PRESCRIBING INFORMATION

PAXIL CR™

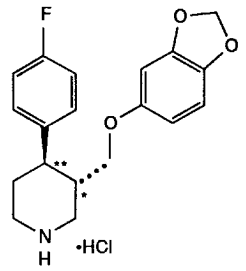
brand of

(paroxetine hydrochloride)

Controlled-Release Tablets

DESCRIPTION

Paxil CR (paroxetine hydrochloride) is an orally administered psychotropic drug with a chemical structure unrelated to other selective serotonin reuptake inhibitors or to tricyclic, tetracyclic or other available antidepressant or antipanic agents. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-*trans*-4*R*-(4'-fluorophenyl)-3*S*-[(3',4'-methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate and has the empirical formula of $C_{19}H_{20}FNO_3 \bullet HCl \bullet 1/2H_2O$. The molecular weight is 374.8 (329.4 as free base). The structural formula is:



paroxetine hydrochloride

Paroxetine hydrochloride is an odorless, off-white powder, having a melting point range of 120° to 138°C and a solubility of 5.4 mg/mL in water.

Each enteric, film-coated, controlled-release tablet contains paroxetine hydrochloride equivalent to paroxetine as follows: 12.5 mg–yellow, 25 mg–pink, 37.5 mg–blue. One layer of the tablet consists of a degradable barrier layer and the other contains the active material in a hydrophilic matrix.

Inactive ingredients consist of hydroxypropyl methylcellulose, polyvinylpyrrolidone, lactose monohydrate, magnesium stearate, colloidal silicon dioxide, glyceryl behenate, methacrylic acid copolymer type C, sodium lauryl sulfate, polysorbate 80, talc, triethyl citrate, and one or more of the following colorants: yellow ferric oxide, red ferric oxide, D&C Red No. 30, D&C Yellow No. 6, D&C Yellow No. 10, FD&C Blue No. 2.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The efficacy of paroxetine in the treatment of major depressive disorder, panic disorder and Premenstrual Dysphoric Disorder (PMDD) is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT). Studies at clinically relevant doses in humans have

demonstrated that paroxetine blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. *In vitro* radioligand binding studies indicate that paroxetine has little affinity for muscarinic, alpha$_1$-, alpha$_2$-, beta-adrenergic-, dopamine (D_2)-, 5-HT_1-, 5-HT_2- and histamine (H_1)-receptors; antagonism of muscarinic, histaminergic and alpha$_1$-adrenergic receptors has been associated with various anticholinergic, sedative and cardiovascular effects for other psychotropic drugs.

Because the relative potencies of paroxetine's major metabolites are at most 1/50 of the parent compound, they are essentially inactive.

Pharmacokinetics

Paxil CR (paroxetine hydrochloride) 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.

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. 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 30 ng/mL, 20 ng/mL and 550 ng.hr./mL, respectively.

Based on studies using immediate-release formulations, steady-state drug exposure based on $AUC_{0\text{-}24}$ was several-fold greater than would have been predicted from single-dose data. The excess accumulation is a consequence of the fact that one of the enzymes that metabolizes paroxetine is readily saturable.

In steady-state dose proportionality studies involving elderly and nonelderly patients, at doses of the immediate-release formulation of 20 to 40 mg daily for the elderly and 20 to 50 mg daily for the nonelderly, some nonlinearity was observed in both populations, again reflecting a saturable metabolic pathway. In comparison to C_{min} values after 20 mg daily, values after 40 mg daily were only about 2 to 3 times greater than doubled.

Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic acid and sulfate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 the potency of

the parent compound at inhibiting serotonin uptake. The metabolism of paroxetine is accomplished in part by cytochrome $P_{450}IID_6$. 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 PRECAUTIONS).

Approximately 64% of a 30 mg oral solution dose of paroxetine was excreted in the urine with 2% as the parent compound and 62% as metabolites over a 10-day post-dosing period. About 36% was excreted in the feces (probably via the bile), mostly as metabolites and less than 1% as the parent compound over the 10-day post-dosing period.

Distribution: Paroxetine distributes throughout the body, including the CNS, with only 1% remaining in the plasma.

Protein Binding: Approximately 95% and 93% of paroxetine is bound to plasma protein at 100 ng/mL and 400 ng/mL, respectively. Under clinical conditions, paroxetine concentrations would normally be less than 400 ng/mL. Paroxetine does not alter the *in vitro* protein binding of phenytoin or warfarin.

Renal and Liver Disease: Increased plasma concentrations of paroxetine occur in subjects with renal and hepatic impairment. The mean plasma concentrations in patients with creatinine clearance below 30 mL/min. was approximately 4 times greater than seen in normal volunteers. Patients with creatinine clearance of 30 to 60 mL/min. and patients with hepatic functional impairment had about a two-fold increase in plasma concentrations (AUC, C_{max}).

The initial dosage should therefore be reduced in patients with severe renal or hepatic impairment, and upward titration, if necessary, should be at increased intervals (see DOSAGE AND ADMINISTRATION).

Elderly Patients: In a multiple-dose study in the elderly at daily doses of 20, 30 and 40 mg of the immediate-release formulation, C_{min} concentrations were about 70% to 80% greater than the respective C_{min} concentrations in nonelderly subjects. Therefore the initial dosage in the elderly should be reduced (see DOSAGE AND ADMINISTRATION).

Clinical Trials

Major Depressive Disorder

The efficacy of *Paxil CR* controlled-release tablets as a treatment for major depressive disorder 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 major depressive disorder as measured by the following: Hamilton Depression Rating Scale (HDRS), the Hamilton depressed mood item, and the Clinical Global Impression (CGI)–Severity of Illness score.

A study of outpatients with 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 a significantly lower relapse rate for patients taking immediate-release paroxetine

tablets (15%) compared to those on placebo (39%). 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 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.

Long-term maintenance effects of the immediate-release formulation of paroxetine in panic disorder were demonstrated in an extension study. Patients who were responders during a 10-week double-blind phase with immediate-release paroxetine and during a 3-month double-blind extension phase were randomized to either immediate-release paroxetine or placebo in a 3-month double-blind relapse prevention phase. Patients randomized to paroxetine were significantly less likely to relapse than comparably treated patients who were randomized to placebo.

Premenstrual Dysphoric Disorder

The effectiveness of *Paxil CR* for the treatment of Premenstrual Dysphoric Disorder has been established in 2 placebo-controlled trials. Patients in these trials met DSM-IV criteria for Premenstrual Dysphoric Disorder (PMDD). In a pool of 1030 patients, the mean duration of the PMDD symptoms was approximately 11±7 years. 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. In both positive studies, patients (N = 672) 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 menstrual cycles. The VAS-Total score is a patient-rated instrument that mirrors the diagnostic criteria of PMDD as identified in the DSM-IV, and includes assessments for mood, physical symptoms and other symptoms. *Paxil CR* 12.5 mg/day and 25 mg/day were significantly more effective than placebo as measured by change from baseline to the endpoint on the luteal phase VAS -Total score.

There is insufficient information to determine the effect of race or age on outcome in these studies.

INDICATIONS AND USAGE

Major Depressive Disorder

Paxil CR (paroxetine hydrochloride) is indicated for the treatment of major depressive disorder.

The efficacy of *Paxil CR* in the treatment of a major depressive episode was established in two 12-week controlled trials of outpatients whose diagnoses corresponded to the DSM-IV category of major depressive disorder (see CLINICAL PHARMACOLOGY).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed mood or loss of interest or pleasure in nearly all activities, representing a change from previous functioning, and includes the presence of at least five of the following nine symptoms during the same two week period: depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The antidepressant action of paroxetine in hospitalized depressed patients has not been adequately studied.

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 major depressive disorder for up to 1 year has been demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY). 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 treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

The efficacy of Paxil CR (paroxetine hydrochloride) controlled-release tablets was established in two 10-week trials in panic disorder patients whose diagnoses corresponded to the DSM-IV category of panic disorder (see CLINICAL PHARMACOLOGY—Clinical Trials).

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.

Long-term maintenance of efficacy with the immediate-release formulation of paroxetine was demonstrated in a 3-month relapse prevention trial. In this trial, patients with panic disorder assigned to immediate-release paroxetine demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY). Nevertheless, the physician who prescribes *Paxil CR* for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Premenstrual Dysphoric Disorder

Paxil CR (paroxetine hydrochloride) is indicated for the treatment of premenstrual dysphoric disorder (PMDD).

The efficacy of *Paxil CR* in the treatment of PMDD was established in 2 placebo-controlled trials (see CLINICAL PHARMACOLOGY- 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 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. In making the diagnosis, care should be taken to rule out other cyclical mood disorders that may be exacerbated by treatment with an antidepressant.

The effectiveness of *Paxil CR* in long-term use, that is, for more than 3 menstrual cycles, has not been systematically 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.

CONTRAINDICATIONS

Concomitant use in patients taking either monoamine oxidase inhibitors (MAOIs) or thioridazine is contraindicated (see WARNINGS and PRECAUTIONS).

Paxil CR is contraindicated in patients with a hypersensitivity to paroxetine or to any of the inactive ingredients in *Paxil CR*.

WARNINGS

Potential for Interaction with Monoamine Oxidase Inhibitors

In patients receiving another serotonin reuptake inhibitor drug in combination with a monoamine oxidase inhibitor (MAOI), 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 that drug and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. While there are no human data showing such an interaction with paroxetine hydrochloride, limited animal data on the effects of combined use of paroxetine and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that Paxil CR (paroxetine hydrochloride) not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. At least 2 weeks should be allowed after stopping *Paxil CR* before starting an MAOI.

Potential Interaction with 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 $P_{450}IID_6$, such as paroxetine, will elevate plasma levels of thioridazine. Therefore, it is recommended that paroxetine not be used in combination with thioridazine (see CONTRAINDICATIONS and PRECAUTIONS).

PRECAUTIONS

General

Activation of Mania/Hypomania: During premarketing testing of immediate-release paroxetine hydrochloride, hypomania or mania occurred in approximately 1.0% of paroxetine-treated unipolar patients compared to 1.1% of active-control and 0.3% of placebo-treated unipolar patients. In a subset of patients classified as bipolar, the rate of manic episodes was 2.2% for immediate-release paroxetine and 11.6% for the combined active-control groups. Among 1441 patients with major depressive disorder, panic disorder or PMDD treated with *Paxil CR* in controlled clinical studies, there were no reports of mania or hypomania. As with all drugs effective in the treatment of major depressive disorder, *Paxil CR* should be used cautiously in patients with a history of mania.

Seizures: During premarketing testing of immediate-release paroxetine hydrochloride, seizures occurred in 0.1% of paroxetine-treated patients, a rate similar to that associated with other drugs effective in the treatment of major depressive disorder.

Among 1441 patients who received *Paxil CR* in controlled clinical trials in major depressive disorder, panic disorder or PMDD, one patient (0.1%) experienced a seizure. *Paxil CR* should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Suicide: The possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Paxil CR (paroxetine hydrochloride) should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Because of well-established comorbidity between major depressive disorder and other psychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric disorders.

***Discontinuation of Treatment with* Paxil CR:** Adverse events while discontinuing therapy with *Paxil CR* were not systematically evaluated in clinical trials; however, in recent placebo-controlled clinical trials 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 their daily dose by 12.5 mg/day to a dose of 25 mg/day for one 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 in those studies, 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 (11.9% vs 1.3%), nausea (5.4% vs 2.7%), nervousness (2.4% vs 1.1%), and additional symptoms described by the investigator as associated with tapering or discontinuing *Paxil CR* (e.g., emotional lability, headache, agitation, electric shock sensations, fatigue, sleep disturbances) (2.4% vs 0.3%).

In clinical trials of immediate-release paroxetine which employed a taper phase with an incremental decrease in the daily dose by 10 mg/day to a total daily dose of 20 mg/day, rather than abrupt discontinuation, events which met the above criteria were: abnormal dreams paresthesia, and dizziness. In the majority of patients, these events were mild to moderate and were self-limiting and did not require medical intervention.

During marketing of immediate-release paroxetine hydrochloride, there have been spontaneous reports of similar adverse events, which may have no causal relationship to the drug, upon the discontinuation of immediate-release paroxetine hydrochloride (particularly when abrupt), including the following: dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), agitation, anxiety, nausea, and sweating. These events are generally self-limiting. Similar events have been reported for other selective serotonin reuptake inhibitors.

Patients should be monitored for these symptoms when discontinuing treatment, regardless of the indication for which *Paxil CR* is being prescribed. 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, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION).

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

Abnormal Bleeding: There have been several reports of abnormal bleeding (mostly ecchymosis and purpura) associated with immediate-release paroxetine hydrochloride 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.

Use in Patients with Concomitant Illness: Clinical experience with immediate-release paroxetine hydrochloride in patients with certain concomitant systemic illness is limited. Caution is advisable in using *Paxil CR* in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

As with other SSRIs, mydriasis has been infrequently reported in premarketing studies with paroxetine hydrochloride. A few cases of acute angle closure glaucoma associated with therapy with immediate-release paroxetine have been reported in the literature. As mydriasis can cause acute angle closure in patients with narrow angle glaucoma, caution should be used when *Paxil CR* is prescribed for patients with narrow angle glaucoma.

Paxil CR or the immediate-release formulation has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during premarket testing. Evaluation of electrocardiograms of 682 patients who received immediate-release paroxetine hydrochloride in double-blind, placebo-controlled trials, however, did not indicate that paroxetine is associated with the development of significant ECG abnormalities. Similarly, paroxetine hydrochloride does not cause any clinically important changes in heart rate or blood pressure.

Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance <30 mL/min.) or severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe *Paxil CR*:

Paxil CR (paroxetine hydrochloride) tablets should not be chewed or crushed, and should be swallowed whole.

Interference with Cognitive and Motor Performance: Any psychoactive drug may impair judgment, thinking or motor skills. Although in controlled studies immediate-release paroxetine hydrochloride has not been shown to impair psychomotor performance, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that *Paxil CR* therapy does not affect their ability to engage in such activities.

Completing Course of Therapy: While patients may notice improvement with *Paxil CR* therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.

Concomitant Medications: Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol: Although immediate-release paroxetine hydrochloride has not been shown to increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking *Paxil CR*.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised to notify their physician if they are breast-feeding an infant (see PRECAUTIONS–Nursing Mothers).

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

Tryptophan: As with other serotonin reuptake inhibitors, an interaction between paroxetine and tryptophan may occur when they are co-administered. Adverse experiences, consisting primarily of headache, nausea, sweating and dizziness, have been reported when tryptophan was administered to patients taking immediate-release paroxetine. Consequently, concomitant use of Paxil CR with tryptophan is not recommended.

Monoamine Oxidase Inhibitors: See CONTRAINDICATIONS and WARNINGS.

Thioridazine: See CONTRAINDICATIONS and WARNINGS.

Warfarin: Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis in the face of unaltered prothrombin time) between paroxetine and warfarin. Since there is little clinical experience, the concomitant administration of Paxil CR and warfarin should be undertaken with caution.

Sumatriptan: There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) is clinically warranted, appropriate observation of the patient is advised.

Drugs Affecting Hepatic Metabolism: The metabolism and pharmacokinetics of paroxetine may be affected by the induction or inhibition of drug-metabolizing enzymes.

Cimetidine—Cimetidine inhibits many cytochrome P_{450} (oxidative) enzymes. In a study where immediate-release paroxetine (30 mg q.d.) was dosed orally for 4 weeks, steady-state plasma concentrations of paroxetine were increased by approximately 50% during co-administration with oral cimetidine (300 mg t.i.d.) for the final week. Therefore, when these drugs are administered concurrently, dosage adjustment of *Paxil CR* after the starting dose should be guided by clinical effect. The effect of paroxetine on cimetidine's pharmacokinetics was not studied.

Phenobarbital—Phenobarbital induces many cytochrome P_{450} (oxidative) enzymes. When a single oral 30 mg dose of immediate-release paroxetine was administered at phenobarbital steady state (100 mg q.d. for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 25% and 38%, respectively) compared to paroxetine administered alone. The effect of paroxetine on phenobarbital pharmacokinetics was not studied. Since paroxetine exhibits nonlinear pharmacokinetics, the results of this study may not address the case where the two drugs are both being chronically dosed. No initial *Paxil CR* dosage adjustment is considered necessary when co-administered with phenobarbital; any subsequent adjustment should be guided by clinical effect.

Phenytoin—When a single oral 30 mg dose of immediate-release paroxetine was administered at phenytoin steady state (300 mg q.d. for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 50% and 35%, respectively) compared to immediate-release paroxetine administered alone. In a separate study, when a single oral 300 mg dose of phenytoin was administered at paroxetine steady state (30 mg q.d. for 14 days), phenytoin AUC was slightly reduced (12% on average) compared to phenytoin administered alone. Since both drugs exhibit nonlinear pharmacokinetics, the above studies may not address the case where the two drugs are both being chronically dosed. No initial dosage adjustments are considered necessary when *Paxil CR* is co-administered with phenytoin; any subsequent adjustments should be guided by clinical effect (see ADVERSE REACTIONS–Postmarketing Reports).

Drugs Metabolized by Cytochrome $P_{450}IID_6$: Many drugs, including most drugs effective in the treatment of major depressive disorder (paroxetine, other SSRIs, and many tricyclics), are metabolized by the cytochrome P_{450} isozyme $P_{450}IID_6$. Like other agents that are metabolized by $P_{450}IID_6$, paroxetine may significantly inhibit the activity of this isozyme. In most patients (>90%), this $P_{450}IID_6$ isozyme is saturated early during paroxetine dosing. In one study, daily dosing of immediate-release paroxetine (20 mg q.d.) under steady-state conditions increased single-dose desipramine (100 mg) C_{max}, AUC, and $T_{½}$ by an average of approximately two-, five-, and three-fold, respectively. Concomitant use of *Paxil CR* with other drugs metabolized by cytochrome $P_{450}IID_6$ has not been formally studied but may require lower doses than usually prescribed for either Paxil CR (paroxetine hydrochloride) or the other drug.

Therefore, co-administration of *Paxil CR* with other drugs that are metabolized by this isozyme, including certain drugs effective in the treatment of major depressive disorder (e.g., nortriptyline, amitriptyline, imipramine, desipramine and fluoxetine), phenothiazines and Type 1C antiarrhythmics (e.g., propafenone, flecainide and encainide), or that inhibit this enzyme (e.g., quinidine), should be approached with caution.

However, due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, paroxetine and thioridazine should not be co-administered (see CONTRAINDICATIONS and WARNINGS).

At steady state, when the $P_{450}IID_6$ pathway is essentially saturated, paroxetine clearance is governed by alternative P_{450} isozymes which, unlike $P_{450}IID_6$, show no evidence of saturation (see PRECAUTIONS–Tricyclic Antidepressants).

Drugs Metabolized by Cytochrome $P_{450}IIIA_4$: An *in vivo* interaction study involving the co-administration under steady-state conditions of paroxetine and terfenadine, a substrate for $P_{450}IIIA_4$, revealed no effect of paroxetine on terfenadine pharmacokinetics. In addition, *in vitro* studies have shown ketoconazole, a potent inhibitor of $P_{450}IIIA_4$ 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* K_i and its lack of effect on terfenadine's *in vivo* clearance predicts its effect on other $IIIA_4$ substrates, paroxetine's extent of inhibition of $IIIA_4$ activity is not likely to be of clinical significance.

Tricyclic Antidepressants (TCAs): Caution is indicated in the co-administration of tricyclic antidepressants (TCAs) with *Paxil CR*, because paroxetine may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is co-administered with *Paxil CR* (see PRECAUTIONS—Drugs Metabolized by Cytochrome $P_{450}IID_6$).

Drugs Highly Bound to Plasma Protein: Because paroxetine is highly bound to plasma protein, 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: Although paroxetine does not increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking *Paxil CR*.

Lithium: A multiple-dose study with immediate-release paroxetine hydrochloride has shown that there is no pharmacokinetic interaction between paroxetine and lithium carbonate. However, since there is little clinical experience, the concurrent administration of Paxil CR (paroxetine hydrochloride) and lithium should be undertaken with caution.

Digoxin: The steady-state pharmacokinetics of paroxetine was not altered when administered with digoxin at steady state. Mean digoxin AUC at steady state decreased by 15% in the presence of paroxetine. Since there is little clinical experience, the concurrent administration of Paxil CR (paroxetine hydrochloride) and digoxin should be undertaken with caution.

Diazepam: Under steady-state conditions, diazepam does not appear to affect paroxetine kinetics. The effects of paroxetine on diazepam were not evaluated.

Procyclidine: Daily oral dosing of immediate-release paroxetine (30 mg q.d.) increased steady-state $AUC_{0\text{-}24}$, C_{max} and C_{min} values of procyclidine (5 mg oral q.d.) by 35%, 37% and 67%, respectively, compared to procyclidine alone at steady state. If anticholinergic effects are seen, the dose of procyclidine should be reduced.

Beta-Blockers: In a study where propranolol (80 mg b.i.d.) was dosed orally for 18 days, the established steady-state plasma concentrations of propranolol were unaltered during co-administration with immediate-release paroxetine (30 mg q.d.) for the final 10 days. The effects of propranolol on paroxetine have not been evaluated (see ADVERSE REACTIONS–Postmarketing Reports).

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

Electroconvulsive Therapy (ECT): There are no clinical studies of the combined use of ECT and *Paxil CR*.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Two-year carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are up to approximately 2 (mouse) and 3 (rat) times the maximum recommended human dose (MRHD) on a mg/m^2 basis. There was a significantly greater number of male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50 and 4/50 for control, low-, middle- and high-dose groups, respectively) and a significantly increased linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The relevance of these findings to humans is unknown.

Mutagenesis: Paroxetine produced no genotoxic effects in a battery of 5 *in vitro* and 2 *in vivo* assays that included the following: bacterial mutation assay, mouse lymphoma mutation assay, unscheduled DNA synthesis assay, and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes and in a dominant lethal test in rats.

Impairment of Fertility: A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of 15 mg/kg/day which is approximately twice the MRHD on a mg/m^2 basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks. These lesions consisted of vacuolation of epididymal tubular epithelium at 50 mg/kg/day and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis at 25 mg/kg/day (approximately 8 and 4 times the MRHD on a mg/m^2 basis).

Pregnancy

Pregnancy Category C

Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately 8 (rat) and 2 (rabbit) times the maximum recommended human dose (MRHD) on a mg/m^2 basis. These studies have

revealed no evidence of teratogenic effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg/day or approximately one-sixth of the MRHD on a mg/m^2 basis. The no-effect dose for rat pup mortality was not determined. The cause of these deaths is not known. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of paroxetine on labor and delivery in humans is unknown.

Nursing Mothers

Like many other drugs, paroxetine is secreted in human milk, and caution should be exercised when Paxil CR (paroxetine hydrochloride) is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

Geriatric Use

In worldwide premarketing clinical trials with immediate-release paroxetine hydrochloride, 17% of paroxetine-treated patients (approximately 700) were 65 years of age or older. Pharmacokinetic studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended; there were, however, no overall differences in the adverse event profile between elderly and younger patients, and effectiveness was similar in younger and older patients (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

In a controlled study focusing specifically on elderly patients with major depressive disorder, *Paxil CR* was demonstrated to be safe and effective in the treatment of elderly patients (>60 years of age) with major depressive disorder. (See CLINICAL TRIALS and ADVERSE REACTIONS—Table 2)

ADVERSE REACTIONS

The information included under the "Adverse Findings Observed in Short-Term, Placebo-Controlled Trials with *Paxil CR*" subsection of ADVERSE REACTIONS is based on data from 9 placebo-controlled clinical trials. Three of these studies were conducted in patients with major depressive disorder, three studies were done in patients with panic disorder, and three studies were done in female patients with PMDD. Two of the studies in major depressive disorder, which enrolled patients in the age range 18 to 65 years, are pooled. Information from a third study of major depressive disorder, which focused on elderly patients (ages 60 to 88), is presented separately as is the information from the panic disorder studies and the information from the PMDD studies. 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).

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials with *Paxil CR*:

Adverse Events Associated with Discontinuation of Treatment

Major Depressive Disorder

Ten percent (21/212) of *Paxil CR* patients discontinued treatment due to an adverse event in a pool of two studies of patients with major depressive disorder. 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 major depressive disorder, 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%

Premenstrual Dysphoric Disorder

Thirteen percent (88/681) of patients treated with *Paxil CR* in PMDD studies discontinued treatment due to an adverse event.

The most common events (≥1%) associated with discontinuation in either *Paxil CR* group with an incidence rate that is at least twice that of placebo in PMDD trials are shown in the following table. This table also shows those events that were dose dependent (indicated with an asterisk) as 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).

	Paxil CR 25 mg N = 348	*Paxil CR* 12.5 mg N = 333	Placebo N = 349
TOTAL	15%	9.9%	6.3%
Nausea*	6.0%	2.4%	0.9%
Asthenia	4.9%	3.0%	1.4%
Somnolence*	4.3%	1.8%	0.3%
Insomnia	2.3%	1.5%	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%
Decreased appetite*	1.4%	0.6%	0.0%
Sweating*	1.4%	0.0%	0.3%
Tremor*	1.4%	0.3%	0.0%
Yawn*	1.1%	0.0%	0.0%
Diarrhea	0.9%	1.2%	0.0%

*Events considered to be dose dependent as 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)

Commonly Observed Adverse Events

Major Depressive Disorder

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 major depressive disorder 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).

Premenstrual Dysphoric 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) were: nausea, asthenia, libido decreased, somnolence, insomnia, female genital disorders, sweating, dizziness, diarrhea and constipation.

Incidence in Controlled Clinical Trials

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 major depressive disorder 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 major depressive disorder 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 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. 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 Major Depressive Disorder[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 Major Depressive Disorder[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/Adverse Event	**% 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		

Body System/Adverse Event	% Reporting Event	
	Paxil CR **(n=444)**	**Placebo (n=445)**
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 Events Occurring in ≥1% of *Paxil CR* Patients in a Pool of Three Premenstrual Dysphoric Disorder Studies[1,2]

	% Reporting Event	
Body System/Adverse Event	***Paxil CR* (n=681)**	**Placebo (n=349)**
Body as a Whole		
Asthenia	17%	6%
Headache	15%	12%
Infection	6%	4%
Cardiovascular System		
Migraine	1%	<1%
Digestive System		
Nausea	17%	7%
Diarrhea	6%	2%
Constipation	5%	1%
Dry Mouth	4%	2%
Increased Appetite	3%	<1%
Decreased Appetite	2%	<1%
Dyspepsia	2%	1%
Musculoskeletal System		
Arthralgia	2%	1%
Nervous System		
Libido Decreased	12%	5%
Somnolence	9%	2%
Insomnia	8%	2%
Dizziness	7%	3%
Tremor	4%	<1%
Concentration Impaired	3%	<1%
Nervousness	2%	<1%
Anxiety	2%	1%
Lack of Emotion	2%	<1%
Abnormal Dreams	1%	<1%
Respiratory System		
Yawn	2%	<1%

Body System/Adverse Event	% Reporting Event *Paxil CR* (n=681)	Placebo (n=349)
Cough Increased	1%	<1%
Skin and Appendages		
Sweating	7%	<1%
Urogenital System		
Female Genital Disorders[3]	8%	1%
Menorrhagia	1%	<1%
Vaginal Monoliasis	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: 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, Low and High Dose Paxil CR Treated Subjects in a Pool of Three Fixed-Dose 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 major depressive disorder 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 major depressive disorder, in the pool of three placebo-controlled trials in patients with panic disorder and in the pool of three placebo-controlled trials in female patients with PMDD are as follows:

	Major Depressive Disorder		**Panic Disorder**		**PMDD**	
	Paxil CR	**Placebo**	***Paxil CR***	**Placebo**	***Paxil CR***	**Placebo**
n (males)	**78**	**78**	**162**	**194**	**n/a**	**n/a**
Decreased libido	10%	5%	9%	6%	n/a	n/a
Ejaculatory disturbance	26%	1%	27%	3%	n/a	n/a
Impotence	5%	3%	10%	1%	n/a	n/a
n (females)	**134**	**133**	**282**	**251**	**681**	**349**
Decreased libido	4%	2%	8%	2%	12%	5%
Orgasmic disturbance	10%	<1%	7%	1%	8%	1%

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.

Weight and Vital Sign Changes: Significant weight loss may be an undesirable result of treatment with paroxetine for some patients but, on average, patients in controlled trials with Paxil CR (paroxetine hydrochloride), or the immediate-release formulation, had minimal weight loss (about 1 pound). No significant changes in vital signs (systolic and diastolic blood pressure, pulse and temperature) were observed in patients treated with *Paxil CR*, or immediate-release paroxetine hydrochloride, in controlled clinical trials.

ECG Changes: In an analysis of ECGs obtained in 682 patients treated with immediate-release paroxetine and 415 patients treated with placebo in controlled clinical trials, no clinically significant changes were seen in the ECGs of either group.

Liver Function Tests: In a pool of two placebo-controlled clinical trials, patients treated with *Paxil CR* or placebo exhibited abnormal values on liver function tests at comparable rates. In particular, the controlled-release paroxetine-vs.-placebo comparisons for alkaline phosphatase,

SGOT, SGPT and bilirubin revealed no differences in the percentage of patients with marked abnormalities.

In a study of elderly patients with major depressive disorder, three of 104 *Paxil CR* patients and none of 109 placebo patients experienced liver transaminase elevations of potential clinical concern.

Two of the *Paxil CR* patients dropped out of the study due to abnormal liver function tests; the third patient experienced normalization of transaminase levels with continued treatment. Also, in the pool of three studies of patients with panic disorder, four of 444 *Paxil CR* patients and none of 445 placebo patients experienced liver transaminase elevations of potential clinical concern. Elevations in all four patients decreased substantially after discontinuation of *Paxil CR*. The clinical significance of these findings is unknown.

In placebo-controlled clinical trials with the immediate release formulation of paroxetine, patients exhibited abnormal values on liver function tests at no greater rate than that seen in placebo-treated patients.

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 major depressive disorder, panic disorder and PMDD, multiple doses of *Paxil CR* were administered to 1441 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 1441 patients exposed to Paxil CR (paroxetine hydrochloride) 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, or 4 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 major depressive

disorder, 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 PRECAUTIONS section.

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

Cardiovascular System: Infrequent were angina pectoris, bradycardia, 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 glossitis, gum hyperplasia, hepatosplenomegaly, increased salivation, intestinal obstruction, peptic ulcer, stomach ulcer, throat tightness; also observed were aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, cholelithiasis, colitis, 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, hypochromic anemia, leukocytosis, leukopenia, lymphadenopathy, purpura; rare were eosinophilia, thrombocytopenia; also observed were anisocytosis, basophilia, bleeding time increased, lymphedema, lymphocytosis, lymphopenia, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia.

Metabolic and Nutritional Disorders: Frequent were weight gain; infrequent were generalized edema, hyperglycemia, 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, diplopia, paranoid reaction, torticollis, withdrawal syndrome; also observed were abnormal gait, akathisis, akinesia, aphasia, choreoathetosis, circumoral paresthesia, delirium, delusions, dysarthria, dyskinesia, euphoria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hostility, 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 abnormality of accommodation, 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 dysmenorrhea*; infrequent were albuminuria, amenorrhea*, breast enlargement*, breast pain*, breast neoplasm*, cystitis, dysuria, prostatitis*, pregnancy and puerperal disorders*, urinary retention, uterine fibroids enlarged*; rare were female lactation, hematuria, kidney calculus, nephritis, nocturia, salpingitis, urinary incontinence; 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.

Postmarketing Reports

Voluntary reports of adverse events in patients taking immediate-release paroxetine hydrochloride that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome-like events; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide, tremor and trismus; serotonin syndrome,

associated in some cases with concomitant use of serotonergic drugs and with drugs which may have impaired paroxetine metabolism (symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor); status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic syndromes (such as Henoch-Schőnlein purpura). There has been a case report of an elevated phenytoin level after 4 weeks of immediate-release paroxetine and phenytoin co-administration. There has been a case report of severe hypotension when immediate-release paroxetine was added to chronic metoprolol treatment.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class*:* Paxil CR (paroxetine hydrochloride) is not a controlled substance.

Physical and Psychologic Dependence*: Paxil CR* has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for history of drug abuse, and such patients should be observed closely for signs of *Paxil CR* misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience: Since the introduction of immediate-release paroxetine hydrochloride in the U.S., 342 spontaneous cases of deliberate or accidental overdosage during paroxetine treatment have been reported worldwide (circa 1999). These include overdoses with paroxetine alone and in combination with other substances. Of these, 48 cases were fatal and, of the fatalities, 17 appeared to involve paroxetine alone. Eight fatal cases which documented the amount of paroxetine ingested were generally confounded by the ingestion of other drugs or alcohol or the presence of significant comorbid conditions. Of 145 non-fatal cases with known outcome, most recovered without sequelae. The largest known ingestion involved 2000 mg of paroxetine (33 times the maximum recommended daily dose) in a patient who recovered.

Commonly reported adverse events associated with paroxetine overdosage include somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other notable signs and symptoms observed with overdoses involving paroxetine (alone or with other substances) include mydriasis, convulsions (including status epilepticus), ventricular dysrhythmias (including torsade de pointes), hypertension, aggressive reactions, syncope, hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction (including hepatic failure, hepatic necrosis, jaundice, hepatitis, and hepatic steatosis), serotonin syndrome, manic reactions, myoclonus, acute renal failure, and urinary retention.

Overdosage Management: Treatment should consist of those general measures employed in the management of overdosage with any drugs effective in the treatment of major depressive disorder.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for paroxetine are known.

A specific caution involves patients taking or recently having taken paroxetine who might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (see Drugs Metabolized by Cytochrome $P_{450}IID_6$ under PRECAUTIONS).

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. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION

Major Depressive Disorder

Usual Initial Dosage: Paxil CR (paroxetine hydrochloride) should be administered as a single daily dose, usually in the morning, with or without food. 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 major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, 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.

Patients should be cautioned that the *Paxil CR* tablet should not be chewed or crushed, and should be swallowed whole.

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. It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Whether the dose of an antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Systematic evaluation of the efficacy of immediate-release paroxetine hydrochloride has shown that efficacy is maintained for periods of up to 1 year with doses that averaged about 30 mg, which corresponds to a 37.5 mg dose of *Paxil CR*, based on relative bioavailability considerations (see Pharmacokinetics).

Panic Disorder

Usual Initial Dosage*: Paxil CR* should be administered as a single daily dose, usually in the morning. 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.

Patients should be cautioned that the *Paxil CR* tablet should not be chewed or crushed, and should be swallowed whole.

Maintenance Therapy*:* Long-term maintenance of efficacy with the immediate-release formulation of paroxetine was demonstrated in a 3-month relapse prevention trial. In this trial, patients with panic disorder assigned to immediate-release paroxetine demonstrated a lower relapse rate compared to patients on placebo. Panic disorder is a chronic condition, and it is reasonable to consider continuation 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: *Paxil CR* should be administered as a single daily dose, usually in the morning, with or without food. The recommended initial dose is 12.5 mg/day. In clinical trials, both 12.5 mg/day and 25 mg/day were shown to be effective. Dose changes should occur at intervals of at least 1 week.

Patients should be cautioned that the *Paxil CR* tablet should not be chewed or crushed, and should be swallowed whole.

Maintenance/Continuation Therapy: The effectiveness of *Paxil CR* for a period exceeding 3 menstrual cycles has not been systematically evaluated in controlled trials. However, women commonly report that symptoms worsen with age until relieved by the onset of menopause. Therefore, it is reasonable to consider continuation of a responding patient. Patients should be periodically reassessed to determine the need for continued treatment.

Dosage for Elderly or Debilitated, and Patients with Severe Renal or Hepatic Impairment: The recommended initial dose of *Paxil CR* is 12.5 mg/day for elderly patients, debilitated patients, and/or patients with severe renal or hepatic impairment. Increases may be made if indicated. Dosage should not exceed 50 mg/day.

Switching Patients to or from a Monoamine Oxidase Inhibitor: At least 14 days should elapse between discontinuation of an MAOI and initiation of *Paxil CR* therapy. Similarly, at least 14 days should be allowed after stopping *Paxil CR* before starting an MAOI.

Discontinuation of Treatment with *Paxil CR:* Symptoms associated with discontinuation of immediate-release paroxetine hydrochloride or *Paxil CR* have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment, regardless of the indication for which *Paxil CR* is being prescribed. 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, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

HOW SUPPLIED

Paxil CR is supplied as an enteric film-coated, controlled-release, round tablet, as follows:

12.5 mg yellow tablets, engraved with Paxil CR and 12.5
NDC 0029-3206-13 Bottles of 30
NDC 0029-3206-20 Bottles of 100

25 mg pink tablets, engraved with Paxil CR and 25
NDC 0029-3207-13 Bottles of 30
NDC 0029-3207-20 Bottles of 100
NDC 0029-3207-21 SUP 100's (intended for institutional use only)

37.5 mg blue tablets, engraved with Paxil CR and 37.5
NDC 0029-3208-13 Bottles of 30

Store at or below 25°C (77°F) [see USP].

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