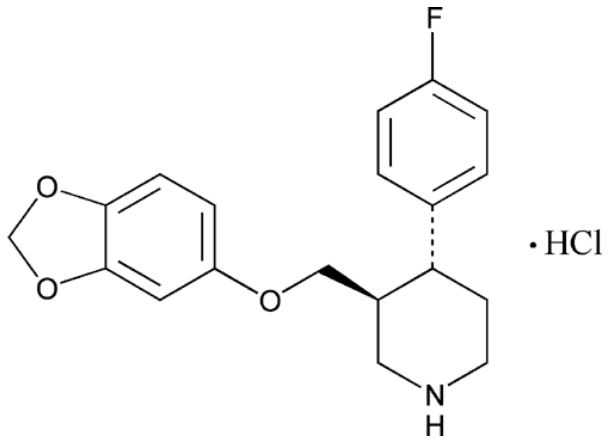
Proper Name**:** Paroxetine hydrochloride

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

Molecular Formula: $C_{19}H_{20}NO_3F \bullet HCl$

Molecular Weight: 365.8 (as anhydrate salt)
329.4 (as free base)

Structural Formula**:**



Physicochemical properties:

Description**:**	A white to off-white crystalline powder
Melting point**:**	115-126°C

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

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

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

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

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

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

CLINICAL TRIALS

Comparative Bioavailability

Two randomized, 2-way crossover, bioequivalence studies were performed using Sandoz Paroxetine 30 mg tablets and Paxil® tablets as a single 30 mg dose in 23 healthy adult males under fasting and in 18 healthy adult males and females under fed conditions. The tables below show that Sandoz Paroxetine and Paxil® (Canadian Reference) are bioequivalent.

Summary Table of the Comparative Bioavailability Data

Fasting Study

Paroxetine hydrochloride (1 x 30 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Sandoz Paroxetine 1 x 30 mg tablet	**Paxil® 30 mg tablets GlaxoSmithKline Inc.	% Ratio of Geometric Means	90 % Confidence Interval
AUC_T (ng·h/mL)	107.52 164.65 (95.3)	101.31 157.13 (90.7)	106.10	92.3%-122.0%
AUC_I (ng·h/mL)	113.62 171.64 (97.0)	107.44 163.40 (90.7)	105.80	93.6%-119.5%
C_{max} (ng/mL)	7.36 10.0500 (9.005)	7.43 10.6091 (78.3)	98.90	85.3%-114.6%
T_{max}* (h)	5.75 (1.0–9.0)	6.00 (4.50–8.0)		
$T_{½}$# (h)	12.394 (26.0)	13.341 (28.6)		

* Expressed as the median (range) only
# Expressed as the arithmetic mean (CV %) only
** Paxil® manufactured by GlaxoSmithKline Inc. was purchased in Canada

Summary Table of the Comparative Bioavailability Data

Fed Study

Paroxetine hydrochloride (1 x 30 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Sandoz Paroxetine 1 x 30 mg tablet	**Paxil® 30 mg tablets GlaxoSmithKline Inc.	% Ratio of Geometric Means	90 % Confidence Interval
AUC_{0-72} (ng·h/mL)	194.76 300.27 (111.39)	197.78 299.43 (105.47)	98.47	83.84%-115.65%
AUC_I (ng·h/mL)	211.53 385.82 (147.24)	215.66 375.99 (137.76)	98.08	84.78%-113.48%
C_{max} (ng/mL)	10.68 12.66 (63.58)	10.37 12.22 (63.49)	103.02	91.15%-116.44%
T_{max}* (h)	5.50 (2.00-10.00)	5.50 (2.00-10.1)		
$T_{½}$# (h)	15.24 (84.07)	14.97 (81.93)		

* Expressed as the median (range) only
# Expressed as the arithmetic mean (CV %) only
** Paxil® manufactured by GlaxoSmithKline Inc. was purchased in Canada

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

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

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

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

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

Panic Disorder
One fixed dose and three flexible dose placebo-controlled clinical trials of 10 to 12 weeks in duration have been performed to investigate the efficacy of paroxetine in panic disorder. The fixed dose study and two of the three flexible dose studies were supportive of differences from placebo in favor of paroxetine for measures of panic attack frequency. At endpoint, in the fixed dose study, the proportion of patients who were free of panic attacks was 44% (29/66) for the placebo group, 56% (33/59) for the 10 mg/day paroxetine group, 57% (35/61) for the 20 mg/day paroxetine group, and 76% (47/62) for the 40 mg/day paroxetine group.

Social Phobia (Social Anxiety Disorder)
One fixed dose and two flexible dose placebo-controlled clinical trials of 12 weeks in duration have been performed to investigate the efficacy of paroxetine in social phobia (social anxiety disorder). These studies showed statistically significant differences from placebo in favor of paroxetine in terms of mean change from baseline to endpoint on the Liebowitz Social Anxiety Scale and the percentage of therapeutic responders according to the Clinical Global Impression of Improvement. In the fixed dose study, the proportion of patients who were considered to be much or very much improved at week 12 of treatment according to the Clinical Global Impression of Improvement was 28.3% (26/92) in the placebo group, 44.9% (40/89) in the 20 mg/day group, 46.6% (41/88) in the 40 mg/day group, and 42.9% (39/91) in the 60 mg/day group. In the two flexible dose (20-50 mg/day) studies, placebo response rates according to this criterion were 23.9% (22/92) and 32.4% (47/145), while paroxetine response rates were 54.9% (50/91) and 65.7% (90/137), respectively.

Generalized Anxiety Disorder
The effectiveness of paroxetine in the treatment of Generalized Anxiety Disorder (GAD) (DSM IV) was demonstrated in two 8-week, multicentre, placebo-controlled studies. One trial was a flexible dose (20 to 50 mg/day) study while the other was a multiple fixed dose (20 or 40 mg/day) study. In both studies paroxetine demonstrated statistically significant superiority over placebo on the primary outcome measure - the Hamilton Rating Scale for Anxiety (HAM-A) total score, and on a number of secondary outcomes including the

HAM-A anxiety and tension items, the Clinical Global Impression (CGI) responder criterion and the Sheehan Disability Scale (SDS). An additional 8-week flexible dose study did not demonstrate a significant difference between paroxetine (20 to 50 mg/day), and placebo on the primary outcome measure. However, paroxetine (20 to 50 mg/day) was more effective than placebo on many secondary study outcomes.

Posttraumatic Stress Disorder
The efficacy of paroxetine in the treatment of Posttraumatic Stress Disorder (PTSD) was demonstrated in two 12 week, multicentre placebo controlled studies (Study 1 and Study 2) in adult patients who met the DSM-IV criteria for PTSD. Study outcome was assessed by (i) the Clinician Administered PTSD Scale Part (CAPS-2) score and (ii) the Clinical Global Impression Global Improvement Item (CGI-I). The CAPS-2 is a multi-item instrument that measures the three PTSD diagnostic symptom clusters of: re-experiencing/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 mg/day or 40 mg/day to placebo. Paroxetine 20 mg and 40 mg were demonstrated to be significantly superior to placebo for the CAPS-2 total score, and on proportion of responders on the CGI-I.

Study 2 was a 12-week flexible-dose study comparing paroxetine (20 mg to 50 mg daily) to placebo. Paroxetine was demonstrated to be significantly superior to placebo for the CAPS-2 total scorer, and on proportion of responders on the CGI-I.

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

DETAILED PHARMACOLOGY

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

Radioligand binding techniques in rat brain, *in vitro*, have indicated that paroxetine has little affinity for α_1, α_2 and β-adrenoceptors, dopamine (D_2), 5-HT_1-like, 5-HT_2 and histamine (H_1) receptors at concentrations below 1 mcM. This lack of interaction with post-synaptic

receptors *in vitro* is substantiated by *in vivo* studies which demonstrate a lack of CNS depressant and hypotensive properties.

In vivo: In mice, paroxetine (ED_{50}=0.4 mg/kg PO) was associated with potent and prolonged potentiation of the hypermotility induced by the 5-HT precursor, 5-hydroxytryptophan. Similarly, the anticonvulsant effects of 5-hydroxytryptophan in a mouse electroshock model were potentiated by paroxetine (ED_{50}=0.4 mg/kg PO). In rats paroxetine (ED_{50}=0.8 mg/kg PO) inhibited the hypermotility induced by p-chloroamphetamine, an agent which depletes neuronal 5-HT stores. Paroxetine, 1 mg/kg IP, 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 IP, 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.

Behavioral 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 IP). Paroxetine caused seizures in mice at a lethal dose of 300 mg/kg PO At a dose of 50 mg/kg PO, 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 anesthetized dog, IV 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 IV 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 IP in mice and rats, 1 to 7.5 mg/kg PO 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 LD_{50} 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 tumors 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 (IM and SC) injected with paroxetine in Freund's adjuvant. In addition as a positive control, sera were obtained from NZW rabbits which had been immunized by IM and SC 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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PART III: CONSUMER INFORMATION

[Pr] Sandoz Paroxetine
paroxetine hydrochloride tablets

This leaflet is part III of a three-part "Product Monograph" published when Sandoz 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 Sandoz 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:
Sandoz 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 behavior, 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:
Sandoz Paroxetine belongs to the family of medicines called selective serotonin reuptake inhibitors. 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 Sandoz 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:
Nonmedicinal ingredients include microcrystalline cellulose, mannitol, copovidone, sodium starch, glycolate, silica colloidal anhydrous, magnesium stearate, hypermellose, talc, titanium dioxide, lemon yellow #10 (10mg only) sunset yellow # 6 (10mg only) allura red lake # 40 (20 and 30 mg), brilliant blue lake (20 and 30 mg), indigotine lake (20 and 30 mg).

There is no ethanol, gluten, lactose, sulfite, or tartrazine in Sandoz Paroxetine.

What dosage forms it comes in:
Sandoz Paroxetine is available as a 10 mg yellow tablet, a 20 mg pink tablet, and a 30 mg blue tablet.

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.

Sandoz 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 Sandoz 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 Sandoz 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 Sandoz Paroxetine on your own.

Taking Sandoz 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 Sandoz Paroxetine may affect your sperm. Fertility in some men may be reduced while taking Sandoz Paroxetine.

BEFORE you use Sandoz 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

Effects on Pregnancy and Newborns
As stated above, ask your doctor or pharmacist for advice before taking any medicine including Sandoz Paroxetine. **If you are already taking/using Sandoz 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 Sandoz 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 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 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.

Taking Sandoz Paroxetine in Later Stages of Pregnancy

Possible complications at birth (from taking any newer antidepressant, including Sandoz 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 Sandoz Paroxetine:
The use of Sandoz 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 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:
Sandoz Paroxetine can cause an acute attack of glaucoma. Having your eyes examined before you take Sandoz 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 Sandoz 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 anticoagulants (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 Sandoz Paroxetine
- certain medicines used to treat cough, such as dextromethorphan

PROPER USE OF THIS MEDICATION

Usual Dose:

- It is very important that you take Sandoz Paroxetine exactly as your doctor has instructed. Generally most people take between 20 mg to 40 mg of Sandoz 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 think you have taken too much Sandoz Paroxetine, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medications, Sandoz 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 Sandoz 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).

Sandoz Paroxetine 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.

Sandoz Paroxetine may raise cholesterol levels in some patients.

Discontinuation Symptoms

Contact your doctor before stopping or reducing your dosage of Sandoz 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 Sandoz Paroxetine, 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 Sandoz 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 Sandoz 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	
Uncommon	Hallucinations [strange visions or sounds]		√	
Uncommon	Uncontrollable movements of the body or face		√	
Uncommon	Inability to urinate or loss of control of the bladder (urinary incontinence).		√	
Uncommon	Dilated pupils		√	
Uncommon	Low blood pressure (may cause dizziness, lightheadedness or fainting when standing up from a sitting down or lying position)		√	
Uncommon	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]			√
Rare	Allergic reactions (skin rash alone)		√	
Rare	Low sodium level in blood [symptoms of tiredness, weakness, confusion combined with achy, stiff or uncoordinated muscles		√	
Rare	Akathisia [feeling restless and unable to sit or stand still]		√	
Rare	Mania [overactive behaviour and thoughts]		√	
Rare	Seizures [loss of consciousness with uncontrollable shaking ("fit")]			√
Rare	Restless Legs Syndrome (irresistible urge to move the legs)		√	
Rare	Angle-Closure Glaucoma [eye pain, changes in vision and swelling or redness in or around the eye]			√
Rare	Abnormal secretion of breast milk in men and women		√	
Rare	Increased sensitivity of the skin to sunlight	√		
Rare	Swelling of hands, ankles or feet		√	
Rare	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.			√
Very Rare	Gastrointestinal bleeding [vomiting			√

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	
	blood or passing blood in stools]			
Very Rare	Liver disorder [symptoms include nausea, vomiting, loss of appetite combined with itching, yellowing of the skin or eyes, dark urine]		√	
Very Rare	A severe widespread rash with blisters and peeling skin often with sores or pain in the mouth or eyes			√
Very Rare	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 Sandoz Paroxetine, contact your doctor or pharmacist.

HOW TO STORE IT

- Keep all medicines out of reach and sight of children.
- Store at room temperature between 15 and 30°C in a dry place
- Keep container tightly closed
- If your doctor tells you to stop taking Sandoz 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.

If you want more information about Sandoz Paroxetine:

- Talk to your healthcare profession
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.sandoz.ca or by calling 1-800-361-3062

or

by written request at:

110 Rue de Lauzon

Boucherville, (QC), Canada

J4B 1E6

Or by e-mail at :
medinfo@sandoz.com

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