GlaxoSmithKline

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IMPORTANT PRESCRIBING INFORMATION

Dear Healthcare Professional:

GlaxoSmithKline (GSK) would like to advise you of important changes to the **Clinical Worsening and Suicide Risk** subsection of the WARNINGS section in the labels for PAXIL® (paroxetine HCl) and PAXIL CR® (paroxetine HCl Controlled-Release Tablets). These labeling changes relate to your adult patients, particularly those who are younger adults. **Please read the full text of the added WARNINGS following this letter.** Full copies of the revised package inserts for PAXIL and PAXIL CR are enclosed.

Current prescribing information for paroxetine – and for all other antidepressants – contains information in the **WARNINGS** section (**Clinical Worsening and Suicide Risk** subsection) stating that "patients with MDD, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs."

GSK has recently conducted a new meta-analysis (an addition to numerous prior analyses) of suicidal behavior and ideation in placebo-controlled clinical trials of paroxetine in adult patients with psychiatric disorders including Major Depressive Disorder (MDD), other depression and non-depression disorders (e.g., dysthymia, panic disorder, generalized anxiety disorder, obsessive compulsive disorder). These trials included 8958 patients treated with paroxetine and 5953 with placebo.

Results of this analysis showed a higher frequency of suicidal behavior in young adults (prospectively defined as age 18-24) treated with paroxetine compared with placebo (17/776 [2.19%] versus 5/542 [0.92%]). In the older age groups (25-64 years and ≥65 years), no such increase was observed. This finding in young adults was not statisticially significant; however, the difference was observed in paroxetine-treated patients with both depressive and non-depressive conditions.

Further, in the analysis of adults with MDD (all ages), the frequency of suicidal behavior was higher in patients treated with paroxetine compared with placebo (11/3455 [0.32%] versus 1/1978 [0.05%]). This difference was statistically significant; however as the absolute number and incidence of events are small, these data should be interpreted with caution. All of the reported events of suicidal behavior in the adult patients with MDD were non-fatal suicide attempts, and the majority of these attempts (8 of 11) were in younger adults aged 18-30. These MDD data suggest that the higher frequency observed in the younger adult population across psychiatric disorders may extend beyond the age of 24.

The possible increase in risk of suicidal behavior in the MDD studies was observed despite substantial evidence for efficacy in the paroxetine-treated patients (compared with placebo) as determined by standardized disease-specific instruments (e.g., Hamilton Depression

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Rating Scale and Montgomery-Asberg Depression Rating Scale for depression). Most patients had an identified social stressor at the time of the event.

It is therefore important that all patients, especially young adults and those who are improving, receive careful monitoring during paroxetine therapy regardless of the condition being treated.

It is difficult to conclude a causal relationship between paroxetine and suicidality due to the small incidence and absolute number of events, the retrospective nature of this meta-analysis, and potential for confounding by the fact that the events of interest are a symptom of the psychiatric illnesses themselves. However, GSK believes it is important to draw your attention to these findings and is voluntarily amending the paroxetine labeling to reflect this new information and to emphasize the importance of careful monitoring of all patients during paroxetine therapy. **Please read the full text of the added WARNINGS following this letter.** Full copies of the revised package inserts for PAXIL and PAXIL CR are enclosed.

GSK continues to believe that the overall risk:benefit of paroxetine in the treatment of adult patients with MDD and other non-depressive psychiatric disorders remains positive.

PAXIL is indicated for the treatment of major depressive disorder, obsessive-compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder, and posttraumatic stress disorder in adults; PAXIL CR is indicated for the treatment of major depressive disorder, panic disorder, social anxiety disorder, and premenstrual dysphoric disorder in adults.

The medical community can further our understanding of PAXIL and PAXIL CR by reporting adverse events to GlaxoSmithKline at 1-888-825-5249 or to FDA's MedWatch Adverse Event Reporting program online (at www.fda.gov/MedWatch/report.htm), by phone (1-800-FDA-1088), or by returning the postage-paid FDA form 3500 (which may be downloaded from www.fda.gov/MedWatch/getforms.htm) by mail (to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787) or fax (1-800-FDA-0178).

GlaxoSmithKline encourages you to familiarize yourself with these revisions to labeling. If you have any questions about the new information, please contact our Customer Response Center at 1-888-825-5249. You can find other useful information related to this issue at gsk.com and to clinical trials involving all other GSK products at our Clinical Trial Registry website (http://ctr.gsk.co.uk/welcome.asp).

Sincerely,

John E. Kraus, MD, PhD
Director, Clinical Development
Clinical Psychiatry- North America
Neurosciences Medicines Development Center
GlaxoSmithKline

PAXIL®
(paroxetine hydrochloride)
Tablets and Oral Suspension

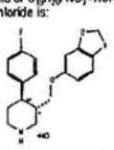
Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of PAXIL or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. PAXIL is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS—Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

PAXIL (paroxetine hydrochloride) is an orally administered psychotropic drug. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-*trans*-4*R*-(4′-fluorophenyl)-3*S*-[(3′,4′-methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate and has the empirical formula of $C_{19}H_{20}FNO_3 \cdot HCl \cdot 1/2H_2O$. The molecular weight is 374.8 (329.4 as free base). The structural formula of paroxetine hydrochloride is:



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, hypromellose, magnesium stearate, polyethylene glycols, polysorbate 80, sodium starch glycolate, titanium dioxide, and 1 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 major depressive disorder, social anxiety disorder, obsessive compulsive disorder (OCD), panic disorder (PD), generalized anxiety disorder (GAD), and posttraumatic stress disorder (PTSD) 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 hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt. The mean elimination half-life is approximately 21 hours (CV 32%) after oral dosing of 30 mg tablets of PAXIL daily for 30 days. Paroxetine is extensively metabolized and the metabolites are considered to be inactive. Nonlinearity in pharmacokinetics is observed with increasing doses. Paroxetine metabolism is mediated in part by CYP2D6, and the metabolites are primarily excreted in the urine and to some extent in the feces. Pharmacokinetic behavior of paroxetine has not been evaluated in subjects who are deficient in CYP2D6 (poor metabolizers).

Absorption and Distribution: 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 hours (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 1 of the enzymes that metabolizes paroxetine is readily saturable.

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% greater, while the time to reach peak plasma concentration decreased from 6.4 hours post-dosing to 4.9 hours.

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

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.

Metabolism and Excretion: The mean elimination half-life is approximately 21 hours (CV 32%) after oral dosing of 30 mg tablets daily for 30 days of PAXIL. In steady-state dose proportionality studies involving elderly and nonelderly patients, at doses of 20 mg to 40 mg daily for the elderly and 20 mg to 50 mg daily for the nonelderly, some nonlinearity was observed in both populations, again reflecting a saturable metabolic pathway. In comparison to $C_{ss,in}$ values after 20 mg daily, values after 40 mg daily were only about 2 to 3 times greater than doubled.

Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic acid and sulfate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 the potency of the parent compound at inhibiting serotonin uptake. The metabolism of paroxetine is accomplished in part by CYP2D6. 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.

Other Clinical Pharmacology Information: ***Specific Populations: 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_{max} concentrations were about 70% to 80% greater than the respective C_{max} concentrations in nonelderly subjects. Therefore the initial dosage in the elderly should be reduced (see DOSAGE AND ADMINISTRATION).

Drug-Drug Interactions: In vitro drug interaction studies reveal that paroxetine inhibits CYP2D6. Clinical drug interaction studies have been performed with substrates of CYP2D6 and show that paroxetine can inhibit the metabolism of drugs metabolized by CYP2D6 including desipramine, risperidone, and atomoxetine (see PRECAUTIONS—Drug Interactions).

Clinical Trials

Major Depressive Disorder: The efficacy of PAXIL as a treatment for major depressive disorder has been established in 6 placebo-controlled studies of patients with major depressive disorder (aged 18 to 73). In these studies, PAXIL was shown to be significantly more effective than placebo in treating major depressive disorder by at least 2 of the following measures: Hamilton Depression Rating Scale (HDRS), the Hamilton depressed mood item, and the Clinical Global Impression (CGI)-Severity of Illness. PAXIL was significantly better than placebo in improvement of the HDRS sub-factor scores, including the depressed mood item, sleep disturbance factor, and anxiety factor.

A study of outpatients with major depressive disorder 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 28. 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 provides the outcome classification by treatment group on Global Improvement items of the Clinical Global Impression (CGI) scale for Study 1.

Outcome Classification (%) on CGI-Global Improvement Item for Completers in Study 1				
Outcome Classification	Placebo (n = 74)	PAXIL 20 mg (n = 78)	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 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, 2, and 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 Impression (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 mg and 60 mg/day dose groups. There was no indication in this study of any additional benefit for doses higher than 20 mg/day.

Subgroup analyses generally did not indicate differences in treatment outcomes as a function of age, race, or gender.

Generalized Anxiety Disorder: The effectiveness of PAXIL in the treatment of Generalized Anxiety Disorder (GAD) was demonstrated in two 8-week, multicenter, placebo-controlled studies (Studies 1 and 2) of adult outpatients with Generalized Anxiety Disorder (DSM-IV).

Study 1 was an 8-week study comparing fixed paroxetine doses of 20 mg or 40 mg/day with placebo. Doses of 20 mg or 40 mg of PAXIL were both demonstrated to be significantly superior to placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score. There was not sufficient evidence in this study to suggest a greater benefit for the 40 mg/day dose compared to the 20 mg/day dose.

Study 2 was a flexible-dose study comparing paroxetine (20 mg to 50 mg daily) and placebo. PAXIL demonstrated statistically significant superiority over placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score. A third study, also flexible-dose comparing paroxetine (20 mg to 50 mg daily), did not demonstrate statistically significant superiority of PAXIL over placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score, the primary outcome.

Subgroup analyses did not indicate differences in treatment outcomes as a function of race or gender. There were insufficient elderly patients to conduct subgroup analyses on the basis of age.

In a longer-term trial, 566 patients meeting DSM-IV criteria for Generalized Anxiety Disorder, who had responded during a single-blind, 8-week acute treatment phase with 20 to 50 mg/day of PAXIL, were randomized to continuation of PAXIL at their same dose, or to placebo, for up to 24 weeks of observation for relapse. Response during the single-blind phase was defined by having a decrease of ≥2 points compared to baseline on the CGI-Severity of Illness scale, to a score of ≤3. Relapse during the double-blind phase was defined as an increase of ≥2 points compared to baseline on the CGI-Severity of Illness scale to a score of ≥4, or withdrawal due to lack of efficacy. Patients receiving continued PAXIL experienced a significantly lower relapse rate over the subsequent 24 weeks compared to those receiving placebo.

Posttraumatic Stress Disorder: The effectiveness of PAXIL in the treatment of Posttraumatic Stress Disorder (PTSD) was demonstrated in two 12-week, multicenter, placebo-controlled studies (Studies 1 and 2) of adult outpatients who met DSM-IV criteria for PTSD. The mean duration of PTSD symptoms for the 2 studies combined was 13 years (ranging from .1 year to 57 years). The percentage of patients with secondary major depressive disorder or non-PTSD anxiety disorders in the combined 2 studies was 41% (356 out of 858 patients) and 40% (345 out of 858 patients), respectively. Study outcome was assessed by (i) the Clinician-Administered PTSD Scale Part 2 (CAPS-2) score and (ii) the Clinical Global Impression-Global Improvement Scale (CGI-I). The CAPS-2 is a multi-item instrument that measures 3 aspects of PTSD with the following symptom clusters: Reexperiencing/Intrusion, avoidance/numbing and hyperarousal. The 2 primary outcomes for each trial were (i) change from baseline to endpoint on the CAPS-2 total score (17 items), and (ii) proportion of responders on the CGI-I, where responders were defined as patients having a score of 1 (very much improved) or 2 (much improved).

Study 1 was a 12-week study comparing fixed paroxetine doses of 20 mg or 40 mg/day to placebo. Doses of 20 mg and 40 mg of PAXIL were demonstrated to be significantly superior to placebo on change from baseline for the CAPS-2 total score and on proportion of responders on the CGI-I. There was not sufficient evidence in this study to suggest a greater benefit for the 40 mg/day dose compared to the 20 mg/day dose.

Study 2 was a 12-week flexible-dose study comparing paroxetine (20 to 50 mg daily) to placebo. PAXIL was demonstrated to be significantly superior to placebo on change from baseline for the CAPS-2 total score and on proportion of responders on the CGI-I.

A third study, also a flexible-dose study comparing paroxetine (20 to 50 mg daily) to placebo, demonstrated PAXIL to be significantly superior to placebo on change from baseline for CAPS-2 total score, but not on proportion of responders on the CGI-I.

The majority of patients in these trials were women (68% women: 377 out of 551 subjects in Study 1 and 66% women: 202 out of 303 subjects in Study 2). Subgroup analyses did not indicate differences in treatment outcomes as a function of gender. There were an insufficient number of patients who were 65 years and older or were non-Caucasian to conduct subgroup analyses on the basis of age or race, respectively.

INDICATIONS AND USAGE

Major Depressive Disorder: PAXIL is indicated for the treatment of major depressive disorder.

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—Clinical Trials). 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 effects of PAXIL in hospitalized depressed patients have not been adequately studied.

The efficacy of PAXIL in maintaining a response in major depressive disorder for up to 1 year was demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY—Clinical Trials). 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—Clinical Trials). 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 was established in three 10- to 12-week trials in panic disorder patients whose diagnoses corresponded to the DSM-III-R 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 4 (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—Clinical Trials). 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 1 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 psychopharmacological treatment.

The efficacy of PAXIL was established in three 12-week trials in adult patients with social anxiety 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 efficacy of PAXIL in maintaining a response in patients with Generalized Anxiety Disorder, who responded during an 8-week acute treatment phase while taking PAXIL and were then observed for relapse during a period of up to 24 weeks, was demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY—Clinical Trials). 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).

Posttraumatic Stress Disorder: PAXIL is indicated for the treatment of Posttraumatic Stress Disorder (PTSD).

The efficacy of PAXIL in the treatment of PTSD was established in two 12-week placebo-controlled trials in adults with PTSD (DSM-IV) (see CLINICAL PHARMACOLOGY—Clinical Trials).

PTSD, as defined by DSM-IV, requires exposure to a traumatic event that involved actual or threatened death or serious injury, or threat to the physical integrity of self or others, and a response that involves intense fear, helplessness, or horror. Symptoms that occur as a result of exposure to the traumatic event include reexperiencing of the event in the form of intrusive thoughts, flashbacks, or dreams, and intense psychological distress and physiological reactivity on exposure to cues to the event; avoidance of situations reminiscent of the traumatic event, inability to recall details of the event, and/or numbing of general responsiveness manifested as diminished interest in significant activities, estrangement from others, restricted range of affect, or sense of foreshortened future; and symptoms of autonomic arousal including hypervigilance, exaggerated startle response, sleep disturbance, impaired concentration, and irritability or outbursts of anger. A PTSD diagnosis requires that the symptoms are present for at least a month and that they cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

The efficacy of PAXIL in longer-term treatment of PTSD, i.e., for more than 12 weeks, has not been systematically evaluated in placebo-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).

CONTRAINDICATIONS

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

Concomitant use in patients taking pimozide is contraindicated (see PRECAUTIONS).

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

WARNINGS

Clinical Worsening and Suicide Risk: Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in any of these trials. It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

Young adults, especially those with MDD, may be at increased risk for suicidal behavior during treatment with paroxetine. An analysis of placebo-controlled trials of adults with psychiatric disorders showed a higher frequency of suicidal behavior in young adults (prospectively defined as aged 18-24 years) treated with paroxetine compared with placebo (17/778 [2.19%] versus 5/542 [0.92%]), although this difference was not statistically significant. In the older age groups (aged 25-64 years and ≥65 years), no such increase was observed. In adults with MDD (all ages), there was a statistically significant increase in the frequency of suicidal behavior in patients treated with paroxetine compared with placebo (11/3,455 [0.32%] versus 1/1,978 [0.05%]); all of the events were suicide attempts. However, the majority of these attempts for paroxetine (8 of 11) were in younger adults aged 18-30 years. These MDD data suggest that the higher frequency observed in the younger adult population across psychiatric disorders may extend beyond the age of 24.

In addition, patients with a history of suicidal behavior or thoughts, those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at an increased risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION—Discontinuation of Treatment With PAXIL, for a description of the risks of discontinuation of PAXIL).

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. 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. Families and caregivers of adults being treated for depression should be similarly advised.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that PAXIL is not approved for use in treating bipolar depression.

Potential for Interaction With Monoamine Oxidase Inhibitors: In patients receiving another serotonin reuptake inhibitor drug in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued that drug and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. While there are no human data showing such an interaction with 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 not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. At least 2 weeks should be allowed after stopping PAXIL before starting an MAOI.

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

An in vivo study suggests that drugs which inhibit CYP2D6, 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).

Usage in Pregnancy: ***Teratogenic Effects:*** Epidemiological studies have shown that infants born to women who had first trimester paroxetine exposure had an increased risk of cardiovascular malformations, primarily ventricular and atrial septal defects (VSDs and ASDs). In general, septal defects range from those that are symptomatic and may require surgery to those that are asymptomatic and may resolve spontaneously. If a patient becomes pregnant while taking paroxetine, she should be advised of the potential harm to the fetus. Unless the benefits of paroxetine to the mother justify continuing treatment, consideration should be given to either discontinuing paroxetine therapy or switching to another antidepressant (see PRECAUTIONS—Discontinuation of Treatment with PAXIL). For women who intend to become pregnant or are in their first trimester of pregnancy, paroxetine should only be initiated after consideration of the other available treatment options.

A study based on Swedish national registry data evaluated infants of 6,898 women exposed to antidepressants in early pregnancy (5,123 women exposed to SSRIs; including 815 for paroxetine). Infants exposed to paroxetine in early pregnancy had an increased risk of cardiovascular malformations (primarily VSDs and ASDs) compared to the entire registry population (OR 1.8; 95% confidence interval 1.1-2.8). The rate of cardiovascular malformations following early pregnancy paroxetine exposure was 2% vs. 1% in the entire registry population. Among the same paroxetine exposed infants, an examination of the data showed no increase in the overall risk for congenital malformations.

A separate retrospective cohort study using US United Healthcare data evaluated 5,956 infants of mothers dispensed paroxetine or other antidepressants during the first trimester (n = 815 for paroxetine). This study showed a trend towards an increased risk for cardiovascular malformations for paroxetine compared to other antidepressants (OR 1.5; 95% confidence interval 0.8-2.9). The prevalence of cardiovascular malformations following first trimester dispensing was 1.5% for paroxetine vs. 1% for other antidepressants. Nine out of 12 infants with cardiovascular malformations whose mothers were dispensed paroxetine in the first trimester had VSDs. This study also suggested an increased risk of overall major congenital malformations (inclusive of the cardiovascular defects) for paroxetine compared to other antidepressants (OR 1.8; 95% confidence interval 1.2-2.8). The prevalence of all congenital malformations following first trimester exposure was 4% for paroxetine vs. 2% for other antidepressants.

Animal Findings: Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately 8 (rat) and 2 (rabbit) times the MRHD on an mg/m² basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg/day or approximately one-sixth of the MRHD on an mg/m² basis. The no-effect dose for rat pup mortality was not determined. The cause of these deaths is not known.

Nonteratogenic Effects: Neonates exposed to PAXIL and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS—Potential for Interaction With Monoamine Oxidase Inhibitors).

Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN is associated with substantial neonatal morbidity and mortality. In a case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. PPHN occurs in 1 – 2 per 1,000 live births in the general population.

There have also been postmarketing reports of premature births in pregnant women exposed to paroxetine or other SSRIs.

When treating a pregnant woman with paroxetine during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION). Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

PRECAUTIONS

General: ***Activation of Mania/Hypomania:*** During premarketing testing, hypomania or mania occurred in approximately 1.0% of unipolar patients treated with PAXIL 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 11.5% for the combined active-control groups. As with all drugs effective in the treatment of major depressive disorder, PAXIL should be used cautiously in patients with a history of mania.

Seizures: During premarketing testing, seizures occurred in 0.1% of patients treated with PAXIL, a rate similar to that associated with other drugs effective in the treatment of major depressive disorder. PAXIL should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Discontinuation of Treatment With PAXIL: Recent clinical trials supporting the various approved indications for PAXIL employed a taper-phase regimen, rather than an abrupt discontinuation of treatment. The taper-phase regimen used in GAD and PTSD clinical trials involved an incremental decrease in the daily dose by 10 mg/day at weekly intervals. When a daily dose of 20 mg/day was reached, patients were continued on this dose for 1 week before treatment was stopped.

With this regimen in those studies, the following adverse events were reported at an incidence of 2% or greater for PAXIL and were at least twice that reported for placebo: Abnormal dreams, paresthesia, and dizziness. In the majority of patients, these events were mild to moderate and were self-limiting and did not require medical intervention.

During marketing of PAXIL and other SSRIs and SNRIs, there have been spontaneous reports of adverse events occurring, upon the discontinuation of these drugs (particularly when abrupt), including the following: Dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations and tinnitus), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with PAXIL. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION).

See also PRECAUTIONS—Pediatric Use, for adverse events reported upon discontinuation of treatment with PAXIL in pediatric patients.

Akathisia: The use of paroxetine or other SSRIs has been associated with the development of akathisia, which is characterized by an inner sense of restlessness and psychomotor agitation such as an inability to sit or stand still usually associated with subjective distress. This is most likely to occur within the first few weeks of treatment.

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

Serotonin Syndrome: The development of a serotonin syndrome may occur in association with treatment with paroxetine, particularly with concomitant use of serotonergic drugs and with drugs which may have impaired metabolism of paroxetine. Symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia, and tremor. The concomitant use of PAXIL with serotonin precursors (such as tryptophan) is not recommended (see WARNINGS—Potential for Interaction with Monoamine Oxidase Inhibitors and PRECAUTIONS—Drug Interactions).

Abnormal Bleeding: Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic agents that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In 2 studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID)

or aspirin potentiated the risk of bleeding (see Drug Interactions). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of paroxetine with NSAIDs, aspirin, or other drugs that affect coagulation.

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.

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

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 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: Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with PAXIL and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for PAXIL. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Information from clinical trials has suggested that young adults, particularly those with depression, may be at an increased risk of suicidal behavior (including suicide attempts) when treated with PAXIL. The majority of attempted suicides in clinical trials in depression involved patients aged 18-30 years.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking PAXIL.

Clinical Worsening and Suicide Risk: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.): Patients should be cautioned about the concomitant use of paroxetine and NSAIDs, aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding.

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 therapy with PAXIL does not affect their ability to engage in such activities.

Completing Course of Therapy: While patients may notice improvement with treatment with PAXIL 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 (see WARNINGS—Usage in Pregnancy: *Teratogenic and Nonteratogenic Effects*).

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 coadministered. Adverse experiences, consisting primarily of headache, nausea, sweating, and dizziness, have been reported when tryptophan was administered to patients taking PAXIL. Consequently, concomitant use of PAXIL with tryptophan is not recommended (see Serotonin Syndrome).

Monoamine Oxidase Inhibitors: See CONTRAINDICATIONS and WARNINGS.

Pimozide: In a controlled study of healthy volunteers, after PAXIL was titrated to 60 mg daily, co-administration of a single dose of 2 mg pimozide was associated with mean increases in pimozide AUC of 151% and C_{max} of 62%, compared to pimozide administered alone. Due to the narrow therapeutic index of pimozide and its known ability to prolong the QT interval, concomitant use of pimozide and PAXIL is contraindicated (see CONTRAINDICATIONS).

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

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 (see *Drugs That Interfere With Hemostasis*).

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

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 once daily) was dosed orally for 4 weeks, steady-state plasma concentrations of paroxetine were increased by approximately 50% during coadministration with oral cimetidine (300 mg three times daily) for the final week. Therefore, when these drugs are administered concurrently, dosage adjustment of PAXIL after the 20-mg starting dose should be guided by clinical effect. The effect of paroxetine on cimetidine's pharmacokinetics was not studied.

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

Drugs Metabolized by CYP2D6: Many drugs, including most drugs effective in the treatment of major depressive disorder (paroxetine, other SSRIs and many tricyclics), are metabolized by the cytochrome P_{450} isozyme CYP2D6. Like other agents that are metabolized by CYP2D6, paroxetine may significantly inhibit the activity of this isozyme. In most patients (>90%), this CYP2D6 isozyme is saturated early during dosing with PAXIL. In 1 study, daily dosing of PAXIL (20 mg once daily) under steady-state conditions increased single dose desipramine (100 mg) C_{max}, AUC, and $T_{1/2}$ by an average of approximately 2-, 5-, and 3-fold, respectively. Concomitant use of paroxetine with risperidone, a CYP2D6 substrate has also been evaluated. In 1 study, daily dosing of paroxetine 20 mg in patients stabilized on risperidone (4 to 8 mg/day) increased mean plasma concentrations of risperidone approximately 4-fold, decreased 9-hydroxyrisperidone concentrations approximately 10%, and increased concentrations of the active moiety (the sum of risperidone plus 9-hydroxyrisperidone) approximately 1.4-fold. The effect of paroxetine on the pharmacokinetics of atomoxetine has been evaluated when both drugs were at steady state. In healthy volunteers who were extensive metabolizers of CYP2D6, paroxetine 20 mg daily was given in combination with 20 mg atomoxetine every 12 hours. This resulted in increases in steady state atomoxetine AUC values that were 6- to 8-fold greater and in atomoxetine C_{max} values that were 3- to 4-fold greater than when atomoxetine was given alone. Dosage adjustment of atomoxetine may be necessary and it is recommended that atomoxetine be initiated at a reduced dose when it is given with paroxetine.

Concomitant use of PAXIL with other drugs metabolized by cytochrome CYP2D6 has not been formally studied but may require lower doses than usually prescribed for either PAXIL or the other drug.

Therefore, coadministration of PAXIL with other drugs that are metabolized by this isozyme, including certain drugs effective in the treatment of major depressive disorder (e.g., nortriptyline, amitriptyline, imipramine, desipramine, and fluoxetine), phenothiazines, risperidone, 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 coadministered (see CONTRAINDICATIONS and WARNINGS).

At steady state, when the CYP2D6 pathway is essentially saturated, paroxetine clearance is governed by alternative P_{450} isozymes that, unlike CYP2D6, show no evidence of saturation (see PRECAUTIONS—*Tricyclic Antidepressants*).

Drugs Metabolized by Cytochrome CYP3A4: An in vivo interaction study involving the coadministration under steady-state conditions of paroxetine and terfenadine, a substrate for cytochrome CYP3A4, revealed no effect of paroxetine on terfenadine pharmacokinetics. In addition, in vitro studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several substrates for this enzyme, including terfenadine, astemizole, cisapride, triazolam, and cyclosporine. 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 CYP3A4 substrates, paroxetine's extent of inhibition of CYP3A4 activity is not likely to be of clinical significance.

Tricyclic Antidepressants (TCAs): Caution is indicated in the coadministration 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 coadministered with PAXIL (see PRECAUTIONS—*Drugs Metabolized by Cytochrome CYP2D6*).

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.

Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.): Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentiated the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with paroxetine.

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.

Lithium: A multiple-dose study has shown that there is no pharmacokinetic interaction between PAXIL and lithium carbonate. However, due to the potential for serotonin syndrome, caution is advised when PAXIL is coadministered with lithium.

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 once daily) increased steady-state $AUC_{T,24}$, C_{max}, and $C_{T,0}$ values of procyclidine (5 mg oral once daily) by 35%, 37%, and 67%, respectively, compared to procyclidine alone at steady state. If anticholinergic effects are seen, the dose of procyclidine should be reduced.

Beta-Blockers: In a study where propranolol (80 mg twice daily) was dosed orally for 18 days, the established steady-state plasma concentrations of propranolol were unaltered during coadministration with PAXIL (30 mg once daily) 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 treatment with PAXIL 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.

Fosamprenavir/Ritonavir: Co-administration of fosamprenavir/ritonavir with paroxetine significantly decreased plasma levels of paroxetine. Any dose adjustment should be guided by clinical effect (tolerability and efficacy).

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 major depressive disorder, social anxiety disorder, GAD, and PTSD on a mg/m² basis. Because the MRHD for major depressive disorder is slightly less than that for OCD (50 mg versus 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 major depressive disorder, social anxiety disorder, GAD, and PTSD or 2.4 times the MRHD for OCD on a mg/m² basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks. These lesions 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 major depressive disorder, social anxiety disorder, and GAD; 8.2 and 4.1 times the MRHD for OCD and PD on a mg/m² basis).

Pregnancy: Pregnancy Category D. See WARNINGS—Usage in Pregnancy: *Teratogenic and Nonteratogenic Effects*.

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 is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS—Clinical Worsening and Suicide Risk). Three placebo-controlled trials in 752 pediatric patients with MDD have been conducted with PAXIL, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of PAXIL in a child or adolescent must balance the potential risks with the clinical need.

In placebo-controlled clinical trials conducted with pediatric patients, the following adverse events were reported in at least 2% of pediatric patients treated with PAXIL and occurred at a rate at least twice that for pediatric patients receiving placebo: emotional lability (including self-harm, suicidal thoughts, attempted suicide, crying, and mood fluctuations), hostility, decreased appetite, tremor, sweating, hyperkinesia, and agitation.

Events reported upon discontinuation of treatment with PAXIL in the pediatric clinical trials that included a taper phase regimen, which occurred in at least 2% of patients who received PAXIL and which occurred at a rate at least twice that of placebo, were: emotional lability (including suicidal ideation, suicide attempt, mood changes, and tearfulness), nervousness, dizziness, nausea, and abdominal pain (see Discontinuation of Treatment With PAXIL).

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

ADVERSE REACTIONS

Associated With Discontinuation of Treatment: Twenty percent (1,199/6,145) of patients treated with PAXIL in worldwide clinical trials in major depressive disorder and 16.1% (84/522), 11.8% (64/542), 9.4% (44/469), 10.7% (79/735), and 11.7% (79/676) of patients treated with PAXIL in worldwide trials in social anxiety disorder, OCD, panic disorder, GAD, and PTSD, 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:

	Major Depressive Disorder		OCD		Panic Disorder		Social Anxiety Disorder		Generalized Anxiety Disorder		PTSD	
	PAXIL	Placebo	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%	2.8%	0.6%
Insomnia	–	–	1.7%	0%	1.3%	0.3%	3.1%	0%			–	–
Agitation	1.1%	0.5%	–								–	–
Tremor	1.1%	0.3%	–				1.7%	0%			1.0%	0.2%
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%	2.2%	0.6%
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%	1.6%	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 patients treated with PAXIL was not >1% or was not greater than or equal to 2 times the incidence of placebo.

1. Incidence corrected for gender.

Commonly Observed Adverse Events: ***Major Depressive 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 1) 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) 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) 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) 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) were: Asthenia, infection, constipation, decreased appetite, dry mouth, nausea, libido decreased, somnolence, tremor, sweating, and abnormal ejaculation.

Posttraumatic Stress 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) were: Asthenia, sweating, nausea, dry mouth, diarrhea, decreased appetite, somnolence, libido decreased, abnormal ejaculation, female genital disorders, and impotence.

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 that 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.

Major Depressive Disorder: 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 mg to 50 mg/day. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

Table 1. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Major Depressive Disorder[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 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."

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 mg 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 mg to 60 mg/day or among patients with social anxiety disorder on PAXIL who participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a range of 20 mg to 50 mg/day.

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

		Obsessive Compulsive Disorder		Panic Disorder		Social Anxiety Disorder	
Body System	Preferred Term	PAXIL (n = 542)	Placebo (n = 265)	PAXIL (n = 469)	Placebo (n = 324)	PAXIL (n = 425)	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%
Cardiovascular	Vasodilation	4%	1%	–	–	–	–
	Palpitation	2%	0%	–	–	–	–
Dermatologic	Sweating	9%	3%	14%	6%	9%	2%
	Rash	3%	2%	–	–	–	–
Gastrointestinal	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%

continued

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

		Obsessive Compulsive Disorder		Panic Disorder		Social Anxiety Disorder	
Body System	Preferred Term	PAXIL (n = 542)	Placebo (n = 265)	PAXIL (n = 469)	Placebo (n = 324)	PAXIL (n = 425)	Placebo (n = 339)
Musculoskeletal	Myalgia	–	–	–	–	4%	3%
Nervous System	Insomnia	24%	13%	18%	10%	21%	10%
	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 in patients treated with PAXIL 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.

Generalized Anxiety Disorder and Posttraumatic Stress 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 or among PTSD patients on PAXIL who participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a range of 20 mg/day to 50 mg/day.

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

		Generalized Anxiety Disorder		Posttraumatic Stress Disorder	
Body System	Preferred Term	PAXIL (n = 736)	Placebo (n = 529)	PAXIL (n = 676)	Placebo (n = 604)
Body as a Whole	Asthenia	14%	6%	12%	4%
	Headache	17%	14%	–	–
	Infection	6%	3%	5%	4%
	Abdominal Pain			4%	3%
	Trauma			6%	5%
Cardiovascular	Vasodilation	3%	1%	2%	1%
Dermatologic	Sweating	6%	2%	5%	1%
Gastrointestinal	Nausea	20%	5%	19%	8%
	Dry Mouth	11%	5%	10%	5%
	Constipation	10%	2%	5%	3%
	Diarrhea	9%	7%	11%	5%
	Decreased Appetite	5%	1%	6%	3%
	Vomiting	3%	2%	3%	2%
	Dyspepsia	–	–	5%	3%
Nervous System	Insomnia	11%	8%	12%	11%
	Somnolence	15%	5%	16%	5%
	Dizziness	6%	5%	6%	5%
	Tremor	5%	1%	4%	1%
	Nervousness	4%	3%	–	–
	Libido Decreased	9%	2%	5%	2%
	Abnormal Dreams			3%	2%
Respiratory System	Respiratory Disorder	7%	5%	–	–
	Sinusitis	4%	3%	–	–
	Yawn	4%	–	2%	<1%
Special Senses	Abnormal Vision	2%	1%	3%	1%
Urogenital System	Abnormal Ejaculation[2]	25%	2%	13%	2%
	Female Genital Disorder[2]	4%	1%	5%	1%
	Impotence[2]	4%	3%	9%	1%

1. Events reported by at least 2% of GAD and PTSD in patients treated with PAXIL are included, except the following events which had an incidence on placebo ≥PAXIL [GAD]: Abdominal pain, back pain, trauma, dyspepsia, myalgia, and pharyngitis. [PTSD]: Back pain, headache, anxiety, depression, nervousness, respiratory disorder, pharyngitis, and sinusitis.
2. Percentage corrected for gender.

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

Table 4. Treatment-Emergent Adverse Experience Incidence in a Dose-Comparison Trial in the Treatment of Major Depressive Disorder*

	Placebo	PAXIL			
Body System/Preferred Term	n = 51	10 mg n = 102	20 mg n = 104	30 mg n = 101	40 mg n = 102
Body as a Whole					
Asthenia	0.0%	2.9%	10.6%	13.9%	12.7%
Dermatology					
Sweating	2.0%	1.0%	6.7%	8.9%	11.8%
Gastrointestinal					
Constipation	5.9%	4.9%	7.7%	9.9%	12.7%
Decreased Appetite	2.0%	2.0%	5.8%	4.0%	4.9%
Diarrhea	7.8%	9.8%	19.2%	7.9%	14.7%
Dry Mouth	2.0%	10.8%	18.3%	15.8%	20.6%
Nausea	13.7%	14.7%	26.9%	34.7%	36.3%
Nervous System					
Anxiety	0.0%	2.0%	5.8%	5.9%	5.9%
Dizziness	3.9%	8.9%	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%

continued

Table 4. Treatment-Emergent Adverse Experience Incidence in a Dose-Comparison Trial in the Treatment of Major Depressive Disorder* *(continued)*

Body System/Preferred Term	Placebo n = 51	PAXIL 10 mg n = 102	PAXIL 20 mg n = 104	PAXIL 30 mg n = 101	PAXIL 40 mg n = 102
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 1 of paroxetine groups and ≥ twice the placebo incidence for at least 1 paroxetine group.

In a fixed-dose study comparing placebo and 20, 40, and 60 mg of PAXIL in the treatment of OCD, there was no clear relationship between adverse events and the dose of PAXIL to which patients were assigned. No new adverse events were observed in the group treated with 60 mg of PAXIL compared to any of the other treatment groups.

In a fixed-dose study comparing placebo and 10, 20, and 40 mg of PAXIL 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, dry mouth, anxiety, libido decreased, tremor, and abnormal ejaculation. In flexible-dose studies, no new adverse events were observed in patients receiving 60 mg of PAXIL compared to any of the other treatment groups.

In a fixed-dose study comparing placebo and 20, 40, and 60 mg of PAXIL 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 to which patients were assigned.

In a fixed-dose study comparing placebo and 20 and 40 mg of PAXIL 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 to which patients were assigned, except for the following adverse events: Asthenia, constipation, and abnormal ejaculation.

In a fixed-dose study comparing placebo and 20 and 40 mg of PAXIL in the treatment of posttraumatic stress disorder, for most of the adverse events, there was no clear relationship between adverse events and the dose of PAXIL to which patients were assigned, except for impotence and abnormal ejaculation.

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

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 3,200 patients, the ranges for the reported incidence of sexual side effects in males and females with major depressive disorder, OCD, panic disorder, social anxiety disorder, GAD, and PTSD are displayed in Table 5.

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

	PAXIL	Placebo
n (males)	1446	1042
Decreased Libido	6-15%	0-5%
Ejaculatory Disturbance	13-28%	0-2%
Impotence	2-9%	0-3%
n (females)	1822	1340
Decreased Libido	0-9%	0-2%
Orgasmic Disturbance	2-9%	0-1%

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 versus 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-versus-placebo comparisons for alkaline phosphatase, SGOT, SGPT, and bilirubin revealed no differences in the percentage of patients with marked abnormalities.

Hallucinations: In pooled clinical trials of immediate-release paroxetine hydrochloride, hallucinations were observed in 22 of 9089 patients receiving drug and 4 of 3187 patients receiving placebo.

Other Events Observed During the Premarketing Evaluation of PAXIL: During its premarketing assessment in major depressive disorder, 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, generalized anxiety disorder, and posttraumatic stress disorder, 542, 469, 522, 735, and 676 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 9,089 patients exposed to multiple doses of PAXIL who experienced an event of the type cited on at least 1 occasion while receiving PAXIL. All reported events are included except those already listed in Tables 1 to 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 1 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 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients. Events of major clinical importance are also described in the PRECAUTIONS section.

Body as a Whole: *Infrequent:* Allergic reaction, chills, face edema, malaise, neck pain; *rare:* Adrenergic syndrome, cellulitis, moniliasis, neck rigidity, pelvic pain, peritonitis, sepsis, ulcer.

Cardiovascular System: *Frequent:* Hypertension, tachycardia; *infrequent:* Bradycardia, hematoma, hypotension, migraine, syncope; *rare:* Angina pectoris, arrhythmia nodal, 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, cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, intestinal obstruction, jaundice, melena, mouth ulceration, peptic ulcer, salivary gland enlargement, sialadenitis, stomach ulcer, stomatitis, tongue discoloration, tongue edema, tooth caries.

Endocrine System: *Rare:* Diabetes mellitus, goiter, hyperthyroidism, hypothyroidism, thyroiditis.

Hemic and Lymphatic Systems: *Infrequent:* Anemia, leukopenia, lymphadenopathy, purpura; *rare:* Abnormal erythrocytes, basophilia, bleeding time increased, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia, thrombocytopenia.

Metabolic and Nutritional: *Frequent:* Weight gain; *infrequent:* Edema, peripheral edema, SGOT increased, SGPT increased, thirst, weight loss; *rare:* Alkaline phosphatase increased, 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.

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, dystonia, dyskinesia, euphoria, hallucinations, hostility, hypertonia, hypesthesia, hypokinesia, incoordination, lack of emotion, libido increased, manic reaction, neurosis, paralysis, paranoid reaction; *rare:* Abnormal gait, akinesia, antisocial reaction, aphasia, choreoathetosis, circumoral paresthesias, convulsion, delirium, 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, psychosis, 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, stridor, voice alteration.

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

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

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

Postmarketing Reports: Voluntary reports of adverse events in patients taking PAXIL 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, serotonin syndrome; 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; status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic syndromes (such as Henoch-Schönlein purpura). There has been a case report of an elevated phenytoin level after 4 weeks of PAXIL and phenytoin coadministration. 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 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 misuse or abuse of PAXIL (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience: Since the introduction of PAXIL in the United States, 342 spontaneous cases of deliberate or accidental overdosage during paroxetine treatment have been reported worldwide (circa 1999). These include overdoses with paroxetine alone and in combination with other substances. Of these, 48 cases were fatal and of the fatalities, 17 appeared to involve paroxetine alone. Eight fatal cases that 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 2,000 mg of paroxetine (33 times the maximum recommended daily dose) in a patient who recovered.

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

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

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

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

A specific caution involves patients who are taking or have recently taken paroxetine who might ingest excessive quantities 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 PRECAUTIONS—*Drugs Metabolized by Cytochrome CYP2D6*).

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

DOSAGE AND ADMINISTRATION

Major Depressive Disorder: ***Usual Initial Dosage:*** PAXIL 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 effectiveness of PAXIL in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, the full effect may be delayed. Some patients not responding to a 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 major depressive disorder require several months or longer of sustained pharmacologic therapy. Whether the dose 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 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 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—Clinical Trials). 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—Clinical Trials). 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—Clinical Trials).

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 demonstrated in patients dosed in a range of 20 to 50 mg/day. The recommended starting dosage and the established effective dosage is 20 mg/day. There is not sufficient evidence to suggest 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: Systematic evaluation of continuing PAXIL for periods of up to 24 weeks in patients with Generalized Anxiety Disorder who had responded while taking PAXIL during an 8-week acute treatment phase has demonstrated a benefit of

such maintenance (see CLINICAL PHARMACOLOGY—Clinical Trials). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

Posttraumatic Stress Disorder: ***Usual Initial Dosage:*** PAXIL should be administered as a single daily dose with or without food, usually in the morning. The recommended starting dosage and the established effective dosage is 20 mg/day. In 1 clinical trial, the effectiveness of PAXIL was demonstrated in patients dosed in a range of 20 to 50 mg/day. However, in a fixed dose study, there was not sufficient evidence to suggest a greater benefit for a dose of 40 mg/day compared to 20 mg/day. Dose changes, if indicated, 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 12 weeks of dosing has not been demonstrated in controlled clinical trials, PTSD 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.

Special Populations: ***Treatment of Pregnant Women During the Third Trimester:*** Neonates exposed to PAXIL and other SSRIs or SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see WARNINGS). When treating pregnant women with paroxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering paroxetine in the third trimester.

Dosage for Elderly or Debilitated Patients, 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 an MAOI and initiation of therapy with PAXIL. Similarly, at least 14 days should be allowed after stopping PAXIL before starting an MAOI.

Discontinuation of Treatment With PAXIL: Symptoms associated with discontinuation of PAXIL have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment, regardless of the indication for which PAXIL is being prescribed. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

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 0029-3211-59 Bottles of 90
NDC 0029-3211-21 SUP 100s (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).

PAXIL is a registered trademark of GlaxoSmithKline.

Medication Guide
PAXIL® (PAX-il) (paroxetine hydrochloride) Tablets and Oral Suspension
About Using Antidepressants in Children and Teenagers

What is the most important information I should know if my child is being prescribed an antidepressant?

Parents or guardians need to think about 4 important things when their child is prescribed an antidepressant:
1. There is a risk of suicidal thoughts or actions
2. How to try to prevent suicidal thoughts or actions in your child
3. You should watch for certain signs if your child is taking an antidepressant
4. There are benefits and risks when using antidepressants

1. There Is a Risk of Suicidal Thoughts or Actions

Children and teenagers sometimes think about suicide, and many report trying to kill themselves.

Antidepressants increase suicidal thoughts and actions in some children and teenagers. But suicidal thoughts and actions can also be caused by depression, a serious medical condition that is commonly treated with antidepressants. Thinking about killing yourself or trying to kill yourself is called *suicidality* or *being suicidal.*

A large study combined the results of 24 different studies of children and teenagers with depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an antidepressant for 1 to 4 months. ***No one committed suicide in these studies,*** but some patients became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4 out of every 100 patients became suicidal.

For some children and teenagers, the risks of suicidal actions may be especially high. These include patients with
- Bipolar illness (sometimes called manic-depressive illness)
- A family history of bipolar illness
- A personal or family history of attempting suicide

If any of these are present, make sure you tell your healthcare provider before your child takes an antidepressant.

2. How to Try to Prevent Suicidal Thoughts and Actions

To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her or his moods or actions, especially if the changes occur suddenly. Other important people in your child's life can help by paying attention as well (e.g., your child, brothers and sisters, teachers, and other important people). The changes to look out for are listed in Section 3, on what to watch for.

Whenever an antidepressant is started or its dose is changed, pay close attention to your child.
After starting an antidepressant, your child should generally see his or her healthcare provider:
- Once a week for the first 4 weeks
- Every 2 weeks for the next 4 weeks
- After taking the antidepressant for 12 weeks
- After 12 weeks, follow your healthcare provider's advice about how often to come back
- More often if problems or questions arise (see Section 3)

You should call your child's healthcare provider between visits if needed.

3. You Should Watch for Certain Signs if Your Child Is Taking an Antidepressant

Contact your child's healthcare provider ***right away*** if your child exhibits any of the following signs for the first time, or if they seem worse, or worry you, your child, or your child's teacher:
- Thoughts about suicide or dying
- Attempts to commit suicide
- New or worse depression
- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Difficulty sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry, or violent
- Acting on dangerous impulses
- An extreme increase in activity and talking
- Other unusual changes in behavior or mood

Never let your child stop taking an antidepressant without first talking to his or her healthcare provider. Stopping an antidepressant suddenly can cause other symptoms.

4. There Are Benefits and Risks When Using Antidepressants

Antidepressants are used to treat depression and other illnesses. Depression and other illnesses can lead to suicide. In some children and teenagers, treatment with an antidepressant increases suicidal thinking or actions. It is important to discuss all the risks of treating depression and also the risks of not treating it. You and your child should discuss all treatment choices with your healthcare provider, not just the use of antidepressants.

Other side effects can occur with antidepressants (see section below).

Of all the antidepressants, only fluoxetine (Prozac®)* has been FDA approved to treat pediatric depression.

For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine (Prozac®)*, sertraline (Zoloft®)*, fluvoxamine, and clomipramine (Anafranil®)*.

Your healthcare provider may suggest other antidepressants based on the past experience of your child or other family members.

Is this all I need to know if my child is being prescribed an antidepressant?

No. This is a warning about the risk for suicidality. Other side effects can occur with antidepressants. Be sure to ask your healthcare provider to explain all the side effects of the particular drug he or she is prescribing. Also ask about drugs to avoid when taking an antidepressant. Ask your healthcare provider or pharmacist where to find more information.

*The following are registered trademarks of their respective manufacturers: Prozac®/Eli Lilly and Company; Zoloft®/Pfizer Pharmaceuticals; Anafranil®/Mallinckrodt Inc.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

MG-PX:2

GlaxoSmithKline

GlaxoSmithKline
Research Triangle Park, NC 27709

May 2006

PX:L41

PAXIL CR®
(paroxetine hydrochloride)
Controlled-Release Tablets

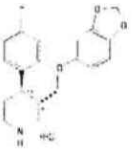
Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of PAXIL CR or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. PAXIL CR is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS—Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

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



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

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

Inactive ingredients consist of hypromellose, polyvinylpyrrolidone, lactose monohydrate, magnesium stearate, colloidal silicon dioxide, glyceryl behenate, methacrylic acid copolymer type C, sodium lauryl sulfate, polysorbate 80, talc, triethyl citrate, and 1 or more of the following colorants: Yellow ferric oxide, red ferric oxide, D&C Red No. 30, D&C Yellow No. 6, D&C Yellow No. 10, FD&C Blue No. 2.

CLINICAL PHARMACOLOGY

Pharmacodynamics: The efficacy of paroxetine in the treatment of major depressive disorder, panic disorder, social anxiety disorder, and premenstrual dysphoric disorder (PMDD) is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT). Studies at clinically relevant doses in humans have demonstrated that paroxetine blocks the uptake of serotonin into human platelets. In vitro studies in animals also suggest that paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. In vitro radioligand binding studies indicate that paroxetine has little affinity for muscarinic, $alpha_1$-, $alpha_2$-, beta-adrenergic-, dopamine (D_2)-, $5\text{-}HT_1$-, $5\text{-}HT_2$-, and histamine (H_1)-receptors; antagonism of muscarinic, histaminergic, and $alpha_1$-adrenergic receptors has been associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs.

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

Pharmacokinetics: Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt. The elimination half-life is approximately 15 to 20 hours after a single dose of PAXIL CR. Paroxetine is extensively metabolized and the metabolites are considered to be inactive. Nonlinearity in pharmacokinetics is observed with increasing doses. Paroxetine metabolism is mediated in part by CYP2D6, and the metabolites are primarily excreted in the urine and to some extent in the feces. Pharmacokinetic behavior of paroxetine has not been evaluated in subjects who are deficient in CYP2D6 (poor metabolizers).

Absorption and Distribution: Tablets of PAXIL CR contain a degradable polymeric matrix (GEOMATRIX™) designed to control the dissolution rate of paroxetine over a period of approximately 4 to 5 hours. In addition to controlling the rate of drug release in vivo, an enteric coat delays the start of drug release until tablets of PAXIL CR have left the stomach.

Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt. In a study in which normal male and female subjects (n = 23) received single oral doses of PAXIL CR at 4 dosage strengths (12.5 mg, 25 mg, 37.5 mg, and 50 mg), paroxetine C_{max} and $AUC_{0-\infty}$ increased disproportionately with dose (as seen also with immediate-release formulations). Mean C_{max} and $AUC_{0-\infty}$ values at these doses were 2.0, 5.5, 9.0, and 12.5 ng/mL, and 121, 261, 338, and 540 ng•hr./mL, respectively. T_{max} was observed typically between 6 and 10 hours post-dose, reflecting a reduction in absorption rate compared with immediate-release formulations. The bioavailability of 25 mg PAXIL CR is not affected by food.

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

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.

Metabolism and Excretion: The mean elimination half-life of paroxetine was 15 to 20 hours throughout a range of single doses of PAXIL CR (12.5 mg, 25 mg, 37.5 mg, and 50 mg). During repeated administration of PAXIL CR (25 mg once daily), steady state was reached within 2 weeks (i.e., comparable to immediate-release formulations). In a repeat-dose study in which normal male and female subjects (n = 23) received PAXIL CR (25 mg daily), mean steady state C_{max}, C_{min}, and AUC_{0-24} values were 30 ng/mL, 20 ng/mL, and 550 ng•hr./mL, respectively.

Based on studies using immediate-release formulations, steady-state drug exposure based on AUC_{0-24} was several-fold greater than would have been predicted from single-dose data. The excess accumulation is a consequence of the fact that 1 of the enzymes that metabolizes paroxetine is readily saturable.

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

Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic acid and sulfate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 the potency of the parent compound at inhibiting serotonin uptake. The metabolism of paroxetine is accomplished in part by CYP2D6. 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.

Other Clinical Pharmacology Information: ***Specific Populations: 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 doses of 20, 30, and 40 mg of the immediate-release formulation, C_{min} concentrations were about 70% to 80% greater than the respective C_{min} concentrations in nonelderly subjects. Therefore the initial dosage in the elderly should be reduced (see DOSAGE AND ADMINISTRATION).

Drug-Drug Interactions: In vitro drug interaction studies reveal that paroxetine inhibits CYP2D6. Clinical drug interaction studies have been performed with substrates of CYP2D6 and show that paroxetine can inhibit the metabolism of drugs metabolized by CYP2D6 including desipramine, risperidone, and atomoxetine (see PRECAUTIONS—Drug Interactions).

Clinical Trials

Major Depressive Disorder: The efficacy of PAXIL CR controlled-release tablets as a treatment for major depressive disorder has been established in two 12-week, flexible-dose, placebo-controlled studies of patients with DSM-IV Major Depressive Disorder. One study included patients in the age range 18 to 65 years, and a second study included elderly patients, ranging in age from 60 to 88. In both studies, PAXIL CR was shown to be significantly more effective than placebo in treating major depressive disorder as measured by the following: Hamilton Depression Rating Scale (HDRS), the Hamilton depressed mood item, and the Clinical Global Impression (CGI)–Severity of Illness score.

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

Panic Disorder: The effectiveness of PAXIL CR in the treatment of panic disorder was evaluated in three 10-week, multicenter, flexible-dose studies (Studies 1, 2, and 3) comparing paroxetine controlled-release (12.5 to 75 mg daily) to placebo in adult outpatients who had panic disorder (DSM-IV), with or without agoraphobia. These trials were assessed on the basis of their outcomes on 3 variables: (1) the proportions of patients free of full panic attacks at endpoint; (2) change from baseline to endpoint in the median number of full panic attacks; and (3) change from baseline to endpoint in the median Clinical Global Impression Severity score. For Studies 1 and 2, PAXIL CR was consistently superior to placebo on 2 of these 3 variables. Study 3 failed to consistently demonstrate a significant difference between PAXIL CR and placebo on any of these variables.

For all 3 studies, the mean dose of PAXIL CR for completers at endpoint was approximately 50 mg/day. Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

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

Social Anxiety Disorder: The efficacy of PAXIL CR as a treatment for social anxiety disorder has been established, in part, on the basis of extrapolation from the established effectiveness of the immediate-release formulation of paroxetine. In addition, the effectiveness of PAXIL CR in the treatment of social anxiety disorder was demonstrated in a 12-week, multicenter, double-blind, flexible-dose, placebo-controlled study of adult outpatients with a primary diagnosis of social anxiety disorder (DSM-IV). In the study, the effectiveness of PAXIL CR (12.5 to 37.5 mg daily) compared to placebo was evaluated on the basis of (1) change from baseline in the Liebowitz Social Anxiety Scale (LSAS) total score and (2) the proportion of responders who scored 1 or 2 (very much improved or much improved) on the Clinical Global Impression (CGI) Global Improvement score.

PAXIL CR demonstrated statistically significant superiority over placebo on both the LSAS total score and the CGI Improvement responder criterion. For patients who completed the trial, 64% of patients treated with PAXIL CR compared to 34.7% of patients treated with placebo were CGI Improvement responders.

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of gender. Subgroup analyses of studies utilizing the immediate-release formulation of paroxetine generally did not indicate differences in treatment outcomes as a function of age, race, or gender.

Premenstrual Dysphoric Disorder: The effectiveness of PAXIL CR for the treatment of PMDD utilizing a continuous dosing regimen has been established in 2 placebo-controlled trials. Patients in these trials met DSM-IV criteria for PMDD. In a pool of 1,030 patients, treated with daily doses of PAXIL CR 12.5 or 25 mg/day, or placebo the mean duration of the PMDD symptoms was approximately 11 ± 7 years. Patients on systemic hormonal contraceptives were excluded from these trials. Therefore, the efficacy of PAXIL CR in combination with systemic (including oral) hormonal contraceptives for the continuous daily treatment of PMDD is unknown. In both positive studies, patients (N = 672) were treated with 12.5 mg/day or 25 mg/day of PAXIL CR or placebo continuously throughout the menstrual cycle for a period of 3 menstrual cycles. The VAS-Total score is a patient-rated instrument that mirrors the diagnostic criteria of PMDD as identified in the DSM-IV, and includes assessments for mood, physical symptoms, and other symptoms. 12.5 mg/day and 25 mg/day of PAXIL CR were significantly more effective than placebo as measured by change from baseline to the endpoint on the luteal phase VAS-Total score.

In a third study employing intermittent dosing, patients (N = 366) were treated for the 2 weeks prior to the onset of menses (luteal phase dosing, also known as intermittent dosing) with 12.5 mg/day or 25 mg/day of PAXIL CR or placebo for a period of 3 months. 12.5 mg/day and 25 mg/day of PAXIL CR, as luteal phase dosing, was significantly more effective than placebo as measured by change from baseline luteal phase VAS total score.

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

INDICATIONS AND USAGE

Major Depressive Disorder: PAXIL CR is indicated for the treatment of major depressive disorder.

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

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed mood or loss of interest or pleasure in nearly all activities, representing a change from previous functioning, and includes the presence of at least 5 of the following 9 symptoms during the same 2-week period: Depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt, or suicidal ideation.

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

PAXIL CR has not been systematically evaluated beyond 12 weeks in controlled clinical trials; however, the effectiveness of immediate-release paroxetine hydrochloride in maintaining a response in major depressive disorder for up to 1 year has been demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY–Clinical Trials). The physician who elects to use PAXIL CR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

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

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

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

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

Social Anxiety Disorder: PAXIL CR 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 1 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 psychopharmacological treatment.

The efficacy of PAXIL CR as a treatment for social anxiety disorder has been established, in part, on the basis of extrapolation from the established effectiveness of the immediate-release formulation of paroxetine. In addition, the efficacy of PAXIL CR was established in a 12-week trial, in adult outpatients with social anxiety disorder (DSM-IV). PAXIL CR has not been studied in children or adolescents with social phobia (see CLINICAL PHARMACOLOGY—Clinical Trials).

The effectiveness of PAXIL CR 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 CR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Premenstrual Dysphoric Disorder: PAXIL CR is indicated for the treatment of PMDD.

The efficacy of PAXIL CR in the treatment of PMDD has been established in 3 placebo-controlled trials (see CLINICAL PHARMACOLOGY–Clinical Trials).

The essential features of PMDD, according to DSM-IV, include markedly depressed mood, anxiety or tension, affective lability, and persistent anger or irritability. Other features include decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. Physical symptoms associated with PMDD include breast tenderness, headache, joint and muscle pain, bloating, and weight gain. These symptoms occur regularly during the luteal phase and remit within a few days following the onset of menses; the disturbance markedly interferes with work or school or with usual social activities and relationships with others. In making the diagnosis, care should be taken to rule out other cyclical mood disorders that may be exacerbated by treatment with an antidepressant.

The effectiveness of PAXIL CR in long-term use, that is, for more than 3 menstrual cycles, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use PAXIL CR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

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

Concomitant use in patients taking pimozide is contraindicated (see PRECAUTIONS).

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

WARNINGS

Clinical Worsening and Suicide Risk: Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

Young adults, especially those with MDD, may be at increased risk for suicidal behavior during treatment with paroxetine. An analysis of placebo-controlled trials of adults with psychiatric disorders showed a higher frequency of suicidal behavior in young adults (prospectively defined as aged 18-24 years) treated with paroxetine compared with placebo (17/776 [2.19%] versus 5/542 [0.92%]), although this difference was not statistically significant. In the older age groups (aged 25-64 years and ≥65 years), no such increase was observed. In adults with MDD (all ages), there was a statistically significant increase in the frequency of suicidal behavior in patients treated with paroxetine compared with placebo (11/3,455 [0.32%] versus 1/1,978 [0.05%]); all of the events were suicide attempts. However, the majority of these attempts for paroxetine (8 of 11) were in younger adults aged 18-30 years. These MDD data suggest that the higher frequency observed in the younger adult population across psychiatric disorders may extend beyond the age of 24.

In addition, patients with a history of suicidal behavior or thoughts, those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at an increased risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION—Discontinuation of Treatment With PAXIL CR, for a description of the risks of discontinuation of PAXIL CR).

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for PAXIL CR should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that PAXIL CR is not approved for use in treating bipolar depression.

Potential for Interaction With Monoamine Oxidase Inhibitors: In patients receiving another serotonin reuptake inhibitor drug in combination with an MAOI, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued that drug and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. While there are no human data showing such an interaction with paroxetine hydrochloride, limited animal data on the effects of combined use of paroxetine and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that PAXIL CR not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. At least 2 weeks should be allowed after stopping PAXIL CR before starting an MAOI.

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

An in vivo study suggests that drugs which inhibit CYP2D6, 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).

Usage in Pregnancy: ***Teratogenic Effects:*** Epidemiological studies have shown that infants born to women who had first trimester paroxetine exposure had an increased risk of cardiovascular malformations, primarily ventricular and atrial septal defects (VSDs and ASDs). In general, septal defects range from those that are symptomatic and may require surgery to those that are asymptomatic and may resolve spontaneously. If a patient becomes pregnant while taking paroxetine, she should be advised of the potential harm to the fetus. Unless the benefits of paroxetine to the mother justify continuing treatment, consideration should be given to either discontinuing paroxetine therapy or switching to another antidepressant (see PRECAUTIONS—Discontinuation of Treatment with PAXIL CR). For women who intend to become pregnant or are in their first trimester of pregnancy, paroxetine should only be initiated after consideration of the other available treatment options.

A study based on Swedish national registry data evaluated infants of 6,896 women exposed to antidepressants in early pregnancy (5,123 women exposed to SSRIs; including 815 for paroxetine). Infants exposed to paroxetine in early pregnancy had an increased risk of cardiovascular malformations (primarily VSDs and ASDs) compared to the entire registry population (OR 1.8; 95% confidence interval 1.1-2.8). The rate of cardiovascular malformations following early pregnancy paroxetine exposure was 2% vs. 1% in the entire registry population. Among the same paroxetine exposed infants, an examination of the data showed no increase in the overall risk for congenital malformations.

A separate retrospective cohort study using US United Healthcare data evaluated 5,956 infants of mothers dispensed paroxetine or other antidepressants during the first trimester (n = 815 for paroxetine). This study showed a trend towards an increased risk for cardiovascular malformations for paroxetine compared to other antidepressants (OR 1.5; 95% confidence interval 0.8-2.9). The prevalence of cardiovascular malformations following first trimester dispensing was 1.5% for paroxetine vs. 1% for other antidepressants. Nine out of 12 infants with cardiovascular malformations whose mothers were dispensed paroxetine in the first trimester had VSDs. This study also suggested an increased risk of overall major congenital malformations (inclusive of the cardiovascular defects) for paroxetine compared to other antidepressants (OR 1.8; 95% confidence interval 1.2-2.8). The prevalence of all congenital malformations following first trimester exposure was 4% for paroxetine vs. 2% for other antidepressants.

Animal Findings: Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately 8 (rat) and 2 (rabbit) times the MRHD on an mg/m² basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg/day or approximately one-sixth of the MRHD on an mg/m² basis. The no-effect dose for rat pup mortality was not determined. The cause of these deaths is not known.

Nonteratogenic Effects: Neonates exposed to PAXIL CR and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS—Potential for Interaction With Monoamine Oxidase Inhibitors).

Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN is associated with substantial neonatal morbidity and mortality. In a case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. PPHN occurs in 1 – 2 per 1,000 live births in the general population.

There have also been postmarketing reports of premature births in pregnant women exposed to paroxetine or other SSRIs.

When treating a pregnant woman with paroxetine during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION). Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

PRECAUTIONS

General: ***Activation of Mania/Hypomania:*** During premarketing testing of immediate-release paroxetine hydrochloride, hypomania or mania occurred in approximately 1.0% of paroxetine-treated unipolar patients compared to 1.1% of active-control and 0.3% of placebo-treated unipolar patients. In a subset of patients classified as bipolar, the rate of manic episodes was 2.2% for immediate-release paroxetine and 11.6% for the combined active-control groups. Among 1,627 patients with major depressive disorder, panic disorder, social anxiety disorder, or PMDD treated with PAXIL CR in controlled clinical studies, there were no reports of mania or hypomania. As with all drugs effective in the treatment of major depressive disorder, PAXIL CR should be used cautiously in patients with a history of mania.

Seizures: During premarketing testing of immediate-release paroxetine hydrochloride, seizures occurred in 0.1% of paroxetine-treated patients, a rate similar to that associated with other drugs effective in the treatment of major depressive disorder. Among 1,627 patients who received PAXIL CR in controlled clinical trials in major depressive disorder, panic disorder, social anxiety disorder, or PMDD, 1 patient (0.1%) experienced a seizure. PAXIL CR should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Discontinuation of Treatment With PAXIL CR: Adverse events while discontinuing therapy with PAXIL CR were not systematically evaluated in most clinical trials; however, in recent placebo-controlled clinical trials utilizing daily doses of PAXIL CR up to 37.5 mg/day, spontaneously reported adverse events while discontinuing therapy with PAXIL CR were evaluated. Patients receiving 37.5 mg/day underwent an incremental decrease in the daily dose by 12.5 mg/day to a dose of 25 mg/day for 1 week before treatment was stopped. For patients receiving 25 mg/day or 12.5 mg/day, treatment was stopped without an incremental decrease in dose. With this regimen in those studies, the following adverse events were reported for PAXIL CR, at an incidence of 2% or greater for PAXIL CR and were at least twice that reported for placebo: Dizziness, nausea, nervousness, and additional symptoms described by the investigator as associated with tapering or discontinuing PAXIL CR (e.g., emotional lability, headache, agitation, electric shock sensations, fatigue, and sleep disturbances). These events were reported as serious in 0.3% of patients who discontinued therapy with PAXIL CR.

During marketing of PAXIL CR and other SSRIs and SNRIs, there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs (particularly when abrupt), including the following: Dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations and tinnitus), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with PAXIL CR. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION).

See also PRECAUTIONS—Pediatric Use, for adverse events reported upon discontinuation of treatment with paroxetine in pediatric patients.

Akathisia: The use of paroxetine or other SSRIs has been associated with the development of akathisia, which is characterized by an inner sense of restlessness and psychomotor agitation such as an inability to sit or stand still usually associated with subjective distress. This is most likely to occur within the first few weeks of treatment.

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

Serotonin Syndrome: The development of a serotonin syndrome may occur in association with treatment with paroxetine, particularly with concomitant use of serotonergic drugs and with drugs which may have impaired metabolism of immediate-release paroxetine hydrochloride. Symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia, and tremor. The concomitant use of PAXIL CR with serotonin precursors (such as tryptophan) is not recommended (see WARNINGS—Potential for Interaction With Monoamine Oxidase Inhibitors and PRECAUTIONS—Drug Interactions).

Abnormal Bleeding: Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In 2 studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (see Drug Interactions). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of paroxetine with NSAIDs, aspirin, or other drugs that affect coagulation.

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

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

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

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

Information for Patients: Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with PAXIL CR and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for PAXIL CR. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Information from clinical trials has suggested that young adults, particularly those with depression, may be at an increased risk of suicidal behavior (including suicide attempts) when treated with PAXIL CR. The majority of attempted suicides in clinical trials in depression involved patients aged 18-30 years.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking PAXIL CR.

Clinical Worsening and Suicide Risk: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

PAXIL CR should not be chewed or crushed, and should be swallowed whole.

Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.): Patients should be cautioned about the concomitant use of paroxetine and NSAIDs, aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding.

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

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

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

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

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy (see WARNINGS—Usage in Pregnancy: *Teratogenic and Nonteratogenic Effects*).

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 coadministered. Adverse experiences, consisting primarily of headache, nausea, sweating, and dizziness, have been reported when tryptophan was administered to patients taking immediate-release paroxetine. Consequently, concomitant use of PAXIL CR with tryptophan is not recommended (see Serotonin Syndrome).

Monoamine Oxidase Inhibitors: See CONTRAINDICATIONS and WARNINGS.

Pimozide: In a controlled study of healthy volunteers, after immediate-release paroxetine hydrochloride was titrated to 60 mg daily, co-administration of a single dose of 2 mg pimozide was associated with mean increases in pimozide AUC of 151% and C_{max} of 62%, compared to pimozide administered alone. Due to the narrow therapeutic index of pimozide and its known ability to prolong the QT interval, concomitant use of pimozide and PAXIL CR is contraindicated (see CONTRAINDICATIONS).

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

Thioridazine: See CONTRAINDICATIONS and WARNINGS.

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

Triptans: There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination

following the use of an SSRI and sumatriptan. If concomitant treatment with a triptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) is clinically warranted, appropriate observation of the patient is advised (see Serotonin Syndrome).

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

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

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

Phenytoin: When a single oral 30-mg dose of immediate-release paroxetine was administered at phenytoin steady state (300 mg once daily for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 50% and 35%, respectively) compared to immediate-release paroxetine administered alone. In a separate study, when a single oral 300-mg dose of phenytoin was administered at paroxetine steady state (30 mg once daily 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 2 drugs are both being chronically dosed. No initial dosage adjustments are considered necessary when PAXIL CR is coadministered with phenytoin; any subsequent adjustments should be guided by clinical effect (see ADVERSE REACTIONS—Postmarketing Reports).

Drugs Metabolized by CYP2D6: Many drugs, including most drugs effective in the treatment of major depressive disorder (paroxetine, other SSRIs, and many tricyclics), are metabolized by the cytochrome P_{450} isozyme CYP2D6. Like other agents that are metabolized by CYP2D6, paroxetine may significantly inhibit the activity of this isozyme. In most patients (>90%), this CYP2D6 isozyme is saturated early during paroxetine dosing. In 1 study, daily dosing of immediate-release paroxetine (20 mg once daily) under steady-state conditions increased single-dose desipramine (100 mg) C_{max}, AUC, and $T_{1/2}$ by an average of approximately 2-, 5-, and 3-fold, respectively. Concomitant use of paroxetine with risperidone, a CYP2D6 substrate has also been evaluated. In 1 study, daily dosing of paroxetine 20 mg in patients stabilized on risperidone (4 to 8 mg/day) increased mean plasma concentrations of risperidone approximately 4-fold, decreased 9-hydroxyrisperidone concentrations approximately 10%, and increased concentrations of the active moiety (the sum of risperidone plus 9-hydroxyrisperidone) approximately 1.4-fold. The effect of paroxetine on the pharmacokinetics of atomoxetine has been evaluated when both drugs were at steady state. In healthy volunteers who were extensive metabolizers of CYP2D6, paroxetine 20 mg daily was given in combination with 20 mg atomoxetine every 12 hours. This resulted in increases in steady state atomoxetine AUC values that were 6- to 8-fold greater and in atomoxetine C_{max} values that were 3- to 4-fold greater than when atomoxetine was given alone. Dosage adjustment of atomoxetine may be necessary and it is recommended that atomoxetine be initiated at a reduced dose when given with paroxetine.

Concomitant use of PAXIL CR with other drugs metabolized by cytochrome CYP2D6 has not been formally studied but may require lower doses than usually prescribed for either PAXIL CR or the other drug.

Therefore, coadministration of PAXIL CR with other drugs that are metabolized by this isozyme, including certain drugs effective in the treatment of major depressive disorder (e.g., nortriptyline, amitriptyline, imipramine, desipramine, and fluoxetine), phenothiazines, risperidone, 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 coadministered (see CONTRAINDICATIONS and WARNINGS).

At steady state, when the CYP2D6 pathway is essentially saturated, paroxetine clearance is governed by alternative P_{450} isozymes that, unlike CYP2D6, show no evidence of saturation (see PRECAUTIONS—Tricyclic Antidepressants).

Drugs Metabolized by Cytochrome CYP3A4: An in vivo interaction study involving the coadministration under steady-state conditions of paroxetine and terfenadine, a substrate for CYP3A4, revealed no effect of paroxetine on terfenadine pharmacokinetics. In addition, in vitro studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several substrates for this enzyme, including terfenadine, astemizole, cisapride, triazolam, and cyclosporine. 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 CYP3A4 substrates, paroxetine's extent of inhibition of CYP3A4 activity is not likely to be of clinical significance.

Tricyclic Antidepressants (TCAs): Caution is indicated in the coadministration of TCAs with PAXIL CR, because paroxetine may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is coadministered with PAXIL CR (see PRECAUTIONS—Drugs Metabolized by Cytochrome CYP2D6).

Drugs Highly Bound to Plasma Protein: Because paroxetine is highly bound to plasma protein, administration of PAXIL CR to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events. Conversely, adverse effects could result from displacement of paroxetine by other highly bound drugs.

Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.): Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentiated the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with paroxetine.

Alcohol: Although paroxetine does not increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking PAXIL CR.

Lithium: A multiple-dose study with immediate-release paroxetine hydrochloride has shown that there is no pharmacokinetic interaction between paroxetine and lithium carbonate. However, due to the potential for serotonin syndrome, caution is advised when immediate-release paroxetine hydrochloride is coadministered with lithium.

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

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

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

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

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

Fosamprenavir/Ritonavir: Co-administration of fosamprenavir/ritonavir with paroxetine significantly decreased plasma levels of paroxetine. Any dose adjustment should be guided by clinical effect (tolerability and efficacy).

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

Carcinogenesis, Mutagenesis, Impairment of Fertility: ***Carcinogenesis:*** Two-year carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are up to approximately 2 (mouse) and 3 (rat) times the maximum recommended human dose (MRHD) on a mg/m² basis. There was a significantly greater number of male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50, and 4/50 for control, low-, middle-, and high-dose groups, respectively) and a significantly increased linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The relevance of these findings to humans is unknown.

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

Impairment of Fertility: A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of 15 mg/kg/day, which is approximately twice the MRHD on a mg/m² basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks. These lesions consisted of vacuolation of epididymal tubular epithelium at 50 mg/kg/day and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis at 25 mg/kg/day (approximately 8 and 4 times the MRHD on a mg/m² basis).

Pregnancy: Pregnancy Category D. See WARNINGS—Usage in Pregnancy: *Teratogenic and Nonteratogenic Effects.*

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

Nursing Mothers: Like many other drugs, paroxetine is secreted in human milk, and caution should be exercised when PAXIL CR is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS—Clinical Worsening and Suicide Risk). Three placebo-controlled trials in 752 pediatric patients with MDD have been conducted with PAXIL, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of PAXIL CR in a child or adolescent must balance the potential risks with the clinical need.

In placebo-controlled clinical trials conducted with pediatric patients, the following adverse events were reported in at least 2% of pediatric patients treated with immediate-release paroxetine hydrochloride and occurred at a rate at least twice that for pediatric patients receiving placebo: emotional lability (including self-harm, suicidal thoughts, attempted suicide, crying, and mood fluctuations), hostility, decreased appetite, tremor, sweating, hyperkinesia, and agitation.

Events reported upon discontinuation of treatment with immediate-release paroxetine hydrochloride in the pediatric clinical trials that included a taper phase regimen, which occurred in at least 2% of patients who received immediate-release paroxetine hydrochloride and which occurred at a rate at least twice that of placebo, were: emotional lability (including suicidal ideation, suicide attempt, mood changes, and tearfulness), nervousness, dizziness, nausea, and abdominal pain (see Discontinuation of Treatment With PAXIL CR).

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

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

ADVERSE REACTIONS

The information included under the "Adverse Findings Observed in Short-Term, Placebo-Controlled Trials With PAXIL CR" subsection of ADVERSE REACTIONS is based on data from 11 placebo-controlled clinical trials. Three of these studies were conducted in patients with major depressive disorder, 3 studies were done in patients with panic disorder, 1 study was conducted in patients with social anxiety disorder, and 4 studies were done in female patients with PMDD. Two of the studies in major depressive disorder, which enrolled patients in the age range 18 to 65 years, are pooled. Information from a third study of major depressive disorder, which focused on elderly patients (60 to 88 years), is presented separately as is the information from the panic disorder studies and the information from the PMDD studies. Information on additional adverse events associated with PAXIL CR and the immediate-release formulation of paroxetine hydrochloride is included in a separate subsection (see Other Events).

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials With PAXIL CR:

Adverse Events Associated With Discontinuation of Treatment: ***Major Depressive Disorder:*** Ten percent (21/212) of patients treated with PAXIL CR discontinued treatment due to an adverse event in a pool of 2 studies of patients with major depressive disorder. The most common events (≥1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate approximately twice or greater for PAXIL CR compared to placebo) included the following:

	PAXIL CR (n=212)	Placebo (n=211)
Nausea	3.7%	0.5%
Asthenia	1.9%	0.5%
Dizziness	1.4%	0.0%
Somnolence	1.4%	0.0%

In a placebo-controlled study of elderly patients with major depressive disorder, 13% (13/104) of patients treated with PAXIL CR discontinued due to an adverse event. Events meeting the above criteria included the following:

	PAXIL CR (n=104)	Placebo (n=109)
Nausea	2.9%	0.0%
Headache	1.9%	0.9%
Depression	1.9%	0.0%
LFT's abnormal	1.9%	0.0%

Panic Disorder: Eleven percent (50/444) of patients treated with PAXIL CR in panic disorder studies discontinued treatment due to an adverse event. Events meeting the above criteria included the following:

	PAXIL CR (n=444)	Placebo (n=445)
Nausea	2.9%	0.4%
Insomnia	1.8%	0.0%
Headache	1.4%	0.2%
Asthenia	1.1%	0.0%

Social Anxiety Disorder: Three percent (5/186) of patients treated with PAXIL CR in the social anxiety disorder study discontinued treatment due to an adverse event. Events meeting the above criteria included the following:

	PAXIL CR (n=186)	Placebo (n=184)
Nausea	2.2%	0.5%
Headache	1.6%	0.5%
Diarrhea	1.1%	0.5%

Premenstrual Dysphoric Disorder: Spontaneously reported adverse events were monitored in studies of both continuous and intermittent dosing of PAXIL CR in the treatment of PMDD. Generally, there were few differences in the adverse event profiles of the 2 dosing regimens. Thirteen percent (88/681) of patients treated with PAXIL CR in PMDD studies of continuous dosing discontinued treatment due to an adverse event.

The most common events (≥1%) associated with discontinuation in either group treated with PAXIL CR with an incidence rate that is at least twice that of placebo in PMDD trials that employed a continuous dosing regimen are shown in the following table. This table also shows those events that were dose dependent (indicated with an asterisk) as defined as events having an incidence rate with 25 mg of PAXIL CR that was at least twice that with 12.5 mg of PAXIL CR (as well as the placebo group).

	PAXIL CR 25 mg (n=348)	PAXIL CR 12.5 mg (n=333)	Placebo (n=349)
TOTAL	15%	9.9%	6.3%
Nausea*	6.0%	2.4%	0.9%
Asthenia	4.9%	3.0%	1.4%
Somnolence*	4.3%	1.8%	0.3%
Insomnia	2.3%	1.5%	0.0%
Concentration Impaired*	2.0%	0.6%	0.3%
Dry mouth*	2.0%	0.6%	0.3%
Dizziness*	1.7%	0.6%	0.6%
Decreased Appetite*	1.4%	0.6%	0.0%
Sweating*	1.4%	0.0%	0.3%
Tremor*	1.4%	0.3%	0.0%
Yawn*	1.1%	0.0%	0.0%
Diarrhea	0.9%	1.2%	0.0%

* Events considered to be dose dependent are defined as events having an incidence rate with 25 mg of PAXIL CR that was at least twice that with 12.5 mg of PAXIL CR (as well as the placebo group).

Commonly Observed Adverse Events: ***Major Depressive Disorder:*** The most commonly observed adverse events associated with the use of PAXIL CR in a pool of 2 trials (incidence of 5.0% or greater and incidence for PAXIL CR at least twice that for placebo, derived from Table 1) were: Abnormal ejaculation, abnormal vision, constipation, decreased libido, diarrhea, dizziness, female genital disorders, nausea, somnolence, sweating, trauma, tremor, and yawning.

Using the same criteria, the adverse events associated with the use of PAXIL CR in a study of elderly patients with major depressive disorder were: Abnormal ejaculation, constipation, decreased appetite, dry mouth, impotence, infection, libido decreased, sweating, and tremor.

Panic Disorder: In the pool of panic disorder studies, the adverse events meeting these criteria were: Abnormal ejaculation, somnolence, impotence, libido decreased, tremor, sweating, and female genital disorders (generally anorgasmia or difficulty achieving orgasm).

Social Anxiety Disorder: In the social anxiety disorder study, the adverse events meeting these criteria were: Nausea, asthenia, abnormal ejaculation, sweating, somnolence, impotence, insomnia, and libido decreased.

Premenstrual Dysphoric Disorder: The most commonly observed adverse events associated with the use of PAXIL CR either during continuous dosing or luteal phase dosing (incidence of 5% or greater and incidence for PAXIL CR at least twice that for placebo, derived from Table 5) were: Nausea, asthenia, libido decreased, somnolence, insomnia, female genital disorders, sweating, dizziness, diarrhea, and constipation.

In the luteal phase dosing PMDD trial, which employed dosing of 12.5 mg/day or 25 mg/day of PAXIL CR limited to the 2 weeks prior to the onset of menses over 3 consecutive menstrual cycles, adverse events were evaluated during the first 14 days of each off-drug phase. When the 3 off-drug phases were combined, the following adverse events were reported at an incidence of 2% or greater for PAXIL CR and were at least twice the rate of that reported for placebo: infection (5.3% versus 2.5%), depression (2.8% versus 0.8%), insomnia (2.4% versus 0.8%), sinusitis (2.4% versus 0%), and asthenia (2.0% versus 0.8%).

Incidence in Controlled Clinical Trials: Table 1 enumerates adverse events that occurred at an incidence of 1% or more among patients treated with PAXIL CR, aged 18 to 65, who participated in 2 short-term (12-week) placebo-controlled trials in major depressive disorder in which patients were dosed in a range of 25 mg to 62.5 mg/day. Table 2 enumerates adverse events reported at an incidence of 5% or greater among elderly patients (ages 60 to 88) treated with PAXIL CR who participated in a short-term (12-week) placebo-controlled trial in major depressive disorder in which patients were dosed in a range of 12.5 mg to 50 mg/day. Table 3 enumerates adverse events reported at an incidence of 1% or greater among patients (19 to 72 years) treated with PAXIL CR who participated in short-term (10-week) placebo-controlled trials in panic disorder in which patients were dosed in a range of 12.5 mg to 75 mg/day. Table 4 enumerates adverse events reported at an incidence of 1% or greater among adult patients treated with PAXIL CR who participated in a short-term (12-week), double-blind, placebo-controlled trial in social anxiety disorder in which patients were dosed in a range of 12.5 to 37.5 mg/day. Table 5 enumerates adverse events that occurred at an incidence of 1% or more among patients treated with PAXIL CR who participated in three, 12-week, placebo-controlled trials in PMDD in which patients were dosed at 12.5 mg/day or 25 mg/day and in one 12-week placebo-controlled trial in which patients were dosed for 2 weeks prior to the onset of menses (luteal phase dosing) at 12.5 mg/day or 25 mg/day. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Table 1. Treatment-Emergent Adverse Events Occurring in ≥1% of Patients Treated With PAXIL CR in a Pool of 2 Studies in Major Depressive Disorder[1,2]

Body System/Adverse Event	% Reporting Event	
	PAXIL CR (n=212)	Placebo (n=211)
Body as a Whole		
Headache	27%	20%
Asthenia	14%	9%
Infection[3]	8%	5%
Abdominal Pain	7%	4%
Back Pain	5%	3%
Trauma[4]	5%	1%
Pain[5]	3%	1%
Allergic Reaction[6]	2%	1%
Cardiovascular System		
Tachycardia	1%	0%
Vasodilatation[7]	2%	0%
Digestive System		
Nausea	22%	10%
Diarrhea	18%	7%
Dry Mouth	15%	8%
Constipation	10%	4%
Flatulence	6%	4%
Decreased Appetite	4%	2%
Vomiting	2%	1%
Nervous System		
Somnolence	22%	8%
Insomnia	17%	9%
Dizziness	14%	4%
Libido Decreased	7%	3%
Tremor	7%	1%
Hypertonia	3%	1%
Paresthesia	3%	1%
Agitation	2%	1%
Confusion	1%	0%
Respiratory System		
Yawn	5%	0%
Rhinitis	4%	1%
Cough Increased	2%	1%
Bronchitis	1%	0%
Skin and Appendages		
Sweating	6%	2%
Photosensitivity	2%	0%
Special Senses		
Abnormal Vision[8]	5%	1%
Taste Perversion	2%	0%
Urogenital System		
Abnormal Ejaculation[9,10]	26%	1%
Female Genital Disorder[9,11]	10%	<1%
Impotence[9]	5%	3%
Urinary Tract Infection	3%	1%
Menstrual Disorder[9]	2%	<1%
Vaginitis[9]	2%	0%

1. Adverse events for which the PAXIL CR reporting incidence was less than or equal to the placebo incidence are not included. These events are: Abnormal dreams, anxiety, arthralgia, depersonalization, dysmenorrhea, dyspepsia, hyperkinesia, increased appetite, myalgia, nervousness, pharyngitis, purpura, rash, respiratory disorder, sinusitis, urinary frequency, and weight gain.
2. <1% means greater than zero and less than 1%.
3. Mostly flu.
4. A wide variety of injuries with no obvious pattern.
5. Pain in a variety of locations with no obvious pattern.
6. Most frequently seasonal allergic symptoms.
7. Usually flushing.
8. Mostly blurred vision.
9. Based on the number of males or females.
10. Mostly anorgasmia or delayed ejaculation.
11. Mostly anorgasmia or delayed orgasm.

Table 2. Treatment-Emergent Adverse Events Occurring in ≥5% of Patients Treated With PAXIL CR in a Study of Elderly Patients With Major Depressive Disorder[1,2]

Body System/Adverse Event	% Reporting Event	
	PAXIL CR (n=104)	Placebo (n=109)
Body as a Whole		
Headache	17%	13%
Asthenia	15%	14%
Trauma	8%	5%
Infection	6%	2%
Digestive System		
Dry Mouth	18%	7%
Diarrhea	15%	9%
Constipation	13%	5%
Dyspepsia	13%	10%
Decreased Appetite	12%	5%
Flatulence	8%	7%
Nervous System		
Somnolence	21%	12%
Insomnia	10%	8%
Dizziness	9%	5%
Libido Decreased	8%	<1%
Tremor	7%	0%
Skin and Appendages		
Sweating	10%	<1%
Urogenital System		
Abnormal Ejaculation[3,4]	17%	3%
Impotence[3]	9%	3%

1. Adverse events for which the PAXIL CR reporting incidence was less than or equal to the placebo incidence are not included. These events are nausea and respiratory disorder.
2. <1% means greater than zero and less than 1%.
3. Based on the number of males.
4. Mostly anorgasmia or delayed ejaculation.

Table 3. Treatment-Emergent Adverse Events Occurring in ≥1% of Patients Treated With PAXIL CR in a Pool of 3 Panic Disorder Studies[1,2]

Body System/Adverse Event	% Reporting Event	
	PAXIL CR (n=444)	Placebo (n=445)
Body as a Whole		
Asthenia	15%	10%
Abdominal Pain	6%	4%
Trauma[3]	5%	4%
Cardiovascular System		
Vasodilation[4]	3%	2%
Digestive System		
Nausea	23%	17%

continued

Table 3. Treatment-Emergent Adverse Events Occurring in ≥1% of Patients Treated With PAXIL CR in a Pool of 3 Panic Disorder Studies[1,2] *(continued)*

Body System/Adverse Event	% Reporting Event	
	PAXIL CR (n=444)	Placebo (n=445)
Digestive System *(cont'd)*		
Dry Mouth	13%	9%
Diarrhea	12%	9%
Constipation	9%	6%
Decreased Appetite	8%	6%
Metabolic/Nutritional Disorders		
Weight Loss	1%	0%
Musculoskeletal System		
Myalgia	5%	3%
Nervous System		
Insomnia	20%	11%
Somnolence	20%	9%
Libido Decreased	9%	4%
Nervousness	8%	7%
Tremor	8%	2%
Anxiety	5%	4%
Agitation	3%	2%
Hypertonia[5]	2%	<1%
Myoclonus	2%	<1%
Respiratory System		
Sinusitis	8%	5%
Yawn	3%	0%
Skin and Appendages		
Sweating	7%	2%
Special Senses		
Abnormal Vision[6]	3%	<1%
Urogenital System		
Abnormal Ejaculation[7,8]	27%	3%
Impotence[7]	10%	1%
Female Genital Disorders[9,10]	7%	1%
Urinary Frequency	2%	<1%
Urination Impaired	2%	<1%
Vaginitis[9]	1%	<1%

1. Adverse events for which the reporting rate for PAXIL CR was less than or equal to the placebo rate are not included. These events are: Abnormal dreams, allergic reaction, back pain, bronchitis, chest pain, concentration impaired, confusion, cough increased, depression, dizziness, dysmenorrhea, dyspepsia, fever, flatulence, headache, increased appetite, infection, menstrual disorder, migraine, pain, paresthesia, pharyngitis, respiratory disorder, rhinitis, tachycardia, taste perversion, thinking abnormal, urinary tract infection, and vomiting.
2. <1% means greater than zero and less than 1%.
3. Various physical injuries.
4. Mostly flushing.
5. Mostly muscle tightness or stiffness.
6. Mostly blurred vision.
7. Based on the number of male patients.
8. Mostly anorgasmia or delayed ejaculation.
9. Based on the number of female patients.
10. Mostly anorgasmia or difficulty achieving orgasm.

Table 4. Treatment-Emergent Adverse Effects Occurring in ≥1% of Patients Treated With PAXIL CR in a Social Anxiety Disorder Study[1,2]

Body System/Adverse Event	% Reporting Event	
	PAXIL CR (n=186)	Placebo (n=184)
Body as a Whole		
Headache	23%	17%
Asthenia	18%	7%
Abdominal Pain	5%	4%
Back Pain	4%	1%
Trauma[3]	3%	<1%
Allergic Reaction[4]	2%	<1%
Chest Pain	1%	<1%
Cardiovascular System		
Hypertension	2%	0%
Migraine	2%	1%
Tachycardia	2%	1%
Digestive System		
Nausea	22%	6%
Diarrhea	9%	8%
Constipation	5%	2%
Dry Mouth	3%	2%
Dysoepsia	2%	<1%
Decreased Appetite	1%	<1%
Tooth Disorder	1%	0%
Metabolic/Nutritional Disorders		
Weight Gain	3%	1%
Weight Loss	1%	0%
Nervous System		
Insomnia	9%	4%
Somnolence	9%	4%
Libido Decreased	8%	1%
Dizziness	7%	4%
Tremor	4%	2%
Anxiety	2%	1%
Concentration Impaired	2%	0%
Depression	2%	1%
Myoclonus	1%	<1%
Paresthesia	1%	<1%
Respiratory System		
Yawn	2%	0%
Skin and Appendages		
Sweating	14%	3%
Eczema	1%	0%
Special Senses		
Abnormal Vision[5]	2%	0%
Abnormality of Accommodation	2%	0%
Urogenital System		
Abnormal Ejaculation[6,7]	15%	1%
Impotence[6]	9%	0%
Female Genital Disorders[8,9]	3%	0%

1. Adverse events for which the reporting rate for PAXIL CR was less than or equal to the placebo rate are not included. These events are: Dysmenorrhea, flatulence, gastroenteritis, hypertonia, infection, pain, pharyngitis, rash, respiratory disorder, rhinitis, and vomiting.
2. <1% means greater than zero and less than 1%.
3. Various physical injuries.
4. Most frequently seasonal allergic symptoms.
5. Mostly blurred vision.
6. Based on the number of male patients.
7. Mostly anorgasmia or delayed ejaculation.
8. Based on the number of female patients.
9. Mostly anorgasmia or difficulty achieving orgasm.

Table 5. Treatment-Emergent Adverse Events Occurring in ≥1% of Patients Treated With PAXIL CR in a Pool of 3 Premenstrual Dysphoric Disorder Studies With Continuous Dosing or in 1 Premenstrual Dysphoric Disorder Study With Luteal Phase Dosing[1,2,3]

	% Reporting Event			
	Continuous Dosing		Luteal Phase Dosing	
Body System/Adverse Event	PAXIL CR (n=681)	Placebo (n=349)	PAXIL CR (n=246)	Placebo (n=120)
Body as a Whole				
Asthenia	17%	6%	15%	4%
Headache	15%	12%	—	—
Infection	6%	4%	—	—
Abdominal pain	—	—	3%	0%
Cardiovascular System				
Migraine	1%	<1%	—	—
Digestive System				
Nausea	17%	7%	18%	2%
Diarrhea	6%	2%	6%	0%
Constipation	5%	1%	2%	<1%
Dry Mouth	4%	2%	2%	<1%
Increased Appetite	3%	<1%	—	—
Decreased Appetite	2%	<1%	2%	0%
Dyspepsia	2%	1%	2%	2%
Gingivitis	—	—	1%	0%
Metabolic and Nutritional Disorders				
Generalized Edema	—	—	1%	<1%
Weight Gain	—	—	1%	<1%
Musculoskeletal System				
Arthralgia	2%	1%	—	—
Nervous System				
Libido Decreased	12%	5%	9%	6%
Somnolence	9%	2%	3%	<1%
Insomnia	8%	2%	7%	3%
Dizziness	7%	3%	6%	3%
Tremor	4%	<1%	5%	0%
Concentration Impaired	3%	<1%	1%	0%
Nervousness	2%	<1%	3%	2%
Anxiety	2%	1%	—	—
Lack of Emotion	2%	<1%	—	—
Depression	—	—	2%	<1%
Vertigo	—	—	2%	<1%
Abnormal Dreams	1%	<1%	—	—
Amnesia	—	—	1%	0%
Respiratory System				
Sinusitis	—	—	4%	2%
Yawn	2%	<1%	—	—
Bronchitis	—	—	2%	0%
Cough Increased	1%	<1%	—	—
Skin and Appendages				
Sweating	7%	<1%	6%	<1%
Special Senses				
Abnormal Vision	—	—	1%	0%
Urogenital System				
Female Genital Disorders[4]	8%	1%	2%	0%
Menorrhagia	1%	<1%	—	—
Vaginal Moniliasis	1%	<1%	—	—
Menstrual Disorder	—	—	1%	0%

1. Adverse events for which the reporting rate of PAXIL CR was less than or equal to the placebo rate are not included. These events for continuous dosing are: Abdominal pain, back pain, pain, trauma, weight gain, myalgia, pharyngitis, respiratory disorder, rhinitis, sinusitis, pruritus, dysmenorrhea, menstrual disorder, urinary tract infection, and vomiting. The events for luteal phase dosing are: Allergic reaction, back pain, headache, infection, pain, trauma, myalgia, anxiety, pharyngitis, respiratory disorder, cystitis, and dysmenorrhea.
2. <1% means greater than zero and less than 1%.
3. The luteal phase and continuous dosing PMDD trials were not designed for making direct comparisons between the 2 dosing regimens. Therefore, a comparison between the 2 dosing regimens of the PMDD trials of incidence rates shown in Table 5 should be avoided.
4. Mostly anorgasmia or difficulty achieving orgasm.

Dose Dependency of Adverse Events: The following table shows results in PMDD trials of common adverse events, defined as events with an incidence of ≥1% with 25 mg of PAXIL CR that was at least twice that with 12.5 mg of PAXIL CR and with placebo.

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

Common Adverse Event	PAXIL CR 25 mg (n=348)	PAXIL CR 12.5 mg (n=333)	Placebo (n=349)
Sweating	8.9%	4.2%	0.9%
Tremor	6.0%	1.5%	0.3%
Concentration Impaired	4.3%	1.5%	0.6%
Yawn	3.2%	0.9%	0.3%
Paresthesia	1.4%	0.3%	0.3%
Hyperkinesia	1.1%	0.3%	0.0%
Vaginitis	1.1%	0.3%	0.3%

A comparison of adverse event rates in a fixed-dose study comparing immediate-release paroxetine with placebo in the treatment of major depressive disorder revealed a clear dose dependency for some of the more common adverse events associated with the use of immediate-release paroxetine.

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

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

The percentage of patients reporting symptoms of sexual dysfunction in the pool of 2 placebo-controlled trials in nonelderly patients with major depressive disorder, in the pool of 3 placebo-controlled trials in patients with panic disorder, in the placebo-controlled trial in patients with social anxiety disorder, and in the intermittent dosing and the pool of 3 placebo-controlled continuous dosing trials in female patients with PMDD are as follows:

	Major Depressive Disorder		Panic Disorder		Social Anxiety Disorder		PMDD Continuous Dosing		PMDD Luteal Phase Dosing	
	PAXIL CR	Placebo	PAXIL CR	Placebo	PAXIL CR	Placebo	PAXIL CR	Placebo	PAXIL CR	Placebo
n (males)	78	78	162	194	88	97	n/a	n/a	n/a	n/a
Decreased Libido	10%	5%	9%	6%	13%	1%	n/a	n/a	n/a	n/a
Ejaculatory Disturbance	26%	1%	27%	3%	15%	1%	n/a	n/a	n/a	n/a
Impotence	5%	3%	10%	1%	9%	0%	n/a	n/a	n/a	n/a
n (females)	134	133	282	251	98	87	681	349	246	120
Decreased Libido	4%	2%	8%	2%	4%	1%	12%	5%	9%	6%
Orgasmic Disturbance	10%	<1%	7%	1%	3%	0%	8%	1%	2%	0%

There are no adequate, controlled studies examining sexual dysfunction with paroxetine treatment.

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

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

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

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

Liver Function Tests: In a pool of 2 placebo-controlled clinical trials, patients treated with PAXIL CR or placebo exhibited abnormal values on liver function tests at comparable rates. In particular, the controlled-release paroxetine-versus-placebo comparisons for alkaline phosphatase, SGOT, SGPT, and bilirubin revealed no differences in the percentage of patients with marked abnormalities.

In a study of elderly patients with major depressive disorder, 3 of 104 patients treated with PAXIL CR and none of 109 placebo patients experienced liver transaminase elevations of potential clinical concern.

Two of the patients treated with PAXIL CR dropped out of the study due to abnormal liver function tests; the third patient experienced normalization of transaminase levels with continued treatment. Also, in the pool of 3 studies of patients with panic disorder, 4 of 444 patients treated with PAXIL CR and none of 445 placebo patients experienced liver transaminase elevations of potential clinical concern. Elevations in all 4 patients decreased substantially after discontinuation of PAXIL CR. The clinical significance of these findings is unknown.

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

Hallucinations: In pooled clinical trials of immediate-release paroxetine hydrochloride, hallucinations were observed in 22 of 9089 patients receiving drug and in 4 of 3187 patients receiving placebo.

Other Events Observed During the Clinical Development of Paroxetine: The following adverse events were reported during the clinical development of PAXIL CR and/or the clinical development of the immediate-release formulation of paroxetine.

Adverse events for which frequencies are provided below occurred in clinical trials with the controlled-release formulation of paroxetine. During its premarketing assessment in major depressive disorder, panic disorder, social anxiety disorder, and PMDD multiple doses of PAXIL CR were administered to 1,627 patients in phase 3 double-blind, controlled, outpatient studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a COSTART-based dictionary. The frequencies presented, therefore, represent the proportion of the 1,627 patients exposed to PAXIL CR who experienced an event of the type cited on at least 1 occasion while receiving PAXIL CR. All reported events are included except those already listed in Tables 1 through 5 and those events where a drug cause was remote. If the COSTART term for an event was so general as to be uninformative, it was deleted or, when possible, replaced with a more informative term. It is important to emphasize that although the events reported occurred during treatment with paroxetine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: Frequent adverse events are those occurring on 1 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 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients.

Adverse events for which frequencies are not provided occurred during the premarketing assessment of immediate-release paroxetine in phase 2 and 3 studies of major depressive disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder, and posttraumatic stress disorder. The conditions and duration of exposure to immediate-release paroxetine varied greatly and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose and titration studies. Only those events not previously listed for controlled-release paroxetine are included. The extent to which these events may be associated with PAXIL CR is unknown.

Events are listed alphabetically within the respective body system. Events of major clinical importance are also described in the PRECAUTIONS section.

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

Cardiovascular System: Infrequent were angina pectoris, bradycardia, hematoma, hypertension, hypotension, palpitation, postural hypotension, supraventricular tachycardia, syncope; rare were bundle branch block; also observed were arrhythmia nodal, atrial fibrillation, cerebrovascular accident, congestive heart failure, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, vascular headache, ventricular extrasystoles.

Digestive System: Infrequent were bruxism, dysphagia, eructation, gastritis, gastroenteritis, gastroesophageal reflux, gingivitis, hemorrhoids, liver function test abnormal, melena, pancreatitis, rectal hemorrhage, toothache, ulcerative stomatitis; rare were colitis, glossitis, gum hyperplasia, hepatosplenomegaly, increased salivation, intestinal obstruction, peptic ulcer, stomach ulcer, throat tightness; also observed were aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, jaundice, mouth ulceration, salivary gland enlargement, sialadenitis, stomatitis, tongue discoloration, tongue edema.

Endocrine System: Infrequent were ovarian cyst, testes pain; rare were diabetes mellitus, hyperthyroidism; also observed were goiter, hypothyroidism, thyroiditis.

Hemic and Lymphatic System: Infrequent were anemia, eosinophilia, hypochromic anemia, leukocytosis, leukopenia, lymphadenopathy, purpura; rare were thrombocytopenia; also observed were anisocytosis, basophilia, bleeding time increased, lymphedema, lymphocytosis, lymphopenia, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia.

Metabolic and Nutritional Disorders: Infrequent were generalized edema, hyperglycemia, hypokalemia, peripheral edema, SGOT increased, SGPT increased, thirst; rare were bilirubinemia, dehydration, hyperkalemia, obesity; also observed were alkaline phosphatase increased, BUN increased, creatinine phosphokinase increased, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, hyperphosphatemia, hypocalcemia, hypoglycemia, hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased.

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

Nervous System: Frequent were depression; infrequent were amnesia, convulsion, depersonalization, dystonia, emotional lability, hallucinations, hyperkinesia, hypesthesia, hypokinesia, incoordination, libido increased, neuralgia, neuropathy, nystagmus, paralysis, vertigo; rare were ataxia, coma, diplopia, dyskinesia, hostility, paranoid reaction, torticollis, withdrawal syndrome; also observed were abnormal gait, akathisia, akinesia, aphasia, choreoathetosis, circumoral paresthesia, delirium, delusions, dysarthria, euphoria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hyperalgesia, irritability, manic reaction, manic-depressive reaction, meningitis, myelitis, peripheral neuritis, psychosis, psychotic depression, reflexes decreased, reflexes increased, stupor, trismus.

Respiratory System: Frequent were pharyngitis; infrequent were asthma, dyspnea, epistaxis, laryngitis, pneumonia; rare were stridor; also observed were dysphonia, emphysema, hemoptysis, hiccups, hyperventilation, lung fibrosis, pulmonary edema, respiratory flu, sputum increased.

Skin and Appendages: Frequent were rash; infrequent were acne, alopecia, dry skin, eczema, pruritus, urticaria; rare were exfoliative dermatitis, furunculosis, pustular rash, seborrhea; also observed were angioedema, ecchymosis, erythema multiforme, erythema nodosum, hirsutism, maculopapular rash, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash.

Special Senses: Infrequent were conjunctivitis, earache, keratoconjunctivitis, mydriasis, photophobia, retinal hemorrhage, tinnitus; rare were blepharitis, visual field defect; also observed were amblyopia, aniscoria, blurred vision, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, glaucoma, hyperacusis, night blindness, parosmia, ptosis, taste loss.

Urogenital System: Frequent were dysmenorrhea*; infrequent were albuminuria, amenorrhea*, breast pain*, cystitis, dysuria, prostatitis*, urinary retention; rare were breast enlargement*, breast neoplasm*, female lactation, hematuria, kidney calculus, metrorrhagia*, nephritis, nocturia, pregnancy and puerperal disorders*, salpingitis, urinary incontinence, uterine fibroids enlarged*; also observed were breast atrophy, ejaculatory disturbance, endometrial disorder, epididymitis, fibrocystic breast, leukorrhea, mastitis, oliguria, polyuria, pyuria, urethritis, urinary casts, urinary urgency, urolith, uterine spasm, vaginal hemorrhage.

*Based on the number of men and women as appropriate.

Postmarketing Reports: Voluntary reports of adverse events in patients taking immediate-release paroxetine hydrochloride that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome–like events, serotonin syndrome; 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; status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic syndromes (such as Henoch-Schönlein purpura). There has been a case report of an elevated phenytoin level after 4 weeks of immediate-release paroxetine and phenytoin coadministration. There has been a case report of severe hypotension when immediate-release paroxetine was added to chronic metoprolol treatment.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: PAXIL CR is not a controlled substance.

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

OVERDOSAGE

Human Experience: Since the introduction of immediate-release paroxetine hydrochloride in the United States, 342 spontaneous cases of deliberate or accidental overdosage during paroxetine treatment have been reported worldwide (circa 1999). These include overdoses with paroxetine alone and in combination with other substances. Of these, 48 cases were fatal and of the fatalities, 17 appeared to involve paroxetine alone. Eight fatal cases that 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 2,000 mg of paroxetine (33 times the maximum recommended daily dose) in a patient who recovered.

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

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

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

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

A specific caution involves patients taking or recently having taken paroxetine who might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (see PRECAUTIONS—*Drugs Metabolized by Cytochrome CYP2D6*).

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

DOSAGE AND ADMINISTRATION

Major Depressive Disorder: ***Usual Initial Dosage:*** PAXIL CR should be administered as a single daily dose, usually in the morning, with or without food. The recommended initial dose is 25 mg/day. Patients were dosed in a range of 25 mg to 62.5 mg/day in the clinical trials demonstrating the effectiveness of PAXIL CR in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, the full effect may be delayed. Some patients not responding to a 25-mg dose may benefit from dose increases, in 12.5-mg/day increments, up to a maximum of 62.5 mg/day. Dose changes should occur at intervals of at least 1 week.

Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be swallowed whole.

Maintenance Therapy: There is no body of evidence available to answer the question of how long the patient treated with PAXIL CR should remain on it. It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Whether the dose of an antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

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

Panic Disorder: ***Usual Initial Dosage:*** PAXIL CR should be administered as a single daily dose, usually in the morning. Patients should be started on 12.5 mg/day. Dose changes should occur in 12.5-mg/day increments and at intervals of at least 1 week. Patients were dosed in a range of 12.5 to 75 mg/day in the clinical trials demonstrating the effectiveness of PAXIL CR. The maximum dosage should not exceed 75 mg/day.

Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be swallowed whole.

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

Social Anxiety Disorder: ***Usual Initial Dosage:*** PAXIL CR should be administered as a single daily dose, usually in the morning, with or without food. The recommended initial dose is 12.5 mg/day. Patients were dosed in a range of 12.5 mg to 37.5 mg/day in the clinical trial demonstrating the effectiveness of PAXIL CR in the treatment of social anxiety disorder. If the dose is increased, this should occur at intervals of at least 1 week, in increments of 12.5 mg/day, up to a maximum of 37.5 mg/day.

Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be swallowed whole.

Maintenance Therapy: There is no body of evidence available to answer the question of how long the patient treated with PAXIL CR should remain on it. Although the efficacy of PAXIL CR beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials, social anxiety disorder is recognized as a chronic condition, and it is reasonable to consider continuation of treatment for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Premenstrual Dysphoric Disorder: ***Usual Initial Dosage:*** PAXIL CR should be administered as a single daily dose, usually in the morning, with or without food. PAXIL CR may be administered either daily throughout the menstrual cycle or limited to the luteal phase of the menstrual cycle, depending on physician assessment. The recommended initial dose is 12.5 mg/day. In clinical trials, both 12.5 mg/day and 25 mg/day were shown to be effective. Dose changes should occur at intervals of at least 1 week.

Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be swallowed whole.

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

Special Populations: ***Treatment of Pregnant Women During the Third Trimester:*** Neonates exposed to PAXIL CR and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see WARNINGS). When treating pregnant women with paroxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering paroxetine in the third trimester.

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

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

Discontinuation of Treatment With PAXIL CR: Symptoms associated with discontinuation of immediate-release paroxetine hydrochloride or PAXIL CR have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment, regardless of the indication for which PAXIL CR is being prescribed. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

HOW SUPPLIED

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

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

25-mg pink tablets, engraved with PAXIL CR and 25
NDC 0029-3207-13 Bottles of 30

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

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

PAXIL CR is a registered trademark of GlaxoSmithKline.
GEOMATRIX is a trademark of Jago Pharma, Muttenz, Switzerland.

Medication Guide
PAXIL CR® (PAX-il) (paroxetine hydrochloride) Controlled-Release Tablets
About Using Antidepressants in Children and Teenagers

What is the most important information I should know if my child is being prescribed an antidepressant?

Parents or guardians need to think about 4 important things when their child is prescribed an antidepressant:

1. There is a risk of suicidal thoughts or actions
2. How to try to prevent suicidal thoughts or actions in your child
3. You should watch for certain signs if your child is taking an antidepressant
4. There are benefits and risks when using antidepressants

1. There Is a Risk of Suicidal Thoughts or Actions

Children and teenagers sometimes think about suicide, and many report trying to kill themselves.

Antidepressants increase suicidal thoughts and actions in some children and teenagers. But suicidal thoughts and actions can also be caused by depression, a serious medical condition that is commonly treated with antidepressants. Thinking about killing yourself or trying to kill yourself is called *suicidality* or *being suicidal.*

A large study combined the results of 24 different studies of children and teenagers with depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an antidepressant for 1 to 4 months. ***No one committed suicide in these studies,*** but some patients became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4 out of every 100 patients became suicidal.

For some children and teenagers, the risks of suicidal actions may be especially high. These include patients with

- Bipolar illness (sometimes called manic-depressive illness)
- A family history of bipolar illness
- A personal or family history of attempting suicide

If any of these are present, make sure you tell your healthcare provider before your child takes an antidepressant.

2. How to Try to Prevent Suicidal Thoughts and Actions

To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her or his moods or actions, especially if the changes occur suddenly. Other important people in your child's life can help by paying attention as well (e.g., your child, brothers and sisters, teachers, and other important people). The changes to look out for are listed in Section 3, on what to watch for.

Whenever an antidepressant is started or its dose is changed, pay close attention to your child.

After starting an antidepressant, your child should generally see his or her healthcare provider:

- Once a week for the first 4 weeks
- Every 2 weeks for the next 4 weeks
- After taking the antidepressant for 12 weeks
- After 12 weeks, follow your healthcare provider's advice about how often to come back
- More often if problems or questions arise (see Section 3)

You should call your child's healthcare provider between visits if needed.

3. You Should Watch for Certain Signs if Your Child Is Taking an Antidepressant

Contact your child's healthcare provider ***right away*** if your child exhibits any of the following signs for the first time, or if they seem worse, or worry you, your child, or your child's teacher:

- Thoughts about suicide or dying
- Attempts to commit suicide
- New or worse depression
- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Difficulty sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry, or violent
- Acting on dangerous impulses
- An extreme increase in activity and talking
- Other unusual changes in behavior or mood

Never let your child stop taking an antidepressant without first talking to his or her healthcare provider. Stopping an antidepressant suddenly can cause other symptoms.

4. There Are Benefits and Risks When Using Antidepressants

Antidepressants are used to treat depression and other illnesses. Depression and other illnesses can lead to suicide. In some children and teenagers, treatment with an antidepressant increases suicidal thinking or actions. It is important to discuss all the risks of treating depression and also the risks of not treating it. You and your child should discuss all treatment choices with your healthcare provider, not just the use of antidepressants.

Other side effects can occur with antidepressants (see section below).

Of all the antidepressants, only fluoxetine (Prozac®)* has been FDA approved to treat pediatric depression.

For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine (Prozac®)*, sertraline (Zoloft®)*, fluvoxamine, and clomipramine (Anafranil®)*.

Your healthcare provider may suggest other antidepressants based on the past experience of your child or other family members.

Is this all I need to know if my child is being prescribed an antidepressant?

No. This is a warning about the risk for suicidality. Other side effects can occur with antidepressants. Be sure to ask your healthcare provider to explain all the side effects of the particular drug he or she is prescribing. Also ask about drugs to avoid when taking an antidepressant. Ask your healthcare provider or pharmacist where to find more information.

*The following are registered trademarks of their respective manufacturers: Prozac®/Eli Lilly and Company; Zoloft®/Pfizer Pharmaceuticals; Anafranil®/Mallinckrodt Inc.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

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