CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-031/S-030

Name:	Paxil Tablets (paroxetine hydrochloride)
Sponsor:	SmithKline Beecham Pharmaceuticals
Approval Date:	September 28, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-031/S-030

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-031/S-030

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-031/[ ]/S-031
NDA 20-710/[ ]/S-009

SmithKline Beecham Pharmaceuticals
Attention: Thomas Kline
Assistant Director, U.S. Regulatory Affairs
1250 S. Collegeville Road, P.O. Box 5089
Collegeville, PA 19426-0989

Dear Mr. Kline:

Please refer to your supplemental new drug applications [ ] October 3, 2000 (NDAs 20-031/S-031 and 20-710/S-009), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paxil (paroxetine hydrochloride) Immediate Release Tablets (NDA 20-031) and Oral Suspension (NDA 20-710).

We additionally refer to [ ] an Agency approvable letter dated November 3, 2000 for NDAs 20-031/S-031 and 20-710/S-009, and to an Agency approval letter dated May 11, 1999 for 20-031/S-023.

We acknowledge receipt of your submission dated December 15, 2000, providing for a response to our November 3, 2000, Agency letter.

These supplemental new drug applications provide for the following revisions to the prescriber labeling:

[ ]

1. [redacted]
2. [redacted]
3. [redacted]

20-031/S-031 and 20-710/S-009
Revisions to the **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS** sections of labeling to describe a potential interaction between paroxetine and thioridazine.

We have completed the review of supplemental applications 20-031/S-031 and 20-710/S-009 and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted December 15, 2000/Label Code LX18A), which incorporates all of the revisions listed. Accordingly, these supplemental applications are approved effective on the date of this letter.

Labeling changes of the kind which you have proposed under supplemental applications 20-031/S-031 and 20-710/S-009 are permitted by section 314.70(c) of the regulations to be instituted prior to approval of these supplements. It is understood that the changes, described in the above NDA supplements, have been made.

Additionally, we note that the revisions proposed under supplemental applications [ ] were incorporated in the approval of 20-031/S-023 (Agency approval letter dated May 11, 1999), and therefore these applications are superceded by the approval of 20-031/S-023. Therefore, supplemental applications [ ] will be retained in our files.

However, we remind you of your agreement to examine your worldwide safety database to further evaluate, and submit your report to the Agency, of the adverse events glaucoma [ ]. This report incorporating information as requested in the Agency letter dated September 29, 1998, should be submitted within 3 months of receiving this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Mr. Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

/s/

Russell Katz
2/15/01 03:54:10 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-031/S-030

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

NDA 20-031/S-031
NDA 20-710/S-009

NOV - 3 2000

SmithKline Beecham Pharmaceuticals
Attention: Thomas Kline
Assistant Director, U.S. Regulatory Affairs
1250 S. Collegeville Road, P.O. Box 5089
Collegeville, PA 19426-0989

Dear Mr. Kline:

Please refer to your supplemental new drug applications dated October 3, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paxil (paroxetine hydrochloride) Immediate Release Tablets (NDA 20-031) and Oral Suspension (NDA 20-710).

These "prior approval" supplemental new drug applications provide for revisions to the **CONTRAINDICATIONS**, **WARNINGS**, and **PRECAUTIONS** sections of labeling to describe a potential interaction between paroxetine and thioridazine. We note that these changes were requested in Agency letters dated February 24, and August 25, 2000.

We have completed the review of these applications, and they are approvable. Before these applications may be approved, however, it will be necessary for you to submit final printed labeling revised as stated below.

Please note that your proposed changes to the **CONTRAINDICATIONS** and **PRECAUTIONS** sections of Paxil labeling are essentially in compliance with our requests dated February 24, and August 25, 2000.

However, you have substantially reworded our suggested language for the **WARNINGS** section, and it is unacceptable for the following reasons:

1. [redacted]

2. [redacted]

3. [redacted]

Therefore, we request that you revise the **WARNINGS** section of labeling to state the following language (in bolded font):

> **WARNINGS-Potential Interaction with Thioridazine**
> **Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsade de pointes-type arrhythmias, and sudden death. This effect appears to be dose-related.**
>
> **An *in vivo* study suggests that drugs which inhibit P450IID6, such as paroxetine, will elevate plasma levels of thioridazine. Therefore, it is recommended that paroxetine not be used in combination with thioridazine (see CONTRAINDICATIONS and PRECAUTIONS).**

Please submit 20 paper copies of the final printed labeling, 10 of which are mounted individually on heavy-weight paper or similar material, incorporating the above revisions to your proposed language. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDAs* (January 1999).

In addition, all previous revisions as reflected in the most recently approved package insert must be included.

To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of these supplemental applications.

If you have any questions, call Paul David, R.Ph., Regulatory Project Manager, at (301) 594-5530.

Sincerely,

11/3/00

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival NDAs 20-031 & 20-710
HFD-120/Div. Files
HFD-120/P.David 10/17
HFD-120/R.Katz/T.Laughren/G.Dubitsky 10-17-00
DISTRICT OFFICE 10-17-00

10/13/00pd
filename:PAXIL/NDA/20-031 S-031 20-710 S-009 AE LETTER.DOC

APPROVABLE (AE)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-031/S-030

FINAL PRINTED LABELING

PX:L18A

APPROVED

FEB 15 2001

027 7

PRESCRIBING INFORMATION

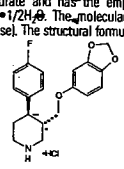
PAXIL®

brand of

paroxetine hydrochloride tablets and oral suspension

DESCRIPTION

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



paroxetine hydrochloride

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

Tablets

Each film-coated tablet contains paroxetine hydrochloride equivalent to paroxetine as follows: 10 mg–yellow; 20 mg–pink (scored); 30 mg–blue, 40 mg–green. Inactive ingredients consist of dibasic calcium phosphate dihydrate, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycols, polysorbate 80, sodium starch glycolate, titanium dioxide and one or more of the following: D&C Red No. 30, D&C Yellow No. 10, FD&C Blue No. 2, FD&C Yellow No. 6.

Suspension for Oral Administration

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

CLINICAL PHARMACOLOGY

Pharmacodynamics

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

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

Pharmacokinetics

Paroxetine is equally bioavailable from oral suspension and tablet.

Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt. In a study in which normal male subjects (n=15) received 30 mg tablets daily for 30 days, steady-state paroxetine concentrations were achieved by approximately 10 days for most subjects, although it may take substantially longer in an occasional patient. At steady state, mean values of C_{max}, T_{max}, C_{min} and $T_{1/2}$ were 61.7 ng/mL (CV 45%), 5.2 hr. (CV 10%), 30.7 ng/mL (CV 67%) and 21.0 hr. (CV 32%), respectively. The steady-state C_{max} and C_{min} values were about 6 and 14 times what would be predicted from single-dose studies. Steady-state drug exposure based on AUC_{0-24} was about 8 times greater than would have been predicted from single-dose data in these subjects. The excess accumulation is a consequence of the fact that one of the enzymes that metabolizes paroxetine is readily saturable.

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

The effects of food on the bioavailability of paroxetine were studied in subjects administered a single dose with and without food. AUC was only slightly increased (6%) when drug was administered with food but the C_{max} was 29% greater, while the time to reach peak plasma concentration decreased from 6.4 hours post-dosing to 4.9 hours.

Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic acid and sulfate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 the potency of the parent compound at inhibiting serotonin uptake. The metabolism of paroxetine is accomplished in part by cytochrome $P_{450}IID_6$. Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. The role of this enzyme in paroxetine metabolism also suggests potential drug-drug interactions (see PRECAUTIONS).

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

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

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

Renal and Liver Disease: Increased plasma concentrations of paroxetine occur in subjects with renal and hepatic impairment. The mean plasma concentrations in patients with creatinine clearance below 30 mL/min. was approximately 4 times greater than seen in normal volunteers. Patients with creatinine clearance of 30 to 60 mL/min. and patients with hepatic functional impairment had about a 2-fold increase in plasma concentrations (AUC, C_{max}).

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

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

Clinical Trials

Depression

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

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

Obsessive Compulsive Disorder

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

The following table provides the outcome classification by treatment group on Global Improvement items of the Clinical Global Impressions (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=75)	*Paxil* 40 mg (n=66)	*Paxil* 60 mg (n=66)
Worse	14%	7%	7%	3%
No Change	44%	35%	22%	19%
Minimally Improved	24%	33%	29%	34%
Much Improved	11%	18%	22%	24%
Very Much Improved	7%	7%	20%	20%

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

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

Panic Disorder

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

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

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

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

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

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

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

Social Anxiety Disorder

The effectiveness of *Paxil* in the treatment of social anxiety disorder was demonstrated in three 12-week, multicenter, placebo-controlled studies (Studies 1-3) of adult outpatients with social anxiety disorder (DSM-IV). In these studies, the effectiveness of *Paxil* compared to placebo was evaluated on the basis of (1) the proportion of responders, as defined by a Clinical Global Impressions (CGI) Improvement score of 1 (very much improved) or 2 (much improved), and (2) change from baseline in the Liebowitz Social Anxiety Scale (LSAS).

Studies 1 and 2 were flexible-dose studies comparing paroxetine (20 to 50 mg daily) and placebo. Paroxetine demonstrated statistically significant superiority over placebo on both the CGI Improvement responder criterion and the Liebowitz Social Anxiety Scale (LSAS). In Study 1, for patients who completed to week 12, 69% of paroxetine-treated patients compared to 29% of placebo-treated patients were CGI Improvement responders. In Study 2, CGI Improvement responders were 77% and 42% for the paroxetine- and placebo-treated patients, respectively.

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

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

INDICATIONS AND USAGE

Depression

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

The efficacy of *Paxil* in the treatment of a major depressive episode was established in 6-week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder (see CLINICAL PHARMACOLOGY). A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

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

The efficacy of *Paxil* in maintaining an antidepressant response for up to 1 year was demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use *Paxil* for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Obsessive Compulsive Disorder

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

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

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

Long-term maintenance of efficacy was demonstrated in a 6-month relapse prevention trial. In this trial, patients assigned to paroxetine showed a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use *Paxil* for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Panic Disorder

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

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

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

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

Social Anxiety Disorder

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

The efficacy of Paxil (paroxetine hydrochloride) 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).

CONTRAINDICATIONS

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

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

WARNINGS

Potential for Interaction with Monoamine Oxidase Inhibitors

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

Potential Interaction with Thioridazine

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

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

PRECAUTIONS

General

Activation of Mania/Hypomania: During premarketing testing, hypomania or mania occurred in approximately 1.0% of *Paxil*-treated unipolar patients compared to 1.1% of active-control and 0.3% of placebo-treated unipolar patients. In a subset of patients classified as bipolar, the rate of manic episodes was 2.2% for *Paxil* and 11.6% for the combined active-control groups. As with all antidepressants, *Paxil* should be used cautiously in patients with a history of mania.

Seizures: During premarketing testing, seizures occurred in 0.1% of *Paxil*-treated patients, a rate similar to that associated with other antidepressants. *Paxil* should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

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

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

Abnormal Bleeding: There have been several reports of abnormal bleeding (mostly ecchymosis and purpura) associated with paroxetine treatment, including a report of impaired platelet aggregation. While a causal relationship to paroxetine is unclear, impaired platelet aggregation may result from platelet serotonin depletion and contribute to such occurrences.

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

Paxil has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. Evaluation of electrocardiograms of 682 patients who received *Paxil* in double-blind, placebo-controlled trials, however, did not indicate that *Paxil* is associated with the development of significant ECG abnormalities. Similarly, Paxil (paroxetine hydrochloride) does not

cause any clinically important changes in heart rate or blood pressure.

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

Information for Patients

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

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

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

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

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

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

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

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

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

Monoamine Oxidase Inhibitors: See CONTRAINDICATIONS and WARNINGS.

Thioridazine: See CONTRAINDICATIONS and WARNINGS.

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

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

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

Cimetidine–Cimetidine inhibits many cytochrome P_{450} (oxidative) enzymes. In a study where *Paxil* (30 mg q.d.) was dosed orally for 4 weeks, steady-state plasma concentrations of paroxetine were increased by approximately 50% during co-administration with oral cimetidine (300 mg t.i.d.) for the final week. Therefore, when these drugs are administered concurrently, dosage adjustment of Paxil (paroxetine hydrochloride) after the 20 mg starting dose should be guided by clinical effect. The effect of paroxetine on cimetidine's pharmacokinetics was not studied.

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

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

Drugs Metabolized by Cytochrome $P_{450}IID_6$: Many drugs, including most antidepressants (paroxetine, other SSRIs and many tricyclics), are metabolized by the cytochrome P_{450} isozyme $P_{450}IID_6$. Like other agents that are metabolized by $P_{450}IID_6$, paroxetine may significantly inhibit the activity of this isozyme. In most patients (>90%), this $P_{450}IID_6$ isozyme is saturated early during *Paxil* dosing. In one study, daily dosing of *Paxil* (20 mg q.d.) under steady-state conditions increased single dose desipramine (100 mg) C_{max}, AUC and $T_{1/2}$ by an average of approximately two-, five- and three-fold, respectively. Concomitant use of *Paxil* with other drugs metabolized by cytochrome $P_{450}IID_6$ has not been formally studied but may require lower doses than usually prescribed for either *Paxil* or the other drug.

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

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

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

Drugs Metabolized by Cytochrome $P_{450}IIA_4$: An *in vivo* interaction study involving the co-administration under steady-state conditions of paroxetine and terfenadine, a substrate for cytochrome $P_{450}IIA_4$, revealed no effect of paroxetine on terfenadine pharmacokinetics. In addition, *in vitro* studies have shown ketoconazole, a potent inhibitor of $P_{450}IIA_4$ activity, to be at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several substrates for this enzyme, including terfenadine, astemizole, cisapride, triazolam, and cyclosporin. Based on the assumption that the relationship between paroxetine's *in vitro* Ki and its lack of effect on terfenadine's *in vivo* clearance predicts its effect on other IIA_4 substrates, paroxetine's extent of inhibition of IIA_4 activity is not likely to be of clinical significance.

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

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

Alcohol: Although *Paxil* does not increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking Paxil (paroxetine hydrochloride).

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

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

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

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

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

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Two-year carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are up to 2.4 (mouse) and 3.9 (rat) times the maximum recommended human dose (MRHD) for depression and social anxiety disorder on a mg/m² basis. Because the MRHD for depression is slightly less than that for OCD (50 mg vs. 60 mg), the doses used in these carcinogenicity studies were only 2.0 (mouse) and 3.2 (rat) times the MRHD for OCD. There was a significantly greater number of male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50 and 4/50 for control, low-, middle- and high-dose groups, respectively) and a significantly increased linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The relevance of these findings to humans is unknown.

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

Impairment of Fertility: A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of 15 mg/kg/day which is 2.9 times the MRHD for depression and social anxiety disorder 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 depression and social anxiety disorder; 8.2 and 4.1 times the MRHD for OCD and PD on a mg/m² basis).

Pregnancy

Teratogenic Effects–Pregnancy Category C

Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are equivalent to 9.7 (rat) and 2.2 (rabbit) times the maximum recommended human dose (MRHD) for depression and social anxiety disorder (50 mg) and 8.1 (rat) and 1.9 (rabbit) times the MRHD for OCD, on a 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 0.19 times (mg/m²) the MRHD for depression and social anxiety disorder and at 0.16 times (mg/m²) the MRHD for OCD. The no-effect dose for rat pup mortality was not determined. The cause of these deaths is not known. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

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

	Depression		OCD		Panic Disorder		Social Anxiety Disorder	
	Paxil	Placebo	*Paxil*	Placebo	*Paxil*	Placebo	*Paxil*	Placebo
CNS								
Somnolence	2.3%	0.7%	—		1.9%	0.3%	3.4%	0.3%
Insomnia	—	—	1.7%	0%	1.3%	0.3%	3.1%	0%
Agitation	1.1%	0.5%	—					
Tremor	1.1%	0.3%	—				1.7%	0%
Anxiety	—	—	—				1.1%	0%
Dizziness	—	—	1.5%	0%			1.9%	0%
Gastrointestinal								
Constipation	—		1.1%	0%				
Nausea	3.2%	1.1%	1.5%	0%	3.2%	1.2%	4.0%	0.3%
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%
Abnormal ejaculation[1]	1.6%	0%	2.1%	0%			4.9%	0.6%
Sweating	1.0%	0.3%	—				1.1%	0%
Impotence[1]	—		1.5%	0%				
Libido Decreased							1.0%	0%

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

1. Incidence corrected for gender.

Commonly Observed Adverse Events

Depression

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

Obsessive Compulsive Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for *Paxil* at least twice that of placebo, derived from Table 2 below) were: nausea, dry mouth, decreased appetite, constipation, dizziness, somnolence, tremor, sweating, impotence and abnormal ejaculation.

Panic Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for *Paxil* at least twice that for placebo, derived from Table 2 below) were: asthenia, sweating, decreased appetite, libido decreased, tremor, abnormal ejaculation, female genital disorders and impotence.

Social Anxiety Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for *Paxil* at least twice that for placebo, derived from Table 2 below) were: sweating, nausea, dry mouth, constipation, decreased appetite, somnolence, tremor, libido decreased, yawn, abnormal ejaculation, female genital disorders and impotence.

Incidence in Controlled Clinical Trials

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

Depression

Table 1 enumerates adverse events that occurred at an incidence of 1% or more among paroxetine-treated patients who participated in short-term (6-week) placebo-controlled trials in which patients were dosed in a range of 20 to 50 mg/day. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

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

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

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

Obsessive Compulsive Disorder, Panic Disorder and Social Anxiety Disorder

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

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%
Musculoskeletal	Myalgia	—	—	—	—	4%	3%
Nervous System	Insomnia	24%	13%	18%	10%	21%	16%
	Somnolence	24%	7%	19%	11%	22%	5%
	Dizziness	12%	6%	14%	10%	11%	7%
	Tremor	11%	1%	9%	1%	9%	1%
	Nervousness	9%	8%	—	—	8%	7%
	Libido Decreased	7%	4%	9%	1%	12%	1%
	Agitation	—	—	5%	4%	3%	1%
	Anxiety	—	—	5%	4%	5%	4%
	Abnormal Dreams	4%	1%	—	—	—	—
	Concentration Impaired	3%	2%	—	—	4%	1%
	Depersonalization	3%	0%	—	—	—	—
	Myoclonus	3%	0%	3%	2%	2%	1%
	Amnesia	2%	1%	—	—	—	—
Respiratory System	Rhinitis	—	—	3%	0%	—	—
	Pharyngitis	—	—	—	—	4%	2%
	Yawn	—	—	—	—	5%	1%
Special Senses	Abnormal Vision	4%	2%	—	—	4%	1%
	Taste Perversion	2%	0%	—	—	—	—
Urogenital System	Abnormal Ejaculation[2]	23%	1%	21%	1%	28%	1%
	Dysmenorrhea	—	—	—	—	5%	4%
	Female Genital Disorder[2]	3%	0%	9%	1%	9%	1%
	Impotence[2]	8%	1%	5%	0%	5%	1%
	Urinary Frequency	3%	1%	2%	0%	—	—
	Urination Impaired	3%	0%	—	—	—	—
	Urinary Tract Infection	2%	1%	2%	1%	—	—

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

2. Percentage corrected for gender.

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

Table 3. Treatment-Emergent Adverse Experience Incidence in a Depression Dose-Comparison Trial*

Body System/ Preferred Term	Placebo n=51	Paxil 10 mg n=102	Paxil 20 mg n=104	Paxil 30 mg n=101	Paxil 40 mg n=102
Body as a Whole					
Asthenia	0.0%	2.9%	10.6%	13.9%	12.7%
Dermatology					
Sweating	2.0%	1.0%	6.7%	8.9%	11.8%
Gastrointestinal					
Constipation	5.9%	4.9%	7.7%	9.9%	12.7%
Decreased Appetite	2.0%	2.0%	5.8%	4.0%	4.9%
Diarrhea	7.8%	9.8%	19.2%	7.9%	14.7%
Dry Mouth	2.0%	10.8%	18.3%	15.8%	20.6%
Nausea	13.7%	14.7%	26.9%	34.7%	36.3%
Nervous System					
Anxiety	0.0%	2.0%	5.8%	5.9%	5.9%
Dizziness	3.9%	6.9%	6.7%	8.9%	12.7%
Nervousness	0.0%	5.9%	5.8%	4.0%	2.9%
Paresthesia	0.0%	2.9%	1.0%	5.0%	5.9%
Somnolence	7.8%	12.7%	18.3%	20.8%	21.6%
Tremor	0.0%	0.0%	7.7%	7.9%	14.7%
Special Senses					
Blurred Vision	2.0%	2.9%	2.9%	2.0%	7.8%
Urogenital System					
Abnormal Ejaculation	0.0%	5.8%	6.5%	10.6%	13.0%
Impotence	0.0%	1.9%	4.3%	6.4%	1.9%
Male Genital Disorders	0.0%	3.8%	8.7%	6.4%	3.7%

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

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

In a fixed-dose study comparing placebo and *Paxil* 10, 20 and 40 mg in the treatment of panic disorder, there was no clear relationship between adverse events and the dose of *Paxil* to which patients were assigned, except for asthenia, dry mouth, anxiety, libido decreased, tremor and abnormal ejaculation. In flexible dose studies, no new adverse events were observed in patients receiving *Paxil* 60 mg compared to any of the other treatment groups.

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

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 1,800 patients, the ranges for the reported incidence of sexual side effects in males and females with depression, OCD, panic disorder, and social anxiety disorder are displayed in Table 4 below.

Table 4. Incidence of Sexual Adverse Events in Controlled Clinical Trials

	Paxil	Placebo
n (males)	**925**	**655**
Decreased libido	6%–14%	0%–5%
Ejaculatory disturbance	13%–28%	0%–1%
Impotence	2%–8%	0%–1%
n (females)	**932**	**694**
Decreased libido	1%–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 vs. smaller changes on placebo and active control. No significant changes in vital signs (systolic and diastolic blood pressure, pulse and temperature) were observed in patients treated with *Paxil* in controlled clinical trials.

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

Liver Function Tests: In placebo-controlled clinical trials, patients treated with *Paxil* exhibited abnormal values on liver function tests at no greater rate than that seen in placebo-treated patients. In particular, the *Paxil*-vs.-placebo comparisons for alkaline phosphatase, SGOT, SGPT and bilirubin revealed no differences in the percentage of patients with marked abnormalities.

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

During its premarketing assessment in depression, multiple doses of *Paxil* were administered to 6,145 patients in phase 2 and 3 studies. The conditions and duration of exposure to *Paxil* varied greatly and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose and titration studies. During premarketing clinical trials in OCD, panic disorder, and social anxiety disorder, 542, 469, and 522 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 7,678 patients exposed to multiple doses of Paxil (paroxetine hydrochloride) who experienced an event of the type cited on at least one occasion while receiving *Paxil*. All reported events are included except those already listed in Tables 1 and 2, those reported in terms so general as to be uninformative and those events where a drug cause was remote. It is important to emphasize that although the events reported occurred during treatment with paroxetine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in the PRECAUTIONS section.

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

Cardiovascular System: *frequent:* hypertension, syncope, tachycardia; *infrequent:* bradycardia, hematoma, hypotension, migraine; *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, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileus, intestinal obstruction, jaundice, melena, mouth ulceration, peptic ulcer, salivary gland enlargement, stomach ulcer, stomatitis, tongue discoloration, tongue edema, tooth caries.

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

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

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

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

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

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

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

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

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

Postmarketing Reports

Voluntary reports of adverse events in patients taking Paxil (paroxetine hydrochloride) that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome-like events; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide, tremor and trismus, serotonin syndrome, associated in some cases with concomitant use of serotonergic drugs and with drugs which may have impaired *Paxil* metabolism (symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor), status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia, and events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis). There have been spontaneous reports that discontinuation (particularly when abrupt) may lead to symptoms such as dizziness, sensory disturbances, agitation or anxiety, nausea and sweating; these events are generally self-limiting. There has been a case report of an elevated phenytoin level after 4 weeks of *Paxil* and phenytoin co-administration. There has been a case report of severe hypotension when *Paxil* was added to chronic metoprolol treatment.

DRUG ABUSE AND DEPENDENCE

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

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

OVERDOSAGE

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

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

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

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

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

A specific caution involves patients 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 Drugs Metabolized by Cytochrome $P_{450}IID_6$ under PRECAUTIONS).

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

DOSAGE AND ADMINISTRATION

Depression

Usual Initial Dosage: Paxil (paroxetine hydrochloride) should be administered as a single daily dose with or without food, usually in the morning. The recommended initial dose is 20 mg/day. Patients were dosed in a range of 20 to 50 mg/day in the clinical trials demonstrating the antidepressant effectiveness of *Paxil*. As with all antidepressants, the full antidepressant effect may be delayed. Some patients not responding to a 20 mg dose may benefit from dose increases, in 10 mg/day increments, up to a maximum of 50 mg/day. Dose changes should occur at intervals of at least 1 week.

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

Systematic evaluation of the efficacy of Paxil (paroxetine hydrochloride) has shown that efficacy is maintained for periods of up to 1 year with doses that averaged about 30 mg.

Obsessive Compulsive Disorder

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

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

Panic Disorder

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

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

Social Anxiety Disorder

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

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

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

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

NOTE: SHAKE SUSPENSION WELL BEFORE USING.

HOW SUPPLIED

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

10 mg yellow tablets engraved on the front with PAXIL and on the back with 10. NDC 0029-3210-13 Bottles of 30

20 mg pink, scored tablets engraved on the front with PAXIL and on the back with 20. NDC 0029-3211-13 Bottles of 30
NDC 0029-3211-20 Bottles of 100
NDC 0029-3211-21 SUP 100's (intended for institutional use only)

30 mg blue tablets engraved on the front with PAXIL and on the back with 30. NDC 0029-3212-13 Bottles of 30

40 mg green tablets engraved on the front with PAXIL and on the back with 40. NDC 0029-3213-13 Bottles of 30

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

Oral Suspension: Orange-colored, orange-flavored, 10 mg/5 mL, in 250 mL white bottles. NDC 0029-3215-48

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

DATE OF ISSUANCE DEC. 2000

R_x only

SmithKline Beecham Pharmaceuticals
Philadelphia, PA 19101
PX:L18A
Printed in U.S.A.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-031/S-030

MEDICAL REVIEW(S)

OCT 12 2000

Review and Evaluation of Clinical Data
NDA #20-031

Sponsor:	SmithKline Beecham Pharmaceuticals
Drug:	Paxil (paroxetine HCl)
Indication:	Depression, Panic Disorder, OCD, Social Anxiety Disorder
Material Reviewed:	Response to Request for Labeling Change RE: Mellaril/Paxil Interaction (SLR-031)
Date Submitted:	October 3, 2000
Date Received:	October 4, 2000
Related NDA's:	20-710 (Paxil Oral Suspension) (SLR-009)

I. Background

On 2-24-00, we sent a letter to the sponsor (SB) requesting changes to the CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS sections of Paxil labeling to describe a potential interaction between paroxetine and thioridazine. The reasons for this request were elaborated in that letter.

SB responded on 5-3-00, stating that such a contraindication was unwarranted since a search of their serious adverse event database [ ] revealed no relevant reports of a dangerous interaction between these two agents and, thus, there was no known hazard.

On 8-25-00, the Division issued a second letter explaining that their response was inadequate to reasonably rule out a clinically significant interaction and we again requested the above described labeling revisions.

This submission contains the sponsor's response to our 8-25-00 letter.

II. Review of Response to 8-25-00 Letter

This submission contains draft labeling to contraindicate the co-administration of Paxil and thioridazine. The cover letter also respectfully requests that we consider similar labeling changes for Prozac and Zoloft and two articles

which purport to support these changes to Zoloft labeling have been included in this submission.

The indicated changes to the CONTRAINDICATIONS and PRECAUTIONS sections of Paxil labeling are essentially in compliance with our request and are acceptable.

However, the sponsor has substantially reworded our suggested language for the WARNINGS section (see page 9 of the submission). The sponsor's proposal is not totally acceptable, in my opinion, for the following reasons:

III. Recommendations

The sponsor's proposed changes to Paxil labeling are acceptable except for those to the WARNINGS section. Based on the above discussion, I recommend the following revision of the sponsor's proposal for that section:

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

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

Upon the sponsor's agreement with this wording or the crafting of other mutually acceptable language for the WARNINGS section, this supplement may be approved.

Finally, the sponsor's comments and data regarding Prozac and Zoloft have been forwarded to the Medical Officer for those drugs, Andrew Mosholder, M.D.

Gregory M. Dubitsky, M.D.
October 12, 2000

10-12-00

cc: NDA# 20-031 (Paxil Tablets)
NDA# 20-710 (Paxil Oral Suspension)
HFD-120 (Div. Files)
HFD-120/GDubitsky
/TLaughren
/PDavid

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-031/S-030

ADMINISTRATIVE

REGULATORY PROJECT MANAGER
LABELING REVIEW

Date: February 9, 2001
NDA: 20-031 (Tablets) & 20-710 (Oral Suspension)
DRUG: Paxil (paroxetine HCl) Tablets and Oral Suspension
Sponsor: SmithKline Beecham (SB)
Indication: Depression/OCD/Social Anxiety Disorder
Supplements:

NDA	Supplement	Dated	Action
[redacted]			
20-031	SLR-031	10-3-00 and amended on 12-15-00	AE Letter Dated 11-3-00
[redacted]			
20-710	SLR-009	10-3-00 and amended on 12-15-00	AE Letter Dated 11-3-00

Notes of interest:

- The last approved labeling revision was 20-031/SLR-030 and 20-710/SLR-008 approved in an Agency letter dated 9-28-00. These supplemental applications were submitted under CBE with a label code of PX:L17. See my labeling review dated 9/21/00.
- A new indication for Paxil in the treatment of social anxiety disorder, submitted in 20-031/SE1-023, was approved in an Agency letter dated 5-11-99.
- The Agency incorporated some of the labeling revisions submitted under [redacted] into the approval of SE1-023 (new indication for social anxiety disorder). However, there were 2 labeling revisions, which were glaucoma and [redacted], that were not incorporated into the approval of 20-031/SE1-023 since more data were needed prior to enacting the labeling change. Therefore, SB was requested to evaluate these adverse events using their worldwide safety database.

REVIEW

[redacted]

[redacted]

20-031/SLR-031
20-710/SLR-009
Dated: 9-18-98
CBE: Yes
Label Code: PX: LX18A
Reviewed by Medical Officer: Yes, acceptable.

The supplement provides for revisions to the **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS** sections of labeling to describe a potential interaction between paroxetine and thioridazine.

CONCLUSIONS

1. Supplements 20-031/SLR-031 nad 20-710SLR-009 only provide for the labeling revisions listed above. Please see attached documentation denoting the revisions made to labeling compared to the last approved FPL for Paxil (Label Code PX:L17; approval letter dated 9-28-00).

2. I recommend issuing an approval letter for supplements 20-031/SLR-031 and 20-710/SLR-009.

3. In lieu of maintaining open supplements [redacted] in the records, I recommend issuing a letter superceding these applications since the majority of changes provided for in these applications were incorporated into the approval of social anxiety disorder (20-01/SE1-023; approval letter dated 5-11-99). We can remind the sponsor as well as provide a 3 month due date to submit their report to the Agency with information on these adverse events.

Paul David. RPh
Regulatory Project Manager

John Purvis
Supervisory Consumer Safety Officer

8 page(s) of draft labeling has been removed from this portion of the review.

Admin: Labeling Review (S-031)

/s/

Paul David
2/14/01 03:01:02 PM
CSO

Paul David
2/14/01 03:16:18 PM
CSO

Robbin Nighswander
2/15/01 08:59:31 AM
CSO
Signed for Jack Purvis, SCSO.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-031/S-030

CORRESPONDENCE

SB
SmithKline Beecham
Pharmaceuticals

ORIGINAL

December 15, 2000

NDA 20-031/S-031 Paxil® (paroxetine hydrochloride) Tablets
NDA 20-710/S-009 Paxil® (paroxetine hydrochloride) Oral Suspension

Russell Katz, M.D., Director
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products (HFD-120)
Document Control Room 10B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA SUPP AMEND
SLR-031-AF

Final Printed Labeling
FPL for supplements NDA 20-031/S-031 and 20-710/S-009

Dear Dr. Katz:

Reference is made to SmithKline Beecham's New Drug Applications for Paxil® (paroxetine hydrochloride) Tablets and Oral Suspension, NDA 20-031 and NDA 20-710, respectively. Please refer also to the Agency letters dated February 24, and August 25, 2000, and the undated letter received by SB on November 21, 2000. These FDA letters, and SB's October 3, 2000 response, regard updates to the CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS section of labeling to describe a potential interaction between paroxetine and thioridazine.

Submitted herein is final printed labeling (FPL) incorporating changes as requested in the above mentioned FDA letters. For reviewer convenience, a copy of the current approved labeling, highlighted to reflect changes in this submission, is provided in Attachment 1. Twenty copies of final printed labeling, mounted on heavy-weight paper, is provided in Attachment 2.

This new version of labeling (code PX:L18A) is intended to replace the currently approved labeling code L17A, and is scheduled to be implemented within the next couple months.

Please do not hesitate to contact me at (610) 917-5970 if you have any questions regarding this submission.

Sincerely,

Thomas F. Kline
Assistant Director
U.S. Regulatory Affairs

000001

1250 S. Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989. Telephone (610) 917 7000. Fax (610) 917 7665.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-031/S-031

SmithKline Beecham Pharmaceuticals
1250 S. Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-0989

OCT 15 2000

Attention: Thomas F. Kline
Assistant Director
U.S. Regulatory Affairs

Dear Mr. Kline:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Paxil® (paroxetine hydrochloride) Tablets

NDA Number: 20-031

Supplement Number: S-031

Date of Supplement: October 3, 2000

Date of Receipt: October 4, 2000

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on December 3, 2000 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Attention: Document Control Room 4008
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

10-15-00

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 20-031/S-031
HFD-120/Div. Files
HFD-120/CSO/David

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SUPPLEMENT ACKNOWLEDGEMENT

SmithKline Beecham
Pharmaceuticals

ORIGINAL

NDA SUPPLEMENT

October 3, 2000

NDA 20-031 Paxil® (paroxetine hydrochloride) Tablets
NDA 20-710 Paxil® (paroxetine hydrochloride) Oral Suspension

CENTER FOR DRUG EVALUATION AND RESEARCH

OCT 04 2000

RECEIVED HFD-120

Russell Katz, M.D., Director
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products (HFD-120)
Document Control Room 10B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA NO. 20-031 REF NO. SLR-031
NDA SUPPL FOR LABELING

Response to FDA: Proposed Draft Labeling

Dear Dr. Katz:

Reference is made to our approved New Drug Applications for Paxil® (paroxetine hydrochloride) Tablets, and Oral Suspension, NDA 20-031 and NDA 20-710, respectively. Reference is also made to the FDA letters of February 24th and August 25, 2000 regarding proposed labeling statements relating to concomitant use of thioridazine and paroxetine.

Submitted herein is draft labeling pertaining to the above mentioned letters. Please note, however, that in accepting your proposals to contraindicate the concomitant use of paroxetine and thioridazine, we respectfully request that you consider imposing similar labeling for other drugs also known to inhibit CYP2D6 since, as with paroxetine, there must exist some risk that, in certain patients, concomitant administration could result in potentially hazardous elevations in thioridazine plasma levels.

We note that, among the SSRIs, the 'Sarafem' brand of fluoxetine already carries this contraindication, and therefore other brands of fluoxetine (e.g. Prozac) should be similarly labeled. Regarding sertraline ('Zoloft') , the current labeling notes explicitly its potential for interactions with CYP2D6 substrates, therefore it is logical that the contraindication with thioridazine should be applied here also. Although it is acknowledged that sertraline tends to display less potent inhibition of CYP2D6 *in-vitro* than either paroxetine or fluoxetine/norfluoxetine, significant elevations of, for example, TCA plasma levels have been observed *in-vivo*, especially at higher sertraline doses within the normal therapeutic range [See references 1 and 2, provided in Attachment 2]. Because other CYP2D6 substrates, such as thioridazine, could be similarly affected, it is important that physicians are not given the impression, by inconsistent SSRI labeling, that co-administration of sertraline and thioridazine is risk-free.

1250 S. Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989. Telephone (610) 917 7000. Fax (610) 917 7665.

Please do not hesitate to contact me at (610) 917-5970 if you have any questions regarding this submission.

Sincerely,

Thomas F. Kline
Assistant Director
U.S. Regulatory Affairs

References:
(copy provided in Attachment 2 of this submission)
1. Kurtz DL et al (1997), Clin Pharm Ther 62: 145-156.
2. Solai LK et al (1997), J Clin Psychiatry 58: 440-443