Use Parnate (tranylcypromine sulfate) with caution in hyperthyroid patients because of their increased sensitivity to pressor amines.

Parnate should be administered with caution to patients receiving Antabuse®‡. In a single study, rats given high intraperitoneal doses of *d* or *l* isomers of tranylcypromine sulfate plus disulfiram experienced severe toxicity including convulsions and death. Additional studies in rats given high oral doses of racemic tranylcypromine sulfate (*Parnate*) and disulfiram produced no adverse interaction.

ADVERSE REACTIONS

Overstimulation which may include increased anxiety, agitation and manic symptoms is usually evidence of excessive therapeutic action. Dosage should be reduced, or a phenothiazine tranquilizer should be administered concomitantly. Patients may experience restlessness or insomnia; may notice some weakness, drowsiness, episodes of dizziness or dry mouth; or may report nausea, diarrhea, abdominal pain or constipation. Most of these effects can be relieved by lowering the dosage or by giving suitable concomitant medication.

Tachycardia, significant anorexia, edema, palpitation, blurred vision, chills and impotence have each been reported.

Headaches without blood pressure elevation have occurred. There are instances of hepatitis and skin rash have been reported.

Impaired water excretion compatible with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) has been reported.

Tinnitus, muscle spasm, tremors, myoclonic jerks, numbness, paresthesia, urinary retention and retarded ejaculation have been reported.

Hematologic disorders including anemia, leukopenia, granulocytosis and thrombocytopenia have been reported.

Post-Introduction Reports

The following are spontaneously reported adverse events temporally associated with *Parnate* therapy. No clear relationship between *Parnate* and these events has been established. Localized scleroderma, flare-up of cystic acne, ataxia, confusion, disorientation, memory loss, urinary frequency, urinary incontinence, urticaria, fissuring in corner of mouth, akinesia.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted to the requirements of the individual patient. Improvement should be seen within 48 hours to 3 weeks after starting therapy.

The usual effective dosage is 30 mg per day, usually given in divided doses. If there are no signs of improvement after a reasonable period (up to 2 weeks), then the dosage may be increased in 10 mg per day increments at intervals of 1 to 3 weeks; the dosage range may be extended to a maximum of 60 mg per day from the usual 30 mg per day.

OVERDOSAGE

SYMPTOMS: The characteristic symptoms that may be caused by overdosage are usually those described above.

However, an intensification of these symptoms and sometimes severe additional manifestations may be seen, depending on the degree of overdosage and on individual susceptibility. Some patients exhibit insomnia, restlessness and anxiety, progressing in severe cases to agitation, mental confusion and incoherence. Hypotension, dizziness, weakness and drowsiness may occur, progressing in severe cases to extreme dizziness and shock. A few patients have displayed hypertension with severe headache and other symptoms. Rare instances have been reported in which hypertension was accompanied by twitching or myoclonic fibrillation of skeletal muscles with hyperpyrexia, sometimes progressing to generalized rigidity and coma.

TREATMENT: Gastric lavage is helpful if performed early. Treatment should normally consist of general supportive measures, close observation of vital signs and steps to counteract specific symptoms as they occur, since MAO inhibition may persist. The management of hypertensive crises is described under WARNINGS in the HYPERTENSIVE CRISES section.

External cooling is recommended if hyperpyrexia occurs. Barbiturates have been reported to help relieve myoclonic reactions, but frequency of administration should be controlled carefully because Parnate (tranylcypromine sulfate) may prolong barbiturate activity. When hypotension requires treatment, the standard measures for managing circulatory shock should be initiated. If pressor agents are used, the rate of infusion should be regulated by careful observation of the patient because an exaggerated pressor response sometimes occurs in the presence of MAO inhibition. Remember that the toxic effect of *Parnate* may be delayed or prolonged following the last dose of the drug. Therefore, the patient should be closely observed for at least a week. It is not known if tranylcypromine is dialyzable.

HOW SUPPLIED

Parnate is supplied as round, rose-red, film-coated tablets imprinted with the product name PARNATE and SB and contains tranylcypromine sulfate equivalent to 10 mg of tranylcypromine, in bottles of 100 with a desiccant, manufactured by Abbott Laboratories, North Chicago, IL 60064.

10 mg 100's: NDC 0007-4471-20

Store between 15° and 30°C (59° and 86°F)

‡disulfiram, Wyeth-Ayerst Laboratories.

GlaxoSmithKline, Research Triangle Park, NC 27709

January 1998/PT:L63

Shown in Product Identification Guide, page 317

PAXIL® ℞

[pax'il]

brand of paroxetine hydrochloride tablets and oral suspension

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 $C_{19}H_{20}FNO_3 \bullet HCl \bullet 1/2H_2O$. The molecular weight is 374.8 (329.4 as free base).

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.

Tablets

Each film-coated tablet contains paroxetine hydrochloride equivalent to paroxetine as follows: 10 mg-yellow (scored); 20 mg-pink (scored); 30 mg-blue, 40 mg-green. 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, D&C Yellow No. 10, FD&C Blue No. 2, FD&C Yellow No. 6.

Suspension for Oral Administration

Each 5 mL of orange-colored, orange-flavored liquid contains paroxetine hydrochloride equivalent to paroxetine, 10 mg. Inactive ingredients consist of polacrilin potassium, microcrystalline cellulose, propylene glycol, glycerin, sorbitol, methyl paraben, propyl paraben, sodium citrate dihydrate, citric acid anhydrate, sodium saccharin, flavorings, FD&C Yellow No. 6 and simethicone emulsion, USP.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The efficacy of paroxetine in the treatment of depression, social anxiety disorder, obsessive compulsive disorder (OCD), panic disorder (PD), and generalized anxiety disorder (GAD) 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

Paroxetine is equally bioavailable from the oral suspension and tablet.

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_{0-24} 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.

The effects of food on the bioavailability of paroxetine were studied in subjects administered a single dose with and without food. AUC was only slightly increased (6%) when drug was administered with food but the C_{max} was 29% 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

Depression

The efficacy of Paxil (paroxetine hydrochloride) 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 (paroxetine hydrochloride) 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.

Obsessive Compulsive Disorder

The effectiveness of *Paxil* in the treatment of obsessive compulsive disorder (OCD) was demonstrated in two 12-week multicenter placebo-controlled studies of adult outpatients (Studies 1 and 2). Patients in all studies had moderate to severe OCD (DSM-IIIR) with mean baseline ratings on the Yale Brown Obsessive Compulsive Scale (YBOCS) total score ranging from 23 to 26. Study 1, a dose-range finding study where patients were treated with fixed doses of 20, 40 or 60 mg of paroxetine/day demonstrated that daily doses of paroxetine 40 and 60 mg are effective in the treatment of OCD. Patients receiving doses of 40 and 60 mg paroxetine experienced a mean reduction of approximately 6 and 7 points, respectively, on the YBOCS total score which was significantly greater than the approximate 4 point reduction at 20 mg and a 3 point reduction in the placebo-treated patients. Study 2 was a flexible dose study comparing paroxetine (20 to 60 mg daily) with clomipramine (25 to 250 mg daily). In this study, patients receiving paroxetine experienced a mean reduction of approximately 7 points on the YBOCS total score which was significantly greater than the mean reduction of approximately 4 points in placebo-treated patients.

The following table pro
treatment group on Glo
ical Global Impressions

This product informati

Paxil—Cont.

Outcome Classification (%) on CGI-Global Improvement Item for Completers in Study 1

Outcome Classification	Placebo (n=74)	*Paxil* 20 mg (n=75)	*Paxil* 40 mg (n=66)	*Paxil* 60 mg (n=66)
Worse	14%	7%	7%	3%
No Change	44%	35%	22%	19%
Minimally Improved	24%	33%	29%	34%
Much Improved	11%	18%	22%	24%
Very Much Improved	7%	7%	20%	20%

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

The long-term maintenance effects of *Paxil* in OCD were demonstrated in a long-term extension to Study 1. Patients who were responders on paroxetine during the 3-month double-blind phase and a 6-month extension on open-label paroxetine (20 to 60 mg/day) were randomized to either paroxetine or placebo in a 6-month double-blind relapse prevention phase. Patients randomized to paroxetine were significantly less likely to relapse than comparably treated patients who were randomized to placebo.

Panic Disorder

The effectiveness of Paxil (paroxetine hydrochloride) in the treatment of panic disorder was demonstrated in three 10- to 12-week multicenter, placebo-controlled studies of adult outpatients (Studies 1–3). Patients in all studies had panic disorder (DSM-IIIR), with or without agoraphobia. In these studies, *Paxil* was shown to be significantly more effective than placebo in treating panic disorder by at least 2 out of 3 measures of panic attack frequency and on the Clinical Global Impression Severity of Illness score.

Study 1 was a 10-week dose-range finding study; patients were treated with fixed paroxetine doses of 10, 20, or 40 mg/day or placebo. A significant difference from placebo was observed only for the 40 mg/day group. At endpoint, 76% of patients receiving paroxetine 40 mg/day were free of panic attacks, compared to 44% of placebo-treated patients.

Study 2 was a 12-week flexible-dose study comparing paroxetine (10 to 60 mg daily) and placebo. At endpoint, 51% of paroxetine patients were free of panic attacks compared to 32% of placebo-treated patients.

Study 3 was a 12-week flexible-dose study comparing paroxetine (10 to 60 mg daily) to placebo in patients concurrently receiving standardized cognitive behavioral therapy. At endpoint, 33% of the paroxetine-treated patients showed a reduction to 0 or 1 panic attacks compared to 14% of placebo patients.

In both Studies 2 and 3, the mean paroxetine dose for completers at endpoint was approximately 40 mg/day of paroxetine.

Long-term maintenance effects of *Paxil* in panic disorder were demonstrated in an extension to Study 1. Patients who were responders during the 10-week double-blind phase and during a 3-month double-blind extension phase were randomized to either paroxetine (10, 20, or 40 mg/day) or placebo in a 3-month double-blind relapse prevention phase. Patients randomized to paroxetine were significantly less likely to relapse than comparably treated patients who were randomized to placebo.

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

Social Anxiety Disorder

The effectiveness of *Paxil* in the treatment of social anxiety disorder was demonstrated in three 12-week, multicenter, placebo-controlled studies (Studies 1–3) of adult outpatients with social anxiety disorder (DSM-IV). In these studies, the effectiveness of *Paxil* compared to placebo was evaluated on the basis of (1) the proportion of responders, as defined by a Clinical Global Impressions (CGI) Improvement score of 1 (very much improved) or 2 (much improved), and (2) change from baseline in the Liebowitz Social Anxiety Scale (LSAS). Studies 1 and 2 were flexible-dose studies comparing paroxetine (20 to 50 mg daily) and placebo. Paroxetine demonstrated statistically significant superiority over placebo on both the CGI Improvement responder criterion and the Liebowitz Social Anxiety Scale (LSAS). In Study 1, for patients who completed to week 12, 69% of paroxetine-treated patients compared to 29% of placebo-treated patients were CGI Improvement responders. In Study 2, CGI Improvement responders were 77% and 42% for the paroxetine- and placebo-treated patients, respectively.

Study 3 was a 12-week study comparing fixed paroxetine doses of 20, 40 or 60 mg/day with placebo. Paroxetine 20 mg was demonstrated to be significantly superior to placebo on both the LSAS Total Score and the CGI Improvement responder criterion; there were trends for superiority over placebo for the 40 and 60 mg/day dose groups. There was no indication in this study of any additional benefit for doses

INDICATIONS AND USAGE

Depression

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.

Obsessive Compulsive Disorder

Paxil is indicated for the treatment of obsessions and compulsions in patients with obsessive compulsive disorder (OCD) as defined in the DSM-IV. The obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of *Paxil* was established in two 12-week trials with obsessive compulsive outpatients whose diagnoses corresponded most closely to the DSM-IIIR category of obsessive compulsive disorder (see CLINICAL PHARMACOLOGY—Clinical Trials).

Obsessive compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses or images (obsessions) that are ego-dystonic and/or repetitive, purposeful and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

Long-term maintenance of efficacy was demonstrated in a 6-month relapse prevention trial. In this trial, patients assigned to paroxetine showed a lower relapse rate compared to patients on placebo (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 (see DOSAGE AND ADMINISTRATION).

Panic Disorder

Paxil is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

The efficacy of Paxil (paroxetine hydrochloride) was established in three 10- to 12-week trials in panic disorder patients whose diagnoses corresponded to the DSM-IIIR category of panic disorder (see CLINICAL PHARMACOLOGY—Clinical Trials).

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

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

Social Anxiety Disorder

Paxil is indicated for the treatment of social anxiety disorder, also known as social phobia, as defined in DSM-IV (300.23). Social anxiety disorder is characterized by a marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. Exposure to the feared situation almost invariably provokes anxiety, which may approach the intensity of a panic attack. The feared situations are avoided or endured with intense anxiety or distress. The avoidance, anxious anticipation, or distress in the feared situation(s) interferes significantly with the person's normal routine, occupational or academic functioning, or social activities or relationships, or there is marked distress about having the phobias. Lesser degrees of performance anxiety or shyness generally do not require psychoanxiety disorder (DSM-IV). *Paxil* has not been studied in children or adolescents with social phobia (see CLINICAL PHARMACOLOGY—Clinical Trials).

The effectiveness of *Paxil* in long-term treatment of social anxiety disorder, i.e., for more than 12 weeks, has not been systematically evaluated in adequate and well-controlled trials. Therefore, the physician who elects to prescribe *Paxil* for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Generalized Anxiety Disorder

Paxil is indicated for the treatment of Generalized Anxiety Disorder (GAD), as defined in DSM-IV. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

The efficacy of *Paxil* in the treatment of GAD was established in two 8-week placebo-controlled trials in adults with GAD. *Paxil* has not been studied in children or adolescents with Generalized Anxiety Disorder (see CLINICAL PHARMACOLOGY—Clinical Trials).

Generalized Anxiety Disorder (DSM-IV) is characterized by excessive anxiety and worry (apprehensive expectation) that is persistent for at least 6 months and which the person finds difficult to control. It must be associated with at least 3 of the following 6 symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, sleep disturbance.

The effectiveness of *Paxil* in the long-term treatment of GAD, that is, for more than 8 weeks, has not been systematically evaluated in controlled trials. 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 (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

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

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

WARNINGS

Potential for Interaction with Monoamine Oxidase Inhibitors

In patients receiving another serotonin reuptake inhibitor or 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.

Potential Interaction with Thioridazine

Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsade de pointes-type arrhythmias, and sudden death. This effect appears to be dose-related.

An *in vivo* study suggests that drugs which inhibit P450IID6, such as paroxetine, will elevate plasma levels of thioridazine. Therefore, it is recommended that paroxetine not be used in combination with thioridazine (see CONTRAINDICATIONS and PRECAUTIONS).

PRECAUTIONS

General

Activation of Mania/Hypomania: During premarketing testing, 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

Abnormal Bleeding: There have been several reports of abnormal bleeding (mostly ecchymosis and purpura) associated with paroxetine 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 *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 682 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.

Thioridazine: See CONTRAINDICATIONS and WARNINGS.

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

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 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 these drugs are co-administered; 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 *Paxil* dosing. In one study, daily dosing of *Paxil* (20 mg q.d.) under steady-state conditions increased single dose desipramine (100 mg) C_{max}, AUC and $T_{1/2}$ by an average of approximately two-, five- and three-fold, respectively. Concomitant use of *Paxil* 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* or the other drug.

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 and Type 1C antiarrhythmics (e.g., propafenone, flecainide and encainide), or that inhibit this enzyme (e.g., quinidine), should be approached with caution.

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

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

Drugs Metabolized by Cytochrome $P_{450}IIIA_4$: An *in vivo* interaction study involving the co-administration under steady-state conditions of paroxetine and terfenadine, a substrate for cytochrome $P_{450}IIIA_4$, revealed no effect of paroxetine on terfenadine pharmacokinetics. In addition, *in vitro* studies have shown ketoconazole, a potent inhibitor of $P_{450}IIIA_4$ activity, to be at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several substrates for this enzyme, including terfenadine, astemizole, cisapride, triazolam, and cyclosporin. Based on the assumption that the relationship between paroxetine's *in vitro* K_i and its lack of effect on terfenadine's *in vivo* clearance predicts its effect on other $IIIA_4$ substrates, paroxetine's extent of inhibition of $IIIA_4$ activity is not likely to be of clinical significance.

Tricyclic Antidepressants (TCA): Caution is indicated in the co-administration of tricyclic antidepressants (TCAs) with *Paxil,* 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* (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* 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.) in

linergic 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 *Paxil* (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 *Paxil* treatment have been reported. While this interaction has not been formally studied, it is recommended that theophylline levels be monitored when these drugs are concurrently administered.

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 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 2.4 (mouse) and 3.9 (rat) times the maximum recommended human dose (MRHD) for depression, social anxiety disorder and GAD on a mg/m^2 basis. Because the MRHD for depression is slightly less than that for OCD (50 mg vs. 60 mg), the doses used in these carcinogenicity studies were only 2.0 (mouse) and 3.2 (rat) times the MRHD for OCD. 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 2.9 times the MRHD for depression, social anxiety disorder and GAD or 2.4 times the MRHD for OCD 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 (9.8 and 4.9 times the MRHD for depression, social anxiety disorder and GAD; 8.2 and 4.1 times the MRHD for OCD and PD on a mg/m^2 basis).

Pregnancy

Teratogenic Effects—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 equivalent to 9.7 (rat) and 2.2 (rabbit) times the maximum recommended human dose (MRHD) for depression, social anxiety disorder and GAD (50 mg) and 8.1 (rat) and 1.9 (rabbit) times the MRHD for OCD, 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 0.19 times (mg/m^2) the MRHD for depression, social anxiety disorder and GAD and at 0.16 times (mg/m^2) the MRHD for OCD. 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. Because animal reproduction studies are not always predictive of human response, 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 (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 *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).

Continued on next page

This product information is based on labeling in effect

Paxil—Cont.

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Twenty percent (1,199/6,145) of *Paxil* patients in worldwide clinical trials in depression and 16.1% (84/522), 11.8% (64/542), 9.4% (44/469) and 10.7% (79/735) of *Paxil* patients in worldwide trials in social anxiety disorder, OCD, panic disorder and GAD, respectively, 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 the following:

[See first table at right]

Commonly Observed Adverse Events

Depression

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 Table 1 below) were: asthenia, sweating, nausea, decreased appetite, somnolence, dizziness, insomnia, tremor, nervousness, ejaculatory disturbance and other male genital disorders.

Obsessive Compulsive Disorder

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 of placebo, derived from Table 2 below) were: nausea, dry mouth, decreased appetite, constipation, dizziness, somnolence, tremor, sweating, impotence and abnormal ejaculation.

Panic Disorder

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 Table 2 below) were: asthenia, sweating, decreased appetite, libido decreased, tremor, abnormal ejaculation, female genital disorders and impotence.

Social Anxiety Disorder

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 Table 2 below) were: sweating, nausea, dry mouth, constipation, decreased appetite, somnolence, tremor, libido decreased, yawn, abnormal ejaculation, female genital disorders and impotence.

Generalized Anxiety Disorder

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 Table 3 below) were: asthenia, infection, constipation, decreased appetite, dry mouth, nausea, libido decreased, somnolence, tremor, sweating, and abnormal ejaculation.

Incidence in Controlled Clinical Trials

The prescriber should be aware that the figures in the tables following 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 populations studied.

Depression

Table 1 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.

[See table 1 above]

Obsessive Compulsive Disorder, Panic Disorder and Social Anxiety Disorder

Table 2 enumerates adverse events that occurred at a frequency of 2% or more among OCD patients on *Paxil* who participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a range of 20 to 60 mg/day or among patients with panic disorder on *Paxil* who participated in placebo-controlled trials of 10- to 12-weeks duration in which patients were dosed in a range of 10 to 60 mg/day or among patients with social anxiety disorder on Paxil (paroxetine hydrochloride) who participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a range of 20 to 50 mg/day.

[See table 2 at top of next page]

Generalized Anxiety Disorder

Table 3 enumerates adverse events that occurred at a frequency of 2% or more among GAD patients on *Paxil* who participated in placebo-controlled trials of 8 weeks duration in which patients were dosed in a range of 10 mg/day to 50 mg/day.

[See table 3 at top of page 1614]

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 in the treatment of depression, a fixed-dose study comparing placebo and *Paxil* 20, 40 and 60 mg in the treatment of OCD, there was no clear relationship between adverse events and the dose of Paxil (paroxetine hydrochloride) to which patients were assigned. No new adverse events were observed in the *Paxil* 60 mg dose group compared to any of the other treatment groups.

In a fixed-dose study comparing placebo and *Paxil* 10, 20 and 40 mg in the treatment of panic disorder, there was no clear relationship between adverse events and the dose of *Paxil* to which patients were assigned, except for asthenia,

In a fixed-dose study comparing placebo and *Paxil* 20, 40 and 60 mg in the treatment of social anxiety disorder, for most of the adverse events, there was no clear relationship between adverse events and the dose of Paxil (paroxetine hydrochloride) to which patients were assigned.

In a fixed-dose study comparing placebo and *Paxil* 20 and 40 mg in the treatment of generalized anxiety disorder, for most of the adverse events, there was no clear relationship between adverse events and the dose of Paxil (paroxetine hydrochloride) to which patients were assigned, except for

	Depression		OCD		Panic Disorder		Social Anxiety Disorder		Generalized Anxiety Disorder	
	Paxil	Placebo	*Paxil*	Placebo	*Paxil*	Placebo	*Paxil*	Placebo	*Paxil*	Placebo
CNS										
Somnolence	2.3%	0.7%	—		1.9%	0.3%	3.4%	0.3%	2.0%	0.2%
Insomnia	—	—	1.7%	0%	1.3%	0.3%	3.1%	0%		
Agitation	1.1%	0.5%	—							
Tremor	1.1%	0.3%	—				1.7%	0%		
Anxiety	—	—	—				1.1%	0%		
Dizziness	—	—	1.5%	0%			1.9%	0%	1.0%	0.2%
Gastro-intestinal										
Constipation	—		1.1%	0%						
Nausea	3.2%	1.1%	1.9%	0%	3.2%	1.2%	4.0%	0.3%	2.0%	0.2%
Diarrhea	1.0%	0.3%	—							
Dry mouth	1.0%	0.3%	—							
Vomiting	1.0%	0.3%	—				1.0%	0%		
Flatulence							1.0%	0.3%		
Other										
Asthenia	1.6%	0.4%	1.9%	0.4%			2.5%	0.6%	1.8%	0.2%
Abnormal ejaculation[1]	1.6%	0%	2.1%	0%			4.9%	0.6%	2.5%	0.5%
Sweating	1.0%	0.3%	—				1.1%	0%	1.1%	0.2%
Impotence[1]	—		1.5%	0%						
Libido Decreased							1.0%	0%		

Where numbers are not provided the incidence of the adverse events in Paxil (paroxetine hydrochloride) patients was not >1% or was not greater than or equal to two times the incidence of placebo.

1. Incidence corrected for gender.

Table 1. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Depression[1]

Body System	Preferred Term	*Paxil* (n=421)	Placebo (n=421)
Body as a Whole	Headache	18%	17%
	Asthenia	15%	6%
Cardiovascular	Palpitation	3%	1%
	Vasodilation	3%	1%
Dermatologic	Sweating	11%	2%
	Rash	2%	1%
Gastrointestinal	Nausea	26%	9%
	Dry Mouth	18%	12%
	Constipation	14%	9%
	Diarrhea	12%	8%
	Decreased Appetite	6%	2%
	Flatulence	4%	2%
	Oropharynx Disorder[2]	2%	0%
	Dyspepsia	2%	1%
Musculoskeletal	Myopathy	2%	1%
	Myalgia	2%	1%
	Myasthenia	1%	0%
Nervous System	Somnolence	23%	9%
	Dizziness	13%	6%
	Insomnia	13%	6%
	Tremor	8%	2%
	Nervousness	5%	3%
	Anxiety	5%	3%
	Paresthesia	4%	2%
	Libido Decreased	3%	0%
	Drugged Feeling	2%	1%
	Confusion	1%	0%
Respiration	Yawn	4%	0%
Special Senses	Blurred Vision	4%	1%
	Taste Perversion	2%	0%
Urogenital System	Ejaculatory Disturbance[3,4]	13%	0%
	Other Male Genital Disorders[3,5]	10%	0%
	Urinary Frequency	3%	1%
	Urination Disorder[6]	3%	0%
	Female Genital Disorders[3,7]	2%	0%

1. Events reported by at least 1% of patients treated with Paxil (paroxetine hydrochloride) are included, except the following events which had an incidence on placebo ≥ *Paxil:* abdominal pain, agitation, back pain, chest pain, CNS stimulation, fever, increased appetite, myoclonus, pharyngitis, postural hypotension, respiratory disorder (includes mostly "cold symptoms" or "URI"), trauma and vomiting.
2. Includes mostly "lump in throat" and "tightness in throat."
3. Percentage corrected for gender.
4. Mostly "ejaculatory delay."
5. Includes "anorgasmia," "erectile difficulties," "delayed ejaculation/orgasm," and "sexual dysfunction," and "impotence."
6. Includes mostly "difficulty with micturition" and "urinary hesitancy."
7. Includes mostly "anorgasmia" and "difficulty reaching climax/orgasm."

verse events with continued therapy (e.g., nausea and dizziness), but less to other effects (e.g., dry mouth, somnolence and asthenia).

Male and Female Sexual Dysfunction with SSRIs: Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences.

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

In placebo-controlled clinical trials involving more than 2,500 patients, the ranges for the reported incidence of sexual side effects in males and females with depression, OCD, panic disorder, social anxiety disorder, and GAD are displayed in Table 5 below.

[See table 5 on next page]

There are no adequate and well-controlled studies examining sexual dysfunction with paroxetine treatment.

Paroxetine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Weight and Vital Sign Changes: Significant weight loss may be an undesirable result of treatment with *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 comparisons for alkaline phosphatase, SGOT, SGPT and bilirubin revealed no differences in the percentage of patients with marked abnormalities.

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

During its premarketing assessment in depression, multiple doses of *Paxil* were administered to 6,145 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. During premarketing clinical trials in OCD, panic disorder, social anxiety disorder, and generalized anxiety disorder, 542, 469, 522, and 735 patients, respectively, received multiple doses of *Paxil*. 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 8,413 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 Tables 1-3, 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, face edema, moniliasis, neck pain; *rare*: adrenergic syndrome, cellulitis, neck rigidity, pelvic pain, peritonitis, ulcer.

Table 2: Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Obsessive Compulsive Disorder, Panic Disorder and Social Anxiety Disorder[1]

Body System	Preferred Term	Obsessive Compulsive Disorder *Paxil* (n=542)	Obsessive Compulsive Disorder Placebo (n=265)	Panic Disorder *Paxil* (n=469)	Panic Disorder Placebo (n=324)	Social Anxiety Disorder *Paxil* (n=425)	Social Anxiety Disorder Placebo (n=339)
Body as a Whole	Asthenia	22%	14%	14%	5%	22%	14%
	Abdominal Pain	—	—	4%	3%	—	—
	Chest Pain	3%	2%	—	—	—	—
	Back Pain	—	—	3%	2%	—	—
	Chills	2%	1%	2%	1%	—	—
	Trauma	—	—	—	—	3%	1%
Cardio-vascular	Vasodilation	4%	1%	—	—	—	—
	Palpitation	2%	0%	—	—	—	—
Dermatologic	Sweating	9%	3%	14%	6%	9%	2%
	Rash	3%	2%	—	—	—	—
Gastro-intestinal	Nausea	23%	10%	23%	17%	25%	7%
	Dry Mouth	18%	9%	18%	11%	9%	3%
	Constipation	16%	6%	8%	5%	5%	2%
	Diarrhea	10%	10%	12%	7%	9%	6%
	Decreased Appetite	9%	3%	7%	3%	8%	2%
	Dyspepsia	—	—	—	—	4%	2%
	Flatulence	—	—	—	—	4%	2%
	Increased Appetite	4%	3%	2%	1%	—	—
	Vomiting	—	—	—	—	2%	1%
Musculo-skeletal	Myalgia	—	—	—	—	4%	3%
Nervous System	Insomnia	24%	13%	18%	10%	21%	16%
	Somnolence	24%	7%	19%	11%	22%	5%
	Dizziness	12%	6%	14%	10%	11%	7%
	Tremor	11%	1%	9%	1%	9%	1%
	Nervousness	9%	8%	—	—	8%	7%
	Libido Decreased	7%	4%	9%	1%	12%	1%
	Agitation	—	—	5%	4%	3%	1%
	Anxiety	—	—	5%	4%	5%	4%
	Abnormal Dreams	4%	1%	—	—	—	—
	Concentration Impaired	3%	2%	—	—	4%	1%
	Depersonalization	3%	0%	—	—	—	—
	Myoclonus	3%	0%	3%	2%	2%	1%
	Amnesia	2%	1%	—	—	—	—
Respiratory System	Rhinitis	—	—	3%	0%	—	—
	Pharyngitis	—	—	—	—	4%	2%
	Yawn	—	—	—	—	5%	1%
Special Senses	Abnormal Vision	4%	2%	—	—	4%	1%
	Taste Perversion	2%	0%	—	—	—	—
Urogenital System	Abnormal Ejaculation[2]	23%	1%	21%	1%	28%	1%
	Dysmenorrhea	—	—	—	—	5%	4%
	Female Genital Disorder[2]	3%	0%	9%	1%	9%	1%
	Impotence[2]	8%	1%	5%	0%	5%	1%
	Urinary Frequency	3%	1%	2%	0%	—	—
	Urination Impaired	3%	0%	—	—	—	—
	Urinary Tract Infection	2%	1%	2%	1%	—	—

1. Events reported by at least 2% of OCD, panic disorder, and social anxiety disorder *Paxil*-treated patients are included, except the following events which had an incidence on placebo ≥*Paxil*: [OCD]: abdominal pain, agitation, anxiety, back pain, cough increased, depression, headache, hyperkinesia, infection, paresthesia, pharyngitis, respiratory disorder, rhinitis and sinusitis. [panic disorder]: abnormal dreams, abnormal vision, chest pain, cough increased, depersonalization, depression, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, myalgia, nervousness, palpitation, paresthesia, pharyngitis, rash, respiratory disorder, sinusitis, taste perversion, trauma, urination impaired and vasodilation. [social anxiety disorder]: abdominal pain, depression, headache, infection, respiratory disorder and sinusitis.
2. Percentage corrected for gender.

atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, heart block, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, varicose vein, vascular headache, ventricular extrasystoles.

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

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

increased, hypochromic anemia, iron deficiency anemia, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia, thrombocytopenia.

Metabolic and Nutritional: *frequent:* weight gain, weight loss; *infrequent:* alkaline phosphatase increased, edema, peripheral edema, SGOT increased, SGPT increased, thirst; *rare:* bilirubinemia, BUN increased, creatinine phosphokinase increased, dehydration, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, hyperglycemia, hyperkalemia, hyperphosphatemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased.

Continued on next page

Paxil—Cont.

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

Nervous System: *frequent:* emotional lability, vertigo; *infrequent:* abnormal thinking, alcohol abuse, ataxia, delirium, dystonia, dyskinesia, euphoria, hallucinations, hostility, hypertonia, hypesthesia, hypokinesia, incoordination, lack of emotion, libido increased, manic reaction, neurosis, paralysis, paranoid reaction, psychosis; *rare:* abnormal gait, akinesia, antisocial reaction, aphasia, choreoathetosis, circumoral paresthesias, convulsion, delusions, diplopia, drug dependence, dysarthria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hyperalgesia, hysteria, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, peripheral neuritis, psychotic depression, reflexes decreased, reflexes increased, stupor, torticollis, trismus, withdrawal syndrome.

Respiratory System: *infrequent:* asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu; *rare:* emphysema, hemoptysis, hiccups, lung fibrosis, pulmonary edema, sputum increased, voice alteration.

Skin and Appendages: *frequent:* pruritus; *infrequent:* acne, alopecia, contact dermatitis, dry skin, ecchymosis, eczema, herpes simplex, maculopapular rash, photosensitivity, urticaria; *rare:* angioedema, erythema nodosum, erythema multiforme, exfoliative dermatitis, fungal dermatitis, herpes zoster, hirsutism, seborrhea, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash.

Special Senses: *frequent:* tinnitus; *infrequent:* abnormality of accommodation, conjunctivitis, ear pain, eye pain, mydriasis, otitis media, photophobia; *rare:* amblyopia, anisocoria, blepharitis, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, keratoconjunctivitis, night blindness, otitis externa, parosmia, ptosis, retinal hemorrhage, taste loss, visual field defect.

Urogenital System: *infrequent:* abortion, amenorrhea, breast pain, cystitis, dysuria, hematuria, menorrhagia, nocturia, polyuria, urinary incontinence, urinary retention, urinary urgency, vaginal moniliasis, vaginitis; *rare:* breast atrophy, breast enlargement, endometrial disorder, epididymitis, female lactation, fibrocystic breast, kidney calculus, kidney pain, leukorrhea, mastitis, metrorrhagia, nephritis, oliguria, pyuria, urethritis, uterine spasm, urolith, vaginal hemorrhage.

Postmarketing Reports

Voluntary reports of adverse events in patients taking Paxil (paroxetine hydrochloride) that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome-like events; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide, tremor and trismus; serotonin syndrome, associated in some cases with concomitant use of serotonergic drugs and with drugs which may have impaired *Paxil* metabolism (symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor), status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia, and events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis). There have been spontaneous reports that discontinuation (particularly when abrupt) 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 *Paxil* and phenytoin co-administration. There has been a case report of severe hypotension when *Paxil* was added to chronic metoprolol treatment.

DRUG ABUSE AND DEPENDENCE

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

Physical and Psychologic 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).

Table 3. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder[1]

		Generalized Anxiety Disorder	
Body System	Preferred Term	*Paxil* (n=735)	Placebo (n=529)
Body as a Whole	Asthenia	14%	6%
	Headache	17%	14%
	Infection	6%	3%
Cardiovascular	Vasodilation	3%	1%
Dermatologic	Sweating	6%	2%
Gastrointestinal	Nausea	20%	5%
	Dry Mouth	11%	5%
	Constipation	10%	2%
	Diarrhea	9%	7%
	Decreased Appetite	5%	1%
	Vomiting	3%	2%
Nervous System	Insomnia	11%	8%
	Somnolence	15%	5%
	Dizziness	6%	5%
	Tremor	5%	1%
	Nervousness	4%	3%
	Libido Decreased	9%	2%
Respiratory System	Respiratory Disorder	7%	5%
	Sinusitis	4%	3%
	Yawn	4%	–
Special Senses	Abnormal Vision	2%	1%
Urogenital System	Abnormal Ejaculation[2]	25%	2%
	Female Genital Disorder[2]	4%	1%
	Impotence[2]	4%	3%

1. Events reported by at least 2% of *Paxil*-treated patients are included, except the following events which had an incidence on placebo ≥*Paxil:* abdominal pain, back pain, trauma, dyspepsia, myalgia, and pharyngitis.
2. Percentage corrected for gender.

Table 4. Treatment-Emergent Adverse Experience Incidence in a Depression Dose-Comparison Trial*

	Placebo	*Paxil*			
Body System/ Preferred Term		10 mg	20 mg	30 mg	40 mg
	n=51	n=102	n=104	n=101	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%	36.3%
Nervous System					
Anxiety	0.0%	2.0%	5.8%	5.9%	5.9%
Dizziness	3.9%	6.9%	6.7%	8.9%	12.7%
Nervousness	0.0%	5.9%	5.8%	4.0%	2.9%
Paresthesia	0.0%	2.9%	1.0%	5.0%	5.9%
Somnolence	7.8%	12.7%	18.3%	20.8%	21.6%
Tremor	0.0%	0.0%	7.7%	7.9%	14.7%
Special Senses					
Blurred Vision	2.0%	2.9%	2.9%	2.0%	7.8%
Urogenital System					
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%

*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.

Table 5. Incidence of Sexual Adverse Events in Controlled Clinical Trials

	Paxil	Placebo
n (males)	**1208**	**852**
Decreased Libido	6%-14%	0%-5%
Ejaculatory Disturbance	13%-28%	0%-2%
Impotence	2%-8%	0%-3%
n (females)	**1384**	**1026**
Decreased Libido	0%-9%	0%-2%
Orgasmic Disturbance	2%-9%	0%-1%

worldwide (circa 1999). These include overdoses with paroxetine alone and in combination with other substances. Of these, 48 cases were fatal and, of the fatalities, 17 appeared to involve paroxetine alone. Eight fatal cases which documented the amount of paroxetine ingested were generally confounded by the ingestion of other drugs or alcohol or the presence of significant comorbid conditions. Of 145 non-fatal cases with known outcome, most recovered without sequelae. The largest known ingestion involved 2000 mg of paroxetine (33 times the maximum recommended daily dose) in a patient who recovered.

Commonly reported adverse events associated with paroxetine overdosage include somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other notable signs and symptoms observed with overdoses involving paroxetine (alone or with other substances) include mydriasis, convulsions (including status epilepticus), hepatic dysfunction (including hepatic failure, hepatic n crosis, jaundice, hepatitis, and hepatic steatosis), seroton syndrome, manic reactions, myoclonus, acute renal failur and urinary retention.

Overdosage Management: Treatment should consist those general measures employed in the management overdosage with any antidepressant.

Ensure an adequate airway, oxygenation, and ventilatio Monitor cardiac rhythm and vital signs. General supporti and symptomatic measures are also recommended. Indu tion of emesis is not recommended. Gastric lavage with large-bore orogastric tube with appropriate airway prote tion, if needed, may be indicated if performed soon after i gestion, or in symptomatic patients.

Activated charcoal should be administered. Due to the lar volume of distribution of this drug, forced diuresis, dialys hemoperfusion and exchange transfusion are unlikely to

tities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and/or 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

Depression

Usual Initial Dosage: Paxil (paroxetine hydrochloride) should be administered as a single daily dose with or without food, 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.

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.

Obsessive Compulsive Disorder

Usual Initial Dosage: Paxil (paroxetine hydrochloride) should be administered as a single daily dose with or without food, usually in the morning. The recommended dose of *Paxil* in the treatment of OCD is 40 mg daily. Patients should be started on 20 mg/day and the dose can be increased in 10 mg/day increments. Dose changes should occur at intervals of at least 1 week. Patients were dosed in a range of 20 to 60 mg/day in the clinical trials demonstrating the effectiveness of *Paxil* in the treatment of OCD. The maximum dosage should not exceed 60 mg/day.

Maintenance Therapy: Long-term maintenance of efficacy was demonstrated in a 6-month relapse prevention trial. In this trial, patients with OCD assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY). OCD is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Panic Disorder

Usual Initial Dosage: *Paxil* should be administered as a single daily dose with or without food, usually in the morning. The target dose of *Paxil* in the treatment of panic disorder is 40 mg/day. Patients should be started on 10 mg/day. Dose changes should occur in 10 mg/day increments and at intervals of at least 1 week. Patients were dosed in a range of 10 to 60 mg/day in the clinical trials demonstrating the effectiveness of *Paxil*. The maximum dosage should not exceed 60 mg/day.

Maintenance Therapy: Long-term maintenance of efficacy was demonstrated in a 3-month relapse prevention trial. In this trial, patients with panic disorder assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY). Panic disorder is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Social Anxiety Disorder

Usual Initial Dosage: *Paxil* should be administered as a single daily dose with or without food, usually in the morning. The recommended and initial dosage is 20 mg/day. In clinical trials the effectiveness of *Paxil* was demonstrated in patients dosed in a range of 20 to 60 mg/day. While the safety of *Paxil* has been evaluated in patients with social anxiety disorder at doses up to 60 mg/day, available information does not suggest any additional benefit for doses above 20 mg/day. (See CLINICAL PHARMACOLOGY).

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. Although the efficacy of *Paxil* beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials, social anxiety disorder is recognized as a chronic condition, and it is reasonable to consider continuation of treatment for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Generalized Anxiety Disorder

Usual Initial Dosage: *Paxil* should be administered as a single daily dose with or without food, usually in the morning. In clinical trials the effectiveness of *Paxil* was demon-gest a greater benefit to doses higher than 20 mg/day. Dose changes should occur in 10 mg/day increments and at intervals of at least 1 week.

Maintenance Therapy: There is no body of evidence available to answer the question of how long the patient treated with *Paxil* should remain on it. Although the efficacy of *Paxil* beyond 8 weeks of dosing has not been demonstrated in controlled clinical trials, generalized anxiety disorder is recognized as a chronic condition, and it is reasonable to consider continuation of treatment for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Dosage for Elderly or Debilitated, and Patients with Severe Renal or Hepatic Impairment: The recommended initial dose is 10 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 40 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* therapy. Similarly, at least 14 days should be allowed after stopping Paxil (paroxetine hydrochloride) before starting a MAOI.

NOTE: SHAKE SUSPENSION WELL BEFORE USING.

HOW SUPPLIED

Tablets: Film-coated, modified-oval as follows:

10 mg yellow, scored tablets engraved on the front with PAXIL and on the back with 10.

NDC 0029-3210-13 Bottles of 30

20 mg pink, scored 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 (intended for institutional use only)

30 mg blue tablets engraved on the front with PAXIL and on the back with 30.

NDC 0029-3212-13 Bottles of 30

40 mg green tablets engraved on the front with PAXIL and on the back with 40.

NDC 0029-3213-13 Bottles of 30

Store tablets between 15° and 30°C (59° and 86°F).

Oral Suspension: Orange-colored, orange-flavored, 10 mg/5 mL, in 250 mL white bottles.

NDC 0029-3215-48

Store suspension at or below 25° C (77° F).

GlaxoSmithKline, Research Triangle, NC 27709

April 2001/PX:20

Shown in Product Identification Guide, page 317

PURINETHOL® ℞

[pur 'ĭn-thawl]

(mercaptopurine)

50-mg Scored Tablets

CAUTION: PURINETHOL (mercaptopurine) is a potent drug. It should not be used unless a diagnosis of acute lymphatic leukemia has been adequately established and the responsible physician is knowledgeable in assessing response to chemotherapy.

DESCRIPTION

PURINETHOL (mercaptopurine) was synthesized and developed by Hitchings, Elion, and associates at the Wellcome Research Laboratories.[1] It is one of a large series of purine analogues which interfere with nucleic acid biosynthesis and has been found active against human leukemias.

Mercaptopurine, known chemically as 1,7-dihydro-6*H*-purine-6-thione monohydrate, is an analogue of the purine bases adenine and hypoxanthine.

PURINETHOL is available in tablet form for oral administration. Each scored tablet contains 50 mg mercaptopurine and the inactive ingredients corn and potato starch, lactose, magnesium stearate, and stearic acid.

CLINICAL PHARMACOLOGY

Clinical studies have shown that the absorption of an oral dose of mercaptopurine in humans is incomplete and variable, averaging approximately 50% of the administered dose.[2] The factors influencing absorption are unknown. Intravenous administration of an investigational preparation of mercaptopurine revealed a plasma half-disappearance time of 21 minutes in pediatric patients and 47 minutes in adults. The volume of distribution usually exceeded that of the total body water.[2]

Following the oral administration of ^{35}S-6-mercaptopurine in one subject, a total of 46% of the dose could be accounted for in the urine (as parent drug and metabolites) in the first 24 hours. Metabolites of mercaptopurine were found in urine within the first 2 hours after administration. Radioactivity (in the form of sulfate) could be found in the urine for weeks afterwards.[3]

There is negligible entry of mercaptopurine into cerebrospinal fluid.

Plasma protein binding averages 19% over the concentra-

Monitoring of plasma levels of mercaptopurine during therapy is of questionable value.[3] There is technical difficulty in determining plasma concentrations which are seldom greater than 1 to 2 mcg/mL after a therapeutic oral dose. More significantly, mercaptopurine enters rapidly into the anabolic and catabolic pathways for purines, and the active intracellular metabolites have appreciably longer half-lives than the parent drug. The biochemical effects of a single dose of mercaptopurine are evident long after the parent drug has disappeared from plasma. Because of this rapid metabolism of mercaptopurine to active intracellular derivatives, hemodialysis would not be expected to appreciably reduce toxicity of the drug. There is no known pharmacologic antagonist to the biochemical actions of mercaptopurine in vivo.

Mercaptopurine competes with hypoxanthine and guanine for the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRTase) and is itself converted to thioinosinic acid (TIMP). This intracellular nucleotide inhibits several reactions involving inosinic acid (IMP), including the conversion of IMP to xanthylic acid (XMP) and the conversion of IMP to adenylic acid (AMP) via adenylosuccinate (SAMP). In addition, 6-methylthioinosinate (MTIMP) is formed by the methylation of TIMP. Both TIMP and MTIMP have been reported to inhibit glutamine-5-phosphoribosylpyrophosphate amidotransferase, the first enzyme unique to the de novo pathway for purine ribonucleotide synthesis.[3]

Experiments indicate that radiolabeled mercaptopurine may be recovered from the DNA in the form of deoxythioguanosine.[4] Some mercaptopurine is converted to nucleotide derivatives of 6-thioguanine (6-TG) by the sequential actions of inosinate (IMP) dehydrogenase and xanthylate (XMP) aminase, converting TIMP to thioguanylic acid (TGMP).

Animal tumors that are resistant to mercaptopurine often have lost the ability to convert mercaptopurine to TIMP. However, it is clear that resistance to mercaptopurine may be acquired by other means as well, particularly in human leukemias.

It is not known exactly which of any one or more of the biochemical effects of mercaptopurine and its metabolites are directly or predominantly responsible for cell death.[5]

The catabolism of mercaptopurine and its metabolites is complex. In humans, after oral administration of ^{35}S-6-mercaptopurine, urine contains intact mercaptopurine, thiouric acid (formed by direct oxidation by xanthine oxidase, probably via 6-mercapto-8-hydroxypurine), and a number of 6-methylated thiopurines. The methylthiopurines yield appreciable amounts of inorganic sulfate.[3] The importance of the metabolism by xanthine oxidase relates to the fact that ZYLOPRIM® (allopurinol) inhibits this enzyme and retards the catabolism of mercaptopurine and its active metabolites. A significant reduction in mercaptopurine dosage is mandatory if a potent xanthine oxidase inhibitor and mercaptopurine are used simultaneously in a patient (see PRECAUTIONS).

INDICATIONS AND USAGE

PURINETHOL (mercaptopurine) is indicated for remission induction and maintenance therapy of acute lymphatic leukemia. The response to this agent depends upon the particular subclassification of acute lymphatic leukemia and the age of the patient (pediatric patient or adult).

Acute Lymphatic (Lymphocytic, Lymphoblastic) Leukemia: Given as a single agent for remission induction, PURINETHOL induces complete remission in approximately 25% of pediatric patients and 10% of adults. However, reliance upon PURINETHOL alone is not justified for initial remission induction of acute lymphatic leukemia since combination chemotherapy with vincristine, prednisone, and L-asparaginase results in more frequent complete remission induction than with PURINETHOL alone or in combination. The duration of complete remission induced in acute lymphatic leukemia is so brief without the use of maintenance therapy that some form of drug therapy is considered essential. PURINETHOL, as a single agent, is capable of significantly prolonging complete remission duration; however, combination therapy has produced remission duration longer than that achieved with PURINETHOL alone.

Acute Myelogenous (and Acute Myelomonocytic) Leukemia: As a single agent, PURINETHOL will induce complete remission in approximately 10% of pediatric patients and adults with acute myelogenous leukemia or its subclassifications. These results are inferior to those achieved with combination chemotherapy employing optimum treatment schedules.

Central Nervous System Leukemia: PURINETHOL is not effective for prophylaxis or treatment of central nervous system leukemia.

Other Neoplasms: PURINETHOL is not effective in chronic lymphatic leukemia, the lymphomas (including Hodgkin's Disease), or solid tumors.

CONTRAINDICATIONS

PURINETHOL should not be used unless a diagnosis of acute lymphatic leukemia has been adequately established and the responsible physician is knowledgeable in assessing response to chemotherapy.

Continued on next page

This product information is based on labeling in effect

Purinethol—Cont.

PURINETHOL should not be used in patients whose disease has demonstrated prior resistance to this drug. In animals and humans, there is usually complete cross-resistance between mercaptopurine and thioguanine.

WARNINGS

SINCE DRUGS USED IN CANCER CHEMOTHERAPY ARE POTENTIALLY HAZARDOUS, IT IS RECOMMENDED THAT ONLY PHYSICIANS EXPERIENCED WITH THE RISKS OF PURINETHOL AND KNOWLEDGEABLE IN THE NATURAL HISTORY OF ACUTE LEUKEMIAS ADMINISTER THIS DRUG.

Bone Marrow Toxicity: The most consistent, dose-related toxicity is bone marrow suppression. This may be manifest by anemia, leukopenia, thrombocytopenia, or any combination of these. Any of these findings may also reflect progression of the underlying disease. Since mercaptopurine may have a delayed effect, it is important to withdraw the medication temporarily at the first sign of an abnormally large fall in any of the formed elements of the blood.

There are rare individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effects of mercaptopurine and prone to developing rapid bone marrow suppression following the initiation of treatment.[6,7] Substantial dosage reductions may be required to avoid the development of life-threatening bone marrow suppression in these patients. This toxicity may be more profound in patients treated with concomitant allopurinol (see PRECAUTIONS: Drug Interactions).

Hepatotoxicity: Mercaptopurine is hepatotoxic in animals and humans. A small number of deaths have been reported which may have been attributed to hepatic necrosis due to administration of mercaptopurine. Hepatic injury can occur with any dosage, but seems to occur with more frequency when doses of 2.5 mg/kg/day are exceeded. The histologic pattern of mercaptopurine hepatotoxicity includes features of both intrahepatic cholestasis and parenchymal cell necrosis, either of which may predominate. It is not clear how much of the hepatic damage is due to direct toxicity from the drug and how much may be due to a hypersensitivity reaction. In some patients jaundice has cleared following withdrawal of mercaptopurine and reappeared with its reintroduction.[8]

Published reports have cited widely varying incidences of overt hepatotoxicity. In a large series of patients with various neoplastic diseases, mercaptopurine was administered orally in doses ranging from 2.5 mg/kg to 5.0 mg/kg without any evidence of hepatotoxicity. It was noted by the authors that no definite clinical evidence of liver damage could be ascribed to the drug, although an occasional case of serum hepatitis did occur in patients receiving 6-MP who previously had transfusions.[8] In reports of smaller cohorts of adult and pediatric leukemic patients, the incidence of hepatotoxicity ranged from 0% to 6%.[9-11] In an isolated report by Einhorn and Davidsohn, jaundice was observed more frequently (40%), especially when doses exceeded 2.5 mg/kg.[12] Usually, clinically detectable jaundice appears early in the course of treatment (1 to 2 months). However, jaundice has been reported as early as 1 week and as late as 8 years after the start of treatment with mercaptopurine.[13]

Monitoring of serum transaminase levels, alkaline phosphatase, and bilirubin levels may allow early detection of hepatotoxicity. It is advisable to monitor these liver function tests at weekly intervals when first beginning therapy and at monthly intervals thereafter. Liver function tests may be advisable more frequently in patients who are receiving mercaptopurine with other hepatotoxic drugs or with known pre-existing liver disease.

The concomitant administration of mercaptopurine with other hepatotoxic agents requires especially careful clinical and biochemical monitoring of hepatic function. Combination therapy involving mercaptopurine with other drugs not felt to be hepatotoxic should nevertheless be approached with caution. The combination of mercaptopurine with doxorubicin was reported to be hepatotoxic in 19 of 20 patients undergoing remission-induction therapy for leukemia resistant to previous therapy.[14]

The hepatotoxicity has been associated in some cases with anorexia, diarrhea, jaundice, and ascites. Hepatic encephalopathy has occurred.

The onset of clinical jaundice, hepatomegaly, or anorexia with tenderness in the right hypochondrium are immediate indications for withholding mercaptopurine until the exact etiology can be identified. Likewise, any evidence of deterioration in liver function studies, toxic hepatitis, or biliary stasis should prompt discontinuation of the drug and a search for an etiology of the hepatotoxicity.

Immunosuppression: Mercaptopurine recipients may manifest decreased cellular hypersensitivities and impaired allograft rejection. Induction of immunity to infectious agents or vaccines will be subnormal in these patients; the degree of immunosuppression will depend on antigen dose and temporal relationship to drug. This immunosuppressive effect should be carefully considered with regard to intercurrent infections and risk of subsequent neoplasia.

Pregnancy: Pregnancy Category D. Mercaptopurine can cause fetal harm when administered to a pregnant woman. The effect of mercaptopurine on human fertility is unknown for either males or females.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category D. See WARNINGS section.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from mercaptopurine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: See DOSAGE AND ADMINISTRATION section.

ADVERSE REACTIONS

The principal and potentially serious toxic effects of PURINETHOL are bone marrow toxicity and hepatotoxicity (see WARNINGS).

Hematologic: The most frequent adverse reaction to PURINETHOL is myelosuppression. The induction of complete remission of acute lymphatic leukemia frequently is associated with marrow hypoplasia. Maintenance of remission generally involves multiple-drug regimens whose component agents cause myelosuppression. Anemia, leukopenia, and thrombocytopenia are frequently observed. Dosages and schedules are adjusted to prevent life-threatening cytopenias.

Renal: Hyperuricemia may occur in patients receiving PURINETHOL as a consequence of rapid cell lysis accompanying the antineoplastic effect. Adverse effects can be minimized by increased hydration, urine alkalinization, and the prophylactic administration of a xanthine oxidase inhibitor such as allopurinol. The dosage of PURINETHOL should be reduced to one third to one quarter of the usual dose if allopurinol is given concurrently.

Gastrointestinal: Intestinal ulceration has been reported.[20] Nausea, vomiting, and anorexia are uncommon during initial administration. Mild diarrhea and sprue-like symptoms have been noted occasionally, but it is difficult at present to attribute these to the medication. Oral lesions are rarely seen, and when they occur they resemble thrush rather than antifolic ulcerations.

An increased risk of pancreatitis may be associated with the investigational use of PURINETHOL in inflammatory bowel disease.[21-23]

Miscellaneous: While dermatologic reactions can occur as a consequence of disease, the administration of PURINETHOL has been associated with skin rashes and hyperpigmentation.[24]

Drug fever has been very rarely reported with PURINETHOL. Before attributing fever to PURINETHOL, every attempt should be made to exclude more common causes of pyrexia, such as sepsis, in patients with acute leukemia.

OVERDOSAGE

Signs and symptoms of overdosage may be immediate such as anorexia, nausea, vomiting and diarrhea; or delayed such as myelosuppression, liver dysfunction, and gastroenteritis. Dialysis cannot be expected to clear mercaptopurine. Hemodialysis is thought to be of marginal use due to the rapid intracellular incorporation of mercaptopurine into active metabolites with long persistence. The oral LD_{50} of mercaptopurine was determined to be 480 mg/kg in the mouse and 425 mg/kg in the rat.[25]

There is no known pharmacologic antagonist of mercaptopurine. The drug should be discontinued immediately if unintended toxicity occurs during treatment. If a patient is seen immediately following an accidental overdosage of the drug, it may be useful to induce emesis.

DOSAGE AND ADMINISTRATION

Induction Therapy: PURINETHOL is administered orally. The dosage which will be tolerated and be effective varies from patient to patient, and therefore careful titration is necessary to obtain the optimum therapeutic effect without incurring excessive, unintended toxicity. The usual initial dosage for pediatric patients and adults is 2.5 mg/kg of body weight per day (100 to 200 mg in the average adult and 50 mg in an average 5-year-old child). Pediatric patients with acute leukemia have tolerated this dose without difficulty in most cases; it may be continued daily for several weeks or more in some patients. If, after 4 weeks at this dosage, there is no clinical improvement and no definite evidence of leukocyte or platelet depression, the dosage may be increased up to 5 mg/kg daily. A dosage of 2.5 mg/kg per day may result in a rapid fall in leukocyte count within 1 to 2 weeks in some adults with acute lymphatic leukemia and high total leukocyte counts.

The total daily dosage may be given at one time. It is calculated to the nearest multiple of 25 mg. The dosage of PURINETHOL should be reduced to one third to one quarter of the usual dose if allopurinol is given concurrently. Because the drug may have a delayed action, it should be discontinued at the first sign of an abnormally large or rapid fall in the leukocyte or platelet count. If subsequently the leukocyte count or platelet count remains constant for 2 or 3 days, or rises, treatment may be resumed.

Maintenance Therapy: Once a complete hematologic remission is obtained, maintenance therapy is considered essential. Maintenance doses will vary from patient to patient. A usual daily maintenance dose of PURINETHOL is