PX:L3 PRESCRIBING INFORMATION

PX:L3

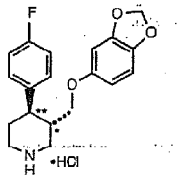
# PAXIL™

*brand of*

## *paroxetine hydrochloride tablets*

### DESCRIPTION

Paxil (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 (-)-*trans*-4*R*-(4'-fluorophenyl)-3*S*-[(3',4'-methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate and has the empirical formula of $C_{19}H_{20}FNO_3 \cdot HCl \cdot 1/2H_2O$. 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 film-coated tablet contains paroxetine hydrochloride equivalent to paroxetine as follows: 20 mg–pink (scored); 30 mg–blue. Inactive ingredients consist of dibasic calcium phosphate dihydrate, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycols, polysorbate 80, sodium starch glycolate, titanium dioxide and one or more of the following: D&C Red No. 30, FD&C Blue No. 2.

### 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-$HT_{1A}$, 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**

Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt. In a study in which normal male subjects (n=15) received 30 mg tablets daily for 30 days, steady-state paroxetine concentrations were achieved by approximately 10 days for most subjects, although it may take substantially longer in an occasional patient. At steady state, mean values of $C_{max}$, $T_{max}$, $C_{min}$ and $T_{1/2}$ were 61.7 ng/mL (CV 45%), 5.2 hr. (CV 10%), 30.7 ng/mL (CV 67%) and 21.0 hr. (CV 32%), respectively. The steady-state $C_{max}$ and $C_{min}$ values were about 6 and 14 times what would be predicted from single-dose studies. Steady-state drug exposure based on $AUC_{24}$ was about 8 times greater than would have been predicted from single-dose data in these subjects. 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 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 2-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 paroxetine doses of 20, 30 and



40 mg, $C_{min}$ 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* as a treatment for depression has been established in 6 placebo-controlled studies of patients with depression (ages 18 to 73). In these studies *Paxil* was shown to be significantly more effective than placebo in treating depression by at least 2 of the following measures: Hamilton Depression Rating Scale (HDRS), the Hamilton depressed mood item, and the Clinical Global Impression (CGI)–Severity of Illness. *Paxil* was significantly better than placebo in improvement of the HDRS sub-factor scores, including the depressed mood item, sleep disturbance factor and anxiety factor.

A study of depressed outpatients who had responded to *Paxil* (HDRS total score ≤8) during an initial 8-week open-treatment phase and were then randomized to continuation on *Paxil* or placebo for 1 year demonstrated a significantly lower relapse rate for patients taking *Paxil* (15%) compared to those on placebo (39%). Effectiveness was similar for male and female patients.

### INDICATIONS AND USAGE

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

The efficacy of *Paxil* in the treatment of a major depressive episode was established in 6-week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder (see CLINICAL PHARMACOLOGY).

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

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

The efficacy of *Paxil* in maintaining an antidepressant response for up to 1 year was demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use *Paxil* 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).

### 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 *Paxil*, 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 (paroxetine hydrochloride) 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* before starting a MAOI.**



### PRECAUTIONS

**General**

***Activation of Mania/Hypomania:*** During premarketing testing, hypomania or mania occurred in approximately 1.0% of *Paxil*-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 *Paxil* and 11.6% for the combined active-control groups. As with all antidepressants, *Paxil* should be used cautiously in patients with a history of mania.

***Seizures:*** During premarketing testing, seizures occurred in 0.1% of *Paxil*-treated patients, a rate similar to that associated with other antidepressants. *Paxil* 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* 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. The hyponatremia appeared to be reversible when *Paxil* was discontinued. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted.

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

*Paxil* 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 the product's premarket testing. Evaluation of electrocardiograms of 882 patients who received *Paxil* in double-blind, placebo-controlled trials, however, did not indicate that *Paxil* is associated with the development of significant ECG abnormalities. Similarly, Paxil (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*:

***Interference with Cognitive and Motor Performance:*** Any psychoactive drug may impair judgment, thinking or motor skills. Although in controlled studies *Paxil* 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* therapy does not affect their ability to engage in such activities.

***Completing Course of Therapy:*** While patients may notice improvement with *Paxil* 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 *Paxil* 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*.

***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 Paxil (paroxetine hydrochloride). Consequently, concomitant use of *Paxil* 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* and warfarin should be undertaken with caution.

***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 *Paxil* (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* after the 20 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 *Paxil* 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 *Paxil* exhibits nonlinear pharmacokinetics, the results of this study may not address the case where the 2 drugs are both being chronically dosed. No initial *Paxil* 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 *Paxil* 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 *Paxil* 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 co-administered alone. Since both drugs exhibit nonlinear pharmacokinetics, the above studies may not address the case where the 2 drugs are both being chronically dosed. No initial dosage adjustments are considered necessary when these drugs are co-administered; any subsequent adjustments should be guided by clinical effect.

***Drugs Metabolized by Cytochrome $P_{450}IID_6$:*** Concomitant use of *Paxil* with drugs metabolized by cytochrome $P_{450}IID_6$ has not been formally studied but may require lower doses than usually prescribed for either *Paxil* or the other drug. Many drugs, including most antidepressants (paroxetine, other SSRIs and many tricyclics), are metabolized by this cytochrome $P_{450}$ isozyme $P_{450}IID_6$. In most patients (>90%), this $P_{450}IID_6$ isozyme is saturated early during *Paxil* dosing. Like other agents that are metabolized by $P_{450}IID_6$, paroxetine may significantly inhibit the activity of this isozyme.

Therefore, co-administration of *Paxil* 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.

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

***Lithium:*** A multiple-dose study has shown that there is no pharmacokinetic interaction between *Paxil* and lithium carbonate. However, since there is little clinical experience, the concurrent administration of paroxetine 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 paroxetine 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 *Paxil* (30 mg q.d.) increased steady-state $AUC_{24}$, $C_{max}$ 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.

***Propranolol:*** In a study where propranolol (60 mg b.i.d.) was dosed orally for 14 days, the established steady-state plasma concentrations of propranolol were unaltered during co-administration with *Paxil* (30 mg q.d.) for the final 10 days. The effects of propranolol on paroxetine have not been evaluated.

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

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

***Carcinogenesis:*** Two-year carcinogenicity studies were conducted in mice and rats given paroxetine in the diet at 1, 5 and 25 mg/kg/day (mice) and 1, 5 and 20 mg/kg/day (rats). The maximum doses in these studies were approximately 25 (mouse) and 20 (rat) times the maximum dose recommended for human use on a mg/kg basis or 2.5 (mouse) and 5.8 (rat) times the maximum recommended human dose 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 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.



Plaintiff Exhibit

PTX-048

***Impairment of Fertility:*** Serotonergic compounds are known to affect reproductive function in animals. Impaired reproductive function (i.e., reduced pregnancy rate, increased pre- and post-implantation losses, decreased viability of pups) was found in reproduction studies in rats at doses of paroxetine which were 15 or more times the highest recommended human dose on a mg/kg basis, or 4.4 times on a mg/m² basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks. These lesions, which consisted of vacuolation of epididymal tubular epithelium and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis occurred at doses which were 25 times the highest recommended human dose on a mg/kg basis or 7.3 times on a mg/m² basis.

**Pregnancy**

**Teratogenic Effects–Pregnancy Category B:** Reproduction studies performed in rats and rabbits at doses up to 50 and 6 times the maximum recommended human dose on a mg/kg basis or 10 and 2 times on a mg/m² basis, respectively, have revealed no evidence of teratogenic effects. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**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 (paroxetine hydrochloride) is administered to a nursing woman.

**Usage in Children**

Safety and effectiveness in children have not been established.

**Geriatric Use**

In worldwide *Paxil* clinical trials, 17% of *Paxil*-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.)

## ADVERSE REACTIONS

### Associated with Discontinuation of Treatment

Twenty-one percent (88/4,126) of *Paxil* patients in worldwide clinical trials discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate approximately twice or greater for *Paxil* compared to placebo) included:

**CNS**

| | |
|---|---|
| Somnolence | 2.3% |
| Insomnia | 1.9% |
| Agitation | 1.3% |
| Tremor | 1.3% |
| Anxiety | 1.1% |

**Gastrointestinal**

| | |
|---|---|
| Nausea | 3.4% |
| Diarrhea | 1.0% |
| Dry mouth | 1.0% |
| Vomiting | 1.0% |

**Other**

| | |
|---|---|
| Asthenia | 1.7% |
| Abnormal ejaculation | 1.6% |
| Sweating | 1.1% |

### Incidence in Controlled Trials

***Commonly Observed Adverse Events in Controlled Clinical Trials:*** The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for *Paxil* at least twice that for placebo, derived from 1% table below) were: asthenia, sweating, nausea, decreased appetite, somnolence, dizziness, insomnia, tremor, nervousness, ejaculatory disturbance and other male genital disorders.



***Adverse Events Occurring at an Incidence of 1% or More Among Paroxetine-Treated Patients:*** The table that follows enumerates adverse events that occurred at an incidence of 1% or more among paroxetine-treated patients who participated in short-term (6-week) placebo-controlled trials in which patients were dosed in a range of 20 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 Experience Incidence in Placebo-Controlled Clinical Trials[1]**

| Body System | Preferred Term | *Paxil* (n=421) | Placebo (n=421) |
|---|---|---|---|
| Body as a Whole | Headache | 17.6% | 17.3% |
| | Asthenia | 15.0% | 5.0% |
| | Abdominal Pain | 3.1% | 4.0% |
| | Fever | 1.7% | 1.7% |
| | Chest Pain | 1.4% | 2.1% |
| | Trauma | 1.4% | 0.5% |
| | Back Pain | 1.2% | 2.4% |
| Cardiovascular | Palpitation | 2.9% | 1.4% |
| | Vasodilation | 2.6% | 0.7% |
| | Postural Hypotension | 1.2% | 0.5% |
| Dermatologic | Sweating | 11.2% | 2.4% |
| | Rash | 1.7% | 0.7% |
| Gastrointestinal | Nausea | 25.7% | 9.3% |
| | Dry Mouth | 18.1% | 12.1% |
| | Constipation | 13.8% | 8.6% |
| | Diarrhea | 11.6% | 7.6% |
| | Decreased Appetite | 6.4% | 1.9% |
| | Flatulence | 4.0% | 1.7% |
| | Vomiting | 2.4% | 1.2% |
| | Oropharynx Disorder[2] | 2.1% | 0.0% |
| | Dyspepsia | 1.9% | 1.0% |
| | Increased Appetite | 1.4% | 0.5% |
| Musculoskeletal | Myopathy | 2.4% | 1.4% |
| | Myalgia | 1.7% | 0.7% |
| | Myasthenia | 1.4% | 0.2% |
| Nervous System | Somnolence | 23.3% | 8.0% |
| | Dizziness | 13.3% | 5.5% |
| | Insomnia | 13.3% | 6.2% |
| | Tremor | 8.3% | 1.9% |
| | Nervousness | 5.2% | 2.6% |
| | Anxiety | 5.0% | 2.9% |
| | Paresthesia | 3.8% | 1.7% |
| | Libido Decreased | 3.3% | 0.0% |
| | Agitation | 2.1% | 1.9% |
| | Drugged Feeling | 1.7% | 0.7% |
| | Myoclonus | 1.4% | 0.2% |
| | CNS Stimulation | 1.2% | 0.5% |
| | Confusion | 1.2% | 0.2% |
| Respiration | Respiratory Disorder[3] | 5.9% | 6.4% |
| | Yawn | 3.8% | 0.0% |
| | Pharyngitis | 2.1% | 2.9% |
| Special Senses | Blurred Vision | 3.6% | 1.4% |
| | Taste Perversion | 2.4% | 0.2% |
| Urogenital System | Ejaculatory Disturbance[4,5] | 12.8% | 0.0% |
| | Other Male Genital Disorders[4,6] | 10.0% | 0.0% |
| | Urinary Frequency | 3.1% | 0.7% |
| | Urination Disorder[7] | 2.6% | 0.2% |
| | Female Genital Disorders[4,8] | 1.8% | 0.0% |

1. Events reported by at least 1% of patients treated with Paxil (paroxetine hydrochloride) are included.
2. Includes mostly "lump in throat" and "tightness in throat."
3. Includes mostly "cold symptoms" or "URI."
4. Percentage corrected for gender.
5. Mostly "ejaculatory delay."
6. Includes "anorgasmia," "erectile difficulties," "delayed ejaculation/orgasm," and "sexual dysfunction," and "impotence."
7. Includes mostly "difficulty with micturition" and "urinary hesitancy."
8. Includes mostly "anorgasmia" and "difficulty reaching climax/orgasm."



***Dose Dependency of Adverse Events:*** A comparison of adverse event rates in a fixed-dose study comparing *Paxil* 10, 20, 30 and 40 mg/day with placebo revealed a clear dose dependency for some of the more common adverse events associated with *Paxil* use, as shown in the following table:

**Table 2. Treatment-Emergent Adverse Experience Incidence in a Dose-Comparison Trial[4]**

| Body System/ Preferred Term | Placebo n=51 | *Paxil* 10 mg n=102 | *Paxil* 20 mg n=104 | *Paxil* 30 mg n=101 | *Paxil* 40 mg n=102 |
|---|---|---|---|---|---|
| Body as a Whole | | | | | |
| Asthenia | 0.0% | 2.9% | 10.6% | 13.9% | 12.7% |
| Dermatology | | | | | |
| Sweating | 2.0% | 1.0% | 6.7% | 8.9% | 11.8% |
| Gastrointestinal | | | | | |
| Constipation | 5.9% | 4.9% | 7.7% | 9.9% | 12.7% |
| Decreased Appetite | 2.0% | 2.0% | 5.8% | 4.0% | 4.9% |
| Diarrhea | 7.8% | 9.8% | 19.2% | 7.9% | 14.7% |
| Dry Mouth | 2.0% | 10.8% | 18.3% | 15.8% | 20.6% |
| Nausea | 13.7% | 14.7% | 26.9% | 34.7% | 35.3% |
| Nervous System | | | | | |
| Anxiety | 0.0% | 2.0% | 5.8% | 5.9% | 5.5% |
| Dizziness | 3.9% | 5.9% | 6.7% | 8.9% | 12.7% |
| Nervousness | 0.0% | 5.9% | 5.9% | 4.0% | 2.9% |
| Paresthesia | 0.0% | 2.9% | 1.0% | 5.0% | 5.9% |
| Somnolence | 7.8% | 12.7% | 18.3% | 26.8% | 21.6% |
| Tremor | 0.0% | 0.0% | 7.7% | 7.9% | 14.7% |
| Special Senses | | | | | |
| Blured Vision | 2.0% | 2.9% | 2.9% | 2.0% | 7.8% |
| Urogenital | | | | | |
| Abnormal Ejaculation | 0.0% | 5.8% | 6.5% | 10.6% | 13.0% |
| Impotence | 0.0% | 1.9% | 4.3% | 6.4% | 1.9% |
| Male Genital Disorders | 0.0% | 3.8% | 8.7% | 6.4% | 3.7% |

[4]Rule for including adverse events in table: incidence at least 5% for one of paroxetine groups and ≥ twice the placebo incidence for at least one paroxetine group.

***Adaptation to Certain Adverse Events:*** Over a 4- to 6-week period, there was evidence of adaptation to some adverse events with continued therapy (e.g., nausea and dizziness), but less to other effects (e.g., dry mouth, somnolence and asthenia).

***Weight and Vital Sign Changes:*** Significant weight loss may be an undesirable result of treatment with *Paxil* for some patients but, on average, patients in controlled trials had minimal (about 1 pound) weight loss vs. smaller changes on placebo and active control. No significant changes in vital signs (systolic and diastolic blood pressure, pulse and temperature) were observed in patients treated with *Paxil* in controlled clinical trials.

***ECG Changes:*** In an analysis of ECGs obtained in 682 patients treated with *Paxil* 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 placebo-controlled clinical trials, patients treated with *Paxil* exhibited abnormal values on liver function tests at no greater rate than that seen in placebo-treated patients. In particular, the *Paxil*-vs.-placebo comparison for alkaline phosphatase was 0% vs. 0%, SGOT 0.3% vs. 0.3%, SGPT 1% vs. 0.3% and bilirubin 0% vs. 0.8%.

### Other Events Observed During the Premarketing Evaluation of Paxil (paroxetine hydrochloride)

During its premarketing assessment, multiple doses of *Paxil* were administered to 4,126 patients in phase 2 and 3 studies. The conditions and duration of exposure to *Paxil* 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. 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 standard



COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 4,126 patients exposed to multiple doses of Paxil (paroxetine hydrochloride) who experienced an event of the type cited on at least one occasion while receiving *Paxil*. All reported events are included except those already listed in Table 1, 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; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in the PRECAUTIONS section.

***Body as a Whole: frequent:*** chills, malaise; *infrequent:* allergic reaction, carcinoma, face edema, moniliasis, neck pain; *rare:* abscess, adrenergic syndrome, cellulitis, neck rigidity, pelvic pain, peritonitis, ulcer.

***Cardiovascular System: frequent:*** hypertension, syncope, tachycardia; *infrequent:* bradycardia, conduction abnormalities, electrocardiogram abnormal, hypotension, migraine, peripheral vascular disorder; *rare:* angina pectoris, arrhythmia, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombosis, varicose vein, vascular headache, ventricular extrasystoles.

***Digestive System: infrequent:*** bruxism, dysphagia, eructation, gastritis, glossitis, increased salivation, liver function tests abnormal, mouth ulceration, rectal hemorrhage; *rare:* aphthous stomatitis, bloody diarrhea, bulimia, colitis, duodenitis, esophagitis, fecal impactions, fecal incontinence, gastritis, gastroenteritis, gingivitis, hematemesis, hepatitis, ileus, jaundice, melena, peptic ulcer, salivary gland enlargement, stomach ulcer, stomatitis, tongue edema, tooth caries.

***Endocrine System: rare:*** diabetes mellitus, hyperthyroidism, hypothyroidism, thyroiditis.

***Hemic and Lymphatic Systems: infrequent:*** anemia, leukopenia, lymphadenopathy, purpura; *rare:* abnormal erythrocytes, eosinophilia, leukocytosis, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia.

***Metabolic and Nutritional: frequent:*** edema, weight gain, weight loss; *infrequent:* hyperglycemia, peripheral edema, thirst; *rare:* alkaline phosphatase increased, bilirubinemia, dehydration, gout, hypercholesteremia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, SGOT increased, SGPT increased.

***Musculoskeletal System:*** *infrequent:* arthralgia, arthritis; *rare:* arthrosis, bursitis, myositis, osteoporosis, tetany.

***Nervous System: frequent:*** amnesia, CNS stimulation, concentration impaired, depression, emotional lability, vertigo; *infrequent:* abnormal thinking, akinesia, alcohol abuse, ataxia, convulsion, depersonalization, hallucinations, hyperkinesia, hypertonia, incoordination, lack of emotion, manic reaction, paranoid reaction; *rare:* abnormal electroencephalogram, abnormal gait, antisocial reaction, choreoathetosis, delirium, delusions, diplopia, drug dependance, dysarthria, dyskinesia, dystonia, euphoria, fasciculations, grand mal convulsion, hostility, hyperalgesia, hypokinesia, hysteria, libido increased, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, paralysis, psychosis, psychotic depression, reflexes increased, stupor, withdrawal syndrome.

***Respiratory System:*** *frequent:* cough increased, rhinitis; *infrequent:* asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu, sinusitis; *rare:* carcinoma of lung, hiccups, lung fibrosis, sputum increased.

***Skin and Appendages:*** *frequent:* pruritus; *infrequent:* acne, alopecia, dry skin, ecchymosis, eczema, furunculosis, urticaria; *rare:* angioedema, contact dermatitis, erythema nodosum, maculopapular rash, photosensitivity, skin discoloration, skin melanoma.

***Special Senses:*** *infrequent:* abnormality of accommodation, ear pain, eye pain, mydriasis, otitis media, taste loss, tinnitus; *rare:* amblyopia, cataract, conjunctivitis, corneal ulcer, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, otitis externa, photophobia.

***Urogenital System:*** *infrequent:* abortion, amenorrhea, breast pain, cystitis, dysmenorrhea, dysuria, menorrhagia, nocturia, polyuria, urethritis, urinary incontinence, urinary retention, urinary urgency, vaginitis; *rare:* breast atrophy, breast carcinoma, breast neoplasm, female lactation, hematuria, kidney calculus, kidney function abnormal, kidney pain, mastitis, nephritis, oliguria, prostatic carcinoma, vaginal moniliasis.

**Non-U.S. Postmarketing Reports**

Voluntary reports of adverse events in patients taking *Paxil* that have been received since market introduction and may have no causal relationship with the drug include elevated liver function tests (the most severe case was a death due to liver necrosis, and one other case involved grossly elevated transaminases associated with severe liver dysfunction).

## DRUG ABUSE AND DEPENDENCE

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

***Physical and Psychological Dependence:*** *Paxil* 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* misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

## OVERDOSAGE

***Human Experience:*** No deaths were reported following acute overdose with *Paxil* alone or in combination with other drugs and/or alcohol (18 cases, with doses up to 850 mg) during premarketing clinical trials. Signs and symptoms of overdose with *Paxil* included: nausea, vomiting, drowsiness, sinus tachycardia and dilated pupils. There were no reports of ECG abnormalities, coma or convulsions following overdosage with *Paxil* alone.

***Overdosage Management:*** Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. There are no specific antidotes for *Paxil*. Establish and maintain an airway; ensure adequate oxygenation and ventilation. Gastric evacuation either by the induction of emesis or lavage or both should be performed. In most cases, following evacuation, 20 to 30 grams of activated charcoal may be administered every 4 to 6 hours during the first 24 to 48 hours after ingestion. An ECG should be taken and monitoring of cardiac function instituted if there is any evidence of abnormality. Supportive care with frequent monitoring of vital signs and careful observation is indicated. Due to the large volume of distribution of *Paxil*, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit.

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

In managing overdosage, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).



## DOSAGE AND ADMINISTRATION

**Depression**

***Usual Initial Dosage:*** Paxil (paroxetine hydrochloride) should be administered as a single daily dose, usually in the morning. The recommended initial dose is 20 mg/day. Patients were dosed in a range of 20 to 50 mg/day in the clinical trials demonstrating the antidepressant effectiveness of *Paxil*. As with all antidepressants, the full antidepressant effect may be delayed. Some patients not responding to a 20 mg dose may benefit from dose increases, in 10 mg/day increments, up to a maximum of 50 mg/day. Dose changes should occur at intervals of at least 1 week.

***Dosage for Elderly or Debilitated, and Patients with Severe Renal or Hepatic Impairment:*** The recommended initial dose is 10 mg/day for elderly, debilitated patients, and/or patients with severe renal or hepatic impairment. Increases may be made if indicated. Dosage should not exceed 40 mg/day.

***Maintenance Therapy:*** There is no body of evidence available to answer the question of how long the patient treated with *Paxil* 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 Paxil (paroxetine hydrochloride) has shown that efficacy is maintained for periods of up to 1 year with doses that averaged about 30 mg.

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

## HOW SUPPLIED

*Paxil* is supplied as film-coated, modified-oval tablets as follows: 20 mg (scored) in bottles of 30, 100 and Single Unit Packages of 100 (intended for institutional use only); 30 mg in bottles of 30.

*Paxil* 20 mg tablets are pink, scored, film-coated modified-oval tablets engraved on the front with PAXIL and on the back with 20.

NDC 0029-3211-13 Bottles of 30
NDC 0029-3211-20 Bottles of 100
NDC 0029-3211-21 SUP 100's

*Paxil* 30 mg tablets are blue, film-coated modified-oval tablets engraved on the front with PAXIL and on the back with 30.

NDC 0029-3212-13 Bottles of 30

Store at controlled room temperature (15° to 30°C: 59° to 86°F).

DATE OF ISSUANCE DEC. 1992



**SmithKline Beecham Pharmaceuticals**
Philadelphia, PA 19101

PX:L3

Printed in U.S.A.