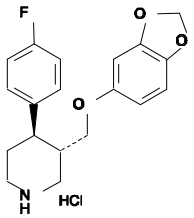
ATTACHMENT

FINAL LABELING

PAXIL® CR™
(paroxetine hydrochloride) Controlled-Release Tablets

DESCRIPTION

Paxil CR (paroxetine hydrochloride) is an orally administered antidepressant with a chemical structure unrelated to other selective serotonin reuptake inhibitors or to tricyclic, tetracyclic or other available antidepressant agents. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (−)-(3*S*,4*R*)-4-[(*p*-fluorophenyl)-3-[(3,4-methylenedioxy)phenoxy]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, bilayer, controlled-release tablet contains paroxetine hydrochloride equivalent to paroxetine as follows: 12.5 mg and 25 mg. One layer of the tablet consists of a degradable barrier layer and the other contains the active material in a hydrophilic matrix. The barrier layer is pale yellow and pink for the 12.5 mg and 25 mg strength tablets, respectively; the active layer is white.

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.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The antidepressant action of paroxetine 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 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 Cmax and $AUC_{0-\infty}$ increased disproportionately with dose (as seen also with immediate-release formulations). Mean Cmax and $AUC_{0-\infty}$ 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. Tmax 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 25mg 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 Cmax, Cmin and AUC_{0-24} 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_{0-24} 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

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 (HDRS), the Hamilton depressed mood item, and the Clinical Global Impression (CGI)-Severity of Illness score.

A study of depressed outpatients 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.

INDICATIONS AND USAGE

Paxil CR (paroxetine hydrochloride) is indicated for the treatment of depression.

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 an antidepressant response for up to 1 year has been demonstrated in a placebo-controlled trial. 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.

CONTRAINDICATIONS

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

Paxil 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 a 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 not be used in combination with a MAOI, or within 14 days of discontinuing treatment with a MAOI. At least 2 weeks should be allowed after stopping Paxil CR before starting a MAOI.

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. As with all antidepressants, 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 antidepressants. 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 depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Paxil CR should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

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.

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 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 Medication: 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.

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 25 mg 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 antidepressants (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 or the other drug.

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

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 coadministration 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} $IIIA_4$, 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 vitro* clearance predicts its effect on other $IIIA_4$ substrates, paroxetine's extent of inhibition of $IIIA_4$ activity is not likely to be of clinial significance.

Tricyclic Antidepressants (TCA) - 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 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 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_{0-24}, 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, Paxil CR 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.)

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 three placebo-controlled clinical trials in depressed patients. Two studies, which are pooled in the following tables, enrolled patients in the age range 18 to 65 years. A third study, presented separately, focused on elderly patients (ages 60 to 88). 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

Ten percent (21/212) of Paxil CR patients discontinued treatment due to an adverse event in a pool of two studies of depressed patients. 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 depressed, elderly patients, 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%

Commonly Observed Adverse Events

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 were: abnormal ejaculation, constipation, decreased appetite, dry mouth, impotence, infection, libido decreased, sweating, and tremor.

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 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. 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 PAROXETINE CR PATIENTS IN A POOL OF TWO STUDIES [1,2]

Body System/Adverse Event	% Reporting Event	
	Par 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%

1 Adverse events for which the paroxetine CR 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.

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%

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 PAROXETINE CR PATIENTS IN A STUDY OF ELDERLY PATIENTS [1,2]		
Body System/Adverse Event	**% Reporting Event**	
	Par 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 paroxetine CR 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.

Dose Dependency of Adverse Events

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

In the pool of two placebo-controlled clinical trials in depressed patients in the age range 18-65, the reported incidence of decreased libido, abnormal ejaculation (mostly delayed ejaculation), and impotence in male patients receiving Paxil CR (n=78) was 10%, 26%, and 5%, respectively. In female patients receiving Paxil CR (n=134), the reported incidence of decreased libido and either anorgasmia or delayed orgasm was 4% and 10%, respectively. The reported incidence of each of these adverse events was ≤5% among male and female patients receiving placebo.

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 SSRI's, 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, 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 depressed patients, 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. The clinical significance of these findings is unknown.

In placebo-controlled clincial 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 depression, multiple doses of Paxil CR were administered to 316 inpatients in Phase 3 double-blind, controlled, inpatient 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 316 inpatients 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 and 2, those reported in terms so general as to be uninformative and those events where a drug cause was remote. 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.

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 and panic 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 cellulitis, chest pain, chills, fever, malaise, neoplasm, rheumatoid arthritis; also observed were abscess, adrenergic syndrome, carcinoma, face edema, flu syndrome, moniliasis, neck pain, neck rigidity, pelvic pain, peritonitis, ulcer.

Cardiovascular System: Frequent were hypertension, hypotension; Infrequent were angina pectoris, arrhythmia, bradycardia, bundle branch block, palpitation, postural hypotension, syncope, vascular disorder; also observed were atrial fibrillation, cerebral ischemia, cerebrovascular accident, conduction abnormalities, congestive heart failure, electrocardiogram abnormal, heart block, hematoma, low cardiac output, migraine, myocardial infarct, myocardial ischemia, pallor, peripheral vascular disorder, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, varicose vein, vascular headache, ventricular extrasystoles.

Digestive System: Frequent were liver function tests abnormal, tooth disorder; Infrequent were bruxism, dysphagia, eructation, gastroenteritis, gastrointestinal disorder, gingivitis, glossitis, hepatosplenomegaly, intestinal obstruction, melena, pancreatitis, peptic ulcer, rectal disorder, rectal hemorrhage, stomach ulcer, tooth caries, ulcerative stomatitis; also observed were aphthous stomatitis, bloody diarrhea, bulimia, cholelithiasis, colitis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gastritis, gum hemorrhage, hematemesis, hepatitis, ileus, increased salivation, jaundice, mouth ulceration, oropharynx disorder, salivary

gland enlargement, stomatitis, tongue discoloration, tongue edema, tooth malformation.

Endocrine System: Infrequent were hyperthyroidism, ovary disorder, testes disorder; also observed were diabetes mellitus, hypothyroidism, thyroiditis.

Hemic and Lymphatic System: Infrequent were anemia, chronic lymphocytic leukemia, eosinophilia, leukocytosis, leukopenia; also observed were abnormal erythrocytes, abnormal lymphocytes, basophilia, hypochromic anemia, iron deficiency anemia, lymphadenopathy, lymphedema, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia.

Metabolic and Nutritional Disorders: Infrequent were generalized edema, hyperglycemia, hyperkalemia, hypokalemia, peripheral edema, thirst; also observed were alkaline phosphatase increased, bilirubinemia, BUN increased, creatinine phosphokinase increased, dehydration, edema, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, hyperphosphatemia, hypocalcemia, hypoglycemia, hyponatremia, ketosis, lactic dehydrogenase increased, SGOT increased, SGPT increased, weight loss.

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

Nervous System: Frequent were depression, lack of emotion, myoclonus; Infrequent were amnesia, concentration impaired, diplopia, drug dependence, dystonia, emotional lability, hallucinations, hypokinesia, incoordination, neuralgia, neuropathy, paralysis, thinking abnormal, vertigo; also observed were abnormal electroencephalogram, abnormal gait, abnormal thinking, akinesia, alcohol abuse, antisocial reaction, aphasia, ataxia, choreoathetosis, circumoral paresthesia, CNS stimulation, convulsion, delirium, delusions, drugged feeling, dysarthria, dyskinesia, euphoria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hostility, hyperalgesia, hypesthesia, hysteria, libido increased, manic reaction, manic-depressive reaction, meningitis, myelitis, neurosis, nystagmus, paranoid reaction, peripheral neuritis, psychosis, psychotic depression,

reflexes decreased, reflexes increased, stupor, trismus, vertigo, withdrawal syndrome.

Respiratory System: Infrequent were asthma, dyspnea, epistaxis, larynx disorder, pneumonia, stridor; also observed were emphysema, hemoptysis, hiccups, hyperventilation, lung fibrosis, pulmonary edema, respiratory flu, sputum increased, voice alteration.

Skin and Appendages: Infrequent were acne, alopecia, dry skin, exfoliative dermatitis, furunculosis, herpes simplex, herpes zoster, pruritus, seborrhea, urticaria; also observed were angioedema, contact dermatitis, ecchymosis, eczema, erythema multiforme, erythema nodosum, fungal dermatitis, hirsutism, maculopapular rash, skin discoloration, skin hypertrophy, skin melanoma, skin ulcer, vesiculobullous rash.

Special Senses: Frequent were conjunctivitis; Infrequent were abnormality of accommodation, ear disorder, ear pain, eye appendage disorder, eye disorder, eye hemorrhage, keratoconjunctivitis, mydriasis, otitis media, tinnitus; also observed were amblyopia, anisocoria, blepharitis, blurred vision, cataract, conjunctival edema, conjunctivitis, corneal ulcer, deafness, exophthalmos, eye pain, glaucoma, hyperacusis, night blindness, otitis externa, parosmia, photophobia, ptosis, retinal hemorrhage, taste loss, visual field defect.

Urogenital System: Infrequent were albuminuria, hematuria, kidney calculus, kidney function abnormal, menorrhagia,* prostate disorder,* urinary incontinence, urinary retention, urine abnormality; also observed were abortion, amenorrhea, breast atrophy, breast carcinoma, breast enlargement, breast neoplasm, breast pain, cystitis, dysuria, ejaculatory disturbance, epididymitis, female lactation, fibrocystic breast, kidney pain, leukorrhea, male genital disorder, mastitis, metrorrhagia, nephritis, nocturia, oliguria, other male genital disorders, polyuria, prostatic carcinoma, pyuria, urethritis, urinary urgency, urination disorder, urination impaired, urolith, uterine spasm, vaginal hemorrhage, vaginal moniliasis.

*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, thrombocytopenia, 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; and 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). There have been spontaneous reports that abrupt discontinuation may lead to symptoms such as dizziness, sensory disturbances, agitation or anxiety, nausea and sweating; these events are generally self-limiting. 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

Overdose with immediate-release paroxetine (up to 2000 mg) alone and in combination with other drugs has been reported. Signs and symptoms of overdose with immediate-release paroxetine include nausea, vomiting, sedation, dizziness, sweating, and facial flush. There are no reports of coma or convulsions following overdosage with immediate-release paroxetine alone. A fatal outcome has been reported rarely when immediate-release paroxetine was taken in combination with other agents, or when taken alone.

Overdosage Management

Treatment should consist of those general measures employed in the management of overdosage with any antidepressant.

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

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 antidepressant effectiveness of Paxil CR. As with all antidepressants, the full antidepressant 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 depression require several months or longer of sustained pharmacologic therapy. Whether the dose of an antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Systematic evaluation of the efficacy of immediate-release paroxetine hydrochloride has shown that efficacy is maintained for 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).

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 a MAOI and initiation of Paxil CR therapy. Similarly, at least 14 days should be allowed after stopping Paxil CR before starting a MAOI.

HOW SUPPLIED

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

12.5 mg pale yellow and white tablets, printed with Paxil CR and 12.5
NDC 0029-3206-13 Bottles of 30
NDC 0029-3206-20 Bottles of 100
NDC 0029-3207-21 SUP 100's (intended for institutional use only)

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

Store at controlled room temperature between 20° and 25°C (68° and 77°F) [see USP].

Rx Only

DATE OF ISSUANCE: MONTH YEAR

Manufactured by SmithKline Beecham Pharmaceuticals

DOC: PAXILCR DEP AP2.DOC