PRODUCT MONOGRAPH

PrPAXIL CR™

(paroxetine hydrochloride controlled release tablets)

12.5 or 25 mg paroxetine (as paroxetine hydrochloride)

Selective Serotonin Reuptake Inhibitor

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Table of Contents

PAXIL CR™

paroxetine hydrochloride controlled release tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	12.5 and 25 mg controlled release tablets	Lactose monohydrate. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Adults

Depression
PAXIL CR™ (paroxetine hydrochloride) is indicated for symptomatic relief of Major Depressive Disorder.

PAXIL 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 PAXIL CR™ for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Panic Disorder
PAXIL CR™ is indicated for the symptomatic treatment of panic disorder, with or without agoraphobia.

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

Social Phobia (Social Anxiety Disorder)
PAXIL 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, or social life, or causes marked distress.

Premenstrual Dysphoric Disorder
PAXIL CR™ is indicated for the symptomatic treatment of premenstrual dysphoric disorder (PMDD). The efficacy of PAXIL CR™ in the treatment of PMDD was 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% or 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 PAXIL CR™
The effectiveness of PAXIL 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. The physician who elects to use PAXIL CR™ for extended periods in these indications should periodically re-evaluate the long-term usefulness of the drug for individual patients (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 Special Populations-Geriatrics, ACTIONS AND CLINICAL PHARMACOLOGY; DOSAGE AND ADMINISTRATION).

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

CONTRAINDICATIONS

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

Monoamine Oxidase Inhibitors: In patients receiving serotonin reuptake inhibitors (SSRIs) in combination with a MAO inhibitor, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have begun treatment on a MAO inhibitor. Some cases presented with features resembling serotonin syndrome or neuroleptic malignant syndrome (See WARNINGS AND PRECAUTIONS; Serotonin Syndrome/Neuroleptic Malignant Syndrome). Therefore, PAXIL CR™ should not be used in combination with MAO inhibitors or within a minimum of 2 weeks of terminating treatment with MAO inhibitors. Treatment with PAXIL 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 PAXIL 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, PAXIL 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 PAXIL CR™ therapy before initiating treatment with thioridazine.

Pimozide: The concomitant use of PAXIL 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 Drug Interactions).

WARNINGS AND PRECAUTIONS

General

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

Pediatrics: Placebo-Controlled Clinical Trial Data

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

Discontinuation Symptoms: Patients currently taking PAXIL 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 anti-depressant drug, a gradual reduction in the dose rather than an abrupt cessationis recommended.

Discontinuation of Treatment with PAXIL 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 and electric shock sensations), agitation, anxiety, headache, tremor, confusion, diarrhea, nausea, vomiting and sweating or other symptoms which may be of clinical significance [see ADVERSE REACTIONS, Adverse Events following Discontinuation of Treatment (or Dose Reduction)-Postmarketing]. 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).

PAXIL CR™ Treatment During Pregnancy-Effects on Newborns
Post-marketing reports indicate that some neonates exposed to PAXIL CR™, SSRIs (Selective Serotonin Reuptake Inhibitors), or other newer anti-depressants 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 PAXIL CR™ during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see WARNINGS AND PRECAUTIONS, Special Populations; DOSAGE AND ADMINISTRATION, Special Patient Populations-Treatment of Pregnant Women During the Third Trimester).

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 PAXIL CR™ does not affect them adversely.

The following additional precautions are listed alphabetically.

Carcinogenesis and Mutagenesis
See TOXICOLOGY for animal data.

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

Concomitant Illnesses
Clinical experience with PAXIL CR™ or PAXIL® IR in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using PAXIL CR™ in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Dependence Liability

PAXIL CR™ or PAXIL® IR has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. Physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of PAXIL CR™.

Hematologic

Abnormal Bleeding: There have been several reports of abnormal bleeding (mostly ecchymosis) associated with paroxetine IR treatment, including a report of impaired platelet aggregation. While a causal relationship to paroxetine is unclear, impaired platelet aggregation may result from platelet serotonin depletion and contribute to such occurrences.

Skin and mucous membrane bleedings (including upper gastrointestinal bleeding) have been reported following treatment with paroxetine IR. Paroxetine CR™ should therefore be used with caution in patients concomitantly treated with drugs that give an increased risk for bleeding (e.g. anticoagulants, nonsteroidal anti-inflammatories and ASA) and in patients with a known tendency for bleeding or those with predisposing conditions.

Hepatic/Biliary/Pancreatic

Hepatic Impairment: Pharmacokinetic studies of PAXIL® IR 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. PAXIL 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, Special Patient Populations; ACTIONS AND CLINICAL PHARMACOLOGY, Hepatic Insufficiency).

Neurologic

Epilepsy: As with other antidepressants, PAXIL 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 PAXIL® IR. 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 PAXIL 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 PAXIL 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 supportine symptomatic treatment should be initiated. Due to the risk of serotonergic syndrome or neuroleptic malignant syndrome PAXIL CR™ should not be used in combination with MAO inhibitors or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in patients receiving other serotonergic drugs (triptans, lithium, tramadol, St. John's Wort, most tricyclic antidepressants) or neuroleptics/antipsychotics (see CONTRAINDICATIONS and DRUG INTERACTIONS).

Ophthalmologic

Glaucoma: As with other SSRIs, PAXIL CR™ infrequently causes mydriasis and should be used with caution in patients with narrow angle glaucoma.

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. Not withstanding, 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 PAXIL 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, Potential Association with Behavioural and Emotional Changes, Including Self-Harm**).

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

Renal

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

Special Populations

Pregnant Women: The safety of PAXIL CR™ in human pregnancy has not been established. PAXIL CR™ should not be used during pregnancy unless the potential benefit to the patient outweighs the possible risk to the fetus.

Post-marketing reports indicate that some neonates exposed to PAXIL CR™, SSRIs (Selective Serotonin Reuptake Inhibitors), or other newer anti-depressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and other newer anti-depressants, or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS AND PRECAUTIONS, Neurologic-Serotonin Syndrome/Neuroleptic Malignant Syndrome). When treating a pregnant woman with PAXIL CR™ during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION, Special Patient Populations-Treatment of Pregnant Women During the Third Trimester).

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

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

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

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

Evaluation of approximately 800 elderly patients (≥65 years) treated with PAXIL® IR (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, PAXIL 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-Table 2.). 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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Commonly Observed Adverse Events

Depression
The most commonly observed adverse events associated with the use of PAXIL CR™ in a pool of two trials (incidence of 5.0% or greater and incidence for PAXIL 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 PAXIL 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 PAXIL CR™ (incidence of 5.0% or greater and incidence for PAXIL 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 PAXIL CR™, either during continuous dosing or luteal phase dosing (incidence of 5.0% or greater and incidence for PAXIL 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 PAXIL 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 PAXIL 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 focussed 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 PAXIL CR™ and the immediate-release formulation of paroxetine hydrochloride is included in a separate subsection (see OTHER EVENTS).

Depression
Ten percent (21/212) of PAXIL 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 PAXIL CR™ compared to placebo) included the following:

	PAXIL 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 PAXIL CR™ patients discontinued due to an adverse event. Events meeting the above criteria included the following:

	PAXIL 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 PAXIL CR™ patients in panic disorder studies discontinued treatment due to an adverse event. Events meeting the above criteria included the following:

	PAXIL 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 PAXIL CR™ in the social anxiety disorder study discontinued treatment due to an adverse event. Events meeting the above criteria included the following:

	PAXIL 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 PAXIL CR™ in PMDD studies of continuous dosing discontinued treatment due to an adverse event. Nine percent (34/366) of patients treated with PAXIL 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 PAXIL CR™ compared to placebo) included the following:

	Continuous Dosing			Intermittent Dosing		
	PAXIL CR™ 25 mg (n = 348)	**PAXIL CR™ 12.5 mg (n = 333)**	**Placebo (n = 349)**	**PAXIL CR™ 25 mg (n = 116)**	**PAXIL 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 PAXIL CR™ that was at least twice that with 12.5 mg of PAXIL CR™ (as well as the placebo group).

Adverse Events following Discontinuation of Treatment (or Dose Reduction)

Clinical Trials

Adverse events while discontinuing therapy with PAXIL 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 PAXIL CR™ and 184 on placebo), utilizing daily doses of PAXIL CR™ up to 37.5 mg/day, spontaneously reported adverse events while discontinuing therapy with PAXIL 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 PAXIL 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 PAXIL CR™ including electric shock sensations (5.6% versus 0.6%), including electric shock sensations. These events were reported as serious in 1.7% (3/180) of patients who discontinued therapy with PAXIL CR™.

The following adverse events have been reported at an incidence of 2% or greater for PAXIL® IR 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 PAXIL® and PAXIL CR™ (particularly when abrupt), including but not limited to the following: dizziness, sensory disturbances (including paresthesias and electric shock sensations), 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 PAXIL CR™-treated patients, aged 18-65, 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 PAXIL 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 PAXIL 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 PAXIL CR™ who participated in a short-term (12-week) double-blind, placebo-controlled trial in social anxiety disorder in which patients were dosed at a range of 12.5 to 37.5 mg/day. Table 5 enumerates adverse events that occurred at an incidence of 1% or more among PAXIL 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 PAXIL CR™ Patients in a Pool of Two Studies in Depression[1,2]

Body System/Adverse Event	% Reporting Event	
	PAXIL 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 Paxil 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 PAXIL CR™ Patients in a Study of Elderly Patients with Depression[1,2]

Body System/Adverse Event	% Reporting Event	
	PAXIL 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 Paxil 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 PAXIL CR™ Patients in a Pool of Three Panic Disorder Studies[1,2]

Body System/AdverseEvent %	Reporting Event	
	PAXIL 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 PAXIL 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 PAXIL CR™ in a social phobia (social anxiety disorder) study[1,2].

Body System/Adverse Event	% Reporting Event	
	PAXIL 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 PAXIL 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 PAXIL CR™ Patients in a Pool of Three Premenstrual Dysphoric Disorder Studies [1,2] or in 1 Premenstrual Dysphoric Disorder Study with Luteal Phase Dosing

	% Reporting Event Continuous Dosing		% Reporting Event Luteal Phase Dosing	
Body System/Adverse Event	**PAXIL CR™ (n=681)**	**Placebo (n=349)**	**PAXIL 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 Monoliasis	1%	<1%	-	-
Menstrual Disorder	-	-	1%	0%

1. Adverse events for which the PAXIL 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 PAXIL CR™ that was at least twice that with 12.5 mg of PAXIL CR™ and with placebo.

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

	PAXIL CR™ 25 mg (n = 348)	PAXIL 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.

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.

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:

	Depression		Panic Disorder		Social Anxiety Disorder		PMDD Continuous Dosing		PMDD Luteal Phase Dosing	
	PAXIL CR™	Placebo	PAXIL CR™	Placebo	PAXIL CR™	Placebo	PAXIL CR™	Placebo	PAXIL 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.

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 PAXIL® IR 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 PAXIL® IR and which occurred at a rate at least twice that of placebo, were: emotional lability (including suicidal ideation, suicide attempt, mood changes, and tearfulness), nervousness, dizziness, nausea, and abdominal pain (see WARNINGS AND PRECAUTIONS, Discontinuation of Treatment With PAXIL CR™).

Other Events Observed During the Clinical Development of Paroxetine
The following adverse events were reported during the clinical development of PAXIL 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 PAXIL 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 PAXIL CR™ controlled release who experienced an event of the type cited on at least one occasion while receiving PAXIL 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 PAXIL 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, anaphylactoid reaction, anticholinergic syndrome, hypothermia; also observed were adrenergic syndrome, neck rigidity, sepsis.

Cardiovascular System: Infrequent were angina pectoris, bradycardia, bundle branch block, hematoma, hypertension, hypotension, palpitation, postural hypotension, supraventricular tachycardia, syncope ; rare were 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 were thrombocytopenia; also observed were anisocytosis, basophilia, bleeding time increased, lymphedema, lymphocytosis, lymphopenia, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia.

Metabolic and Nutritional Disorders: 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, hypercholesteremia, 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 were 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 were pharyngitis; infrequent were asthma, dyspnea, epistaxis, laryngitis, pneumonia; rare were stridor; also observed were dysphonia, emphysema, hemoptysis, hiccups, hyperventilation, lung fibrosis, pulmonary edema, respiratory flu, sputum increased.

Skin and Appendages: Frequent were 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.

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 were dysmennorhea*; infrequent were albuminuria, amenorrhea*, breast pain*, cystitis, dysuria, prostatitis*, urinary retention; rare were breast enlargement*, breast neoplasm*, female lactation, hematuria, kidney calculus, metorrhagia, 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-Market Adverse Drug Reactions

Adverse events not listed above which have been reported since market introduction in patients taking 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, toxic epidermal necrolysis, priapism, thrombocytopenia, aggravated hypertension, syndrome of inappropriate ADH secretion, symptoms suggestive of hyperprolactinemia and galactorrhea, 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, neuroleptic malignant syndrome-like events; serotonin syndrome (See, WARNINGS AND PRECAUTIONS, Neurologic-Serotonin Syndrome/Neuroleptic Malignant Syndrome). There has been a case report of an elevated phenytoin level after 4 weeks of PAXIL® IR and phenytoin co-administration. There has been a case report of severe hypotension when PAXIL® IR was added to chronic metoprolol treatment. The causal relationship between PAXIL® IR and the emergence of these events has not been established.

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

DRUG INTERACTIONS

Serious Drug Interactions

- **Monoamine Oxidase Inhibitors: See CONTRAINDICATIONS**
- **Thioridazine: See CONTRAINDICATIONS**
- **Pimozide: See CONTRAINDICATIONS**

Overview

Like some other selective serotonin re-uptake inhibitors, paroxetine inhibits the specific hepatic cytochrome P450 isozyme CYP2D6 which is responsible for the metabolism of debrisoquine and sparteine. Poor metabolizers of debrisoquine/sparteine represent approximately 5-10% of Caucasians. The median C_{min} (ss) for PAXIL® (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 PAXIL® is co-administered with drugs with a narrow therapeutic index.

PAXIL 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 PAXIL CR™ has been associated with decreased levels of PAXIL CR™ or IR. When co-administered with cimetidine, PAXIL CR™ levels were elevated.

The concomitant use of PAXIL CR™ and alcohol has not been studied.

Drug-Drug Interactions

Monoamine Oxidase Inhibitors: Combined use of PAXIL CR™ and monoamine oxidase inhibitors is contraindicated due to the potential for serious reactions with features resembling serotonin syndrome or neuroleptic malignant syndrome (See CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS, Serotonin Syndrome/Neuroleptic Malignant Syndrome).

Thioridazine: Combined use of PAXIL 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 PAXIL® (titrated to 60 mg daily) was associated with mean increases in pimozide AUC of 151% and Cmax of 62%, compared to pimozide administered alone. Due to the narrow therapeutic index of pimozide and its known ability to prolong the QT interval, and produce severe cardiac arrhythmias including Torsade de Pointes, concomitant use of pimozide and PAXIL CR™ is contraindicated (see CONTRAINDICATIONS).

Drugs Metabolized by Cytochrome P450 (CYP2D6): In two studies, daily dosing of PAXIL® (20 mg qd) under steady state conditions increased the following mean pharmacokinetic parameters for a single (100 mg) dose of *desipramine* in extensive metabolizers: C_{max} (2 fold), AUC (6 fold), and T½ (3-5 fold). Concomitant steady-state PAXIL® 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 PAXIL 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 PAXIL CR™ with other drugs metabolized by CYP2D6 has not been formally studied but may require lower doses than usually prescribed for either PAXIL 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, PAXIL CR™ and thioridazine should not be co-administered (see CONTRAINDICATIONS).

Drugs Metabolized by Cytochrome P450 (CYP3A4): An in vivo interaction study involving the co-administration under steady state conditions of PAXIL® and terfenadine, a substrate for CYP3A4, revealed no effect of PAXIL® 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 PAXIL 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 PAXIL 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 PAXIL CR™ or IR and alcohol has not been studied and is not recommended. Patients should be advised to avoid alcohol while taking PAXIL CR™.

Anti-cholinergic Drugs: PAXIL® IR 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.

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 $T^{1/2}$ of PAXIL® IR were reduced by an average of 25% and 38% respectively compared to PAXIL® IR administered alone. The effect of PAXIL CR™ or IR on *phenobarbital* pharmacokinetics was not studied. No initial PAXIL CR™ or IR 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 PAXIL® IR (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 PAXIL 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 PAXIL CR™ with anticonvulsants may be associated with an increased incidence of adverse experiences.

Antipsychotic Drugs/Neuroleptic Malignant Syndrome: As with other SSRIs, PAXIL 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, Serotonin Syndrome/Neuroleptic Malignant Syndrome).

Serotonergic Drugs: Based on the mechanism of action of paroxetine and the potential for serotonin syndrome, caution is advised when PAXIL CR™ is coadministered with other drugs or agents that may affect the serotonergic neurotransmitter systems, such as tryptophan, triptans, serotonin reuptake inhibitors, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (see WARNINGS AND PRECAUTIONS, Serotonin Syndrome/Neuroleptic Malignant Syndrome).

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 PAXIL 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, Serotonin Syndrome/Neuroleptic Malignant Syndrome).

Tryptophan: *Tryptophan* can be metabolized to serotonin. As with other serotonin reuptake inhibitors, the use of PAXIL 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 PAXIL CR™ with *tryptophan* is not recommended (see WARNINGS AND PRECAUTIONS, Serotonin Syndrome/Neuroleptic Malignant Syndrome).

CNS Drugs: Experience in a limited number of healthy subjects has shown that PAXIL® IR does not increase the sedation and drowsiness associated with *haloperidol, amylbarbitone or oxazepam,* when given in combination. Since the effects of concomitant administration of PAXIL CR™ or IR with neuroleptics have not been studied, the use of PAXIL CR™ with these drugs should be approached with caution.

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

Cardiovascular Drugs: Multiple dose treatment with PAXIL® IR 30 mg/day has little or no effect on the steady-state pharmacokinetics of *digoxin* (0.25 mg qd) or *propanolo*l (80 mg bid).

Theophylline: Reports of elevated theophylline levels associated with PAXIL® 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 PAXIL® (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 PAXIL 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 PAXIL CR™ is not affected by food.

Drug-Herb Interactions

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

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

Lower initial doses of PAXIL CR™ are recommended for elderly and debilitated patients, and patients with renal or hepatic impairment (See DOSAGE AND ADMINISTRATION, Special Patient Populations.)

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

Discontinuation of Treatment with PAXIL CR™:
Symptoms associated with the discontinuation of PAXIL® IR and PAXIL 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 PAXIL CR™ is being prescribed. (See WARNINGS AND PRECAUTIONS, Discontinuation of Treatment With PAXIL CR™ and ADVERSE REACTIONS, Adverse Reactions Following Discontinuation of Treatment).

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

Adults

Depression

Usual 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 PAXIL 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 a patient should continue to be treated with PAXIL CR™ 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 ntidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Systematic evaluation of the efficacy of PAXIL® IR 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 PAXIL 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 PAXIL 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. In the clinical trial demonstrating the effectiveness of PAXIL CR™ in the treatment of social anxiety disorder, patients were dosed in a range of 12.5 mg to 37.5 mg/day. Some patients not responding to a 12.5 mg dose may benefit from dose increases, in 12.5 mg/day increments, 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 PAXIL CR™ should remain on it. Although the efficacy of PAXIL CR™ beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials, social anxiety disorder is recognized 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 PAXIL 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 PAXIL 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 PAXIL CR™ for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

Special Patient Populations

Treatment of Pregnant Women During the Third Trimester: Post-marketing reports indicate that some neonates exposed to PAXIL CR™, SSRIs, or other newer anti-depressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see WARNINGS AND PRECAUTIONS, Special Populations). When treating pregnant women with PAXIL CR™ during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering PAXIL CR™ in the third trimester.

***Geriatrics (>65 years) or Debilitated*:** Administration of PAXIL CR™ to the elderly is associated with increased plasma levels and prolongation of the elimination half life relative to younger adults. (See ACTION AND CLINICAL PHARMACOLOGY).The recommended initial dose of PAXIL CR™ is 12.5 mg/day for elderly patients and debilitated patients. The dose may be increased if indicated up to a maximum of 50 mg/day.

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

Renal/Hepatic Impairment: PAXIL 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 WARNINGS AND PRECAUTIONS; ACTION AND CLINICAL PHARMACOLOGY).

OVERDOSAGE

Symptoms of Overdosage

Patients have generally recovered without serious sequelae even when doses of up to 2000 mg of PAXIL® IR have been taken alone. Events such as coma or ECG changes have occasionally been reported and, very rarely a fatal outcome, but generally when PAXIL CR™ was taken in conjunction with other psychotropic drugs, with or without alcohol.

Experience of PAXIL CR™ in overdose has indicated that, in addition to those symptoms mentioned under 'ADVERSE REACTIONS', vomiting, dilated pupils, fever, blood pressure changes, headache, involuntary muscle contractions, agitation, anxiety and tachycardia have been reported.

Treatment of Overdosage

No specific antidote is known.

Treatment should consist of those general measures employed in the management of overdose with any antidepressant. Establish and maintain an airway; ensure adequate oxygenation and ventilation. Where appropriate, the stomach should be emptied by lavage. Following evacuation, 20 to 30 grams of activated charcoal may be administered every 4 to 6 hours during the first 24 hours after ingestion. An ECG should be taken and monitoring of cardiac function instituted if there is any evidence of abnormality. Supportive care with frequent monitoring of vital signs and careful observation is indicated. Due to the large volume of distribution of PAXIL CR™, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit.

A specific caution involves patients taking or recently having taken PAXIL 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.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Paroxetine is a potent and selective serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitor (SSRI). This activity of the drug on brain neurons is thought to be responsible for its antidepressant and anxiolytic action in the treatment of depression, 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 (α_1, α_2, β), dopaminergic, serotonergic ($5HT_1$, $5HT_2$), or histaminergic receptors of rat brain membrane. A weak affinity for the muscarinic acetylcholine receptor was evident. The predominant metabolites of paroxetine are essentially inactive as 5-HT reuptake inhibitors.

Pharmacokinetics

PAXIL CR™ tablets contain a degradable polymeric matrix (Geomatrix™, a trademark of Jago Pharma, Muttenz, Switzerland) 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 PAXIL 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 PAXIL 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 (IR). The mean elimination half-life of paroxetine was 15 to 20 hours throughout this range of single PAXIL CR™ doses. The bioavailability of 25 mg PAXIL CR™ is not affected by food.

During repeated administration of PAXIL 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 PAXIL CR™ (25 mg daily), mean steady state C_{max}, C_{min} and $AUC_{0\text{-}24}$ values were 30ng/mL, 20ng/mL and 550ng.hr./mL, respectively.

Based on studies using IR 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 IR formulation of 20 to 40mg daily for the elderly and 20 to 50mg daily for the nonelderly, some nonlinearity was observed in both populations, again reflecting a saturable metabolic pathway. In comparison to Cmin 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 paroxetine IR for 15 days, the mean maximal plasma concentration was 41 ng/mL at steady state (see Table 6). Peak plasma levels generally occurred within 3 to 7 hours.

Distribution: At therapeutic concentrations, the plasma protein binding of paroxetine is approximately 95%. After the administration of a single 50 mg oral dose of paroxetine IR to lactating women, the concentrations of paroxetine detected in breast milk were similar to those in plasma.

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

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

Special Populations and Conditions

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

Hepatic Insufficiency: The results from a multiple dose pharmacokinetic study with paroxetine IR, in subjects with severe hepatic dysfunction, suggest that the clearance of paroxetine is markedly reduced in this patient group (see Table 6). As the elimination of paroxetine is dependent upon extensive hepatic metabolism, its use in patients with hepatic impairment should be undertaken with caution (see DOSAGE AND ADMINISTRATION, Special Patient Populations).

Renal Insufficiency: In a single dose pharmacokinetic study in patients with mild to severe renal impairment, plasma levels of paroxetine tended to increase with deteriorating renal function (see Table 7).

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

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

	Young Healthy Subjects [n=22]	Elderly Healthy Subjects [n=22]	Hepatically* Impaired Subjects [n=10]
Cmax (ss) (ng/mL)	41 (12-90)	87 (18-154)	87 (11-147)
Tmax (ss) (hours)	5.0 (3-7)	5.0 (1-10)	6.4 (2-11)
Cmin (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)
T½ (hour)	19 (8-43)	31 (13-92)	66 (17-152)

*Galactose elimination capacity 30-70% of normal.

TABLE 7
Pharmacokinetics of paroxetine IR 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]
Cmax (ng/mL)	46.2 (35.9-56.7)	36 (3.6-59.4)	19.8 (1.4-54.8)
Tmax (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)
T½ (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:
Cmax = maximum plasma concentration; Tmax = time to reach Cmax
AUC_∞ = Area under the plasma concentration time curve at infinity.
T½ = terminal elimination half-life

STORAGE AND STABILITY

Store between 15 and 25°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

PAXIL CR™ is available as round and biconvex, enteric, film-coated, controlled-release tablet containing paroxetine hydrochloride equivalent to paroxetine as follows: 12.5 mg-yellow and 25 mg-pink. The tablets have the product name engraved on one side and strength engraved on the other side. Available in bottles of 30.

PAXIL CR™ tablets contains either 12.5 or 25 mg of Paroxetine, as paroxetine hydrochloride. The tablets also contain the following non-medicinal ingredients: colloidal silicon dioxide, glyceryl behenate, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, methacrylic acid copolymer type C, polyethylene glycol, polysorbate 80, polyvinylpyrrolidone, sodium lauryl sulphate, talc, titanium dioxide, triethyl citrate. PAXIL CR™ 12.5 mg tablets also contain D&C yellow No.10 aluminium lake, FD&C yellow No. 6 aluminium lake, and yellow ferric oxide. PAXIL CR™ 25 mg tablets also contains D&C red No. 30 aluminium lake and red ferric oxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

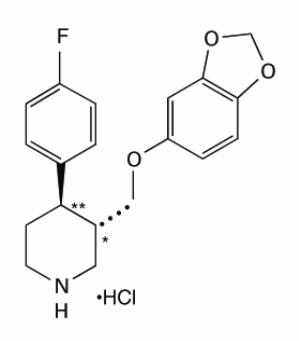
Proper Name: Paroxetine hydrochloride

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

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

Molecular Mass: 374.8 (as hemihydrate salt)
329.4 (as free base)

Structural Formula:



Physicochemical properties:

Description: a white to off-white solid

Melting point: 120-138°C

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

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

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

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

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

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

CLINICAL TRIALS

Depression
The efficacy of PAXIL 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, PAXIL 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 PAXIL® (15%) compared to placebo (39%) met criteria for partial relapse[1]. Criteria for full relapse[2] were met by a significantly lower percentage of PAXIL® treated patients (12%) compared to placebo treated patients (28%). Effectiveness was similar for male and female patients.

Panic Disorder
The effectiveness of PAXIL CR™ in the treatment of panic disorder was evaluated in three 10-week, multicenter, 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

[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).

Impression Severity score. For Studies 1 and 2, PAXIL CR™ was consistently superior to placebo on two of these three variables. Study 3 failed to consistently demonstrate a significant difference between PAXIL CR™ and placebo on any of these variables.

For all three studies, the mean PAXIL 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 PAXIL CR™ in the treatment of social anxiety disorder was demonstrated in a 12-week, multicenter, 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 PAXIL 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.

PAXIL 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 PAXIL 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 PAXIL 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 PAXIL CR™ 12.5 mg/day 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 PAXIL CR™ 12.5 mg/day 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. PAXIL 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. PAXIL CR™ 12.5 mg/day were 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 PAXIL CR™ in combination with systemic (including oral) hormonal contraceptives for the treatment of PMDD is unknown.

DETAILED PHARMACOLOGY

Animal Pharmacology:

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

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

In Vivo: In mice, paroxetine (ED_{50}=0.4 mg/kg p.o.) was associated with potent and prolonged potentiation of the hypermotility induced by the 5-HT precursor, 5-hydroxytryptophan. Similarly, the anticonvulsant effects of 5-hydroxytryptophan in a mouse electroshock model were potentiated by paroxetine (ED_{50}=0.4 mg/kg p.o.). In rats paroxetine (ED50=0.8 mg/kg p.o.) inhibited the hypermotility induced by p-chloroamphetamine, an agent which depletes neuronal 5-HT stores.

Paroxetine, 1 mg/kg i.p., in conscious rats with chronically implanted cortical electrodes, produced essentially no changes in the power spectrum and frequency analysis of the EEG.

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

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

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

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

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

Human Pharmacology: Paroxetine 30 mg administered in single doses to healthy non-depressed volunteers did not impair psychomotor function which was measured by psychomotor tasks such as Morse tapping and motor manipulation, assessment of subjective perception and general assessment of arousal.

Paroxetine at doses of up to 40 mg daily produces no clinically significant changes in blood pressure, heart rate or ECG after administration to healthy subjects.

TOXICOLOGY

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

Acute Toxicity

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

Long-Term Toxicity

The no-toxic effect levels in the rhesus monkeys and rats were 4-10 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.

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PART III: CONSUMER INFORMATION

PAXIL CR ™
paroxetine hydrochloride controlled release tablets

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

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

ABOUT THIS MEDICATION

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

When it should not be used:
Do not use PAXIL CR™ if you are:
- allergic to it or any of the components of its formulation. See list of components at the end of this section.
- currently taking or have recently taken monoamine oxidase inhibitor antidepressants (e.g. phenelzine sulphate, moclobemide).
- currently taking or have recently taken thioridazine or pimozide (Orap®).

What the medicinal ingredient is:
Paroxetine hydrochloride.

What the important nonmedicinal ingredients are:
Lactose monohydrate.
Other non-medicinal ingredients include: colloidal silicon dioxide, glyceryl behenate, hydroxypropyl methylcellulose, magnesium stearate, methacrylic acid copolymer type C, polyethylene glycol, polysorbate 80, polyvinylpyrrolidone, sodium lauryl sulphate, talc, titanium dioxide, triethyl citrate. PAXIL CR™ 12.5 mg tablets also contain D&C yellow No.10 aluminium lake, FD&C yellow No. 6 aluminium lake, and yellow ferric oxide. PAXIL CR™ 25 mg tablets also contains D&C red No. 30 aluminium lake and red ferric oxide.

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

What dosage forms it comes in:
PAXIL CR™ (paroxetine hydrochloride) is available as a 12.5 mg yellow tablet and a 25 mg pink tablet.

WARNINGS AND PRECAUTIONS

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

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

New or Worsened Emotional or Behavioral Problems
Particularly in the first few weeks or when doses are adjusted, a small number of patients taking drugs of this type may feel worse instead of better; for example, they may experience unusual feelings of agitation, hostility or anxiety, or have impulsive or disturbing thoughts such as thoughts of self-harm or harm to others. Should this happen to you, or to those in your care if you are a caregiver or guardian, consult your doctor immediately. Close observation by a doctor is necessary in this situation. **Do not discontinue your medication on your own.**

BEFORE you use PAXIL CR™ tell your doctor or pharmacist:
- all your medical conditions, including a history of seizures, liver or kidney disease, heart problems or history of any abnormal bleeding;
- 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 (Orap®), drugs used to prevent fits (anticonvulsants), drugs for Parkinson's disease, or drugs containing tryptophan;
- if you have ever had any allergic reactions to medications, food etc.
- if you are taking hormonal oral contraceptives and are being prescribed PAXIL 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.

Effects on Pregnancy and Newborns
Post-marketing reports indicate that some newborns whose mothers took an SSRI (selective serotonin reuptake inhibitor) or other newer anti-depressant, 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 anti-depressant was taken during the third trimester of pregnancy. These symptoms are consistent with either a direct adverse effect of the anti-depressant 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.

If you are pregnant and taking an SSRI, or other newer anti-depressant, 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

INTERACTIONS WITH THIS MEDICATION

Do not use PAXIL CR™ if you are taking or have recently taken monoamine oxidase inhibitors, thioridazine or pimozide (Orap®).

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 patients with irregular heart beats (arrhythmias)
- certain medicines used to treat schizophrenia
- certain medicines used to treat bipolar depression, such as lithium
- 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), 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 PAXIL CR™.

PROPER USE OF THIS MEDICATION

Usual dose:
How to take PAXIL CR™

- Depression, Panic Disorder and Social Phobia (social anxiety disorder): It is very important that you take PAXIL 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 PAXIL 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 PAXIL 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, PAXIL 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.

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

The most common side effects of PAXIL CR™ are:

- nausea
- dry mouth
- drowsiness
- weakness
- dizziness
- sweating
- nervousness
- sleep disturbances
- sexual problems
- Although psychiatric disorders are often associated with decreases in sexual desire, performance and satisfaction, treatment with this medication may lead to further decreases.

Other effects may include loss of appetite, constipation, and diarrhea.

PAXIL 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.

New or Worsened Emotional or Behavioral Problems

A small number of patients taking drugs of this type may feel worse instead of better; for example, they may experience new or worsened feelings of agitation, hostility or anxiety, or thoughts about suicide. Your doctor should be informed of such changes immediately. Close observation by a doctor is necessary in this situation. Do not discontinue your medication on your own. See also the WARNINGS AND PRECAUTIONS section.

Discontinuation Symptoms

Contact your doctor before stopping or reducing your dosage of PAXILCR™. Symptoms such as dizziness, lightheadness, nausea, vomiting, agitation/restlessness, anxiety, sweating, headache, sleep disturbance, electric shock sensations and other symptoms have been reported after stopping treatment,-reducing the dosage of PAXIL 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 PAXIL 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 anti-depressant, such as PAXIL 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		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Bruising or unusual bleeding from the skin or other areas		✓	
Uncommon	Hallucinations [strange visions or sounds]		✓	
Uncommon	Uncontrollable movements of the body or face		✓	
Uncommon	Inability to urinate		✓	
Rare	Allergic reactions [red and lumpy skin rash, hives, swelling, trouble breathing]			✓*
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")]		✓*	

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Rare	Serotonin syndrome [a combination of most or all of the following; confusion, restlessness, sweating, shaking, shivering, hallucinations, sudden jerking of the muscles, fast heartbeat]		✓*	
Very Rare	Increased pressure in the eyes [symptoms of eye pain and blurred vision]		✓	
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]		✓*	
See Warnings & Precautions	New or Worsened Emotional or Behavioral Problems		✓*	

*If you think you have these side effects, it is important that you seek medical advice from your doctor straight away

This is not a complete list of side effects. For any unexpected effects while taking PAXIL CR™ contact your doctor or pharmacist.

HOW TO STORE IT

- Keep all medication out of the reach of children.
- Store between 15-25°C.
- Keep container tightly closed.
- If your doctor tells you to stop taking PAXIL CR™ please return any left over medicine to your pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

You may need to read this package insert again. Please do not throw it away until you have finished your medicine. This document plus the full product monograph, prepared for health professionals can be found at: http://www.gsk.ca or by contacting the sponsor,
GlaxoSmithKline Inc.
7333 Mississauga Road North
Mississauga, Ontario
L5N 6L4
1-800-387-7374

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