SEROXAT CR Controlled-Release Tablets
Paroxetine Hydrochloride Hemihydrate

THERAPEUTIC INDICATIONS

Adults

Depression:
SEROXAT CR is indicated for symptomatic relief of Major Depressive Disorder.

SEROXAT CR has not been systematically evaluated beyond 12 weeks in controlled clinical trials; however, the effectiveness of immediate-release paroxetine hydrochloride in maintaining a response in depression for at least 6 months has been demonstrated in a placebo-controlled trial (see *Clinical Trials).* The physician who elects to use SEROXAT CR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Panic Disorder:
SEROXAT CR is indicated for the symptomatic treatment of panic disorder, with or without agoraphobia.
Panic disorder (DSM-IV) is characterised by recurrent unexpected panic attacks, i.e., a discrete period of intense fear or discomfort in which 4 (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):
SEROXAT CR 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.

Premenstrual Dysphoric Disorder:
SEROXAT CR is indicated for the symptomatic treatment of premenstrual dysphoric disorder (PMDD). The efficacy of SEROXAT CR in the treatment of PMDD has been established in 3 placebo-controlled trials (see *Clinical Trials).*

The essential features of PMDD, according to DSM-IV, include markedly depressed mood, anxiety or tension, affective lability, and persistent anger or irritability. Other features include decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. Physical symptoms associated with PMDD include breast tenderness, headache, joint and muscle pain, bloating, and weight gain. These

symptoms occur regularly, in most menstrual cycles, during the luteal phase and remit within a few days following the onset of menses; the disturbance markedly interferes with work or school or with usual social activities and relationships with others. Typically, the symptoms are comparable in severity (but not duration) to those of a major depressive episode. The presence of the cyclical pattern of symptoms must be confirmed by at least two consecutive months of prospective daily symptom ratings. It is estimated that at least 75% of women report minor or isolated premenstrual changes; however, only 3 to 5% of women experience symptoms that may meet the criteria for PMDD. In making the diagnosis, care should be taken to rule out other cyclical mood disorders that may be exacerbated by treatment with an antidepressant.

Long-Term Use of SEROXAT CR
The effectiveness of SEROXAT CR in long-term use (i.e. more than 12 weeks for depression, panic disorder and social phobia and more than 3 menstrual cycles for premenstrual dysmorphic disorder), has not yet been established in controlled trials for depression, panic disorder, social phobia or premenstrual dysmorphic disorder. Therefore, the physician who elects to use SEROXAT CR for extended periods in these indications should periodically re-evaluate the long-term usefulness of the drug for the individual patient. (see *Dosage and Administration)*

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; Pharmacological Properties*; *Dosage and Administration*).

Pediatrics (<18 years of age)
SEROXAT CR is not indicated for use in patients below the age of 18 years (see *Warnings and Precautions*).

DOSAGE AND ADMINISTRATION

General

SEROXAT CR is not indicated for use in children under 18 years of age (see *Warnings and Precautions*).

SEROXAT CR should be administered as a single daily dose, usually in the morning, with or without food. Patients should be cautioned that SEROXAT CR tablet should not be chewed or crushed, and should be swallowed whole.

Discontinuation of Treatment with SEROXAT CR: Symptoms associated with the discontinuation of immediate-release paroxetine and SEROXAT CR 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 SEROXAT CR is being prescribed (see *Warnings and Precautions* and *Adverse Reactions*).
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 Initial Dosage: The recommended initial dose is 25 mg/day. Patients were dosed in a range of 25 mg to 62.5 mg/day in the clinical trials demonstrating the effectiveness of SEROXAT CR in the treatment of depression. As with all drugs effective in the treatment of depression, the full effect may be delayed. Some patients not responding to a 25-mg dose may benefit from dose increases, in 12.5-mg/day increments, up to a maximum of 62.5 mg/day. Dose changes should occur at intervals of at least 1 week.

Maintenance Therapy: There is no body of evidence available to answer the question of how long the patient treated with SEROXAT CR should remain on it for the symptoms of panic and depression. 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 immediate-release paroxetine hydrochloride has shown that efficacy is maintained for at least 6 months with doses that averaged about 30 mg, which corresponds to a 37.5-mg dose of SEROXAT CR, based on relative bioavailability considerations.

Panic Disorder:
Usual Initial Dosage: Patients should be started on 12.5 mg/day. Dose changes should occur in 12.5-mg/day increments and at intervals of at least 1 week. Patients were dosed in a range of 12.5 to 75 mg/day in the clinical trials demonstrating the effectiveness of SEROXAT CR. The maximum dosage should not exceed 75 mg/day.

Maintenance Therapy: Panic disorder is a chronic condition, and it is reasonable to consider continuation of treatment for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Social Phobia (Social Anxiety Disorder):
Usual Initial Dosage: The recommended initial dose is 12.5 mg/day. Patients were dosed in a range of 12.5 mg to 37.5 mg/day in the clinical trial demonstrating the effectiveness of SEROXAT CR in the treatment of social anxiety disorder. Some patients not responding to a 12.5 mg dose may benefit from dose increases, , in increments of 12.5 mg/day, up to a maximum of 37.5 mg/day. Dose changes should occur at intervals of at least 1 week.

Maintenance Therapy: There is no body of evidence available to answer the question of how long the patient treated with SEROXAT CR should remain on it. Although the efficacy of SEROXAT CR beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials, social anxiety disorder is recognised as a chronic condition, and it is reasonable to consider continuation of treatment for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Premenstrual Dysphoric Disorder:

Usual Initial Dosage: In clinical trials, both 12.5 mg/day and 25 mg/day were shown to be effective with continuous dosing, or intermittent luteal phase dosing.
The recommended dose is 12.5 mg/day limited to the luteal phase of the menstrual cycle, starting 14 days prior to the expected onset of menses, and terminating on the first day of menses. Some patients not responding to a 12.5 mg dose may benefit from a dose increase to 25 mg/day. Dose changes should occur at intervals of at least 1 week.
Continuous dosing of SEROXAT CR, administered daily throughout the menstrual cycle may be considered if efficacy with luteal phase dosing is sub-optimal.
Dose changes should occur at intervals of at least 1 week.

Maintenance/Continuation Therapy: The effectiveness of SEROXAT CR in long-term use, that is, for more than 3 menstrual cycles has not been evaluated in controlled trials. Therefore, the physician who elects to use SEROXAT CR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Special 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 SEROXAT CR, she should be informed of the current estimate of risk to the fetus (see *Warnings and Precautions*) and consideration should be given to switching to other treatment options. Treatment with SEROXAT CR 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*).
Post-marketing reports indicate that some neonates exposed to SEROXAT CR, 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*) When treating pregnant women with SEROXAT CR during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.
The physician may consider tapering SEROXAT CR in the third trimester.

Dosage for Elderly (> 65 years) or Debilitated:
Administration of SEROXAT CR to the elderly is associated with increased plasma levels and prolongation of the elimination half life relative to younger adults (see *Pharmacological Properties*). The recommended initial dose of SEROXAT CR is 12.5 mg/day for elderly patients and debilitated patients. Increases may be made if indicated. Dosage should not exceed 50 mg/day.

Pediatrics*: SEROXAT CR is not indicated for use in children under 18 years of age (see *Therapeutic Indications* and *Warnings and Precautions).

Renal/Hepatic Impairment: SEROXAT CR should be used with caution in patients with renal or hepatic impairment. The recommended initial dose is 12.5 mg/day in patients with clinically significant renal or hepatic impairment. A maximum dose of 50 mg/day should not be exceeded (see *Warning and Precautions* and *Pharmacological Properties*).

CONTRAINDICATIONS

Hypersensitivity: SEROXAT CR is contraindicated in patients with known hypersensitivity to active substance(s) or to any of the excipients listed in *Excipients*.

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*). Therefore, SEROXAT CR should not be used in combination with MAO inhibitors [including methylthioninium chloride (methylene blue)] or within a minimum of 2 weeks of terminating treatment with MAO inhibitors. Treatment with SEROXAT CR 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 SEROXAT CR.

SEROXAT CR should not be started in a patient receiving linezolid. Wait until 24 hours after the last dose of linezolid before starting SEROXAT CR.

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 SSRI's such as paroxetine, fluoxetine and fluvoxamine, will elevate plasma levels of thioridazine. Therefore, SEROXAT CR 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 SEROXAT CR therapy before initiating treatment with thioridazine.

Pimozide: The concomitant use of SEROXAT CR 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 *Interactions*).

WARNINGS AND PRECAUTIONS

General

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

Pediatrics: Placebo-Controlled Clinical Trial Data

- **Recent analyses of placebo-controlled clinical trial safety databases from SSRIs and other newer antidepressants suggests that use of these drugs in patients under the age of 18 may be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour over that of placebo.**

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

Adult and Pediatrics: Additional data

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

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

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

Discontinuation Symptoms: Patients currently taking SEROXAT CR 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 SEROXAT CR
When discontinuing treatment, 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*]. 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*).

SEROXAT CR 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 SEROXAT CR, consideration should be given to switching to other treatment options. Treatment with SEROXAT CR should only be continued for an individual pregnant patient, if the potential benefits outweigh the potential risks. Initiation of paroxetine, for women who intend to become pregnant, or are in their first trimester of pregnancy, should be considered only after other treatment options have been evaluated (see *Warnings and Precautions*).

Post-marketing reports indicate that some neonates exposed to SEROXAT CR, 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 SEROXAT CR during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see *Warnings and Precautions* and *Dosage and Administration*).

Sexual Dysfunction
Selective serotonin reuptake inhibitors (SSRIs) may cause symptoms of sexual dysfunction (see ADVERSE REACTIONS). Patients should be informed that there have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs.

Potential for reduced efficacy of Tamoxifen with concomitant SSRI use, including SEROXAT CR
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 *Interactions*). 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 SEROXAT CR 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 SEROXAT CR does not affect them adversely.

Bone fracture risk
Epidemiological studies show an increased risk of bone fracture 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 SEROXAT CR. 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 SEROXAT CR, 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

SEROXAT CR or immediate-release paroxetine have 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 SEROXAT CR or immediate-release paroxetine in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using SEROXAT CR in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Dependence Liability

SEROXAT CR or immediate-release paroxetine have 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 SEROXAT CR.

Endocrine and Metabolism

Serum Cholesterol Elevation: Several public domain studies have shown increased LDL-cholesterol levels of ~10% in volunteers and patients taking paroxetine for 8 to 12 weeks, which generally normalized after paroxetine discontinuation. In addition, of the patients in placebo-controlled clinical trials for whom baseline and on-treatment measurements were taken, total serum levels of cholesterol showed a mean increase of ~ 1.5 mg/dL in paroxetine-treated patients (n = 653), compared to a mean decrease of ~ 5.0 mg/dL in placebo-treated patients (n = 379). Increases from baseline of 45 mg/dL or greater were recorded in 6.6% of paroxetine-treated patients compared to 2.6% of placebo-treated patients (see Monitoring and Laboratory Tests, Serum Cholesterol Elevation). These data should be taken into consideration when treating patients with underlying cardiac risk factors.

Hematologic

Abnormal Bleeding: SSRIs including SEROXAT CR may increase the risk of bleeding events by causing abnormal platelet aggregation. Concomitant use of acetylsalicylic acid (ASA), nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin and other anticoagulants may add to the risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening haemorrhages. Gastrointestinal and gynaecological bleeding have also been reported following treatment with SEROXAT CR.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of SEROXAT CR and NSAIDs, ASA, or other drugs that affect coagulation (see *Interactions*). 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 immediate-release 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. SEROXAT CR 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* and *Pharmacological Properties*).

Immune

Hypersensitivity: The 12.5 mg controlled release tablet coating contains an azo dye (FD&C Yellow No. 6 aluminium lake) which may cause allergic reactions.

Neurologic

Epilepsy: As with other antidepressants, SEROXAT CR 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 immediate-release 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 occured in association with treatment of SEROXAT CR, 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 SEROXAT CR 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 SEROXAT CR should not be used in combination with MAO inhibitors [including 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 *Interactions*).

Ophthalmologic

Angle-Closure Glaucoma: As with other antidepressants, SEROXAT CR can cause mydriasis which may trigger an angle-closure attack in a patient with anatomically narrow ocular angles. Caution should be used when paroxetine is prescribed for patients with untreated narrow angles. Open-angle glaucoma is not a risk factor for angle-closure glaucoma. Patients should be informed to seek immediate medical assistance if they experience eye pain, changes in vision or swelling or redness in or around the eye.

Psychiatric

Suicide: The possibility of a suicide attempt is inherent in depression and may persist until remission occurs. Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications. Notwithstanding, high risk patients should be closely supervised throughout therapy with appropriate consideration to the possible need for hospitalization. In order to minimize the opportunity for overdosage, prescriptions for SEROXAT CR 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*).

Activation of Mania/Hypomania: During clinical testing in a patient population comprised primarily of unipolar depressed patients, approximately 1% of patients treated with immediate-release paroxetine experienced manic reactions. When bipolar patients were considered as a sub-group the incidence of mania was 2%. As with all drugs effective in the treatment of depression, SEROXAT CR 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 SEROXAT CR and ECT have not been studied.

Renal
Hyponatremia: Several cases of hyponatremia have been reported. The hyponatremia appeared to be reversible when immediate-release 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 SEROXAT CR is extensively metabolized by the liver; excretion of unchanged drug in urine is a minor route of elimination. However, single dose pharmacokinetic studies in subjects with clinically significant renal impairment suggest that plasma levels of paroxetine are elevated in such subjects. Paroxetine should therefore be used with caution and the dosage restricted to the lower end of the range in patients with clinically significant renal impairment (see *Dosage and Administration* and *Pharmacological Properties*).

Sexual Function/Reproduction

Sexual Dysfunction: See WARNINGS AND PRECAUTIONS

Sperm Quality: 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 *Toxicology*).

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 SEROXAT CR: Pregnancy, or intent to become pregnant:
If a patient becomes pregnant while taking SEROXAT CR, or intends to become pregnant, she should be informed of the current estimate of increased risk to the fetus with SEROXAT CR over other antidepressants. Examinations of additional databases, as well as updated analyses, may result in changes to the current risk estimates. Consideration should be given to switching to other treatment options, including another antidepressant or non-pharmaceutical treatment such as cognitive behavioural therapy. Treatment with SEROXAT CR 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 SEROXAT CR treatment, a gradual reduction in the dose rather than an abrupt cessation is recommended (see *Warnings and Precautions*; *Adverse Reactions* and *Dosage and Administration*).

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

Complications following late third trimester exposure to SSRIs:
Post-marketing reports indicate that some neonates exposed to SEROXAT CR, 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, hypoglycaemia, 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*). When treating a pregnant woman with SEROXAT CR during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see *Dosage and Administration*).
There have been post-marketing reports of premature birth in pregnant women exposed to paroxetine or other SSRIs. The causal relationship between SEROXAT CR and the emergence of these events has not been established.

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 SEROXAT CR) in pregnancy, particularly use in late pregnancy, was associated with an increased risk of PPHN. PPHN occurs in 1-2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy (Odds Ratio 6.1, 95% CI 2.2-16.8). A study using data from the Swedish Medical Birth Register for 831,324 infants born in 1997-2005 found an increased risk of PPHN of approximately 2-fold associated with patient-reported maternal use of SSRIs in the first trimester of pregnancy (Risk Ratio 2.4, 95% CI 1.2-4.3), and an increased risk of PPHN of approximately 4-fold associated with a combination of patient-reported maternal use of SSRIs in the first trimester and an antenatal SSRI prescription in later pregnancy (Risk Ratio 3.6, 95% CI 1.2-8.3).

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

Pediatrics (< 18 years of age): SEROXAT CR is not indicated for use in patients below the age of 18 years (See *Warnings and Precautions, Therapeutic Indications* and *Dosage and Administration)*.

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

Geriatrics (≥ 65 years of age): Administration of SEROXAT CR to the elderly is associated with increased plasma levels and prolongation of the elimination half life relative to younger adults (see *Pharmacological Properties*). 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 immediate-release paroxetine (10-40 mg daily) in worldwide premarketing clinical trials revealed no unusual pattern of adverse events relative to the clinical experience in younger patients.
In a controlled study focusing specifically on elderly patients with depression, SEROXAT CR (12.5-50 mg daily) was demonstrated to be safe and effective in the treatment of elderly patients (> 60 years of age) with depression (see *Clinical Trials* and *Adverse Reactions*). 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* and *Warnings and Precautions*). These data should be taken into consideration when treating patients with underlying cardiac risk factors.

INTERACTIONS

Serious Drug Interactions (see *Contraindications)*

- Monoamine Oxidase Inhibitors
- Thioridazine
- Pimozide

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 5-10% of Caucasians. The median C_{min} (ss) for paroxetine (20 mg daily) at steady state in poor metabolizers (n=8) was almost triple that reported for extensive metabolizers (n=9). Although the full clinical significance of this effect has not been established, inhibition of CYP2D6 can lead to elevated plasma levels of co-administered drugs which are metabolized by this isozyme. Consideration should be given to decreasing the dose of the CYP2D6 metabolized drug or paroxetine and/or monitoring of drug plasma levels, especially when paroxetine is co-administered with drugs with a narrow therapeutic index. SEROXAT CR co-administration has been associated with elevated levels of the anti-cholinergic procyclidine, certain neuroleptics/antipsychotics (e.g. perphenazine, risperidone), tricyclic antidepressants (e.g. desipramine), atomoxetine, type 1C antiarrhythmics (e.g. propafenone), and theophylline.
Co-administration of phenobarbitol or phenytoin with SEROXAT CR has been associated with decreased levels of SEROXAT CR or immediate-release paroxetine. When co-administered with cimetidine, SEROXAT CR levels were elevated.
The concomitant use of SEROXAT CR and alcohol has not been studied.

Drug-Drug Interactions

Monoamine Oxidase Inhibitors: Combined use of SEROXAT CR and monoamine oxidase inhibitors [including 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*).

Thioridazine: Combined use of SEROXAT CR 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 immediate-release paroxetine (titrated to 60 mg daily) was associated with mean increases in pimozide AUC of 151% and C_{max} of 62%, compared to pimozide administered alone. 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 QT interval, and produce severe cardiac arrhythmias including torsade de pointes, concomitant use of pimozide and SEROXAT CR is contraindicated (see *Contraindications*).

Drugs Metabolized by Cytochrome P450 (CYP2D6): In two studies, daily dosing of immediate-release 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 immediate-release 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 SEROXAT CR, if these drugs are to be used in combination. Plasma tricyclic antidepressant concentrations may need to be monitored in such instances.

Concomitant use of SEROXAT CR with other drugs metabolized by CYP2D6 has not been formally studied but may require lower doses than usually prescribed for either SEROXAT CR 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, SEROXAT CR 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*).

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 (CYP3A4): An *in vivo* interaction study involving the co-administration under steady state conditions of paroxetine and terfenadine, a substrate for cytochrome 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 SEROXAT CR 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 SEROXAT CR 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 SEROXAT CR or immediate-release paroxetine and alcohol has not been studied and is not recommended. Patients should be advised to avoid alcohol while taking SEROXAT CR.

Anti-cholinergic Drugs: Immediate-release 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 immediate-release paroxetine were reduced by an average of 25 and 38% respectively compared to immediate-release paroxetine administered alone. The effect of SEROXAT CR or immediate-release paroxetine on phenobarbital pharmacokinetics was not studied. No initial SEROXAT CR or immediate-release 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 600-900 mg/day, n=6; phenytoin 250-400 mg/day, n=6; sodium valproate 300-2500 mg/day, n=8) the co-administration of immediate-release 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 SEROXAT CR 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 SEROXAT CR with anticonvulsants may be associated with an increased incidence of adverse experiences.

Antipsychotic Drugs/Neuroleptic Malignant Syndrome: As with other SSRIs, SEROXAT CR 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*).

Serotonergic Drugs: Based on the mechanism of action of paroxetine and the potential for serotonin syndrome, caution is advised when SEROXAT CR is coadministered with other drugs or agents that may affect the serotonergic neurotransmitter systems, such as tryptophan, triptans, serotonin reuptake inhibitors, lithium, fentanyl and its anologues, dextromethorphan, tramadol, tapentadol, meperidine, methadone and pentazocine or St. John's Wort. (See *Warnings and Precautions*). Concomitant use of SEROXAT CR and MAO inhibitors 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 SEROXAT CR is initiated or discontinued (see *Warnings and Precautions*).

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 SEROXAT CR is coadministered with lithium.

Triptans: There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and the $5HT_1$ 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*).

Tryptophan: Tryptophan can be metabolized to serotonin. As with other serotonin reuptake inhibitors, the use of SEROXAT CR 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 SEROXAT CR with tryptophan is not recommended (see *Warnings and Precautions*).

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

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

Cardiovascular Drugs: Multiple dose treatment with immediate-release 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 SEROXAT CR towards the lower end of the range when co-administered with known drug metabolizing enzyme inhibitors.

Drug-Food Interactions

At steady state, the bioavailability of 25 mg SEROXAT CR is not affected by food.

Drug-Herb Interactions

St. John's Wort: In common with other SSRI's, pharmacodynamic 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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Commonly Observed Adverse Events

Depression
The most commonly observed adverse events associated with the use of SEROXAT CR in a pool of two trials (incidence of 5.0% or greater and incidence for SEROXAT CR at least twice that for placebo, derived from Table 1 below) were: abnormal ejaculation, abnormal vision, constipation, decreased libido, diarrhea, dizziness, female genital disorders, nausea, somnolence, sweating, trauma, tremor, and yawning.
Using the same criteria, the adverse events associated with the use of SEROXAT CR in a study of elderly patients with depression were: abnormal ejaculation, constipation, decreased appetite, dry mouth, impotence, infection, libido decreased, sweating, and tremor.

Panic Disorder
In the pool of panic disorder studies, the adverse events meeting these criteria were: abnormal ejaculation, somnolence, impotence, libido decreased, tremor, sweating, and female genital disorders (generally anorgasmia or difficulty achieving orgasm).

Social Anxiety Disorder
The most commonly observed adverse events associated with the use of SEROXAT CR (incidence of 5.0% or greater and incidence for SEROXAT CR at least twice that for placebo, derived from Table 4 below) in the social phobia (social anxiety disorder) study were nausea, asthenia, abnormal ejaculation, sweating, somnolence, impotence, insomnia, and libido decreased.

Premenstrual Dysphoric Disorder
The most commonly observed adverse events associated with the use of SEROXAT CR, either during continuous dosing or luteal phase dosing (incidence of 5.0% or greater and incidence for SEROXAT CR at least twice that for placebo, derived from Table 5 below) were: nausea, asthenia, libido decreased, somnolence, insomnia, female genital disorders, sweating, dizziness, diarrhea and constipation.
In the luteal phase dosing PMDD trial, which employed dosing of 12.5 mg/day or 25 mg/day of SEROXAT CR limited to the 2 weeks prior to the onset of menses over 3 consecutive menstrual cycles, adverse events were evaluated during the first 14 days of each off-drug phase. When the 3 off-drug phases were combined, the following adverse events were reported at an incidence of 2% or greater for SEROXAT CR and were at least twice the rate of that reported for placebo: Infection (5.3% versus 2.5%), depression (2.8% versus 0.8%), insomnia (2.4% versus 0.8%), sinusitis (2.4% versus 0%), and asthenia (2.0% versus 0.8%).

Adverse Events Leading to Discontinuation of Treatment
The information included under the "Adverse Events Leading to Discontinuation of Treatment" subsection of ADVERSE REACTIONS is based on data from seven short-term placebo-controlled clinical trials. Three of these studies were conducted in patients with depression, three studies were done in patients with panic disorder, and one study was conducted in patients with social anxiety disorder. Two of the studies in depression, which enrolled patients in the age range 18 to 65 years, are pooled. Information from a third study of depression, which focused on elderly patients (ages 60 to 88), is presented separately as is the

information from the panic disorder studies and the information from the social anxiety disorder study. Information on additional adverse events associated with SEROXAT CR and the immediate-release formulation of paroxetine hydrochloride is included in a separate subsection.

Depression

Ten percent (21/212) of SEROXAT CR patients discontinued treatment due to an adverse event in a pool of two studies of patients with depression. The most common events (≥ 1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate approximately twice or greater for SEROXAT CR compared to placebo) included the following:

	SEROXAT CR (n=212)	**Placebo (n=211)**
Nausea	3.7%	0.5%
Asthenia	1.9%	0.5%
Dizziness	1.4%	0.0%
Somnolence	1.4%	0.0%

In a placebo-controlled study of elderly patients with depression, 13% (13/104) of SEROXAT CR patients discontinued due to an adverse event. Events meeting the above criteria included the following:

	SEROXAT CR (n=104)	**Placebo (n=109)**
Nausea	2.9%	0.0%
Headache	1.9%	0.9%
Depression	1.9%	0.0%
LFT's abnormal	1.9%	0.0%

Panic Disorder

Eleven percent (50/444) of SEROXAT CR patients in panic disorder studies discontinued treatment due to an adverse event. Events meeting the above criteria included the following:

	SEROXAT CR (n=444)	**Placebo (n=445)**
Nausea	2.9%	0.4%
Insomnia	1.8%	0.0%
Headache	1.4%	0.2%
Asthenia	1.1%	0.0%

Social Anxiety Disorder

Three percent (5/186) of patients treated with SEROXAT CR in the social anxiety disorder study discontinued treatment due to an adverse event. Events meeting the above criteria included the following:

	SEROXAT CR (n=186)	**Placebo (n=184)**

Nausea	2.2%	0.5%
Headache	1.6%	0.5%
Diarrhea	1.1%	0.5%

Premenstrual Dysphoric Disorder

Thirteen percent (88/681) of patients treated with SEROXAT CR in PMDD studies of continuous dosing discontinued treatment due to an adverse event. Nine percent (34/366) of patients treated with SEROXAT CR in PMDD studies of luteal phase dosing discontinued treatment due to an adverse event.

The most common events (> 1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate approximately twice or greater for SEROXAT CR compared to placebo) included the following:

	Continuous Dosing			**Intermittent Dosing**		
	SEROXAT CR 25 mg (n = 348)	**SEROXAT CR 12.5 mg (n = 333)**	**Placebo (n = 349)**	**SEROXAT CR 25 mg (n = 116)**	**SEROXAT CR 12.5 mg (n = 130)**	**Placebo (n = 120)**
TOTAL	15%	9.9%	6.3%	5.2%	5.4%	0.0%
Nausea*	6.0%	2.4%	0.9%	3.4%	2.3%	0.0%
Asthenia	4.9%	3.0%	1.4%	0.9%	1.5%	0.0%
Somnolence*	4.3%	1.8%	0.3%	-	-	-
Insomnia	2.3%	1.5%	0.0%	1.7%	3.1%	0.0%
Concentration Impaired *	2.0%	0.6%	0.3%	-	-	-
Dry mouth*	2.0%	0.6%	0.3%	-	-	-
Dizziness*	1.7%	0.6%	0.6%	2.6%	0.8%	0.0%
Decreased Appetite*	1.4%	0.6%	0.0%	-	-	-
Sweating*	1.4%	0.0%	0.3%	-	-	-
Tremor*	1.4%	0.3%	0.0%	1.7%	0.8%	0.0%
Yawn*	1.1%	0.0%	0.0%	-	-	-
Diarrhea	0.9%	1.2%	0.0%	-	-	-

*Events considered to be dose dependent are defined as events having an incidence rate with 25 mg of SEROXAT CR that was at least twice that with 12.5 mg of SEROXAT CR (as well as the placebo group).

Adverse Events following Discontinuation of Treatment (or Dose Reduction)

Clinical Trials

Adverse events while discontinuing therapy with SEROXAT CR were not systematically evaluated in most clinical trials; however, in one placebo-controlled clinical trial in social anxiety disorder involving 370 patients (186 on SEROXAT CR and 184 on placebo), utilizing daily doses of SEROXAT CR up to 37.5 mg/day, spontaneously reported adverse events while discontinuing therapy with SEROXAT CR were evaluated. Patients receiving 37.5 mg/day underwent an incremental decrease in the daily dose by 12.5 mg/day to a dose of 25 mg/day for 1 week before treatment was stopped. For patients receiving 25 mg/day or 12.5 mg/day, treatment was stopped without an incremental decrease in dose. With this regimen, the following adverse events were reported at an incidence of 2% or greater for SEROXAT CR and were at least twice that reported for placebo: dizziness (13.9 versus 2.2%), insomnia (4.4 versus 2.2%), paresthesia (4.4 versus 0%) vertigo (3.3 versus 0%), and additional symptoms described by the investigator as associated with tapering or discontinuing SEROXAT CR including electric shock sensations (5.6 versus 0.6%). These events were reported as serious in 1.7% (3/180) of patients who discontinued therapy with SEROXAT CR.
The following adverse events have been reported at an incidence of 2% or greater for immediate-release paroxetine and were at least twice that reported for placebo: abnormal dreams (2.3 vs 0.5%), paresthesias (2.0 vs 0.4%), and dizziness (7.1 vs 1.5%). The majority of these events were mild to moderate, self-limiting and did not require medical intervention. These adverse events were noted in GAD and PTSD clinical trials employing a taper phase regimen for discontinuation of treatment. This regimen involved an incremental decrease in the daily dose by 10 mg/day at weekly intervals. When a daily dose of 20 mg/day was reached, patients were continued on this dose for 1 week before treatment was stopped.

Post-Marketing
There have been spontaneous reports of adverse events upon the discontinuation of paroxetine and SEROXAT CR (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 (2-3 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. 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

Table 1 enumerates adverse events that occurred at an incidence of 1% or more among SEROXAT CR-treated patients, aged 18 to 65, who participated in two short-term (12-week) placebo-controlled trials in depression in which patients were dosed in a range of 25 to 62.5 mg/day. Table 2 enumerates adverse events reported at an incidence of 5% or greater among elderly SEROXAT CR-treated patients (ages 60-88) who participated in a short-term (12-week) placebo-controlled trial in depression in which patients were dosed in a range of 12.5 to 50 mg/day. Table 3 enumerates adverse events reported at an incidence of 1% or greater among SEROXAT CR treated patients (ages 19-72) who participated in short-term (10-week) placebo-controlled trials in panic disorder in which patients were dosed in a range of 12.5 to 75 mg/day. Table 4 enumerates adverse events reported at an incidence of 1% or greater among adult patients treated with SEROXAT CR who participated in a short-term (12-week) double-blind, placebo-controlled trial in Table 5 social anxiety disorder in which patients were dosed at a range of 12.5 to 37.5 mg/day enumerates adverse events that occurred at an incidence of 1% or more among SEROXAT CR treated patients who participated in three 12-week placebo-controlled trials in PMDD in which patients were dosed at 12.5 mg/day or 25 mg/day and in one 12-week placebo-controlled trial in which patients were dosed for 2 weeks prior to the onset of menses (luteal phase dosing) at 12.5 mg/day or 25 mg/day. Reported adverse events were classified using a standard COSTART-based dictionary terminology. 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 frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Table 1 Treatment-Emergent Adverse Events Occurring In ≥ 1% of SEROXAT CR Patients in a Pool of Two Studies in Depression[1,2]

Body System/Adverse Event	% Reporting Event	
	SEROXAT CR (n=212)	**Placebo (n=211)**
Body as a Whole		
Headache	27%	20%
Asthenia	14%	9%
Infection[3]	8%	5%
Abdominal Pain	7%	4%
Back Pain	5%	3%
Trauma[4]	5%	1%
Pain[5]	3%	1%
Allergic Reaction[6]	2%	1%
Cardiovascular System		
Tachycardia	1%	0%
Vasodilatation[7]	2%	0%
Digestive System		
Nausea	22%	10%
Diarrhea	18%	7%
Dry Mouth	15%	8%
Constipation	10%	4%
Flatulence	6%	4%

Decreased Appetite	4%	2%
Vomiting	2%	1%
Nervous System		
Somnolence	22%	8%
Insomnia	17%	9%
Dizziness	14%	4%
Libido Decreased	7%	3%
Tremor	7%	1%
Hypertonia	3%	1%
Paresthesia	3%	1%
Agitation	2%	1%
Confusion	1%	0%
Respiratory System		
Yawn	5%	0%
Rhinitis	4%	1%
Cough Increased	2%	1%
Bronchitis	1%	0%
Skin and Appendages		
Sweating	6%	2%
Photosensitivity	2%	0%
Special Senses		
Abnormal Vision[8]	5%	1%
Taste Perversion	2%	0%
Urogenital System		
Abnormal Ejaculation[9,10]	26%	1%
Female Genital Disorder[9,11]	10%	<1%
Impotence[9]	5%	3%
Urinary Tract Infection	3%	1%
Menstrual Disorder[9]	2%	<1%
Vaginitis[9]	2%	0%

1. Adverse events for which the SEROXAT CR (paroxetine hydrochloride) reporting incidence was less than or equal to the placebo incidence are not included. These events are: abnormal dreams, anxiety, arthralgia, depersonalization, dysmenorrhea, dyspepsia, hyperkinesia, increased appetite, myalgia, nervousness, pharyngitis, purpura, rash, respiratory disorder, sinusitis, urinary frequency, and weight gain.
2. <1% means greater than zero and less than 1%.
3. Mostly flu.
4. A wide variety of injuries with no obvious pattern.
5. Pain in a variety of locations with no obvious pattern.
6. Most frequently seasonal allergic symptoms.
7. Usually flushing.
8. Mostly blurred vision.
9. Based on the number of males or females.
10. Mostly anorgasmia or delayed ejaculation.
11. Mostly anorgasmia or delayed orgasm.

Table 2 Treatment-Emergent Adverse Events Occurring in ≥ 5% of SEROXAT CR Patients in a Study of Elderly Patients with Depression[1,2]

Body System/Adverse Event	**% Reporting Event**	
	SEROXAT CR (n=104)	**Placebo (n=109)**
Body as a Whole		
Headache	17%	13%
Asthenia	15%	14%
Trauma	8%	5%

Infection	6%	2%
Digestive System		
Dry Mouth	18%	7%
Diarrhea	15%	9%
Constipation	13%	5%
Dyspepsia	13%	10%
Decreased Appetite	12%	5%
Flatulence	8%	7%
Nervous System		
Somnolence	21%	12%
Insomnia	10%	8%
Dizziness	9%	5%
Libido Decreased	8%	<1%
Tremor	7%	0%
Skin and Appendages		
Sweating	10%	<1%
Urogenital System		
Abnormal Ejaculation[3,4]	17%	3%
Impotence[3]	9%	3%

1. Adverse events for which the SEROXAT CR (paroxetine hydrochloride) reporting incidence was less than or equal to the placebo incidence are not included. These events are nausea and respiratory disorder.
2. <1% means greater than zero and less than 1%.
3. Based on the number of males.
4. Mostly anorgasmia or delayed ejaculation.

Table 3 Treatment-Emergent Adverse Events Occurring in ≥ 1% of SEROXAT CR Patients in a Pool of Three Panic Disorder Studies[1,2]

Body System/Adverse Event	% Reporting Event	
	SEROXAT CR (n=444)	Placebo (n=445)
Body as a Whole		
Asthenia	15%	10%
Abdominal Pain	6%	4%
Trauma[3]	5%	4%
Cardiovascular System		
Vasodilation[4]	3%	2%
Digestive System		
Nausea	23%	17%
Dry Mouth	13%	9%
Diarrhea	12%	9%
Constipation	9%	6%
Decreased Appetite	8%	6%
Metabolic/Nutritional Disorders		
Weight Loss	1%	0%
Musculoskeletal System		
Myalgia	5%	3%
Nervous System		
Insomnia	20%	11%
Somnolence	20%	9%
Libido Decreased	9%	4%
Nervousness	8%	7%
Tremor	8%	2%
Anxiety	5%	4%
Agitation	3%	2%
Hypertonia[5]	2%	<1%
Myoclonus	2%	<1%
Respiratory System		
Sinusitis	8%	5%
Yawn	3%	0%
Skin and Appendages		
Sweating	7%	2%
Special Senses		
Abnormal Vision[6]	3%	<1%

Urogenital System		
Abnormal Ejaculation[7,8]	27%	3%
Impotence[7]	10%	1%
Female Genital Disorders[9,10]	7%	1%
Urinary Frequency	2%	<1%
Urination Impaired	2%	<1%
Vaginitis[9]	1%	<1%

1. Adverse events for which the SEROXAT CR reporting rate was less than or equal to the placebo rate are not included. These events are: abnormal dreams, allergic reaction, back pain, bronchitis, chest pain, concentration impaired, confusion, cough increased, depression, dizziness, dysmenorrhea, dyspepsia, fever, flatulence, headache, increased appetite, infection, menstrual disorder, migraine, pain, paresthesia, pharyngitis, respiratory disorder, rhinitis, tachycardia, taste perversion, thinking abnormal, urinary tract infection, and vomiting.
2. <1% means greater than zero and less than 1%.
3. Various physical injuries.
4. Mostly flushing.
5. Mostly muscle tightness or stiffness.
6. Mostly blurred vision.
7. Based on the number of male patients.
8. Mostly anorgasmia or delayed ejaculation.
9. Based on the number of female patients.
10. Mostly anorgasmia or difficulty achieving orgasm.

Table 4 Treatment-Emergent Adverse Effects Occurring in ≥ 1% of Patients Treated with SEROXAT CR in a Social Phobia (Social Anxiety Disorder) Study[1,2]

Body System/Adverse Event	**% Reporting Event**	
	SEROXAT CR (n=186)	**Placebo (n=184)**
Body as a Whole		
Headache	23%	17%
Asthenia	18%	7%
Abdominal pain	5%	4%
Back pain	4%	1%
Trauma[3]	3%	<1%
Allergic reaction[4]	2%	<1%
Chest pain	1%	<1%
Cardiovascular System		
Hypertension	2%	0%
Migraine	2%	1%
Tachycardia	2%	1%
Digestive System		
Nausea	22%	6%
Diarrhea	9%	8%
Constipation	5%	2%
Dry mouth	3%	2%
Dyspepsia	2%	<1%
Decreased appetite	1%	<1%
Tooth disorder	1%	0%
Metabolic/Nutritional Disorders		
Weight gain	3%	1%
Weight loss	1%	0%
Nervous System		
Insomnia	9%	4%
Somnolence	9%	4%
Libido decreased	8%	1%
Dizziness	7%	4%
Tremor	4%	2%
Anxiety	2%	1%
Concentration impaired	2%	0%
Depression	2%	1%
Myoclonus	1%	<1%
Paresthesia	1%	<1%
Respiratory System		
Yawn	2%	0%
Skin and Appendages		
Sweating	14%	3%
Eczema	1%	0%

Special Senses		
Abnormal vision[5]	2%	0%
Abnormality of accommodation	2%	0%
Urogenital System		
Abnormal ejaculation[6,7]	15%	1%
Impotence[6]	9%	0%
Female genital disorders[8,9]	3%	0%

1. Adverse events for which the SEROXAT CR reporting rate was less than or equal to the placebo rate are not included. These events are: dysmenorrhea, flatulence, gastroenteritis, hypertonia, infection, pain, pharyngitis, rash, respiratory disorder, rhinitis, and vomiting.
2. <1% means greater than zero and less than 1%
3. Various physical injuries.
4. Most frequently seasonal allergic symptoms.
5. Mostly blurred vision.
6. Based on the number of male patients.
7. Mostly anorgasmia or delayed ejaculation.
8. Based on the number of female patients.
9. Mostly anorgasmia or difficulty achieving orgasm

Table 5 Treatment-Emergent Adverse Events Occurring in >1% of SEROXAT CR Patients in a Pool of Three Premenstrual Dysphoric Disorder Studies [1,2] or in 1 Premenstrual Dysphoric Disorder Study with Luteal Phase Dosing

Body System/Adverse Event	% Reporting Event Continuous Dosing		% Reporting Event Luteal Phase Dosing	
	SEROXAT CR (n=681)	Placebo (n=349)	SEROXAT CR (n=246)	Placebo (n=120)
Body as a Whole				
Asthenia	17%	6%	15%	4%
Headache	15%	12%	-	-
Infection	6%	4%	-	-
Abdominal pain	-	-	3%	0%
Cardiovascular System				
Migraine	1%	<1%	-	-
Digestive System				
Nausea	17%	7%	18%	2%
Diarrhea	6%	2%	6%	0%
Constipation	5%	1%	2%	<1%
Dry Mouth	4%	2%	2%	<1%
Increased Appetite	3%	<1%	-	-
Decreased Appetite	2%	<1%	2%	0%
Dyspepsia	2%	1%	2%	2%
Gingivitis	-	-	1%	0%
Metabolic and Nutritional Disorders				
Generalized Edema	-	-	1%	<1%
Weight Gain	-	-	1%	<1%
Musculoskeletal System				
Arthralgia	2%	1%	-	-
Nervous System				
Libido Decreased	12%	5%	9%	6%
Somnolence	9%	2%	3%	<1%
Insomnia	8%	2%	7%	3%
Dizziness	7%	3%	6%	3%
Tremor	4%	<1%	5%	0%
Concentration Impaired	3%	<1%	1%	0%
Nervousness	2%	<1%	3%	2%
Anxiety	2%	1%	-	-
Lack of Emotion	2%	<1%	-	-
Depression	-	-	2%	<1%
Vertigo	-	-	2%	<1%
Abnormal Dreams	1%	<1%	-	-
Amnesia	-	-	1%	0%
Respiratory System				
Sinusitis	-	-	4%	2%
Yawn	2%	<1%	-	-
Bronchitis	-	-	2%	0%
Cough Increased	1%	<1%	-	-
Skin and Appendages				
Sweating	7%	<1%	6%	<1%
Special Senses				
Abnormal Vision	-	-	1%	0%

Urogenital System				
Female Genital Disorders[3]	8%	1%	2%	0%
Menorrhagia	1%	<1%	-	-
Vaginal Moniliasis	1%	<1%	-	-
Menstrual Disorder	-	-	1%	0%

1. Adverse events for which the SEROXAT CR reporting rate was less than or equal to the placebo rate are not included. These events are: abdominal pain, back pain, pain, trauma, weight gain, myalgia, pharyngitis, respiratory disorder, rhinitis, sinusitis, pruritis, dysmenorrhea, menstrual disorder, urinary tract infection, vomiting
2. <1% means greater than zero and less than 1%
3. Mostly anorgasmia or difficulty achieving orgasm

Dose Dependency of Adverse Events: The following table shows results in PMDD trials of common adverse events, defined as events with an incidence of 1% with 25 mg of SEROXAT CR that was at least twice that with 12.5 mg of SEROXAT CR and with placebo.

Table 6 Incidence of Common Adverse Events in Placebo, 12.5 mg and 25 mg of SEROXAT CR in a Pool of 3 Fixed-Dose Continuous Dosing PMDD Trials

	SEROXAT CR 25 mg (n = 348)	**SEROXAT CR 12.5 mg (n = 333)**	**Placebo (n = 349)**
Common Adverse Event			
Sweating	8.9%	4.2%	0.9%
Tremor	6.0%	1.5%	0.3%
Concentration Impaired	4.3%	1.5%	0.6%
Yawn	3.2%	0.9%	0.3%
Paresthesia	1.4%	0.3%	0.3%
Hyperkinesia	1.1%	0.3%	0.0%
Vaginitis	1.1%	0.3%	0.3%

A comparison of adverse event rates in a fixed-dose study comparing immediate-release paroxetine with placebo in the treatment of depression revealed a clear dose dependency for some of the more common adverse events associated with the use of immediate-release paroxetine.

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

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

Incidence of Sexual Adverse Events in Pooled Data

The percentage of patients reporting symptoms of sexual dysfunction in the pool of two placebo-controlled trials in non-elderly patients with depression, in the pool of three placebo-controlled trials in patients with panic disorder, in the placebo-controlled trial in patients with social anxiety disorder, and in the luteal phase dosing and in the pool of 3 placebo-controlled trials in female patients with PMDD are as follows:

Table 7 The Percentage of Patients Reporting Symptoms of Sexual Dysfunction

	Depression		Panic Disorder		Social Anxiety Disorder		PMDD Continuous Dosing		PMDD Luteal Phase Dosing	
	SEROXAT CR	Placebo	SEROXAT CR	Placebo	SEROXAT CR	Placebo	SEROXAT CR	Placebo	SEROXAT CR	Placebo
n (males)	**78**	**78**	**162**	**194**	**88**	**97**	**n/a**	**n/a**	**n/a**	**n/a**
Decreased libido	10%	5%	9%	6%	13%	1%	n/a	n/a	n/a	n/a
Ejaculatory disturbance	26%	1%	27%	3%	15%	1%	n/a	n/a	n/a	n/a
Impotence	5%	3%	10%	1%	9%	0%	n/a	n/a	n/a	n/a
n (females)	**134**	**133**	**282**	**251**	**98**	**87**	**681**	**349**	**246**	**120**
Decreased libido	4%	2%	8%	2%	4%	1%	12%	5%	9%	6%
Orgasmic disturbance	10%	<1%	7%	1%	3%	0%	8%	1%	2%	0%

There are no adequate, controlled studies examining sexual dysfunction with paroxetine treatment.
Paroxetine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae.
While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Laboratory Changes - Cholesterol
Clinically and statistically relevant increases in cholesterol levels have been noted in studies using paroxetine (see *Warnings and Precautions*).
Of the patients in placebo-controlled clinical trials for whom baseline and on-treatment measurements were taken, total serum levels of cholesterol showed a mean increase of ~ 1.5 mg/dL in paroxetine-treated patients (n = 653), compared to a mean decrease of ~ 5.0 mg/dL in placebo-treated patients (n = 379). Increases from baseline of 45 mg/dL or greater were recorded in 6.6% of paroxetine-treated patients compared to 2.6% of placebo-treated patients.

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

Other Events Observed During the Clinical Development of Paroxetine
The following adverse events were reported during the clinical development of SEROXAT CR tablets and/or the clinical development of the immediate-release formulation of paroxetine. Adverse events for which frequencies are provided below occurred in clinical trials with the controlled release formulation of paroxetine. During its premarketing assessment in depression, panic disorder, social anxiety disorder, and PMDD, multiple doses of SEROXAT CR were administered to 1627 patients in phase 3 double-blind, controlled, outpatient studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.
In the tabulations that follow, reported adverse events were classified using a COSTART-based dictionary. The frequencies presented, therefore, represent the proportion of the 1627 patients exposed to SEROXAT CR controlled release who experienced an event of the type cited on at least one occasion while receiving SEROXAT CR. All reported events are included except those already listed in Tables 1, 2, 3, 4 or 5 and those events where a drug cause was remote. If the COSTART term for an event was so general as to be uninformative, it was deleted or, when possible, replaced with a more informative term. It is important to emphasize that although the events reported occurred during treatment with paroxetine, they were not necessarily caused by it.
Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Adverse events for which frequencies are not provided occurred during the premarketing assessment of immediate-release paroxetine in phase 2 and 3 studies of depression, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder, and posttraumatic stress disorder. The conditions and duration of exposure to immediate-release paroxetine varied greatly and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose and titration studies. Only those events not previously listed for controlled release paroxetine are included. The extent to which these events may be associated with SEROXAT CR is unknown.
Events are listed alphabetically within the respective body system. Events of major clinical importance are also described in the *Warnings and Precautions* section.

Body as a Whole: Infrequent were chills, face edema, fever, flu syndrome, malaise; rare were abscess, anticholinergic syndrome, hypothermia; also observed were adrenergic syndrome, neck rigidity, sepsis.

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

Cardiovascular System: Infrequent were angina pectoris, bradycardia, bundle branch block, hematoma, hypertension, hypotension, palpitation, postural hypotension, supraventricular tachycardia, syncope; rare was bundle branch block; also observed were arrhythmia nodal, atrial fibrillation, cerebrovascular accident, congestive heart failure, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus,

supraventricular extrasystoles, thrombophlebitis, thrombosis, vascular headache, ventricular extrasystoles.

Digestive System: Infrequent were bruxism, dysphagia, eructation, gastritis, gastroenteritis, gastroesophageal reflux, gingivitis, hemorrhoids, liver function tests abnormal, melena, pancreatitis, rectal hemorrhage, toothache, ulcerative stomatitis; rare were colitis, glossitis, gum hyperplasia, hepatosplenomegaly, increased salivation, intestinal obstruction, peptic ulcer, stomach ulcer, throat tightness; also observed were aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, jaundice, mouth ulceration, salivary gland enlargement, sialadenitis, stomatitis, tongue discoloration, tongue edema.

Endocrine System: Infrequent were ovarian cyst, testes pain; rare were diabetes mellitus, hyperthyroidism; also observed were, goiter, hypothyroidism, thyroiditis.

Hemic and Lymphatic System: Infrequent were anemia, eosinophilia, hypochromic anemia, leukocytosis, leukopenia, lymphadenopathy, purpura; rare was thrombocytopenia; also observed were anisocytosis, basophilia, bleeding time increased, lymphedema, lymphocytosis, lymphopenia, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia.

Metabolic and Nutritional Disorders: Frequent were increases in cholesterol levels. Infrequent were generalized edema, hyperglycemia, hyperkalemia, hypokalemia, peripheral edema, SGOT increased, SGPT increased, thirst; rare were billirubinemia, dehydration, hyperkalemia, obesity; also observed were alkaline phosphatase increased, BUN increased, creatinine phosphokinase increased, gamma globulins increased, gout, hypercalcemia, hyperphosphatemia, hypocalcemia, hypoglycemia, hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased.

Musculoskeletal System: Infrequent were arthritis, bursitis, tendonitis; rare were myasthenia, myopathy, myositis; also observed were generalized spasm, osteoporosis, tenosynovitis, tetany.

Nervous System: Frequent was depression; infrequent were amnesia, convulsion, depersonalization, dystonia, emotional lability, hallucinations, hyperkinesia, hypesthesia, hypokinesia, incoordination, libido increased, neuralgia, neuropathy, nystagmus, paralysis, vertigo; rare were ataxia, coma, diplopia, dyskinesia, hostility, paranoid reaction, torticollis, withdrawal syndrome; also observed were abnormal gait, akathisis, akinesia, aphasia, choreoathetosis, circumoral paresthesia, delirium, delusions, dysarthria, euphoria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hyperalgesia, irritability, manic reaction, manic-depressive reaction, meningitis, myelitis, peripheral neuritis, psychosis, psychotic depression, reflexes decreased, reflexes increased, stupor, trismus.

Respiratory System: Frequent was pharyngitis; infrequent were asthma, dyspnea, epistaxis, laryngitis, pneumonia; rare was stridor; also observed were dysphonia, emphysema, hemoptysis, hiccups, hyperventilation, lung fibrosis, pulmonary edema, respiratory flu, sputum increased.

Skin and Appendages: Frequent was rash; infrequent were acne, alopecia, dry skin, eczema, pruritus, urticaria; rare were exfoliative dermatitis, furunculosis, pustular rash, seborrhea; also observed were angioedema, ecchymosis, erythema multiforme, erythema nodosum, hirsutism, maculopapular rash, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased,

vesiculobullous rash; very rare were severe cutaneous adverse reactions (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis).

Special Senses: Infrequent were conjunctivitis, earache, keratoconjunctivitis, mydriasis, photophobia, retinal hemorrhage, tinnitus; rare were blepharitis, visual field defect; also observed were amblyopia, anisocoria, blurred vision, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, glaucoma, hyperacusis, night blindness, parosmia, ptosis, taste loss.

Urogenital System: Frequent was dysmennorhea*; infrequent were albuminuria, amenorrhea*, breast pain*, cystitis, dysuria, prostatitis*, urinary retention; rare were breast enlargement*, breast neoplasm*, female lactation, hematuria, kidney calculus, metrorrhagia, nephritis, nocturia, pregnancy and puerperal disorders*, salpingitis, urinary incontinence, uterine fibroids enlarged*; also observed were breast atrophy, ejaculatory disturbance, endometrial disorder, epididymitis, fibrocystic breast, leukorrhea, mastitis, oliguria, polyuria, pyuria, urethritis, urinary casts, urinary urgency, urolith, uterine spasm, vaginal hemorrhage.

*Based on the number of men and women as appropriate.

Post-Marketing Adverse Drug Reactions

Adverse events not listed above which have been reported since market introduction in patients taking immediate-release paroxetine hydrochloride include acute pancreatitis, hepatic events such as elevation of hepatic enzymes, and hepatitis, sometimes associated with jaundice, and/or liver failure (in very rare circumstances, with fatal outcomes), Guillain-Barré syndrome, priapism, thrombocytopenia, aggravated hypertension, syndrome of inappropriate ADH secretion, symptoms suggestive of hyperprolactinemia and galactorrhea, menstrual disorders (including menorrhagia, metrorrhagia and amenorrhea), blurred vision, extrapyramidal symptoms which have included akathisia, (characterized by an inner sense of restlessness and psychomotor agitation such as an inability to sit or stand still usually associated with subjective distress), bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide, tremor and trismus, abnormal dreams (including nightmares), restless legs syndrome (RLS), vomiting, neuroleptic malignant syndrome-like events; serotonin syndrome (see *Warnings and Precautions*), persistent pulmonary hypertension (PPHN; see also *Warnings and Precautions*). There has been a case report of an elevated phenytoin level after 4 weeks of immediate-release paroxetine and phenytoin co-administration. There has been a case report of severe hypotension when immediate-release paroxetine was added to chronic metoprolol treatment. The causal relationship between immediate-release paroxetine and the emergence of these events has not been established.

There have been spontaneous reports of adverse events upon the discontinuation of SEROXAT CR and other selective serotonin reuptake inhibitors (particularly when abrupt) (see *Warnings and Precautions* and *Adverse Reactions*).

OVERDOSE

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 and Signs

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, tachycardia, hyperhydrosis, mydriasis, convulsion, paraesthesia, 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 or ECG changes have occasionally been reported.

Treatment

No specific antidote is known. The 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 SEROXAT CR, 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.

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

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

PHARMACOLOGICAL PROPERTIES

Mechanism of Action

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

Paroxetine is a phenylpiperidine derivative which is chemically unrelated to the tricyclic or tetracyclic antidepressants. In receptor binding studies, paroxetine did not exhibit significant affinity for the adrenergic (α1, α2, β), dopaminergic, serotonergic ($5HT_1$, $5HT_2$), 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.

Pharmacokinetic properties

SEROXAT CR tablets contain a degradable polymeric matrix designed to control the dissolution rate of paroxetine over a period of approximately 4 to 5 hours. In addition to controlling the rate of drug release *in vivo*, an enteric coat delays the start of drug release until SEROXAT CR tablets have left the stomach.

Absorption

Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt. In a study in which normal male and female subjects (n=23) received single oral doses of SEROXAT CR at four dosage strengths (12.5 mg, 25 mg, 37.5 mg and 50 mg), paroxetine $C_{max.}$and AUC $_{0\text{-}inf}$ increased disproportionately with dose (as seen also with immediate-release formulations). Mean C_{max} and $AUC_{0\text{-}inf}$ values at these doses were 2.0, 5.5, 9.0, and 12.5 ng/mL, and 121, 261, 338, and 540 ng/hr/mL, respectively. T_{max} was observed typically between 6 and 10 hours post-dose, reflecting a reduction in absorption rate compared with immediate-release formulations. The mean elimination half-life of paroxetine was 15 to 20 hours throughout this range of single SEROXAT CR doses. The bioavailability of 25 mg SEROXAT CR is not affected by food.

During repeated administration of SEROXAT CR (25 mg once daily), steady state was reached within two weeks (i.e., comparable to immediate-release formulations). In a repeat-dose study in which normal male and female subjects (n=23) received SEROXAT CR (25 mg daily), mean steady state C_{max}, C_{min} and $AUC_{0\text{-}24}$ values were 30 ng/mL, 20 ng/mL and 550 ng./hr./mL, respectively.
Based on studies using immediate-release formulations, steady-state drug exposure based on $AUC_{0\text{-}24}$ was several-fold greater than would have been predicted from single-dose data. The excess accumulation is a consequence of the fact that one of the enzymes that metabolizes paroxetine is readily saturable.
In steady-state dose proportionality studies involving elderly and nonelderly patients, at doses of the immediate-release formulation of 20 to 40 mg daily for the elderly and 20 to 50 mg daily for the nonelderly, some nonlinearity was observed in both populations, again reflecting a saturable metabolic pathway. In comparison to C_{min} values after 20 mg daily, values after 40 mg daily were only about 2 to 3 times greater than doubled.
In healthy young volunteers receiving a 20 mg daily dose of immediate-release paroxetine for 15 days, the mean maximal plasma concentration was 41 ng/mL at steady state (see Table 8). Peak plasma levels generally occurred within 3 to 7 hours.

Distribution

Approximately 95% of the paroxetine present is protein bound at therapeutic concentrations.

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 (IID_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 *Interactions*). The

majority of the dose appears to be oxidized to a catechol intermediate which is converted to highly polar glucuronide and sulphate metabolites through methylation and conjugation reactions. The glucuronide and sulphate conjugates of paroxetine are about > 10,000 and 3,000 times less potent, respectively, than the parent compound as inhibitors of 5-HT reuptake in rat brain synaptosomes.

Excretion

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

Special Patient Populations

Geriatrics: In elderly subjects, increased steady-state plasma concentrations and prolongation of the elimination half life were observed relative to younger adult controls (Table 8). 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 with immediate-release paroxetine, in subjects with severe hepatic dysfunction, suggest that the clearance of paroxetine is markedly reduced in this patient group (see Table 8). 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*).

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 9).

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*).

Table 8 Steady state pharmacokinetics of immediate-release 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.

Table 9 Pharmacokinetics of immediate-release 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

CLINICAL TRIALS

Depression

The efficacy of SEROXAT CR controlled-release tablets as a treatment for depression has been established in two 12-week, flexible dose, placebo-controlled studies of patients with DSM-IV Major Depressive Disorder. One study included patients in the age range 18-65 years, and a second study included elderly patients, ranging in age from 60-88. In both studies, SEROXAT CR was shown to be significantly more effective than placebo in treating depression as measured by the following: Hamilton Depression Rating Scale Total Score (HDRS), the Hamilton depressed mood item, and the Clinical Global Impression (CGI)-Severity of Illness score.

A study of outpatients with recurrent major depressive disorder who had responded to immediate-release paroxetine tablets (HDRS total score < 8) during an initial 8-week open-treatment phase and were then randomized to continuation on immediate-release paroxetine tablets 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).

Panic Disorder
The effectiveness of SEROXAT CR in the treatment of panic disorder was evaluated in three 10-week, multicentre, flexible dose studies (Studies 1, 2, and 3) comparing paroxetine controlled-release (12.5 to 75 mg daily) to placebo in adult outpatients who had panic disorder (DSM-IV), with or without agoraphobia. These trials were assessed on the basis of their outcomes on three variables: (1) the proportions of patients free of full panic attacks at endpoint; (2) change from baseline to endpoint in the median number of full panic attacks; and (3) change from baseline to endpoint in the median Clinical Global Impression Severity score. For Studies 1 and 2, SEROXAT CR was consistently superior to placebo on two of these three variables. Study 3 failed to consistently demonstrate a significant difference between SEROXAT CR and placebo on any of these variables.
For all three studies, the mean SEROXAT CR dose for completers at endpoint was approximately 50 mg/day. Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

Social Anxiety Disorder
The effectiveness of SEROXAT CR in the treatment of social anxiety disorder was demonstrated in a 12-week, multicentre, double-blind, flexible dose, placebo-controlled study of adult outpatients with a primary diagnosis of social anxiety disorder (DSM-IV). In the study, the effectiveness of SEROXAT CR (12.5 to 37.5 mg daily) compared to placebo was evaluated on the basis of (1) change from baseline in the Liebowitz Social Anxiety Scale (LSAS) total score and (2) the proportion of responders who scored 1 or 2 (very much improved or much improved) on the Clinical Global Impression (CGI) Global Improvement score.
SEROXAT CR demonstrated statistically significant superiority over placebo on both the LSAS total score and the CGI Improvement responder criterion. For patients who completed the trial, 64% of patients treated with SEROXAT CR compared to 34.7% of patients treated with placebo were CGI Improvement responders.
Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of gender. Subgroup analyses of studies utilizing the immediate release formulation of paroxetine generally did not indicate differences in treatment outcomes as a function of age, race or gender.

Premenstrual Dysphoric Disorder (PMDD)
The effectiveness of SEROXAT CR for the treatment for Premenstrual Dysphoric Disorder (PMDD) has been assessed in 4 placebo-controlled trials. Patients in these trials met DSM-IV criteria for PMDD. In 3 studies, patients (n=1030) were treated with SEROXAT CR 12.5 or 25 mg/day or placebo continuously throughout the menstrual cycle for a period of 3 months. In the fourth study, patients (n=366) were treated for the 2 weeks prior to the onset of menses (luteal phase dosing, also known as intermittent dosing) with SEROXAT CR 12.5 or 25 mg/day or placebo for a period of 3 months. The Visual Analogue Scale (VAS)-Mood score which consists of the mean VAS scores for the 4 core PMDD symptoms, irritability, tension, depressed mood and affective lability, was the primary efficacy measure. SEROXAT CR 25 mg/day as continuous dosing and as luteal phase dosing were significantly more effective than placebo as measured by change from baseline luteal phase VAS-Mood score in all 4 studies. SEROXAT CR 12.5 mg/day was significantly more effective than placebo as measured by change from baseline luteal phase VAS-Mood score in 2 of the 3 continuous studies and in the one luteal phase study.
There is insufficient information to determine the effect of race or age on outcome in these studies.

Patients on systemic hormonal contraceptives were excluded from these trials. Therefore, the efficacy of SEROXAT CR in combination with systemic (including oral) hormonal contraceptives for the treatment of PMDD is unknown.

TOXICOLOGY

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

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

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

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

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

Teratology Studies
In male rats, chronic administration of a 50 mg/kg dose has been associated with granulomatous reactions in the epididymides accompanied by atrophy and degeneration of the seminiferous tubules. There were no biologically significant effects on fertility of female rats but corpora lutea count was slightly reduced and preimplantation loss slightly increased at 50 mg/kg in association with marked maternal toxicity.
Reproduction studies were performed in rats and rabbits at doses up to 42 and 5 times the maximum recommended daily human dose (60 mg) on a mg/kg basis. These are 8.3 (rat) and 1.7 (rabbit) times the maximum recommended human dose on a mg/m^2 basis. These studies have revealed no evidence of teratogenic effects or of selective toxicity to the embryo.

Immunotoxicity Studies

Specific studies have demonstrated that paroxetine is unlikely to possess the potential for immunotoxicity.
Serum samples were obtained from depressed patients who had received 30 mg of paroxetine daily for between six and twelve months, from groups of rats on a repeat dose toxicity study in which daily doses of 1, 5 and 25 mg/kg of paroxetine were administered for 52 weeks, from guinea pigs epicutaneously exposed (topically under an occlusive patch) to paroxetine and from New Zealand White (NZW) rabbits parenterally (i.m. and s.c.) injected with paroxetine in Freund's adjuvant. In addition as a positive control, sera were obtained from NZW rabbits which had been immunized by i.m. and s.c. injections of Freund's adjuvant emulsions containing paroxetine chemically conjugated to bovine gamma globulin (BGG).
Serum antibody levels were assessed by enzyme- or radio-immunoassays (ELISA or RIA). No anti-paroxetine antibody activity was detected in serum samples from patients, from rats in the toxicity study, from guinea pigs epicutaneously exposed to paroxetine, or from rabbits parenterally injected with paroxetine. Serum anti-paroxetine antibody was detected in rabbits immunized with Freund's adjuvant emulsions containing paroxetine coupled with BGG, verifying that the RIA system employed was capable of detecting antibodies directed against paroxetine.
Paroxetine also did not induce contact sensitivity reactions in guinea pigs following epicutaneous exposure.

EXCIPIENTS

SEROXAT CR 12.5 mg tablets contain the following excipients:
Lactose Monohydrate, Hypromellose, Povidone, Silicon dioxide, Magnesium Stearate, Glyceryl behenate, Yellow ferric oxide, Methacrylic acid copolymer dispersion, Talc, Triethyl citrate, Opadry Yellow, YS-1-2007 (in which contains FD&C yellow no. 6 Aluminium Lake).

SEROXAT CR 25 mg tablets contain the following excipients:
Lactose Monohydrate, Hypromellose, Povidone, Silicon dioxide, Magnesium Stearate, Glyceryl behenate, Red ferric oxide, Methacrylic acid copolymer dispersion, Talc, Triethyl citrate, Opadry Pink, Y-1-1262.

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Patient Information Leaflet: Information for the users
SEROXAT CR Controlled-Release Tablets
(Paroxetine Hydrochloride Hemihydrate)

ABOUT THIS MEDICATION

What SEROXAT CR is used for:
SEROXAT CR 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
- premenstrual dysphoric disorder (PMDD) - where you may have episodes of major depression, severe mood changes/anxiety, irritability, physical pain and difficulty doing day to day tasks in the few weeks before your period

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

When SEROXAT CR should not be used:
Do not use SEROXAT CR if you are:
- allergic to the medicinal ingredient or any of the components of its formulation
- currently taking or have recently taken monoamine oxidase (MAO) inhibitor antidepressants (e.g. phenelzine sulphate, moclobemide)
- currently taking or have recently taken thioridazine or pimozide

What the medicinal ingredient is:
Paroxetine hydrochloride.

What the important nonmedicinal ingredients are:
Lactose monohydrate.

Other non-medicinal ingredients include:
For SEROXAT CR 12.5 mg tablets:
Hypromellose, Povidone, Silicon dioxide, Magnesium Stearate, Glyceryl behenate, Yellow ferric oxide, Methacrylic acid copolymer dispersion, Talc, Triethyl citrate, Opadry Yellow, YS-1-2007 (in which contains FD&C yellow no. 6 Aluminium Lake).

For SEROXAT CR 25 mg tablets:
Hypromellose, Povidone, Silicon dioxide, Magnesium Stearate, Glyceryl behenate, Red ferric oxide, Methacrylic acid copolymer dispersion, Talc, Triethyl citrate, Opadry Pink, Y-1-1262.

There is no ethanol, gluten, sulfite, or tartrazine in SEROXAT CR.

What dosage forms SEROXAT CR comes in:
SEROXAT CR is available as tablets containing 12.5 mg (yellow) or 25 mg (pink) paroxetine (as paroxetine hydrochloride).

WARNINGS AND PRECAUTIONS

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

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

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

Some patients may feel worse when first starting or changing the dose of drugs such as SEROXAT CR. 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 SEROXAT CR 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 SEROXAT CR on your own.

Taking medicines like SEROXAT CR may increase your risk of experiencing sexual problems, which may continue after SEROXAT CR has been discontinued, including for months or years afterwards in some cases. Tell your doctor if you experience symptoms such as a decrease in sexual desire, performance or satisfaction.
Taking SEROXAT CR 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 SEROXAT CR may affect your sperm. Fertility in some men may be reduced while taking SEROXAT CR.

BEFORE you use SEROXAT CR 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 reactions to medications, food etc.
- if you are taking hormonal oral contraceptives and are being prescribed SEROXAT CR for Premenstrual Dysphoric Disorder
- 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 if you were told you have osteoporosis or risk factors for osteoporosis
- if you have a bleeding disorder or have been told that you have low platelets
- if you are allergic to a particular yellow dye known as FD&C Yellow No. 6 aluminium lake

Effects on Pregnancy and Newborns
As stated above, ask your doctor or pharmacist for advice before taking any medicine including SEROXAT CR. **If you are already taking/using SEROXAT CR 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 SEROXAT CR in early stages of pregnancy:
Some studies have suggested an increased risk of birth defects, particularly heart defects, in babies whose mothers received SEROXAT CR 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 SEROXAT CR 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 SEROXAT CR.

Taking SEROXAT CR in later stages of pregnancy:
Possible complications at birth (from taking any newer antidepressant, including SEROXAT CR):
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 SEROXAT CR:
The use of SEROXAT CR 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 SEROXAT CR 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:

SEROXAT CR can cause an acute attack of glaucoma. Having your eyes examined before you take SEROXAT CR 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 SEROXAT CR if you are taking or have recently taken (within the last 2 weeks) monoamine oxidase inhibitors, methylthioninium chloride (methylene blue), thioridazine or pimozide.

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

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

PROPER USE OF THIS MEDICATION

Usual dose:

How to take SEROXAT CR

- *Depression, Panic Disorder and Social Phobia (social anxiety disorder)*: It is very important that you take SEROXAT CR exactly as your doctor has instructed. The starting dose for depression is 25 mg once daily and for panic disorder it is 12.5 mg once daily. Generally most people take between 12.5 mg to 37.5 mg of SEROXAT CR per day for social phobia (social anxiety disorder).
- *Premenstrual Dysphoric Disorder (PMDD)*: For premenstrual dysphoric disorder (PMDD) the usual dose is 12.5 mg once daily starting 14 days prior to the expected onset of your period, and stopping on the first day of your period. Your doctor may change the dose or dosing schedule,

depending on how you respond to your medication. PMDD is a disorder which should not be confused with the symptoms of Premenstrual Syndrome (PMS). Your doctor must confirm a diagnosis of PMDD before you can take SEROXAT CR.

- Take your tablets in the morning, preferably with food. You should swallow the tablets whole with water. Do not chew or crush 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.
- You should talk to your doctor before you stop taking your medication on your own.

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

Missed Dose:
If you forget to take your tablet in the morning, take it as soon as you remember. Take your next dose at the normal time the next morning, then carry on as before. Do not try to make up for a missed dose by taking a double dose the next time.

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medications, SEROXAT CR 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.

The most common side effects of SEROXAT CR 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 class of medication may lead to further decreases, which may continue after the drug is stopped.

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).

SEROXAT CR 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.

SEROXAT CR may raise cholesterol levels in some patients.

Discontinuation Symptoms

Contact your doctor before stopping or reducing your dosage of SEROXAT CR. 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 SEROXAT CR, 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 SEROXAT CR 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 SEROXAT CR, 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	Low Platelets [bruising or unusual bleeding from the skin or other areas]		√	
Uncommon	Dilated pupils		√	
Uncommon	Low blood pressure (may cause dizziness, lightheadedness or fainting when standing up from a sitting down or lying position)		√	
Rare	Severe allergic reactions [red and lumpy skin rash, itching, hives, 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 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 SEROXAT CR *contact your doctor or pharmacist.*

HOW TO STORE IT

- Keep all medication out of sight and reach of children.
- Store as directed on the carton.
- Keep container tightly closed.
- If your doctor tells you to stop taking SEROXAT CR, please return any leftover medicine to your pharmacist.

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