CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020031/S023

Trade Name: PAXIL TABLETS

Generic Name: PAROXETINE HYDROCHLORIDE

Sponsor: SMITHKLINE BEECHAM PHARMACEUTICALS

Approval Date: 05/11/99

INDICATION(s): TREATMENT OF SOCIAL ANXIETY DISORDER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 020031/S023

CONTENTS

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Application Number: 020031/S023

APPROVAL LETTER

NDA 20-031/S-023

SmithKline Beecham Pharmaceuticals
Attention: Thomas Kline
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426

Dear Mr. Kline:

Please refer to your supplemental new drug application dated May 6, 1998, received May 6, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paxil[R] (paroxetine hydrochloride) Tablets.

The user fee goal date for this application is October 9, 1999.

This supplement provides for the use of Paxil[R] Tablets for the treatment of social anxiety disorder as a new indication.

We acknowledge receipt of your submission dated April 6, 1999. Your submission of April 6, 1999 constituted a complete response to our March 29, 1999 action letter.

We have completed the review of this supplemental application, as amended, 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 enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-031/S-023." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments specified in your submission dated April 6, 1999. These commitments, along with any completion dates agreed upon, are listed below:

1. Completion of a long-term relapse prevention trial for the treatment of social anxiety disorder.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until May 1, 2002. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity [NOTE: You should still submit a pediatric drug development plan.] and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

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, contact Anna Marie Homonnay-Weikel, R.Ph., Project Manager, at (301) 594-5535.

Sincerely,

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020031/S023

FINAL PRINTED LABELING

ATTACHMENT

FDA FINAL APPROVED LABELING

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

[Note: Chemical structure to be inserted]

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 Cmax 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 (paroxetine hydrochloride) 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* 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 generally 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 reevaluate 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 reevaluate 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 reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

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

Paxil is contraindicated in patients with a hypersensitivity to paroxetine or 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.

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.

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 $T_{½}$ 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 (e.g., thioridazine) and Type 1C antiarrhythmics (e.g., propafenone, flecainide and encainide), or that inhibit this enzyme (e.g., quinidine), should be approached with caution.

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

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

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

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

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

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

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

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

Procyclidine: Daily oral dosing of *Paxil* (30 mg q.d.) 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/m^2 basis. Because the MRHD for depression is slightly less than that for OCD (50 mg vs. 60 mg), the doses used in these carcinogenicity studies were only 2.0 (mouse) and 3.2 (rat) times the MRHD for OCD. There was a significantly greater number of male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50 and 4/50 for control, low-, middle- and high-dose groups, respectively) and a significantly increased linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The relevance of these findings to humans is unknown.

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

Impairment of Fertility: A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of 15 mg/kg/day which is 2.9 times the MRHD for depression and social anxiety disorder or 2.4 times the MRHD for OCD on a mg/m^2 basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks. These lesions consisted of vacuolation of epididymal tubular epithelium at 50 mg/kg/day and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis at 25 mg/kg/day (9.8 and 4.9 times the MRHD for depression and social anxiety disorder; 8.2 and 4.1 times the MRHD for OCD and PD on a mg/m^2 basis).

Pregnancy
Teratogenic Effects - Pregnancy Category C

Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are equivalent to 9.7 (rat) and 2.2 (rabbit) times the maximum recommended human dose (MRHD) for depression and social anxiety disorder (50 mg) and 8.1 (rat) and 1.9 (rabbit) times the MRHD for OCD, on a mg/m^2 basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg/day or 0.19 times (mg/m^2) the MRHD for depression and social anxiety disorder and at 0.16 times (mg/m^2) the MRHD for OCD. The no-effect dose for rat pup mortality was not determined. The cause of these deaths is not known. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

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%	1.9%	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* 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, 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*

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

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

In 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, thrombocytopenia, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome-like events; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide, tremor and trismus; and serotonin syndrome, associated in some cases with concomitant use of serotonergic drugs and with drugs which may have impaired *Paxil* metabolism (symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor). There have been spontaneous reports that abrupt discontinuation may lead to symptoms such as dizziness, sensory disturbances, agitation or anxiety, nausea and sweating; these events are generally self-limiting. There has been a case report of an elevated phenytoin level after 4 weeks of *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*:** Overdose with *Paxil* (up to 2000 mg) alone and in combination with other drugs has been reported. Signs and symptoms of overdose with *Paxil* include nausea, vomiting, sedation, dizziness, sweating, and facial flush. There are no reports of coma or convulsions following overdosage with *Paxil* alone. A fatal outcome has been reported rarely when *Paxil* was taken in combination with other agents, or when taken alone.

***Overdosage Management*:**

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

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

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

A specific caution involves patients 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. Manufactured in Crawley, UK, by SmithKline Beecham Pharmaceuticals.
NDC 0029-3215-48

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

DATE OF ISSUANCE xxxxx

SmithKline Beecham Pharmaceuticals
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020031/S023

MEDICAL REVIEW(S)

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 30, 1999

/S/
4-30-99

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for Paxil tablets (paroxetine) for the treatment of social phobia/social anxiety disorder

TO: File NDA 20-031/S-023
[**Note:** This overview should be filed with the 4-6-99 response to our 3-29-99 approvable letter.]

SKB's 4-6-99 response to our 3-29-99 approvable letter represented a complete response to all the issues raised in our letter. Dr. Susan Molchan reviewed the responses to clinical issues in a 4-27-99 review, including labeling, a safety update, a regulatory status update, and a literature update. There were no new safety findings revealed in either the safety update or literature update that would impact on the labeling or an approval action for this supplement. To our knowledge, Paxil is approved for social anxiety disorder in 23 nonUS countries and applications are pending in 33 other nonUS countries.

Labeling:

There were several labeling issues that required consideration and some discussion to obtain agreement.

-Name for the disorder: The sponsor asked that we consider Social Anxiety Disorder as the preferred name for the new indication, rather than Social Phobia (either is acceptable language in DSM-IV). They provided letters of support from experts and other information. Dr. Molchan agreed with the arguments, and I do as well. The disorder is characterized predominantly by social anxiety, which in many cases leads to phobic avoidance of social situations. We have written the new indication in such a way as to encourage use of medication only in patients who are significantly impaired by the disorder rather than for the broader population of individuals with minor social anxiety.

-Whether or not to include results on the Sheehan Disability Scale in the labeling: It has been our policy not to include secondary outcomes in our trial summaries in labeling, since these were not the

subject of primary hypothesis testing. So we have not included these outcomes. The sponsor has alternative ways of conveying such information, e.g., distribution of published papers.

-How best to summarize the sexual dysfunction data for Paxil in the labeling: The sponsor wanted to include the actual risk data in narrative format. However, we were able to reach agreement on a simpler table that provided the ranges across indications.

-There were a number of other changes to labeling, based largely on recalculations for safety findings requested in the approvable letter. Dr. Molchan checked these modifications for accuracy, and has recommended that we accept these other changes. I agree.

We reached agreement with the sponsor on final labeling as of 4-30-99.

Phase IV Studies:

-We had asked for a commitment to conduct a relapse prevention trial of Paxil in social anxiety disorder, and such a trial is already underway.

Conclusions/Recommendations:

To my knowledge, all remaining issues have been resolved, and I recommend that this supplement be approved, with the mutually agreed upon labeling

cc:
Orig NDA 20-031/S-023 (Paxil)
HFD-120/Div File
HFD-120/TLaughren/RKatz/SMolchan/AMHomonnay

For AE package

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 5, 1999

FROM: Thomas P. Laughren, M.D. /S/
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for
Paxil tablets (paroxetine) for the treatment of social phobia

TO: File NDA 20-031/S-023
[**Note:** This overview should be filed with the 5-6-98
original submission.]

1.0 BACKGROUND

Paroxetine is a selective serotonin reuptake inhibitor currently approved and marketed for depression, OCD, and panic disorder in an immediate release tablet, i.e., Paxil (NDA 20-031, originally approved for depression December, 1992). S-023 provides data in support of a new claim for this same Paxil tablet in the treatment of social phobia in a dose range of 20-50 mg/day.

It should be noted that, at the current time, there are no drugs specifically approved in the US for the treatment of social phobia. However, social phobia has long been recognized by the psychiatric community as a legitimate psychiatric disorder and is listed in DSM-IV. Nevertheless, given the symptom overlap between patients with social phobia and those with either depression or other anxiety disorders, one of the concerns identified early in the development of this new indication for Paxil was how this overlap would be sorted out in making a judgement regarding the specific benefit of this product in social phobia.

While we did not have a formal end-of-phase 2 meeting with the sponsor during the development of this indication, we did communicate with them by letter regarding study design and overall development plans.

We met with the sponsor on 2-11-97 for a preNDA meeting, and one issue was our concern about the overlap of social phobia with other anxiety disorders and depression. We also provided technical advice about the submission of the NDA.

Since the proposal is to use the currently approved Paxil immediate release tablets for this expanded population, there was no need for chemistry or pharmacology reviews of this supplement. Since 2 of the key studies used over-encapsulated products of the approved tablets, there was need for a biopharmaceutics review of dissolution data (done by Rae Yuan, Ph.D. from the biopharm group). The focus was on clinical data. The primary review of the efficacy and safety data was done by Susan Molchan, M.D., from the clinical group. Kun Jin, Ph.D., from the Division of Biometrics, also reviewed the efficacy data.

The studies supporting this supplement were conducted under IND The original supplement for this expanded indication (S-023) was submitted 5-6-98.

We decided not to take this supplement to the Psychopharmacological Drugs Advisory Committee.

2.0 CHEMISTRY

As Paxil tablets are already marketed, there were no CMC issues requiring review for this supplement, other than the minor dissolution testing noted above.

3.0 PHARMACOLOGY

As Paxil tablets are already marketed, there were no pharm/tox issues requiring review for this supplement.

4.0 BIOPHARMACEUTICS

As Paxil tablets are already marketed, there were no biopharmaceutics issues requiring review for this supplement, other than the minor dissolution testing noted above.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of efficacy was based on the results of 3 double-blind, randomized, 12-week, placebo-controlled trials (502, 382, 454) in adult outpatients meeting DSM-IV criteria for social phobia (social anxiety disorder). Patients were screened using structured interviews, either the MINJI or a modified SCID. The identified primary outcome measures for these studies were change from baseline for the Liebowitz Social Anxiety Scale (LSAS) total score and the proportion of patients responding to treatment as defined by a CGI Improvement score of 1 (very much improved) or 2 (much improved). The LSAS is a widely used instrument in evaluating treatments for social phobia, and has been shown to be sensitive to drug effects. Its total score ranges from 0 to 144 (24 items with ratings from 0-3 on each of fear/anxiety and avoidance). It was administered by investigators in 2 of the 3 studies, but was used as a patient questionnaire in the 3rd (502). Our focus in these studies was on (1) change from baseline for the LSAS total score, and (2) proportion of responders as defined above for CGI Improvement. In my view, the LSAS is sufficiently specific for the entity "social phobia" that I am not concerned about the blurring of an antidepressant response with a response in this disorder, especially since patients with primary depression diagnoses were excluded from these trials.

Study 470 was a 16-week, double-blind, placebo-controlled relapse prevention trial for responders on Paxil for the 12-week studies and for responders who were switched from placebo to Paxil during a 24-week open phase preceding the double-blind phase. However, the number of randomized patients who completed the double-blind phase was relatively small, and this study on face did not provide any definitive evidence of long-term efficacy and was not reviewed for efficacy.

5.1.2 Summary of Studies Pertinent to Efficacy Claims

5.1.2.1 Study 502

This was a randomized, double-blind, parallel group, 12-week, flexible-dose study (39 non-US sites) comparing paroxetine immediate release tablets (20 to 50 mg/day, taken as a single am dose) and placebo in adult outpatients meeting DSM-IV criteria for social phobia. Patients could not have other Axis I disorders. There were roughly 140 patients per group in the sample analyzed, with the % completing to 12 weeks ranging from 72-75%. The mean dose for completers in the paroxetine group was 35 mg/day.

Overall, the results from this study consistently favored paroxetine over placebo on both primary outcomes, from week 4 on for both LOCF and OC analyses. For both outcomes, the p-values were < 0.001 at week 12 for both LOCF and OC analyses. For the CGI, 77% of paroxetine completers met the response criterion compared to 42% for placebo. For the LSAS, the difference between

paroxetine and placebo in mean change from baseline for completers at 12 weeks was roughly 15 units.

5.1.2.2 Study 382

This was a randomized, double-blind, parallel group, 12-week, flexible-dose study (12 US & 1Canadian site) comparing paroxetine immediate release tablets (20 to 50 mg/day, taken as a single am dose) and placebo in adult outpatients meeting DSM-IV criteria for social phobia. Patients could not have other Axis I disorders. There were roughly 90 patients per group in the sample analyzed, with the % completing to 12 weeks ranging from 66-77%. The mean dose for completers in the paroxetine group was 41 mg/day.

Overall, the results from this study consistently favored paroxetine over placebo on both primary outcomes, from week 4 on for both LOCF and OC analyses. For both outcomes, the p-values were < 0.001 at week 12 for both LOCF and OC analyses. For the CGI, 69% of paroxetine completers met the response criterion compared to 29% for placebo. For the LSAS, the difference between paroxetine and placebo in mean change from baseline for completers at 12 weeks was roughly 19 units.

5.1.2.2 Study 454

This was a randomized, double-blind, parallel group, 12-week, fixed-dose study (21 US & 1Canadian sites) comparing paroxetine immediate release tablets (20, 40, or 60 mg, taken as a single am dose) and placebo in adult outpatients meeting DSM-IV criteria for social phobia. Patients could not have other Axis I disorders. There were roughly 90 patients per group in the sample analyzed, with the % completing to 12 weeks ranging from 58-72%.

Given the multiple active treatment arms in this study (3 dose groups for paroxetine), Dunnet's test was used to establish a criterion p-value for declaring paroxetine/placebo pairwise comparisons significant ($p<0.019$). Using this criterion p-value for LSAS total score, the results from this study favored paroxetine over placebo only for paroxetine 20 mg in both LOCF and OC analyses. However, the results were positive for the 40 mg group in the OC analyses, and the results were certainly trending in a positive direction for all dose groups. For CGI Improvement, the results from this study technically favored paroxetine over placebo only for paroxetine 40 mg in both LOCF and OC analyses, however, the 20 mg group was close enough in my view in the LOCF analysis with a p-value of $p=0.02$. The results were positive for the 20 mg and 60 mg groups in the OC analyses at week 12, and the results were certainly trending in a positive direction for all dose groups. The effect sizes in this study for both the LSAS and CGI Improvement were roughly comparable to those observed in studies 502 & 382.

The results for this study most consistently favored paroxetine over placebo for the 20 mg group, however, there was certainly support for the higher dose groups as well. Nevertheless, there was no indication of additional benefit for the higher dose groups.

5.1.3 Comment on Other Important Clinical Issues Regarding Paxil for Social Phobia

Evidence Bearing on the Question of Dose/Response for Efficacy

Of the 3 studies in the development program, two involved flexible dosing in a range of 20-50 mg/day (502 & 382), and thus, provided no evidence pertinent to the issue of dose response. The mean doses for completers to 12 weeks in these two studies were 35 and 41 mg/day, respectively, but these findings are not interpretable regarding dose response since patients in such trials are generally pushed to the higher end of the permitted dose range, regardless of need. Study 454 was most informative regarding dose response, and this study suggested no advantage at doses beyond 20 mg/day. Thus, while I agree with the sponsor's proposed initial dose of 20 mg/day, labeling must be clear in noting that the only pertinent evidence suggests no benefit in doses above 20 mg/day.

Clinical Predictors of Response

Extensive exploratory analyses were done to detect subgroup interactions on the basis of demographics, severity of illness, comorbid illnesses, or concurrent psychotherapy. Generally these analyses revealed no consistent pattern of findings suggestive of interactions with these covariates. Patients with either higher LSAS scores at baseline or with greater improvement in depression scores during treatment achieved greater improvement in LSAS scores during treatment. However, in both cases, the greater improvement was independent of treatment assignment, i.e.,they improved more whether they got drug or placebo.

Size of Treatment Effect

It is difficult to clinically interpret the effect sizes on the measures observed for these 3 studies in terms of differences between drug and placebo in change from baseline. For LSAS total score, mean baseline scores were roughly 80 and paroxetine patients had decreases to mean scores of roughly 50, compared to decreases to about 65 for placebo patients. As is the case for other psychiatric indications, the mean score after treatment was still within a range that would be considered clinically ill. On the other hand, the finding that roughly 2/3 of drug-treated patients met the CGI Improvement criterion compared to roughly 1/3 of placebo patients suggests to me a clinically relevant treatment effect.

Duration of Treatment

Only study 470 could have provided evidence pertinent to longer-term efficacy, and too few patients entered the double blind phase of this trial (n=55) for it to address the question. While twice as many placebo as paroxetine-treated patiens relapsed during this phase, there was insufficient power for this to be a statistically significant result.

5.1.3 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence to support the claim of a beneficial effect of Paxil tablets in the treatment of Social Phobia. The sponsor's relapse prevention trial failed because of an inadequate sample size, and we will recommend the conduct of an adequate trial of similar design. In addition, since social phobia is also a disorder found in the pediatric population and, once aproved for this indication, Paxil will likely be used in pediatric patients, we will recommend adequate and well-controlled trials of Paxil in this population as well.

5.2 Safety Data

Dr. Molchan's safety review of S-023 was based on an integrated database consisting of a pooling of safety data for the three 12-week studies and also longer-term data from the long-term trial (470). There was no safety update.

Overall, 578 patients were exposed to Paxil in the sponsor's development program for social phobia. Patients in this integrated database were roughly 50% female and predominantly white. 99% of these patients were in a 18-64 year old age range. 82% had mean doses in a range of 20-40 mg/day. Most of the exposure was relatively short-term. The overall person-time for Paxil exposure in this program was 151 PY.

Given our prior knowledge of the risks associated with the immediate release Paxil tablet in the same dose range utilized in this program, the focus in the safety review was on any differences between the recognized safety profile for this drug in its approved indications from that observed in the social phobia population.

5.2.2 Overview of Adverse Event Profile for Paxil Tablets in Social Phobia

Overall, the adverse events profile for Paxil tablets in social phobia was comparable to that observed in patients with depression, OCD, and panic disorder receiving this drug.

5.2.3 Conclusions Regarding Safety of Paxil in Social Phobia

There were no new safety findings to suggest a substantially different safety profile for Paxil tablets in social phobia compared to that observed for the other 3 approved indications, and no basis for substantial changes in the labeling for Paxil from the standpoint of safety.

5.3 Clinical Sections of Labeling

We have modified the clinical sections of the draft labeling that is included with the approvable letter. The explanations for the changes are provided in bracketed comments in the draft labeling.

6.0 WORLD LITERATURE

Dr. Molchan reviewed the published literature for Paxil in social phobia included in the NDA and did not discover any previously unrecognized important safety concerns for this drug. We will ask for a literature update in the approvable letter.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, Paxil is not approved for the treatment of social phobia anywhere at this time. We will ask for an update on the regulatory status of Paxil for social phobia in the approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this supplement to the PDAC.

9.0 DSI INSPECTIONS

Although DSI does not routinely inspect investigative sites for supplements, and did not in this case, none of the listed investigators for these trials was recognized as having had compliance problems in the past.

10.0 LABELING AND APPROVABLE LETTER

10.1 Final Draft of Labeling Attached to Approvable Package

Our proposed draft of labeling is attached to the approvable letter. As noted, we have made changes to the sponsor's draft dated 5-6-98.

10.2 Foreign Labeling

Paxil is not approved for social phobia anywhere at this time.

10.3 Approvable Letter

The approvable letter includes draft labeling and requests for a safety update, a literature update, a regulatory status update, and requests for additional studies of Paxil in social phobia, in particular, (1) a relapse prevention trial, and (2)

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that SKB has submitted sufficient data to support the conclusion that Paxil tablets are effective and acceptably safe in the treatment of social phobia. I recommend that we issue the attached approvable letter with our labeling proposal and the above noted requests for updates, in anticipation of final approval.

cc:
Orig NDA 20-031/S-023
HFD-120
HFD-120/TLaughren/RKatz/SMolchan/GDubitsky/AMHomonnay

APPEARS THIS WAY
ON ORIGINAL

Review and Evaluation of Clinical Data
NDA #20-031

Sponsor: SmithKline Beecham

Drug: Paroxetine

Indication: Social phobia

Material submitted: Response to FDA Approvable Letter, safety update, literature update, draft labeling, foreign regulatory update, phase 4 committments

Correspondence Date: April 6, 1999

Date Received: April 9, 1999

1. Labeling

Two main points are raised by the sponsor in response to our changes in the draft labeling:

- They believe it is important that the term "social anxiety disorder" be included in the labeling, as opposed to just "social phobia" as we had proposed. They provide a rationale for this supported by medical experts in the field of social phobia. Both terms are used in DSM-IV, though "social phobia" is the primary one. Both are used in the literature. Some experts are supporting "social anxiety disorder" as the primary name for the problem, feeling this term better conveys its pervasiveness and impairment.

I think it is reasonable to include both the terms "social anxiety disorder" and "social phobia" in the labeling. The sponsor proposes using both terms in the 'Indications' section and "social anxiety disorder" throughout the rest of the labeling text. I think this is reasonable.

- The sponsor wants to include a description of improvement in patient disability in the labeling (p.20 of current submission). Specifically, they want to include the results of the Sheehan Disability Scale, one of the secondary efficacy measures used in the pivotal studies. They submit that this information is "clinically meaningful" and provide support from a medical expert.

Many secondary efficacy measures were used in these studies and the Division, I believe, has decided to include only primary measures in labeling. I think the benefit of the drug for social phobia is adequately conveyed in the labeling through the results of primary efficacy measures.

Other revisions the sponsor would like in the labeling include:

- On p. 19 of the current submission, the sponsor deletes the information on mean dose for the two flexible dose studies. They note that there is an adequate fixed dose study in which 20 mg was shown effective and the labeling recommends the 20 mg dose as the initial and recommended dose, with no additional benefit suggested for higher doses. The sponsor therefore feels that inclusion of mean dose for the other studies does not serve a useful purpose and may be misleading to prescribers.

Deletion of the mean dose information is reasonable for the reasons noted.

- On p. 22 of the submission, in the description of the anxiety in social phobia, "take the form" was changed to intensity" of a panic attack.

This wording change is reasonable.

- The statement on p. 22 regarding the lack of testing in children has been deleted. It is redundant to the information in the 'Pediatric Use' subsection as the sponsor notes.

Deletion of this statement is reasonable.

- On p. 38 of the submission, the sponsor makes a case for substituting text on sexual dysfunction for Table 4, which enumerates sexual side effects for each of the indications. They note that "there is no physiological evidence that the sexual side effect profile of SSRIs are uniquely attributable to the particular diagnosis..." They also note that some of the information obtained in Table 4 is redundant to that in Tables 1 and 2 ('ejaculatory disturbance' and 'other male genital disorders', which includes impotence, are contained in Table 1 on TEAEs in depression; 'abnormal ejaculation', 'female genital disorder', and impotence' are included in Table 2 which enumerates TEAEs in OCD, panic disorder, and social anxiety disorder).

Unless the Agency is trying to establish a new standard in labeling for sexual side effects by using a table, I do not take issue with the sponsor's proposal on the above point. The text may not direct attention to these side effects as much as the table and the table shows more clearly the low placebo incidence of the sexual side effects. Together with other language the Agency has added on sexual side effects though, I think information on these side effects is considerable and clear.

- The Division had recommended changes in the **"Other Events Observed During the Premarketing Evaluation of Paxil"** section and these were made in a reasonable way. These involved terms that were too general to be informative.

The sponsor notes that issues on interactions with drugs such as astemizole, on mydriasis and glaucoma, and on neuroleptic malignant syndrome are still under discussion with the Agency and are not included in labeling at this time.

2. Safety Update

Safety data was submitted from the only additional ongoing study (study 595: "A Study of the Maintained Efficacy and Safety of Paroxetine vs. Placebo in the Long Term Treatment of Social Phobia") in social phobia patients. No new or unexpected AEs were identified.

In an additional 5 investigator-initiated studies that are ongoing, there have been no SAEs, withdrawals due to AEs, and no new or unexpected AEs identified.

3. Regulatory Status Update

Applications for paroxetine for the treatment of social anxiety disorder have been submitted to 56 countries with approval granted in 23 and 33 pending. The sponsor states that paroxetine has never been withdrawn from any country for safety reasons and there have been no negative actions. Copies of the labeling from countries where Paxil has been recently approved was reviewed and no new information uncovered.

4. World Literature Update

Results of a search of the database for all unsolicited, regulatory, and literature reports of paroxetine AE reports in patients with social phobia revealed no new information.

Dates of this search covered Oct. 16, 1997 through Feb. 12, 1999. Databases included

Clinical information analysts from the SB Information management department conducted the search. The output of the search consisted of abstracts that were reviewed for new safety findings. Complete texts were obtained if there was insufficient detail. Forty citations were generated.

5. Long-Term Efficacy Data

A non-IND, long-term, relapse prevention trial of Paxil in social anxiety disorder is underway.

6. Pediatric Studies

The sponsor has committed to conduct a study in a pediatric population.

/S/
Susan Molchan, M.D.
April 27, 1999

4-30-99
We have reached agreement with S+B on final labeling and this supplement can now be approved. See memo to file for more detailed comments.

/S/
TL, PADP

cc: NDA #20-031
HFD-120
HFD-120/SMolchan
TLaughren
AHomonnay

Review and Evaluation of Clinical Data

Application Information

NDA #: 20-031

Sponsor: SmithKlein Beecham Pharmaceuticals

Clock Date: May 6, 1999

Drug Name

Generic Name: Paroxetine hydrochloride

Trade Name: Paxil

Drug Categorization

Pharmacological Class: Serotonin reuptake inhibitor

Proposed Indication: Social Phobia

NDA Classification: SC 1

Dosage Forms: 10, 20, 30, 40 mg tablets

Route: Oral

Reviewer Information

Clinical Reviewer: Susan Molchan, M.D.

Completion Date: January 11, 1999

TABLE OF CONTENTS		
1.0	**Material Utilized in Review**	4
2.0	**Background**	5
2.1	Indication	5
2.2	Related INDs and NDAs	5
2.3	Administrative History	5
2.4	Proposed Directions for Use	5-6
2.5	Foreign Marketing	6
3.0	**Chemistry**	6
4.0	**Animal Pharmacology**	6
5.0	**Description of Clinical Data Sources**	6
5.1	Primary Development Program	6
5.1.1	Study Type and Design/Patient Enumeration	6-7
5.1.2	Demographics	7
5.1.3	Extent of Exposure	7
5.2	Secondary Source Data	7
5.2.1	Non-IND Studies	7
5.2.2	Post-marketing Experience	8
5.2.3	Literature	8
5.3	Adequacy of Clinical Experience	8
5.4	Data Quality and Completeness	8-9
6.0	**Human Pharmacokinetics**	9
7.0	**Integrated Review of Efficacy**	9
7.1	Overview of Studies Pertinent to Efficacy	9-13
7.2	Summary of Studies Pertinent to Efficacy	13
7.2.1	Study 502	13-18
7.2.2	Study 382	18-23
7.2.3	Study 454	23-28
7.3	Summary of Data Pertinent to Important Clinical Issues	28
7.3.1	Predictors of Response	28-32
7.3.2	Size of Treatment Effect	32
7.3.3	Choice of Dose	32-33
7.3.4	Duration of Treatment	33-34
7.4	Conclusions Regarding Efficacy	34
8.0	**Integrated Review of Safety**	34
8.1	Background and Methodology for Safety Review	34
8.1.1	Deaths	35
8.1.2	Other Serious Adverse Events	35
8.1.3	Dropouts	36
8.1.3.1	Overall Profile of Dropouts	36
8.1.3.2	Dropouts Due to Adverse Events	37-38
8.1.4	Adverse Events	38
8.1.4.1	Establishing Appropriateness of Adverse Event Categorization and Preferred Terms	38
8.1.4.2	Common, Drug-Related Adverse Events	38

APPEARS THIS WAY
ON ORIGINAL

1.0 Material Utilized in Review

This clinical review entailed examination of the following items:

NDA Volumes	Submission Date	Material
1.001	5/6/98	Table of Contents
1.020	5/6/98	Table of Studies
1.003-5	5/6/98	Study report:382
1.006-9	5/6/98	Study report:470
1.010-14	5/6/98	Study report:454
1.015-18	5/6/98	Study report:502
1.019	5/6/98	Integrated summary of efficacy
1.020-1	5/6/98	Integrated summary of safety
1.020	5/6/98	Post-marketing spontaneous reports
1.020	5/6/98	Dropouts-listings, enumeration
1.020	5/6/98	Safety:Laboratory studies, vital signs, ECG
1.020	5/6/98	SAEs-listing
1.012,1.016	5/6/98	Deaths/SAEs-narratives
1.003,1.007, 1.012,1.016	5/6/98	Dropouts-narratives
1.022-24	5/6/98	Clinical literature references
1.020-21	5/6/98	TEAE listings
1.001	5/6/98	Proposed labeling
1.001, CD-ROM	5/6/98	Index to CRFs
-	9/8/98	Adverse event dictionary
CD-ROM	5/6/98	Case report tabulations
CD-ROM	5/6/98	Case report forms

Case report forms for the following patients (by study #, site, patient #) were reviewed to audit the completeness and accuracy of data contained in the corresponding patient narrative summaries.

454-001-00039	470-009-00076
502-010-05344	382-004-00139
502-012-05304	382-011-00057
502-37-5146	454-008-00314

APPEARS THIS WAY
ON ORIGINAL

2.0 Background

2.1 Indication

Paroxetine hydrochloride(Paxil) is a selective serotonin reuptake inhibitor (SSRI) proposed for the treatment of social phobia in a dose range of 20-50 mg daily.

2.2 Related INDs and NDAs

IND for paroxetine hydrochloride tablets in held by SKB. NDA 20-031 for depression was submitted to the Agency November 20, 1989, and supplements for obsessive-compulsive disorder (OCD) and panic disorder May 7, 1996. NDA 20-710 was approved for an oral suspension of paroxetine hydrochloride.

2.3 Administrative History

Paxil was approved for the treatment of major depression in December, 1992 and for OCD and panic disorder in March, 1996.

An initial clinical protocol for a social phobia study was submitted April 12, 1995. The approval letter for the protocol recommended that durability of response over time be examined if the trial showed positive results and to carefully document any psychotherapy treatment that may confound the efficacy analysis.

A pre-NDA meeting for the social phobia indication was held February 11, 1997 and the Agency asserted that at least two efficacy studies needed to be submitted for the NDA. The Agency also recommended that the sponsor obtain independent expert advice on the conduct of social phobia studies especially regarding outcome measures, entry criteria, and comorbidity. This NDA was submitted May 6, 1998.

2.4 Proposed Directions for Use

Directions for use conveyed in the sponsor's proposed labeling are as follows:

Paxil should be administered as a single daily dose, usually in the morning. The recommended initial dosage is 20 mg/day. In clinical trials the effectiveness of Paxil was demonstrated in patients dosed in a range of 20 to 50 mg/day. Some patients not responding to 20 mg may benefit from dosage 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.

In elderly or debilitated patients, and patients with severe renal or hepatic impairment, the recommended initial dose is 10 mg/day. Dose should not exceed 40 mg/day.

2.5 Foreign Marketing

Paroxetine was first approved for marketing for depression, in 1990 in the U.K. and has been approved in 82 countries as of this submission. It was approved in many of the same countries for OCD and panic in 1996.

Applications for the treatment of social phobia have been submitted in Ireland, U.K., and the Netherlands.

No foreign regulatory agency has withdrawn paroxetine from marketing, not approved it, or issued warning letters as of January, 1999.

Dosage formulations for paroxetine available for marketing include: tablets (10, 20, 30, and 40 mg) and an oral suspension.

3.0 Chemistry

Reference is made to approved NDA 20-031 for depression.

4.0 Animal Pharmacology

Reference is made to approved NDA 20-031 for depression.

5.0 Description of Clinical Data Sources

5.1 Primary Development Program

5.1.1 Study Type and Design/Patient Enumeration

The clinical program for the treatment of social anxiety disorder with paroxetine started in April, 1995. Four studies have been completed. The primary efficacy studies are three 12 week double-blind, randomized, placebo-controlled trials (Studies 382, 502, 454). In these studies, 522 patients were assigned to paroxetine and 339 to placebo. A long term, placebo-controlled efficacy trial (study 470), with patients treated up to 52 weeks, was also completed. This was an extension of study 382. A total of 98 patients entered the initial open label phase (42 had been on paroxetine and 56 on placebo in study 382) and 55 of these (27 paroxetine and 28 placebo) went on to the

55 of these (27 paroxetine and 28 placebo) went on to the double-blind phase. Therefore, there were a total of 578 unique patients exposed.

There are no ongoing studies of paroxetine in social phobia being conducted by the sponsor, nor were any planned at the time of the submission.

An enumeration of all subjects is shown in Appendix 5.1.1.1. The studies are summarized in the `Table of all Studies' in Appendix 5.1.1.2.

5.1.2 Demographics

Demographic characteristics of all subjects included in the three 12-week studies are summarized in Appendix 5.1.2.1. There were no statistically significant differences with respect to demographic variables between the paroxetine and placebo groups.

Of the 861 patients enrolled in the three studies, 64% (n=551) of the patients were between the ages of 25-44 years. Only 5% (n=43) were 55 or older. Slightly more males than females were enrolled (54% vs. 46%). 84% (n=723) of the patients were Caucasian.

5.1.3 Extent of Exposure

Duration of exposure and dose for those who received paroxetine in the three 12-week studies and the extension study are shown in Appendix 5.1.3.1; exposure as calculated in patient-years is shown in Appendix 5.1.3.2.

Of the 578 patients studied, 62% (n=358) of patients received paroxetine for at least 85 days and 10% (n=58) for > 24 weeks. Most (82%) received a mean daily dose of 20-40 mg.

5.2 Secondary Source Data

5.2.1 Non-IND Studies

One of the submitted studies, #502, was a non-IND study. The other three studies were under IND .

5.2.2 Post-marketing Experience

In addition to reviewing ADR reports, the sponsor stated that they regularly search databases such as etc., for reports of adverse events associated with paroxetine administration. This submission contains information on ADR reports in patients with social anxiety disorder, with a cutoff date of October 16, 1997. There were four such reports, none SAEs; a listing describing the cases was provided with the submission.

5.2.3 Literature

The sponsor reported that in a search of the literature, two reports of studies and one case report of the use of paroxetine in patients with social anxiety disorder were found. Databases searched included . The cut-off date for this information was February, 1998. The individual performing the search is from SB's Clinical Information group, and has Master's degrees in Biomedical Chemistry and in Neuroscience. A copy of the search sequence utilized was provided which included key words. These included social phobia and paroxetine, including several brand names and compound numbers for the drug. Copies of these reports were provided by the sponsor and safety results were summarized.

5.3 Adequacy of Clinical Experience

Data substantiating efficacy for the treatment of social phobia comes from three placebo-controlled 12-week studies, two flexible dose and one fixed dose. The data presented for these studies is adequate for determining efficacy at the proposed doses.

Safety can be adequately assessed from the extensive post-marketing database, the above noted studies and one additional longer term study.

5.4 Data Quality and Completeness

The quality and completeness of efficacy and safety data was adequate for review. Eight case report forms (CRFs) selected at random were compared to the corresponding narrative summaries to assess the accuracy and completeness of data contained in the summaries. No deficiencies were found.

ECGs were not collected while on drug unless clinically indicated. The sponsor did not provide any systemic analysis of laboratory changes for studies 382 and 470, but the number of outliers was very low and ECG, vital signs, and laboratory data has been extensively evaluated previously for this drug.

6.0 Human Pharmacokinetics and Pharmacodynamics

Reference is made to approved NDA 20-031 for depression. Biopharmaceutics in addition submitted a brief review for this submission because in primary efficacy studies 502 and 454 an over-encapsulated product of the approved tablet was used. Dissolution comparisons were done and the product was found to be bioequivalent to the approved tablets.

7.0 Review of Efficacy

7.1 Overview of Studies Pertinent to Efficacy

The three placebo-controlled acute (12-week) studies provide the primary basis for evaluating the efficacy of paroxetine in the treatment of social anxiety disorder. A fourth study (470) was an extension of one of the acute studies in which patients could have been treated for a total of 52 weeks. The number of patients who completed this relapse prevention extension was small and did not have enough statistical power from which to draw conclusions. Only safety data from it will be considered in this review.

The specified primary efficacy variables specified in the three acute study protocols were the Liebowitz Social Anxiety Scale (LSAS) total score and the proportion of patients responding to treatment as determined by a Clinical Global Impression (CGI) Global Improvement Item score of 1 (very much improved) or 2 (much improved) relative to baseline.

Patients were screened for social anxiety disorder and other comorbidities of interest using structured clinical interviews. In study 502, conducted in Europe and South Africa, the multilingual MINI was used; in studies 382 and 454, conducted in North America, a modified Structured Clinical Interview for DSM (SCID) was used.

The modified SCID was developed with the assistance of academic social anxiety researchers[1] and contains modules for social

[1] Stein MS, Hazen AL. 1995. SCID-SKB Version 4.0. NDA Vol. 1.024, p.171.

anxiety disorder, as well as the more prevalent Axis I comorbidities: panic disorder (with and without agoraphobia), major depression, substance use disorders, and suicidal ideation. In order to ensure a relatively high level of baseline disease severity in these studies, patients were required to meet criteria for the generalized subtype of social anxiety disorder. The modified SCID included specific probes for eight performance situations (e.g., public speaking, eating in front of others) and nine interactional situations (e.g., interacting with strangers, attending social gatherings). Patients endorsing fear of four or more situations in the preceding 6 months, at least two of which were interactional, were considered to meet the DSM definition of the generalized subtype. The modules for social anxiety disorder, panic disorder, major depression, and substance use disorders were designed to ascertain a 6-month prevalence, while the suicidal ideation module was designed to ascertain a 1-month prevalence.

The clinician-rated MINI is another structured diagnostic screening instrument for Axis I DSM-IV disorders developed by researchers at the University of South Florida College of Medicine and at the Hospital de la Salpetriere in Paris, France. It was used in Study 502, which was conducted in six European countries and South Africa. The DSM-III-R version of the instrument has been shown to be reliable and sensitive relative to two criterion instruments: the SCID and the Composite International Diagnostic Interview (CIDI)[2,3]. The modules for social anxiety disorder, panic disorder, and obsessive compulsive disorder (OCD) were designed to ascertain a 1-month prevalence; for major depression, a 2-week prevalence, and for generalized anxiety and substance use disorders, a 6-month prevalence.

The Liebowitz Social Anxiety Scale (LSAS) is one of the most commonly used rating scales developed for the assessment of social anxiety disorder severity. It was designed to assess the range of social interaction and performance situations that individuals with social anxiety disorder may fear and/or avoid. It consists of 24 items rated on 0-3 subscales of fear (0 = none, 1 = mild, 2 = moderate, 3 = severe) and avoidance (0 = never, 1 = occasionally [1-33%], 2 = often [33-67%], 3 = usually [67-100%]). The 24 items can also be divided into subscales that

[2] Sheehan DV, Lecrubier Y, Sheehan KH, et al. 1997. The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. *Eur Psychiatry*, 12:232-241.
[3] Lecrubier Y, Sheehan DV, Weiller E, et al., 1997. The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview:relaibility and validity according to the CIDI. *Eur Psychiatry*, 12:224-231.

assess both fear and avoidance in social interactional and performance situations.

Heimberg et al. recently examined the psychometric characteristics of the LSAS in 382 patients who participated in several studies of pharmacological and cognitive-behavioral treatment[4]. The LSAS total and subscale scores were all normally distributed, with minimal skewness and kurtosis. For all subscales, Cronbach's alphas were high, ranging from 0.81 to 0.92, attesting to a high degree of internal consistency, a type of reliability indicating consistency across the individual items of the scale.

Evidence of the convergent validity of the LSAS was initially presented by Heimberg et al., who reported that scores on the LSAS subscales significantly correlated with scores on the Social Interaction Anxiety Scale and the Social Phobia Scale, two widely used self-report measures of social anxiety disorder with demonstrated reliability and validity[5]. Davidson et al. reported a substantial and statistically significant correlation ($r = 0.70$; $p < 0.0001$) between the LSAS and scores on the Duke Brief Social Phobia Scale, another frequently used measure of social anxiety disorder severity[6].

In the large-scale study of the LSAS conducted by Heimberg et al., the LSAS again demonstrated a high degree of convergent validity with other widely used measures of social anxiety disorder[4,7,8,9]. The LSAS was more highly correlated with the social anxiety disorder measures than with measures of depression (Beck Depression Inventory, Hamilton Rating Scale for Depression), especially after acute treatment.

The LSAS has been widely used in studies of pharmacological treatment of social anxiety disorder, and has also been used in studies of cognitive behavioral group treatment for social

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[4] Heimberg RG, Horner KJ, Juster HR, et al. In press. Psychometric properties of the Leibowitz Anxiety Scale and the Social Phobia Scale. *Psychol Medicine.*

[5] Heimberg RG, Mueller GP, Holt GS, et al. 1992. Assessment of anxiety in social interaction and being observed by others:the Social Interaction Anxiety Scale and the Social Phobia Scale. Behav Ther, 23:57-73.

[6] Davidson JRT, Potts NLS, Richichi EA, et al. 1991. The Brief Social Phobia Scale. *J Clin Psychiatry*, 52 (suppl):48-51.

[7] Watson D, Friend R. 1969. Measurement of social-evocative anxiety. J Consulting and Clin Psychology, 33:448-457.

[8] Marks IM, Mathews AM. 1979. Brief standard self-rating for phobic patients. Behav Res & Ther. 17:263-267.

[9] Dinardo PA, Barlow DH. 1988. The Anxiety Disorders Interview Schedule, Revised (ADIS-R). Albany NY:Graywind Publications.

anxiety[10], [11], [12], [13], [14], [15], [16], [17], [18]. In these studies, the LSAS has been responsive to change both within treatments and in comparisons between active treatments and placebo or waiting list controls. While there is no consensus in the published literature on a minimum change from baseline in the LSAS total score that is considered clinically meaningful, social anxiety disorder researchers have reported within-treatment effects in placebo-controlled acute studies in the range of -12 to -40 points for agents reported to be clinically useful.

Heimberg et al. also examined the treatment sensitivity of the LSAS, i.e., its ability to detect the effects of an intervention. First, they examined whether the LSAS was sensitive to change over time (within-treatment effect)[4]. Effects were calculated for each of the LSAS subscales and for other measures of social anxiety disorder, against which the effects for the LSAS could be evaluated. This analysis was conducted on pretreatment and posttreatment data for patients treated with either the monoamine oxidase inhibitor (MAOI) phenelzine or placebo. A within-treatment effect size of +1.0 represents improvement equal to 1.0 standard deviation unit from pretreatment to posttreatment. Patients treated with phenelzine demonstrated significant within-treatment effects for all measures. Effects for the LSAS scales ranged from 1.15-1.40. These effects were within the range of effects for the other measures (0.92-1.76) and not significantly different from any.

The second analysis of treatment sensitivity examined the ability of the LSAS to detect the effect of phenelzine in

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[10] Davidson JRT, Potts N, Richichi E, et al., 1993. Treatment of social phobia with clonazepam and placebo. J Clin Psychopharmacol, 13:423-428.

[11] Fahlen T, Nilsson HL, BorgG K, et al. 1995. Social phobia: the clinical efficacy and tolerability of the monoamine oxidase-A and serotonin uptake inhibitor brofaromine. *Acta Psychiatr Scand,* 92:351-358.

[12] Lott M, Greist JH, Jefferson JW, et al. 1997. Brofaromine for social phobia: a multicenter, placebo-controlled, double-blind study. *J Clin Psychopharmacology,* 17:255-260.

[13] Katzelnick DJ, Kobak KA, Greist JH, et al. 1995. Sertraline for social phobia: A double-blind, placebo-controlled crossover study. *Am J Psychiatry,* 152:1368-1371.

[14] Liebowitz MR, Schneier F, Campeas R, et al. 1992. Phenelzine vs. atenolol in social phobia: a placebo-controlled comparison. Arch Gen Psychiatry. 49:290-300.

[15] Versiani M, Nardi AE, Mundim FD, et al. 1992. Pharmacotherapy of social phobia: a controlled study with moclobemide and phenelzine. *Br J Psychiatry,* 161, 353-360.

[16]Marshall RD, Schneir FR, Fallon BA, Feerick J, Liebowitz MR. 1994. Medication therapy for social phobia. *J Clin Psychiatry,* 55 (suppl): 33-37.

[17] Munjack DJ, Bruns J, Baltazar PL, et al. 1991. A pilot study of buspirone in the treatment of social phobia. *J Anxiety Disorders*, 5:87-98.

[18] Reich J, Yates W. 1988. A pilot study of treatment of social phobia with alprazolam. *Am J Psychiatry*, 145:590-594.

comparison to placebo. The effects for the LSAS subscales ranged from 0.58 to 0.67, indicating that phenelzine was associated with LSAS scores at posttreatment that surpassed those of placebo patients by one-half a standard deviation or more. The other social anxiety measures had a wider range of effects, from 0.39 to 0.80.

In Studies 382 and 454 the LSAS was clinician-administered. Because of its straightforward format, some investigators have developed alternative forms of the LSAS. Katzelnick et al.[13] administered a computerized patient-rated version of the LSAS in a small (N = 12) double-blind crossover study of the treatment of social anxiety disorder with sertraline. The computerized version appeared to be roughly equivalent to the clinician-administered version (r = 0.89) and the majority of patients preferred the self-administered version. In Study 502, the LSAS was administered as a patient self-report questionnaire.

The Clinical Global Impressions (CGI) items used were the Severity of Illness Item and the Global Improvement Item. The CGI is rated by the clinician based on all information available at the time of the rating. For the Severity of Illness item, clinicians consider their total clinical experience with the particular patient population under study.

Efficacy criteria were similar for each of the acute studies. Secondary efficacy variables in the acute studies were as follows: mean change from baseline in the CGI Severity of Illness Item score (Studies 502 and 454); mean change from baseline in the Fear/Anxiety and Avoidance subscales scores of the LSAS; mean change from baseline in the Social Avoidance and Distress (SAD) Scale score; mean change from baseline in the scores of the items of the Sheehan Disability Scale (SDS); mean change from baseline in the Sheehan Disability Scale (SDS) Total; and the Hamilton Rating Scale for Depression (HAM-D) (17-item) (studies 502 and 454).

The expert consultants used to support the psychometric instruments used were Murray Stein, M.D. from UC-San Diego and Richard Heimberg, Ph.D. from Temple University.

7.2 Summary of Studies Pertinent to Efficacy

7.2.1 Study 502

Investigators/Locations

Principal investigators and study center locations are identified in Appendix 7.2.1. The study was carried out in 39 centers in the U.K., France, Spain, Belgium, Ireland, Germany, and South Africa.

Objectives

The primary objective of this study was to assess the efficacy of paroxetine as compared to placebo in the treatment of social phobia. The secondary objective was to compare the safety of paroxetine to placebo in these patients.

Population

Study participants were outpatients in the age range 18-85 years who had a DSM-IV primary diagnosis of social anxiety disorder using the MINI. Patients on stabilized psychotherapy regimens ongoing for at least 6 months, could be continued. Exclusion criteria included:

- Scored 1 or 2 on the Clinical Global Impressions (global improvement item) at baseline
- Required concomitant therapy with beta adrenergic blockers, monoamine oxidase inhibitors (MAOIs) benzodiazepines, or other psychoactive medications other than chloral hydrate
- Diagnosed with Axis I disorders such as dysthymia, simple phobia, major depression, obsessive compulsive disorder, or panic disorder as a primary diagnosis within 6 months prior to the screen visit
- Diagnosed with body dysmorphic disorder
- History of schizophrenia or bipolar affective disorder
- Previously unresponsive to paroxetine therapy (for depression or other uses)
- Positive pregnancy test or lactating (women)
- For women of child-bearing potential; not practicing a clinically accepted method of contraception
- Presence of any serious medical disorder or condition that would, in the investigator's opinion, have precluded the administration of paroxetine
- History of seizure disorders (except for febrile seizures in childhood)
- Met DSM-IV criteria for substance abuse (alcohol or drugs) within 3 months prior to the trial or substance dependence within 6 months
- Received ECT within 3 months of entry into the study

- Had clinically significant abnormal laboratory, or ECG findings not resolved by the Baseline (Day 0) examinations
- Posed a current, serious suicidal or homicidal risk in the investigator's judgment
- Had taken other psychotropic drugs, or antidepressants (including MAO inhibitors) within 14 days of Baseline, or depot-neuroleptics within 12 weeks
- Had used an investigational drug within the past month (or 5 half-lives, whichever was the longest)
- Had received psychotherapy (except stabilized psychotherapy regimens which have been ongoing for at least 6 months
- Had previous treatment for Social Phobia with SSRIs at a dose and for a duration which would have been adequate to show a response (equivalent to 3 months treatment with Prozac 20-40mg)
- Scored 15 or more on the 17 item HAMD at Baseline

Design

This was a multi-center, randomized, double-blind, placebo-controlled, parallel group study. Doses ranged from 20-50 mg daily (flexible dose), to be taken as a single daily dose each morning. After screening, there was a one-week, single-blind, placebo run-in phase. Baseline evaluations were then conducted to determine eligibility for the treatment phase, which was 12 weeks in duration. For the first two weeks of treatment, all patients randomized to paroxetine were prescribed 20 mg. After week 2, the dose could be titrated up 10 mg/week to a maximum of 50 mg daily, or down-titrated one dose level, according to response and tolerability. At the end of the study or on withdrawal, medication was tapered over 3 weeks.

Analysis

The primary efficacy variables specified in the study protocol were the Liebowitz Social Anxiety Scale (LSAS) total score and the proportion of patients responding to treatment as determined by a Clinical Global Impression (CGI) Global Improvement Item score of 1 (very much improved) or 2 (much improved) relative to baseline.

Secondary efficacy measures included: LSAS subscale scores, CGI Severity of Illness item, SADS Total, and the Sheehan Disability Inventory (SDI).

The proportion of patients achieving a response as defined by CGI Global Improvement of 1 or 2 was analyzed by logistic analysis using the categorical modeling procedure (CATMOD) of the SAS system. Only the treatment effect was included in the model. Due to the small number of patients in treatment-by-investigator cells, no adjustment for investigator was made in the analysis of responders. The mean change from Baseline in LSAS Total and Subscale Scores, CGI Severity of Illness, SADS, and SDS Items were analyzed using parametric analysis of variance using a model with effects for treatment and investigator. The general linear model (GLM) procedure of the SAS system was used to perform these analyses. Type III sums of squares were used.

Tests of hypotheses regarding model assumptions such as the significance of treatment-by-investigator interactions were made at the 10% level. All other statistical tests were two-tailed and performed at the 5% significance level.

The ITT population for analysis of efficacy included all patients who received double-blind medication and for whom at least one valid post-baseline efficacy evaluation was conducted.

Baseline Demographics

Baseline demographic data is displayed in Appendix 7.2.1. Treatment groups were comparable with respect to mean age, age range, gender, and race.

Baseline Severity of Illness

Groups did not significantly differ with respect to baseline scores on the LSAS, LSAS Fear and Avoidance subscales, CGI Severity of Illness, SADS, SDI, and Hamilton Depression scale. Groups did not differ in duration of social phobia. 82% of those randomized to paroxetine and 85% to placebo had social phobia for > 3 years. 5% and 6% of paroxetine and placebo patients, respectively, had received psychotherapy for their social phobia.

Patient Disposition

This study enrolled 323 patients. Of these, 290 patients met criteria for inclusion in the ITT population: 139 were randomized to paroxetine and 151 to placebo. Of the 33 patients who were screened and not randomized, 15 did not meet inclusion/exclusion criteria, 10 were not randomized for 'other'

reason, 4 had protocol violations including noncompliance, 3 were lost to follow-up, and 1 experienced an intercurrent illness adverse event (AE). The numbers of ITT completers at weeks 1, 2, 3, 4, 6, 8, and 12 are displayed in Appendix 7.2.1. Of the ITT samples, 104 (75%) of paroxetine and 109 (72%) of placebo-treated patients completed the study.

Dosing Information

Mean dose by visit is displayed in Appendix 7.2.1. At the final visit, the mean paroxetine dose was 35 mg/day. Further information on dosing in this study will be presented in Section 7.3.3 (Choice of Dose).

Concomitant medications

Concomitant psychotropic medications were prohibited during the study, with the exception of chloral hydrate which was permitted as needed for sleep disturbance. 18 (13%) paroxetine and 26 (17%) placebo patients received chloral hydrate. No paroxetine and 3 placebo patients received alprazolam, one in each group received diazepam, 1 paroxetine and no placebo patients received diphenhydramine, 1 paroxetine and 3 placebo patients received flouxetine. The concomitant medication usage is unlikely to bias the efficacy results in favor of paroxetine.

Efficacy Results

The change from baseline after 12 weeks of treatment for the LSAS total and the proportion of patients who had a CGI-Global Improvement item score of 1 or 2, in the ITT population were the primary efficacy variables. For this analysis, missing datapoints were estimated, i.e. last observation carried forward (LOCF). Results are summarized in Appendix 7.2.1. Observed cases data are also summarized.

Statistically significantly more patients on paroxetine as compared to placebo were shown to have a CGI-Global Improvement score of 1 or 2 ($p<0.001$) at week 12 (85/110 (77%) of paroxetine patients and 46/110 (42%) of placebo patients). Similar results were seen at weeks 4 ($p<0.01$), 6 ($p<0.002$), and 8 ($p<0.001$) for the LOCF analysis. Similar results were seen in the observed cases analysis (weeks 4, 6, 8, and 12).

Statistically significantly greater improvement was also seen in the LSAS total score in patients treated with paroxetine as compared to placebo at week 12 ($p<0.016$), as well as at weeks 4,

6, and 8. Similar results were seen with the observed cases dataset.

Five centers with a small number of enrolled patients enrolled and with missing cells were combined and treated as one site in analyses. This combined site had 7 patients (1 paroxetine and 6 placebo).

In the analysis of LSAS mean change from baseline, the treatment-by-investigator interaction was not found to be significant at endpoint (p=0.896). This interaction was not evaluated for the CGI item, as estimates would be invalid using this categorical measure.

Conclusions

Study 502 demonstrated adequate superiority of paroxetine over placebo in the treatment of patients with social anxiety disorder.

7.2.2 Study 382

Investigators/Locations

Principal investigators and study center locations are identified in Appendix 7.2.2. The study was carried out in 13 centers, 12 in the U.S. and one in Canada.

Objectives

The primary objective of this study was to assess the efficacy of paroxetine as compared to placebo in the treatment of social phobia. The secondary objective was to compare the safety of paroxetine to placebo in these patients.

Population

Study participants were outpatients in the age range 18-80 years who had a DSM-IV primary diagnosis of social anxiety disorder using a modified version of the SCID for DSM-IV. Patients on stabilized psychotherapy regimens ongoing for at least 6 months, could be continued. Exclusion criteria included:

- Scored 1 or 2 on the Clinical Global Impressions (global improvement item) at baseline

- Required concomitant therapy with beta adrenergic blockers, monoamine oxidase inhibitors (MAOIs) benzodiazepines, or other psychoactive medications other than chloral hydrate
- Diagnosed with Axis I disorders such as dysthymia, simple phobia, major depression, obsessive compulsive disorder, or panic disorder as a primary diagnosis within 6 months prior to the screen visit
- Diagnosed with body dysmorphic disorder
- History of schizophrenia or bipolar affective disorder
- Previously unresponsive to paroxetine therapy (for depression or other uses)
- Positive pregnancy test or lactating (women)
- For women of child-bearing potential; not practicing a clinically accepted method of contraception
- Presence of any serious medical disorder or condition that would, in the investigator's opinion, have precluded the administration of paroxetine
- History of seizure disorders (except for febrile seizures in childhood)
- Met DSM-IV criteria for substance abuse (alcohol or drugs) within 3 months prior to the trial or substance dependence within 6 months
- Received ECT within 3 months of entry into the study
- Had clinically significant abnormal laboratory, or ECG findings not resolved by the Baseline (Day 0) examinations
- Posed a current, serious suicidal or homicidal risk in the investigator's judgment
- Had taken other psychotropic drugs, or antidepressants (including MAO inhibitors) within 14 days of Baseline, or depot-neuroleptics within 12 weeks
- Had used an investigational drug within the past month (or 5 half-lives, whichever was the longest) or participated in a clinical trial in the past year.
- Had received psychotherapy (except stabilized psychotherapy regimens which have been ongoing for at least 6 months

Design

This was a multi-center, randomized, double-blind, placebo-controlled, parallel group study. Doses ranged from 20-50 mg daily (flexible dose), to be taken as a single daily dose each morning. After screening, there was a one-week, single-blind, placebo run-in phase. Baseline evaluations were then conducted to determine eligibility for the treatment phase, which was 12 weeks in duration. For the first two weeks of treatment, all

patients randomized to paroxetine were prescribed 20 mg. After week 2, the dose could be titrated up 10 mg/week to a maximum of 50 mg daily, or down-titrated one dose level, according to response and tolerability. At the end of the study or on withdrawal, medication was tapered over 3 weeks.

Analysis

The primary efficacy variables specified in the study protocol were the Liebowitz Social Anxiety Scale (LSAS) total score and the proportion of patients responding to treatment as determined by a Clinical Global Impression (CGI) Global Improvement Item score of 1 (very much improved) or 2 (much improved) relative to baseline.

Secondary efficacy measures included: LSAS subscale scores, SADS Total, and the Sheehan Disability Inventory (SDI) subscales.

The proportion of patients achieving a response (a CGI Global Improvement Item score of 1 or 2 was analyzed by logistic analysis using the categorical modeling procedure(CATMOD) of the SAS system with a model including effects for treatment and Investigator and using maximum likelihood estimates. Change from baseline scores of efficacy scales were analyzed using parametric analysis of variance methodology. The general linear model procedure of the SAS system was used to perform the analyses with a model including effects for treatment and Investigator. Type III sums of squares were used.
The treatment-by-Investigator interaction was found to be non-significant at endpoint for all variables; thus the term was removed from the model.

Because the analyses involve an effect for Investigator, the results may be affected by Investigators who have a small number of patients within a treatment group. Therefore, it was necessary to combine all patients from Investigators having few patients. The ratio of the sample sizes between the treatment groups is 1:1 for paroxetine and placebo respectively. For purposes of statistical analysis, the patients from Investigators having less than a total of ten patients were combined to form one group. Site 013 had less than ten total patients. This Investigator was combined with site 001 having the next smallest number of patients. The total number of patients for these two Investigators was 16. This grouping fell within the range of sizes for the other Investigators, 11 to 16.

Tests of hypothesis regarding model assumptions such as the significance of treatment-by-Investigator interactions were made at the 10% level. All statistical tests were two-tailed and performed at an alpha of 0.05. The comparison of interest was paroxetine versus placebo.

Following the initial efficacy analysis, it was determined that data generated by Center 003 in studies of three other indications, dysthymia, major depression, and panic disorder, had yielded statistically significant treatment-by-center interactions in analyses of efficacy variables. As these data were not representative of the data from the overall study populations in these studies, it was concluded that primary and secondary efficacy variables in Study 382 should be re-evaluated excluding data from Center 003. The results of this re-analysis did not alter the study conclusions, and therefore the presentation of data within this study report includes data from Center 003.

The ITT population included all patients who received double-blind medication and for whom at least one valid post-baseline efficacy evaluation was conducted.

Baseline Demographics

Baseline demographic data is displayed in Appendix 7.2.2. Treatment groups were comparable with respect to mean age, age range, gender, and race.

Baseline Severity of Illness

Groups did not significantly differ with respect to baseline scores on the LSAS, LSAS Fear and Avoidance subscales, SADS, and SDI. Groups did not differ in duration of social phobia. 98% of those randomized to paroxetine and 97% to placebo had social phobia for > 3 years. 3% and 2% of paroxetine and placebo patients, respectively, had received psychotherapy for their social phobia.

Patient Disposition

187 patients met criteria for inclusion in the ITT population: 94 were randomized to paroxetine and 93 to placebo. The numbers of ITT completers at weeks 1, 2, 3, 4, 6, 8, and 12 are displayed in Appendix 7.2.2. Of the ITT samples, 62 (66%) of paroxetine and 72 (77%) of placebo-treated patients completed

the study; these rates were not statistically significantly different.

Dosing Information

Mean dose by visit is displayed in Appendix 7.2.2. At the final visit, the mean paroxetine dose was 41 mg/day. Further information on dosing in this study will be presented in Section 7.3.3 (Choice of Dose).

Concomitant medications

Concomitant psychotropic medications were prohibited during the study, with the exception of chloral hydrate which was permitted as needed for sleep disturbance. No paroxetine and 2 placebo patients received chloral hydrate. Two paroxetine and 1 placebo patient received diazepam, 3 paroxetine and 0 placebo patients received diphenhydramine, and 1 paroxetine and 0 placebo patients received midazolam. This usage is unlikely to bias the efficacy results in favor of paroxetine.

Efficacy Results

The change from baseline after 12 weeks of treatment for the LSAS total and the proportion of patients who had a CGI-Global Improvement item score of 1 or 2, in the ITT population were the primary efficacy variables. For this analysis, missing datapoints were estimated, i.e. last observation carried forward (LOCF). Results are summarized in Appendix 7.2.2. Observed cases data are also summarized.

Statistically significantly more patients on paroxetine as compared to placebo were shown to have a CGI-Global Improvement score of 1 or 2 ($p<0.001$) at week 12 (50/91(55%) of paroxetine patients and 22/92 (24%) of placebo patients). Similar results were seen at weeks 4 ($p<0.005$), 6 ($p<0.003$) and 8 ($p<0.001$) for the LOCF analysis. Similar results were seen in the observed cases analysis (weeks 4, 6, 8, and 12).

Statistically significantly greater improvement was also seen in the LSAS total score in patients treated with paroxetine as compared to placebo at week 12 ($p<0.001$), as well as at weeks 2 through 8 for the LOCF data. Similar results were seen with the observed cases dataset.

In the analysis of LSAS mean change from baseline, the treatment-by-investigator interaction was not found to be

significant. This interaction was not evaluated for the CGI item, as estimates would be invalid using this categorical measure.

Conclusions

Study 382 demonstrated adequate superiority of paroxetine over placebo in the treatment of patients with social anxiety disorder.

7.2.3 Study 454

Investigators/Locations

Principal investigators and study center locations are identified in Appendix 7.2.3. Twenty-one centers were in the U.S. and one was in Canada.

Objectives

The primary objectives of this study were to assess the optimal effective and safe dosage of paroxetine in the treatment of social phobia.

Population

Study participants were outpatients in the age range 18-70 years who had a DSM-IV primary diagnosis of social anxiety disorder using a modified version of the SCID for DSM-IV. Patients on stabilized psychotherapy regimens ongoing for at least 6 months, could be continued. Exclusion criteria included:

- Scored 1 or 2 on the Clinical Global Impressions (global improvement item) at baseline
- HAM-D $\geq$ 15 (17-item)
- Required concomitant therapy with beta adrenergic blockers, monoamine oxidase inhibitors (MAOIs) benzodiazepines, or other psychoactive medications other than chloral hydrate
- Diagnosed with Axis I disorders such as dysthymia, simple phobia, major depression,obsessive compulsive disorder, or panic disorder as a primary diagnosis within 6 months prior to the screen visit
- Diagnosed with body dysmorphic disorder
- History of schizophrenia or bipolar affective disorder
- Previously unresponsive to paroxetine therapy (for depression or other uses)

- Positive pregnancy test or lactating (women)
- For women of child-bearing potential; not practicing a clinically accepted method of contraception
- Presence of any serious medical disorder or condition that would, in the investigator's opinion, have precluded the administration of paroxetine
- History of seizure disorders (except for febrile seizures in childhood)
- Met DSM-IV criteria for substance abuse (alcohol or drugs) within 3 months prior to the trial or substance dependence within 6 months
- Received ECT within 3 months of entry into the study
- Had clinically significant abnormal laboratory, or ECG findings not resolved by the Baseline (Day 0) examinations
- Posed a current, serious suicidal or homicidal risk in the investigator's judgment
- Had taken other psychotropic drugs, or antidepressants (including MAO inhibitors) within 14 days of Baseline, fluoxetine within 5 weeks, or depot-neuroleptics within 12 weeks
- Had used an investigational drug within the past month (or 5 half-lives, whichever was the longest)
- Had received psychotherapy (except stabilized psychotherapy regimens which have been ongoing for at least 6 months
- Lactose intolerance

Design

This was a multi-center, randomized, double-blind, placebo-controlled, parallel group study. Doses ranged from 20-50 mg daily (flexible dose), to be taken as a single daily dose each morning. After screening, there was a one-week, single-blind, placebo run-in phase. Baseline evaluations were then conducted to determine eligibility for the treatment phase, which was 12 weeks in duration. There were four treatment groups: 20, 40, or 60 mg paroxetine, and placebo. For the first week of treatment, all patients randomized to paroxetine were prescribed 20 mg. After week 1, patients assigned to 40 mg were increased to that level, as were the patients assigned to 60 mg. Those assigned to 60 mg were increased to that dose after another week. Dose adjustments were not permitted, though if there was an event felt unrelated to study medication (i.e. intercurrent illness), a maximum of 2 consecutive days of dosage interruption was permitted. At the end of the study or on withdrawal, medication was tapered over 2 weeks.

Analysis

The primary efficacy variables specified in the study protocol were the Liebowitz Social Anxiety Scale (LSAS) total score and the proportion of patients responding to treatment as determined by a Clinical Global Impression (CGI) Global Improvement Item score of 1 (very much improved) or 2 (much improved) relative to baseline.

Secondary efficacy measures included: LSAS subscale scores, CGI Severity of Illness item, SADS Total, and the Sheehan Disability Inventory (SDI). Patients were also administered the HAM-D.

The proportion of patients achieving a response as defined by CGI Global Improvement of 1 or 2 was analyzed by logistic analysis using the categorical modeling procedure (CATMOD) of the SAS system. Only the treatment effect was included in the model. Due to the small number of patients in treatment-by-investigator cells, no adjustment for investigator was made in the analysis of responders. The mean change from Baseline in LSAS Total and Subscale Scores, CGI Severity of Illness, SADS, and SDS Items were analyzed using parametric analysis of variance with a model with effects for treatment and investigator. The general linear model (GLM) procedure of the SAS system was used to perform these analyses. Type III sums of squares were used.

Tests of hypotheses regarding model assumptions such as the significance of treatment-by-investigator interactions were made at the 10% level. All other statistical tests were two-tailed and performed at the 5% significance level. When comparing individual dose groups against the placebo group, Dunnett's multiple comparison procedure was used to maintain an overall alpha level of 0.05.

The ITT population for analysis of efficacy included all patients who received double-blind medication and for whom at least one valid post-baseline efficacy evaluation was conducted.

Prior to unblinding of the data, it was decided to exclude data from center 005, as data recently generated for three other indications had yielded statistically significant treatment x center interactions in analyses of efficacy variables. Safety data from this center was included. A total of 4 patients, one in each treatment arm, were enrolled in center 005.

Baseline Demographics

Baseline demographic data is displayed in Appendix 7.2.3. Treatment groups were comparable with respect to mean age, age range, gender, and race.

Baseline Severity of Illness

Groups were generally similar with respect to baseline scores on the LSAS, LSAS Fear and Avoidance subscales, CGI Severity of Illness, SADS, SDI, and Hamilton Depression scale. The mean scores for the placebo group were numerically lower than scores of those on paroxetine, suggesting that the placebo group may have been less severely ill. This difference reached statistical significance ($p < 0.019$) for the pairwise comparison between placebo and the 20 mg group for the SAD scale and the SDI Social Life item.

Groups did not differ in duration of social phobia. 93-99% of those randomized to paroxetine and 95% to placebo had social phobia for > 3 years. Less than 1% and 1% of paroxetine and placebo patients, respectively, had received psychotherapy for their social phobia.

Patient Disposition

384 patients met criteria for inclusion in the ITT population: 97 each were randomized to the 20 and 60 mg paroxetine groups and 95 each to the 40 mg paroxetine and placebo groups. The numbers of ITT completers at weeks 1, 2, 3, 4, 6, 8, and 12 are displayed in Appendix 7.2.3. 64% of subjects completed the study. A higher percentage of paroxetine patients dropped out within the first two weeks of the study (20-23%) as compared to placebo (9%), though after that rates between drug and placebo were comparable.

Twenty patients (2 in the placebo group and 7, 6, and 5, in the 20, 40, and 60 mg groups, respectively), were withdrawn before and post-baseline efficacy assessments were conducted, so could not be included in the ITT population efficacy analysis. Together with the 4 patients excluded from center 005, this left 360 patients in the analysis.

Dosing Information

Mean dose by visit is displayed in Appendix 7.2.3. At the final visit, the mean paroxetine dose was 35 mg/day. Further

information on dosing in this study will be presented in Section 7.3.3 (Choice of Dose).

Concomitant Medications

Concomitant psychotropic medications were prohibited during the study, with the exception of chloral hydrate which was permitted as needed for sleep disturbance. No significant difference in incidence of concomitant medication use was seen among treatment groups. One placebo patient and 3-4 paroxetine papients within each dosage group received chloral hydrate during the study. Clonazepam was received by 3 patients in the 20 mg group and 1 in the 40 mg group, and sertraline was received by 2 patients in the 60 mg group. No other psychotropic medications were taken by more than one paroxetine patient. The concomitant medication usage is unlikely to bias the efficacy results in favor of paroxetine.

Efficacy Results

The change from baseline after 12 weeks of treatment for the LSAS total and the proportion of patients who had a CGI-Global Improvement item score of 1 or 2, in the ITT population were the primary efficacy variables. For this analysis, missing datapoints were estimated, i.e. last observation carried forward (LOCF). Results are summarized in Appendix 7.2.3. Observed cases data are also summarized.

Statistically significantly greater improvement was seen in the LSAS total score in patients treated with paroxetine 20 mg as compared to placebo at week 12 ($p<0.001$), as well as at week 8 ($p<0.002$). A trend towards significance was shown at 60 mg at 12 weeks ($p<0.024$). In the observed cases dataset, statistical significance was shown at 12 weeks for both the 20 mg and 40 mg doses; significance was also reached at 6 and 8 weeks. The linear p value was significant in the OC dataset at weeks 8 and 12 ($p<0.04$).

There was no consistent evidence of greater improvement at the 60 mg compared to the 40 mg dose or the 40 mg as compared to the 20 mg dose using the LSAS.

Statistically significantly more patients on paroxetine as compared to placebo were shown to have a CGI-Global Improvement score of 1 or 2 ($p<0.012$) at week 12: 47% of paroxetine 40 mg patients and 28% of placebo patients. Statistical significance was also achieved at week 6 for the LOCF analysis. A trend

towards statistical significance was seen for the 20 mg dose (p=0.02). In the observed cases analysis, similar results were shown, with the addition of statistical significance at the 60 mg dose at 12 weeks.

In the analysis of LSAS mean change from baseline, the treatment-by-investigator interaction was statistically significant, though no one or two centers or group of centers was found to be the cause. This interaction was not evaluated for the CGI item, as estimates would be invalid using this categorical measure.

A statistically significant linear trend at week 12 in the observed cases dataset for the LSAS total and at week 12 in the LOCF dataset for the percentage of patients with a CGI Global Improvement score of 1 or 2 were seen.

Conclusions

Study 454 demonstrated adequate superiority of paroxetine over placebo in the treatment of patients with social anxiety disorder at a dose of 20 mg.

7.3 Summary of Data Pertinent to Important Clinical issues

7.3.1 Predictors of Response

Potential interactions between age, gender, race, baseline severity of illness, treatment with psychotherapy, HAM-D total score change, and presence of comorbid psychiatric illness were evaluated. In study 454, each dose group was considered separately.

In the analyses of the pooled dataset from Studies 502 and 382, age was fitted both as a continuous covariate and as the categorical groups 18-34, 35-59, and ≥60 years in separate analyses. No analysis was conducted by age group for Study 454 because of the small number of patients in some cells. The age of patients enrolled in Studies 502 and 382 was not found to have a significant effect on either of the primary efficacy variables, and there were no significant age-by-treatment interactions.

In the analyses of the pooled dataset from Studies 502 and 382 and of Study 454,gender was fitted as a categorical covariate. Gender was not found to have a significant effect on either of the primary efficacy variables in any of the analyses.

The gender-by-treatment interaction was significant in the analysis of the mean change from baseline in the LSAS total score in Study 454 but in no other analysis. As both males and females improved more with paroxetine treatment than with placebo as measured by the LSAS, the appears to be due to a different ordering of improvement between the paroxetine dosage groups, with females responding best to the 20 mg dosage and the males responding essentially equally well to each of the three dosages. This finding was not confirmed in the analysis of response as measured by the CGI Global Improvement Item, where females responded best to the 20 and 60 mg dosages and males to the 40 mg dosage.

In the analyses of the pooled dataset from Studies 502 and 382 and of Study 454,race was fitted as a categorical covariate, Caucasian or non-Caucasian. Race was found to have a significant effect on the mean change from baseline in the LSAS total score in the pooled dataset from Studies 502 and 382 but in no other analysis from those studies. This effect is due to the greater mean improvement seen in non-Caucasians relative to Caucasians.

The race-by-treatment interaction was also significant in the analysis of the mean change from baseline in the LSAS total score in Study 454 but in no other analysis from that study. As both Caucasians and non-Caucasians improved more with paroxetine treatment than with placebo as measured by the LSAS, the significant interaction noted in Study 454 appears to be due to a different ordering of improvement between the paroxetine dosage groups, with non-Caucasians improving the most with the 20 mg dosage and Caucasians improving essentially equally well with each of the three dosages. There were no significant findings in the analysis of response as measured by the CGI Global Improvement Item.

In the analyses of the pooled dataset from Studies 502 and 382 and of Study 454, the baseline LSAS total score was fitted both as a continuous covariate and as three separate groupings of scores: the categorical groups $\leq$53, >53-78, and >78 points in separate analyses. These groupings were selected because they represent the lower, middle and upper tertiles respectively of LSAS total scores observed in another sample of 382 patients with social anxiety disorder.

The analyses using baseline LSAS as a categorical variable (LSAS total score group) resulted in a significant covariate in the mean change from baseline in the LSAS total score. This finding

represents differing degrees of improvement for each level of the covariate in the pooled. The treatment effect p-value in the analysis of Study 454 data is greater than 0.05 (0.07), which reflects the low response in the very small cells in the low LSAS group for the paroxetine patients (N's of 2, 9, and 3). This overly influences the overall treatment comparison, as the covariate groups are considered equally, regardless of sample size, in the this analysis. A significant covariate did not result from analysis of the CGI Global Improvement responders.

Similarly, when baseline LSAS total score was fitted as a continuous variable, it was found to have a significant linear relationship to the endpoint LSAS total score in the pooled dataset from Studies 502 and 382 and in Study 454. Although the baseline LSAS total score-by-treatment interaction was also found to be significant in the analyses of both the LSAS total score change from baseline and the percentage of CGI Global Improvement Item responders in Study 454 when the covariate was fitted as a continuous variable (LSAS total score), the interaction was not found to be significant when the covariate was fitted as a categorical variable (LSAS total score group).

In the analyses of the pooled dataset from Studies 502 and 382, ongoing psychotherapy at the time of entry into the study was fitted as a categorical covariate, yes or no. No analysis was conducted using psychotherapy for Study 454 because of the small number of patients in some cells (n=11 placebo patients, 10 paroxetine patients receiving psychotherapy). Ongoing psychotherapy in these studies was not found to have a significant effect on either of the primary efficacy variables and there were no significant psychotherapy-by-treatment interactions.

Though there was no interaction detected, the number of patients with ongoing psychotherapy were less than 5% of the total sample.

In both of the analyses of Studies 502 and 454, the mean change from baseline to study endpoint in the HAM-D total score was fitted as a continuous covariate; the HAM-D was not employed in Study 382. The change from baseline in the HAM-D total score was found to have a significant linear relationship with the change from baseline in the LSAS total score and was found to be a significant predictor of response based on the CGI Global Improvement. However, there were no significant changes in HAM-D-by-treatment interactions for either variable in either study,

and the magnitude of the treatment effect p-values remains unchanged with the use of this covariate.

In the analyses of the pooled dataset from Studies 502 and 382 and of Study 454, current comorbidity of interest (depression, OCD, panic disorder, and generalized anxiety disorder) was fitted as a categorical covariate, yes or no. This analysis is limited by the low number of patients with comorbidities, 37 of 463 (8.0%) in the pooled analysis of Studies 382 and 502 and 18 of 360 (5.0%) in Study 454. A significant treatment-by-covariate interaction was found for the pooled analysis for both the change from baseline in the LSAS total and the percentage of CGI responders. In both cases the placebo-paroxetine differences were small in the group of patients who had comorbid diagnoses. The sample sizes within this subgroup are too small to allow a conclusion of no efficacy; the 95% confidence interval around the treatment differences are (-14.2, 22.6) for the LSAS total and (-29.0, 35.0) for the CGI, demonstrating the low level of precision available within this subgroup.

Efficacy was, however, evident in the subgroup without comorbidity; the 95% confidence interval around the treatment differences are (-21.0, -10.2) for the LSAS total and (25.0, 43.0) for the CGI. The treatment comparison for the LSAS total change from baseline (p=0.25) is made weighing each level of the covariate equally, thereby allowing the small comorbid group to overly influence the overall comparison. The interpretation of this p-value is suspect given this level of extreme imbalance between the covariate groups. The numbers of patients in each of the paroxetine groups of Study 454 (3, 3, and 4) are too small to draw any meaningful conclusions about the relative efficacy of patients with comorbid conditions.

In summary, covariate analyses on the primary efficacy measures suggested that patients do not differ in their responsiveness to treatment according to age or concurrent psychotherapy. Although patients with greater baseline LSAS total scores on average achieved greater improvement on this measure with treatment, this improvement did not differ according to whether patients were treated with paroxetine or with placebo. Similarly, patients with greater improvement in depressive signs and symptoms as measured by the change in their HAM-D total scores demonstrated greater improvement on the LSAS and response on the CGI Global Improvement Item, but these beneficial effects occurred irrespective of treatment group assignment.

There was evidence that patients responded better to treatment with paroxetine than with placebo irrespective of their gender

or race, but other suggestions with regard to covariate-by-treatment interactions were inconsistent.

Results also suggested that patients with current psychiatric comorbidities that are likely to be responsive to paroxetine treatment are no more likely to improve or respond with paroxetine treatment than patients without such comorbidities.

7.3.2 Size of Treatment Effect

Treatment effect size was examined in terms of the difference between paroxetine and placebo with respect to the least-squares adjusted mean change from baseline to endpoint in LSAS total score (LOCF) for the three 12-week studies. Results are displayed in Table 7.3.2 below.

Table 7.3.2: Treatment Effect Size as Expressed by the LS Mean Change from Baseline to Endpoint in the LSAS Total Score (LOCF)

Study	Paroxetine	Placebo	Difference
502	-29.4	-15.6	13.8
382	-30.5	-14.5	16.0
454 (20 mg)	-31.4	-15.0	16.4
454 (40 mg)	-24.5		9.5
454 (60 mg)	-25.2		10.2

Drug/placebo differences were statistically significant for studies 502, 382, and for the 20 mg dose of study 454. There was a trend towards significance for the other two doses. These reductions in LSAS score are comparable to those achieved in trials of MAOIs which have been demonstarted to be efficacious in 64-80% of patients with social phobia.

Although at the study endpoints, patients continued to have LSAS scores in the 50s on average, the decrease in scores was statistically significant in all three studies. Taken together with the data from the CGI Global Improvement scores, the effect appears to be clinically significant in 47-66% of patients. These results lend support for the efficacy of paroxetine in the treatment of social phobia. Based on the results from study 454, there does not appear to be a dose-response relationship.

7.3.3 Choice of Dose

All three 12 week studies provide support for the approval of paroxetine for the treatment of social phobia. Studies 502 and 382 utilized a flexible dose range of 20-50 mg daily and were

positive on both primary efficacy measures in both the LOCF and the OC datasets. Mean doses at endpoint for completers were 35 and 41 mg. In the fixed dose study, 454, superiority over placebo was demonstrated using the LSAS total at 20 mg, with trends towards significance at the 40 and 60 mg doses. Statistical significance over placebo was shown at 40 mg for the percentage of patients with a CGI Global Improvement score of 1 or 2. There were statistical trends towards significance at the other two doses.

The sponsor proposes an initial daily dosage of 20 mg. For those not responding, dose increases in 10 mg increments, in intervals of a least one week, are recommended, up to a maximum of 50 mg daily. These recommendations are appropriate given the study results obtained.

In the elderly and those with severe renal or hepatic impairment, the initial recommended dose is 10 mg daily, with a maximum recommended dose of 40 mg.

To explore the possible relationship between dose and efficacy, the sponsor performed a linear regression analysis between the mean change from baseline in LSAS total score and the mean daily dose for completers. A similar analysis was done using the percentage of patients achieving a 1 or 2 on the CGI Global Improvement item. No statistically significant linear trend was seen for the LSAS in the LOCF data set, though significance was reached in the OC dataset at weeks 8 and 12 ($p=0.04$). For the CGI measure, statistical significance was achieved at week 12 in the LOCF dataset ($p=0.04$) and at weeks 6 and 12 for the OC dataset ($p=0.04$ and <0.001, respectively).

Since statistical significance was achieved in the LOCF dataset only at 20 mg for the LSAS and only at 40 mg for the CGI measure, and the linear trend was not statistically significant for the LSAS in the LOCF analysis, the bulk of the evidence goes against there being a significant dose-response relationship demonstrated.

7.3.4 Duration of Treatment

The long-term treatment study, 470, ended with lower than projected enrollment and did not have the statistical power to detect a significant difference in incidence of relapse. The number of patients who entered the double-blind phase of the study was 55 (half on paroxetine and half on placebo), 98 were

estimated as needed. Approximately twice as many placebo as paroxetine patients dropped out of the double-blind phase.

7.4 Conclusions Regarding Efficacy

The sponsor provided data from three short-term (12 week), adequate, well-controlled trials supporting the effectiveness of paroxetine in the treatment of social phobia. The two flexible dose studies (502 and 382) were positive on both primary efficacy measures in both the LOCF and the OC datasets. In the fixed dose study, 454, LCOF analysis showed superiority over placebo using the LSAS total at 20 mg, with trends towards significance at the 40 and 60 mg doses. Statistical significance over placebo was shown at 40 mg for the percentage of patients with a CGI Global Improvement score of 1 or 2. There were statistical trends towards significance at the other two doses.

As noted above the dose ranges proposed by the sponsor are appropriate.

As noted above the relapse prevention study that was completed was inadequate and a commitment for performance of a relapse prevention study is recommended.

The sponsor appropriately notes in the proposed labeling that the efficacy of Paxil has not been demonstrated beyond 12 weeks.

8.0 Integrated Review of Safety

8.1 Background and Methodology for Safety Review

The same formulation of paroxetine chloride tablets has been approved for depression, panic disorder, and OCD, in doses similar to those proposed for the current indication of social phobia, so there is extensive pre- and post-marketing experience with the drug. This safety review therefore, will be relatively limited in scope.

This review will focus on the safety data (adverse events, vital signs, and laboratory) from the three acute 12-week studies and one extended use study of paroxetine in patients with social phobia.

8.1.1 Deaths

One death occurred in the four studies of patients with social phobia. Monitoring was done through 30 days after the last dose of study medication.

The death was a suicide in study 502: Patient 502.037.05146 was a 23 year old male with a 3 year history of social anxiety disorder. Approximately 5 weeks after beginning paroxetine treatment, his mother reported that he had stolen and overdosed on his grandmother's medication (bisoprolol, isosorbide dinitrate, nitrazepam). Autopsy had been refused. The investigator felt that the event was probably unrelated to paroxetine.

8.1.2 Other Serious Adverse Events

A serious non-fatal adverse event (SAE) was defined as any event that was life-threatening, permanently or temporarily disabling or incapacitating or resulted in hospitalization, prolonged a hospital stay or was associated with congenital abnormality, cancer or overdose. In addition, it included any experience that the Investigator regarded as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug.

The sponsor reported all SAEs occurring through 30 days after the last dose of study medication.

Among the 3 acute studies, there were 14 SAEs reported by 8 patients. Six (6/522 or 1.1%) of these were on paroxetine and two (2/339 or 0.6%) on placebo. None were felt to be 'Related' to the study medication by the Investigator. In the extension study, two patients experienced SAEs while on paroxetine and one while on placebo. None were felt to be 'Related' to the study medication by the Investigator.

Data for these SAEs are summarized in a patient line listing in Appendix 8.1.2.1.

The patient in the extension study who became paranoid and agitated was found to have used PCP and the unintentional overdose was asymptomatic; the patient had taken the wrong dose (60 mg) during the first two weeks of the extension.

Narrative summaries for all paroxetine-treated patients with SAEs were reviewed to verify the characterization of events listed.

8.1.3 Dropouts

8.1.3.1 Overall Pattern of Dropouts

Table 8.1.3.1.1 displays the numbers (percentages) of patients who completed the three acute studies and dropouts; Table 8.1.3.1.2 shows this information for the extension study.

Table 8.1.3.1.1: Enumeration (Percentages of Randomized) of Premature Terminations by Reason (Studies 502, 382, 454)

	Paroxetine	Placebo
Randomized	522	339
Completed	345 (66%)	249 (73%)
Dropout due to:		
Adverse Event	84 (16%)	13 (4%)
Lack of Efficacy	9 (2%)	39 (11%)
Protocol Deviation	22 (4%)	8 (2%)
Lost to F/U	43 (8%)	21 (6%)
Other	19 (4%)	9 (3%)

Table 8.1.3.1.2: Enumeration (Percentages of Randomized) of Premature Terminations by Reason (Study 470)

	Open-label	Double-Blind	
		Paroxetine	Placebo
Randomized	98	27	28
Completed	64 (65%)	21 (78%)	15 (54%)
Dropout due to:			
Adverse Event	19 (19%)	2 (7%)	4 (14%)
Lack of Efficacy	8 (8%)	2 (7%)	3 (11%)
Protocol Deviation	7 (7%)	2 (7%)	2 (7%)
Lost to F/U	4 (4%)	0 (0%)	2 (7%)
Other	5 (5%)	0 (0%)	2 (7%)

In the pool of the three acute 12-week studies, 66% of the paroxetine and 73% of placebo patients randomized completed the studies. As expected, more active drug patients than placebo patients dropped out for adverse events, the opposite being true for lack of efficacy. A substantial number of patients (6-8%) were lost to follow-up.

In the extension study (470), patients had completed study 382 and enrolled in an open-label phase, with re-randomization to a double-blind phase if they chose to continue, so by the end of the double-blind phase, more patients had dropped out due to adverse events and lack of efficacy in the placebo group. 19% dropped out during the open-label phase due to an adverse event, the majority of these had been on placebo in study 382.

8.1.3.2 Dropouts Due to Adverse Events

Tables 8.1.3.2.1 and 8.1.3.2.2 show the proportions of patients who dropped out due to adverse events in at least 1% of the paroxetine patients. Since the numbers of patients in the extension study was relatively few, only those events are included that occurred in more than one individual while on either open-label or double-blind paroxetine.

Table 8.1.3.2.1: Adverse Events Leading to Dropout in at least 1% of Paroxetine Patients (Studies 502, 382, 454)

Body System/Event	**Paroxetine** (n=522)	**Placebo** (n=339)
Body as a Whole		
Asthenia	2%	<1%
Sweating	1%	0%
Headache	2%	1%
Digestive		
Flatulence	1%	<1%
Nausea	4%	<1%
Vomiting	1%	0%
Nervous		
Anxiety	1%	0%
Dizziness	2%	0%
Insomnia	3%	0%
Libido decreased	1%	0%
Somnolence	3%	<1%
Tremor	2%	0%
Urogenital		
Ejaculation abnormal*	5%	<1%

*Percentage corrected for gender.

Table 8.1.3.2.2: Adverse Events Leading to Dropout in at least 1% of Paroxetine Patients (Study 470)

Body System/Event	**Open-label (n=98)**	**Double-Blind**	
Body as a whole		**Paroxetine** (n=27)	**Placebo** (n=28)
Asthenia	5%	0%	0%
Headache	1%	4%	4%
Nervous			
Depression	0%	7%	0%
Insomnia	1%	4%	0%
Libido decreased	1%	4%	0%
Nervousness	0%	7%	7%
Somnolence	4%	0%	0%
Urogenital*			
Ejaculation abnormal	8%	0%	0%
Female genital disorder	5%	0%	0%
Impotence	3%	0%	0%

*Percentages corrected for gender.

These observations are typical for SSRIs and similar to those observed with paroxetine for its other psychiatric indications.

A review of all listings and narratives of adverse events leading to dropout among paroxetine subjects in the entire safety database. The only one unexpected from prior experience was increased intraocular pressure in one patient in study 382. This was mild, began 4 days after beginning drug, and resolved after discontinuation.

8.1.4 Adverse Events

8.1.4.1 Establishing Appropriateness of Adverse Event Categorization and Preferred Terms

Adverse experiences were coded using the WHO disease codelist and were then classified by the Adverse Drug Event Coding System (ADECS) (COSTART based) to give the body system and preferred term.

The thesaurus used to encode verbatim AE terms to preferred terms was examined to assess the accuracy and usefulness of this coding process. Coding appeared to be reasonable.

8.1.4.2 Common, Drug-Related Adverse Events

Treatment emergent AEs were those events reported for the first time on or after the first day of double-blind medication and up to the last dose in the treatment phase, i.e., prior to taper. This definition also encompasses non-serious AEs during this phase that were rated as more severe relative to baseline.

Appendix 8.1.4.2.1 presents the proportions of paroxetine and placebo patients who experienced TEAEs for those events occurring in at least 1% of patients within the pool of the three acute 12-week studies.

AEs that were common and probably drug-related (i.e., occurring in at least 5% of the paroxetine patients and at an incidence at least twice that in the placebo group) are summarized in Appendix 8.1.4.2.2.

The extension study (470) included patients who had completed study 382 and contained a relatively small number of patients. Adverse events and their incidence were similar to those shown in the Tables for the acute studies.

8.1.4.3 Effects of Age, Gender, and Race on Adverse Event Reporting Incidence

The sponsor explored the effect of demographics on AE incidence by comparing the incidence of AEs that occurred in ≥5% of the paroxetine patients in the three acute studies between gender subgroups, race subgroups (white vs. non-white), and age subgroups (18-34 years, 35-59 years, ≥60 years). Statistical testing of the odds ratios and relative risk were done on TEAEs occurring in ≥5% of paroxetine patients with an incidence at least twice that of placebo for all variable except age, as there were only 13 patients ≥65 years old (3 on paroxetine, 10 on placebo). Results of these analyses revealed that females are at greater risk for constipation and dry mouth than males. Otherwise, AE incidence was not significantly affected by these demographic variables.

8.1.4.4 Dose-Relatedness

The potential relationship between AE incidence and dose was examined separately in the fixed dose study (454) and the two flexible dose studies by the sponsor. The results from the fixed dose study will be considered here, as it has a good number of subjects in each group (about 100 in the ITT population) and a fixed dose study is most appropriately considered for this type of analysis.

In study 454, dose dependency of adverse events was evaluated by determining which commonly reported events (≥ 5% in any treatment group) occurred with at least a 50% greater incidence in the 40 and/or 60 mg groups as compared to the 20 mg and placebo groups. Events meeting this criteria included abnormal ejaculation, yawn, tremor, sweating, constipation, impotence, vomiting, myoclonus, paresthesia, increased apetite, taste perversion, and urination impaired.

8.1.4.5 Other Events Observed During Premarketing Studies of Social Phobia

Events other than those listed in Appendices 8.1.4.2.1 or 8.1.4.2.2 that were reported during all four studies are depicted in Appendix 8.1.4.5 by body system and preferred term.

8.1.5 Laboratory, Vital Sign and ECG Data

8.1.5.1 Laboratory, Vital Sign, and ECG Assessments

Table 8.1.5.1.1 below summarizes the timing of lab and vital signs assessments. For dropouts, lab and vital sign assessments were done at the time of termination. Lab testing in the three acute studies included: hematology (H/H, WBC/diff, platelets), chemistry (electrolytes, BUN, creatinine, ALT, AST, alkaline phosphatase, bilirubin, calcium), thyroid panel, and urinalysis (dipstick for protein, glucose, rbc & wbc count). Vital signs measurements included sitting blood pressure and pulse rate.

Table 8.1.5.1.1: Timing of Laboratory, Vital Sign, and ECG Assessments

	Study 502	Study 382	Study 454	Study 470
Laboratory tests	Screening, week 12	Screening, week 12	Screening, Week 12	Baseline, weeks 24, 40
Vital signs	Screening, baseline, weeks 1-4, 6, 8, 12	Screening, baseline, weeks 1-4, 6, 8, 12	Screening, baseline, weeks 1-4, 6, 8, 12	Baseline, weeks 1-4, 8, 12, 16, 24-28, 30, 32, 36, 40
12-lead ECG	Screening	Screening	Screening	None

8.1.5.2 Analyses of Laboratory, Vital Sign, and ECG Data

For the ISS analyses, the sponsor pooled the data from the two larger acute studies (454 and 502). The sponsor states that lab results for studies 382 and 470 were not routinely reported to the sponsor, nor were they entered into a formal database for analysis. Any abnormality in those studies deemed to be clinically significant by the investigator was recorded in the Case Report Form as an AE and included in the formal analyses of AE incidence. For the pool of studies 454 and 502, acute study 382, and the extension study (470), this review will focus on an analysis of outliers as well as dropouts due to lab or vital signs abnormalities. Any dropouts or AEs associated with ECG abnormalities will be noted.

8.1.5.3 Results of Analyses

8.1.5.3.1 Laboratory Data

Appendix 8.1.5.3.1.1 displays criteria for lab values of potential clinical concern. Appendix 8.1.5.3.1.2 displays proportions of patients in the paroxetine and placebo groups who experienced a laboratory value of PCS (post-baseline up to 14 days after drug discontinuation) for studies 454 and 502. Only those variables for which at least one paroxetine patient had a

flagged value and for which the drug incidence is higher than the placebo incidence are presented. Narratives were reviewed for all laboratory values of PCS.

No statistical analyses were done to compare the fractions of patients with lab values of PCS on paroxetine vs. placebo. None of the abnormalities were serious, most were not clinically significant. The number of abnormalities was also small (<1%) with the exception of eosinophils. None of the increased eosinophil counts in the paroxetine group were considered to be clinically significant by investigators; none were associated with AEs. The patient with an increased ALT had a level of 206 IU/L at week 12; no corrective action was taken and he declined to return for follow-up evaluation. One patient with increased bilirubin had elevated levels on entry; while on drug increases did not exceed 0.5 mg/dl; none of these increases were considered clinically significant. There were no associated AEs.

No patient dropped out due to a laboratory abnormality.

In study 382, laboratory abnormalities that were reported as AEs were: ALT and AST increased slightly in one patient (none on placebo). There were no dropouts due to laboratory abnormalities.

In the extended study 470, there were no dropouts due to laboratory abnormalities and no clinically significant laboratory abnormalities. Abnormalties reported were: hyperthyroidism (1), AST increased (1), ALT increased (1), and hematuria (1).

Regarding LFTs, for the pooled studies 454 and 503, mean changes of $\geq$5% as compared with baseline were found for ALT (+11%), AST (+9%), and total bilirubin (-7%), while on paroxetine and on placebo, these were, respectively, 1%, 3%, and 0%. Despite these increases, mean values at endpoint were all within the normal reference ranges.

In sum, the data in this NDA provide no evidence that paroxetine is associated with any clinically significant laboratory abnormalities.

8.1.5.3.2 Vital Sign Data

Appendix 8.1.5.3.2.1 displays the criteria for vital signs values of PCS. Appendix 8.1.5.3.2.2 displays the proportions of patients in the paroxetine and placebo groups who experienced a

vital signs reading of PCS post-baseline in the pool of the acute studies: 454, 502, and 382. Data is included only when at least one patient on paroxetine had an abnormality.

No SAEs were associated with any of these vital signs changes; concurrent AEs included nocturnal sweating in one patient with decreased DBP and somnolence in the patient with increased SBP. In the extended study (470), the only PCS value reported was decreased pulse; concurrent AEs were transient tremor and dizziness.

No patient withdrew from a study due to an abnormal vital sign parameter. No significant mean changes in vital signs parameters were seen in the pool of the three acute studies.

8.1.5.3.3 ECG Data

No paroxetine patient dropped out due to an abnormal ECG finding. As noted above, ECGs were done as per the protocols only at screening.

8.2 Adequacy of Patient Exposure and Safety Assessments

The same formulation of paroxetine HCl tablets has been approved for three indications, so its safety has been extensively reviewed in the past and there has been a considerable post-marketing database collected. No new safety concerns have been raised in these studies in patients with social phobia, though the database is relatively limited in terms of number of patients tested (578 on paroxetine) and safety assessments, such as the lack of ECG data collection while on drug. In view of the considerable experience with the drug, it is felt that the submitted database is sufficient to reasonably assess the safety of the drug in this population.

8.3 Safety Findings From Post-Marketing Reports and the Literature

As noted in sections 5.2.2 and 5.2.3 above, there were 4 reports of adverse events associated with paroxetine in which social phobia was the reported indication and three literature reports. None of the post-marketing AEs were serious; all are adequately covered by the proposed labeling. They included: panic attack (post-treatment), furuncles and itching, inability to pass urine, and delayed orgasm.

In the literature reports, reported AEs were generally the common ones included in labeling and none were serious.

8.4 Conclusions Regarding Safety

This safety review revealed no major safety concerns that would preclude approval or warrant substantial modification of labeling as it now exists for Paxil. Based on the pool of the three acute studies, the common AE profile seen in patients with social phobia is very similar to that seen for the other indications.

9.0 Labeling

The revised labeling, submitted with this NDA supplement was reviewed. Only sections of the labeling to which information was added are commented on below.

Clinical Trials

In giving the percentage of CGI Global Improvement Item responders, the percentages from the observed cases analysis is used. It would be more legitimate to use the percentages from the LOCF analysis.

A statement defining who is considered a responder (CGI Global Improvement Item score of 1 [very much improved] or 2 [much improved] relative to baseline) should be added to labeling.

In the sentence: "In addition to the significant difference in the LSAS Total Score at week 2, …" the '2' should be '12'-I assume this is a typo.

The information on positive response to the secondary efficacy measures listed may be excluded.

In the paragraph on Study 3, which is fixed dose study 454, the statement: "Paroxetine dosages of 20 and 40 mg/day were demonstrated to be significantly superior to placebo on the LSAS Total Score or the CGI Global Improvement Item Score" is literally correct. It may be a little misleading though, in that on the LOCF analysis of the LSAS the 20 mg and not the 40 mg dose was statistically significant (though both were significant using the OC analysis). Similarly, for the CGI Improvement Item on the LOCF, the 40 mg and not the 20 mg dose came out as statistically significant, though both were significant on the OC analysis. It would be a bit wordy to get into those points

for labeling and I don't think they are clinically significant. I would probably let their statement stand.

Also on Study 3, the statement about "a suggestion of a possible dose response relationship for effectiveness.." is not very definitive and neither is the data on dose-response (section 7.3.1 of the review). I would delete it.

As for the flexible dose studies, for fixed dose Study 3 in labeling the percentages of CGI responders given are from the OC analysis. The LOCF analysis numbers should be used.

The statement on subgroup analyses would be more accurate if it added that there were "no clinically significant" differences in treatment outcomes. A few probably clinically insignificant and inconsistent differences were found for race as discussed in section 7.3.1.

A statement on the range of ages of patients in the trials could be added.

Indications and Usage

This section is adequate as written.

Adverse Reactions

The data in this section is accurate; the section is adequate as written.

Dose Dependency of Adverse Events

The statement here is accurate and adequate as written.

Other Events Observed During the Premarketing Evaluation of Paxil

This section is accurate and adequate as written.

Dosage and Administration

This section is adequate as written.

10.0 Conclusions

The evidence presented is sufficient to support the claim of efficacy of Paxil in the treatment of social phobia in doses of 20-50 mg daily, for up to 12 weeks.

As for the previously approved indications for Paxil, there is adequate evidence of reasonable safety under the conditions of use in the proposed labeling.

11.0 Recommendations

From a clinical standpoint, it is recommended that Paxil be approved for the treatment of social phobia.

It is recommended that the sponsor be requested to conduct a well-controlled relapse prevention study of Paxil in social phobia.

/S/

Susan Molchan, M.D.
January 11, 1999

APPEARS THIS WAY
ON ORIGINAL

3-5-99

I agree that this supplement is approvable. See memo to file for more detailed comments.

/S/
TL, PDP

cc: NDA 20-031
HFD-120
HFD-120/TLaughren
/SMolchan
/AHomonnay

Appendix 5.1.1.1: Patient Enumeration by Study Type		
Completed Phase 3 Studies	Treatment Groups	
Study Type	Paroxetine	Placebo
12-Week Placebo Control		
Flexible Dose	233	244
Fixed Dose	289	95
Subtotal	522	339
Extension Study		
Flexible Dose Open label	98[1]	
Fixed Dose Placebo-Control	27	28
Total unique patients	578	339

[1]Of these 98, 56 had been on placebo & 42 on paroxetine in study 382.

Appendix 5.1.1.2	**Table of All Studies**			
Study #/country	**Design**	**Dose**	**N,parox**	**N, pbo**
Placebo-Controlled, 12-Week				
502 Belgium, Spain, France, Germany, Ireland, UK, S. Africa	Double-blind, randomized, flexible-dose	20-50 mg	139	151
382 USA, Canada	Double-blind, randomized, flexible-dose	20-50 mg	94	93
454 USA, Canada	Double-blind, randomized, fixed-dose	20, 40, 60 mg	289	95
Extension Study (after study 382)				
470 USA	Open-label, flexible-dose x 24 weeks, to double-blind, randomized, pbo-controlled x 16 weeks	20-50 mg	98[1]	28

[1]27 of the 98 went on to paroxetine in the placebo-controlled phase.

APPEARS THIS WAY
ON ORIGINAL

Appendix 5.1.2.1 Demographic Characteristics for Patients in Three 12-Week Studies (ITT)		
	Paroxetine (n=522)	**Placebo** (n=339)
Age (years)		
Mean	37	36
Range	18-70	18-85
Age Groups		
<35	230 (44%)	163 (48%)
35-64	289 (55%)	166 (49%)
>64	3 (0.6%)	10 (2.9%)
Sex		
Female	238 (46%)	159 (47%)
Male	284 (54%)	180 (53%)
Race		
Caucasian	428 (82%)	295 (87%)
Black	48 (9%)	22 (6%)
Oriental	10 (2%)	3 (1%)
Other	36 (7%)	19 (6%)
Weight (kg)		
Mean	75	73
Range	38-155	42-159

Appendix 5.1.3.1 Number of All Patients Receiving Paroxetine: Mean Daily Dose/Duration							
Duration (days)	Mean Paroxetine Dose (mg/day)					Total N	(%)
	20	**21-30**	**31-40**	**41-50**	**51-60**		
1-7	46	0	0	0	0	46	(8)
8-14	17	11	0	0	0	28	(5)
15-28	9	14	13	3	0	39	(7)
29-42	6	2	10	4	1	23	(4)
43-56	4	4	8	1	0	17	(3)
57-70	2	2	13	5	4	26	(4)
71-84	12	3	13	5	6	39	(7)
85-168	93	37	106	19	47	302	(52)
169-252	1	5	5	3	0	14	(2)
253-336	3	7	18	6	0	34	(6)
337-365	0	2	6	2	0	10	(2)
Total	193	87	192	48	58	578	(100)
(%)	(34)	(15)	(33)	(8)	(10)	(100)	

Appendix 5.1.3.2 Person-Time Exposure to Paroxetine and Placebo		
Treatment	**N**	**Patient-Years**
Paroxetine	578	151
Placebo	339	84

Appendix 7.2.1

Study 502: Principal Investigators

Investigators	Ctr	Location
Frank O'Donoghue	001	St Patricks Hospital, Dublin, Ireland
John Lynch	002	St Luke's Hospital, Clonmel, Ireland
David Nutt	003	Bristol Royal Infirmary, Bristol, U.K.
Shashank Chattree	004	Queen's Park Hospital, Blackburn, U.K.
David Baldwin	005	Royal South Hants Hosp, Southampton, U.K.
Jafer Qureshi	008	Newcross Hospital, Wolverhampton, U.K.
John Cookson	010	Royal London Hospital, London, U.K.
David Wheatley	048	Royal Masonic Hospital, London, U.K.
Isaac Marks	049	Maudsley Hospital, London, U.K.
Michel Faure	011	187 Rue Victor Hugo, Tours, France
Joel Gailledreau	012	8 Boulevard Richerand, Villecresnes, France
Christophe Baggot	012	8 Boulevard Richerand, Villecresnes, France
Philippe Leclercq	013	16 Avenue Robert Schuman, Mulhouse, France
Marie-France Moles-Durand	014	26 Rue Du Languedoc, Toulouse, France
Pierre Le Goubey	015	88 Rue Emmanuel Liasis, Cherbough, France
Didier Deroche	016	57 Rue Gamard, Joue Les Tours, France
J Horenstein	017	Centre Mgen, Paris, France
Manuel De Mondragon	018	17 Rue Du Roi Albert, Nantes, France
Laurent Chneiwiss	019	5 Rue Keppler, Paris, France
Christophe Andre	20	Hopital Sainte Anne, 1 Rue Cabanis, Paris, France
Andre De Nayer	021	Clinique Sainte Theresa, Montigny-Sur-Sambre, Belgium
France Bartholome	022	Clinique Sainte-Joseph, Fleron-Retinne, Belgium
Remi Spiers	034	Keistraat 83, De Pinte, Belgium
Koen Demyttenaere	035	University Hospital Gasthuisberg, Leuven, Belgium
C Van Heeringen	036	University Hospital, Zaandam, Belgium
Eugeen De Bleeker	037	Psychiatrische Kliniek St Lucia, St Niklaas, Belgium
Jamie De La Torre	023	Hospital De La Cruz Roja, Barcelona, Spain
Jose Soria	024	Hospital De La Princesa, Madrid, Spain
Pedro Gonzalez-Quiros	025	Hospital Central De Asturias, Oviedo, Spain
Iver Hand	026	Uniuversitaetskrankenhaus Eppendorf, Hamburg, Germany
Fritz Henn	027	Zentralinstitut Fur Seelische Desundheit, Mannheim
Gerhard Buchkremer	029	Klinikum De Eberhard-Karls-Universitat, Tubingen
Gismar Ziegler	030	Institut F. Psychosomat Forschug, Stuttgart, Germany

Appendix 7.2.1

Study 502

Ingebore Scharwachter	033	Burgestrasse 114, Remscheid, Germany
Dan Stein	038	U. of Stellenbosch, Cape Town, S. Africa
Paul Strong	039	Libertas Med Centre, Cape Town, S. Africa
Michael Berk	040	Wits Medical School, Parktown, S. Africa
Jose Gonzalez De Rivera	041	Avda Reyes Catolicos, Madrid, S. Africa
Charl Els	042	125 President Rietz Ave, Bloemfontein, S. Africa
Jeremy Royds	043	Knighten Surgery, Cape Town, S. Africa
Donald Wilson	044	Groote Schuur Hosp., Cape Town, S. Africa
Leon Gittleson	045	38 Cheviot Place, Wigtown Rd.,Cape Town, S. Africa
Graham Futter	046	Suite 7, Highway Medical Centre, Durban, S. Africa
Farouk Randerre	047	1303 Durdoc Centre, Durban, S. Africa

Study 502: Baseline Demographic Characteristics

Treatment	N	Age (yrs)		Sex [N(%)]		Race [N(%)]	
		Mean	Range	Male	Female	White	Non-White
Paroxetine	139	34.7	18-67	64	75	123	16
Placebo	151	37.3	18-85	69	82	136	15

STUDY 502: COMPLETERS BY VISIT

Treatment	ITT	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 12
Paroxetine	139	131 (94%)	129 (93%)	126 (91%)	121 (87%)	118 (85%)	112 (81%)	104 (75%)
Placebo	151	141 (93%)	139 (92%)	134 (89%)	129 (85%)	119 (79%)	110 (73%)	109 (72%)

Study 502: Mean Dose (mg/day) By Visit

Treatment	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 12
Paroxetine	20	35	30	34	35	36	35

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Appendix 7.2.1

Study 502: LS Mean Change From Baseline In LSAS Total Score-LCOF Analysis					
Timepoint	Paroxetine		Placebo		P*
	N	Mean	N	Mean	
Baseline	136	87.6	145	86.1	0.607
Week 1	131	0.3	139	-2.2	0.158
Week 2	136	-2.5	145	-3.6	0.639
Week 3	136	-8.9	145	-5.4	0.160
Week 4	136	-14.3	145	-7.2	0.011
Week 6	136	-20.3	145	-10.2	0.002
Week 8	136	-23.4	145	-12.1	0.001
Week 12	136	-29.4	145	-15.6	<0.001

*2-sided p-values for pairwise comparisons

Study 502: LS Mean Change From Baseline In LSAS Total Score-Observed Cases Analysis					
Timepoint	Paroxetine		Placebo		P*
	N	Mean	N	Mean	
Baseline	136	87.6	145	86.1	0.607
Week 1	131	0.3	139	-2.2	0.158
Week 2	124	-2.7	134	-4.4	0.480
Week 3	120	-9.6	135	-6.4	0.218
Week 4	120	-15.3	131	-8.0	0.016
Week 6	115	-22.4	125	-11.0	0.002
Week 8	115	-26.3	116	-14.8	0.004
Week 12	108	-35.3	109	-20.5	<0.001

*2-sided p-values for pairwise comparisons

Appendix 7.2.1

Study 502: Proportion of Patients Responding with a CGI Global Improvement Score of 1 or 2 - LOCF Analysis				
Timepoint	Paroxetine		Placebo	
	N	%	N	%
Week 1	7/132	5.3	2/140	1.4
Week 2	18/137	13.1	16/145	11.0
Week 3	31/137	22.6	24/145	16.6
Week 4	52/137	38.0*	26/145	17.9
Week 6	70/137	51.1*	31/145	21.4
Week 8	70/137	51.1*	41/145	28.3
Week 12	90/137	65.7*	47/145	32.4

*p<0.001 paroxetine compared to placebo.

Study 502: Proportion of Patients Responding with a CGI Global Improvement Score of 1 or 2 - Observed Cases Analysis				
Timepoint	Paroxetine		Placebo	
	N	%	N	%
Week 1	7/132	5.3	2/140	1.4
Week 2	17/125	13.6	16/134	11.9
Week 3	30/121	24.8	24/135	17.8
Week 4	50/121	41.3*	26/132	19.7
Week 6	66/116	56.9*	30/126	23.8
Week 8	67/116	57.8*	40/116	34.5
Week 12	85/110	77.3*	46/110	41.8

*p<0.001 paroxetine compared to placebo.

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ON ORIGINAL

Appendix 7.2.2

Study 382: Principal Investigators

Investigators	Center	Location
Bijan Bastani, M.D.	Comprehensive Psychiatric Services	Beachwood, OH
Cathryn Clary, M.D.	Clary Research Associates	New Castle, DE
Larry Davis, M.D.	The Davis Clinic	Indianapolis, IN
Eugene DuBoff, M.D.	Center for Behavior Medicine	Denver, CO
Robert DuPont, M.D.	Institute for Behavior and Health	Rockville, MD
James Ferguson, M.D.	Pharmacology Research Corp.	Salt Lake City, UT
James Jefferson, M.D.	Dean Found. for Health Res./Educ.	Madison, WI
Richard Kavoussi, M.D.	Eastern Penn. Psych. Institute	Phil., PA
Michael Liebowitz, M.D.	New York State Psych. Institute	New York, NY
R. Bruce Lydiard, M.D.	Medical U. of South Carolina	Charleston, SC
Robin Reesal, M.D.	W. Canada Behavioural Res. Centre	Calgary, Alberta
Edward Schweizer, M.D.	University of Pennsylvania	Phil., PA
Murray Stein, M.D.	UC San Diego Medical Center	La Jolla, CA

Study 382: Baseline Demographic Characteristics

Treatment	N	Age (yrs)		Sex [N(%)]		Race [N(%)]	
		Mean	Range	Male	Female	White	Non-White
Paroxetine	94	35.9	18-59	50	44	71	23
Placebo	93	36.7	18-76	56	37	80	13

STUDY 382: COMPLETERS BY VISIT

Treatment	ITT	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 12
Paroxetine	94	85 (90%)	82 (87%)	77 (82%)	73 (78%)	71 (75%)	64 (68%)	62 (66%)
Placebo	93	93 (100%)	91 (98%)	89 (96%)	87 (93%)	81 (87%)	75 (81%)	72 (77%)

Study 382: Mean Dose (mg/day) By Visit

Treatment	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 12
Paroxetine	20	23	29	34	38	41	41

Appendix 7.2.2

Study 382: LS Mean Change From Baseline In LSAS Total Score-LCOF Analysis					
Timepoint	Paroxetine		Placebo		P*
	N	Mean	N	Mean	
Baseline	90	78.0	92	83.5	0.100
Week 1	86	-4.1	90	-2.6	0.385
Week 2	90	-10.6	92	-4.1	0.007
Week 3	90	-14.4	92	-7.5	0.010
Week 4	90	-19.0	92	-9.8	0.001
Week 6	90	-22.9	92	-13.9	0.007
Week 8	90	-25.6	92	-14.6	0.002
Week 12	90	-30.5	92	-14.5	<0.001

*ANOVA model including effects for treatment and investigator

Study 382: LS Mean Change From Baseline In LSAS Total Score-Observed Cases Analysis					
Timepoint	Paroxetine		Placebo		P*
	N	Mean	N	Mean	
Baseline	90	78.0	92	83.5	0.100
Week 1	86	-4.1	90	-2.6	0.385
Week 2	80	-10.9	87	-3.9	0.008
Week 3	73	-15.1	84	-8.7	0.033
Week 4	74	-21.7	88	-10.0	<0.001
Week 6	71	-25.3	83	-13.9	0.002
Week 8	67	-30.0	81	-16.1	<0.001
Week 12	64	-37.1	73	-18.1	<0.001

*ANOVA model including effects for treatment and investigator

Appendix 7.2.2

Study 382: Proportion of Patients Responding with a CGI Global Improvement Score of 1 or 2 - LOCF Analysis				
Timepoint	Paroxetine		Placebo	
	N	%	N	%
Week 1	0/87	0.0	3/90	3.3
Week 2	7/91	7.7	5/92	5.4
Week 3	17/91	18.7	9/92	9.8
Week 4	29/91	31.9*	13/92	14.1
Week 6	39/91	42.9*	20/92	21.7
Week 8	46/91	50.5**	25/92	27.2
Week 12	50/91	54.9**	22/92	23.9

*$p \leq 0.005$, **$p \leq 0.001$ paroxetine compared to placebo.

Study 382: Proportion of Patients Responding with a CGI Global Improvement Score of 1 or 2 - Observed Cases Analysis				
Timepoint	Paroxetine		Placebo	
	N	%	N	%
Week 1	0/87	0.0	3/90	3.3
Week 2	7/80	8.8	4/87	4.6
Week 3	15/74	20.3	9/84	10.7
Week 4	28/74	37.8*	13/88	14.8
Week 6	36/71	50.7*	17/83	20.5
Week 8	42/67	62.7*	24/81	29.6
Week 12	44/64	68.8*	21/73	28.8

*$p \leq 0.001$ paroxetine compared to placebo.

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Appendix 7.2.3

Study 454: Principal Investigators

Investigators	Center	Location
Bastani, Bijan MD	N.E. Ohio Health Services	Beachwood, OH
Bielski, Robert MD	Institute for Health Studies	Okemos, MI
Bryer, J, MD	Clary Research Associates	New Castle, DE
Davidson, Jonathan MD	Duke University Medical Ctr	Durham, NC
Davis, Larry MD	Davis Psychiatric Clinic, Inc	Indianapolis, IN
DuBoff, Eugene MD	Center for Behavioral Medicine	Denver, CO
DuPont, Robert MD	Institute for Behavior and Health	Rockville, MD
Ferguson, J, MD; Rasmusen, L, MD	Pharmacology Research Corp.	Salt Lake City UT
Jefferson, James MD	University of Wisconsin	Madison, WI
Kavoussi, Richard MD	Allegheny University	Philadelphia, PA
Liebowitz, Michael MD	NY State Psychiatric Institute	New York, NY
Lydiard, Bruce MD	Medical College of S Carolina	Charleston, SC
Miller, Kevin MD; Gall, Jeff PhD; Busner, Joan PhD	St. Louis University	St. Louis, MO
Munjack, Dennis MD; Murphy, John, MD	Southwestern Research Institute	Beverly Hills, CA
Schweizer, Ed MD	Univ. of Pennsylvania	Philadelphia, PA
Shear, M. Katherine MD	Western Psychiatric Institute	Pittsburgh, PA
Smith, Ward MD	Pacific NW Clinical Research	Portland, OR
Stein, Murray MD	Univ. of California San Diego	La Jolla, CA
Stewart, Rege MD	Univ. of Texas SW Med Center	Dallas, TX
Tancer, Manuel MD	Detroit VA Medical Center	Detroit, MI
Weihs, Karen MD	GW Univ. Medical Center	Washington, DC
Bennet, Vern MD	Royal University	Saskatchewan, Can

Study 454: Baseline Demographic Characteristics

Treatment	N	Age (yrs)		Sex [N(%)]		Race [N(%)]	
		Mean	Range	Male	Female	White	Non-White
Parox 20 mg	97	39.2	20-70	51	46	79	18
Parox 40 mg	95	37.9	20-61	63	32	77	18
Parox 60 mg	97	36.0	20-60	56	41	78	19
Placebo	95	34.7	18-65	55	40	79	16

STUDY 454: COMPLETERS BY VISIT

Treatment	ITT	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 12
Paroxetine 20 mg	97	81 (84%)	75 (77%)	74 (76%)	71 (73%)	69 (71%)	68 (70%)	67 (69%)
Paroxetine 40 mg	95	80 (84%)	75 (79%)	72 (76%)	71 (75%)	66 (69%)	58 (61%)	56 (59%)
Paroxetine 60 mg	97	84 (87%)	78 (80%)	75 (77%)	69 (71%)	64 (66%)	57 (59%)	56 (58%)
Placebo	95	89 (94%)	86 (91%)	86 (91%)	82 (86%)	78 (82%)	69 (73%)	68 (72%)

Appendix 7.2.3

Study 454: Mean Dose (mg/day) By Visit							
Treatment	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 12
Parox 20 mg	20	20	20	20	20	20	20
Parox 40 mg	37	40	40	40	40	40	40
Parox 60 mg	38	59	60	60	60	60	60

Study 454: LS Mean Change From Baseline In LSAS Total Score-LOCF Analysis											
Time-point	Placebo		Paroxetine 20 mg		Paroxetine 40 mg		Paroxetine 60 mg		Pl v. 20 mg	Pl v. 40 mg	Pl v. 60 mg
	N	Mean	N	Mean	N	Mean	N	Mean	p	p	p
Baseline	92	73.3	89	79.8	88	77.5	91	76.9	0.047	0.202	0.261
Week 1	92	-2.8	87	-4.4	88	-3.3	91	-4.0	0.461	0.819	0.571
Week 2	92	-6.8	89	-8.5	88	-4.5	91	-5.6	0.519	0.390	0.665
Week 3	92	-9.2	89	-12.5	88	-9.4	91	-11.0	0.293	0.936	0.560
Week 4	92	-11.8	89	-18.0	88	-13.7	91	-15.3	0.077	0.592	0.316
Week 6	92	-12.9	89	-22.1	88	-19.2	91	-21.5	0.022	0.122	0.031
Week 8	92	-14.2	89	-27.5	88	-24.2	91	-23.6	0.002*	0.022	0.029
Week 12	92	-15.0	89	-31.4	88	-24.5	91	-25.2	<0.001*	0.039	0.024

*Dunnet's test, maintaining overall alpha =0.05 (p<0.019)

Study 454: LS Mean Change From Baseline In LSAS Total Score-Observed Cases Analysis											
Time-point	Placebo		Paroxetine 20 mg		Paroxetine 40 mg		Paroxetine 60 mg		Pl v. 20 mg	Pl v. 40 mg	Pl v. 60 mg
	N	Mean	N	Mean	N	Mean	N	Mean	p	p	p
Baseline	92	73.3	89	79.8	88	77.5	91	76.9	0.047	0.202	0.261
Week 1	92	-2.9	87	-5.8	88	-3.9	91	-4.7	0.160	0.646	0.360
Week 2	86	-7.2	80	-11.3	72	-5.6	80	-4.6	0.115	0.580	0.332
Week 3	77	-8.7	73	-16.0	71	-13.8	73	-12.3	0.027	0.132	0.277
Week 4	81	-13.1	70	-21.5	68	-18.4	71	-14.5	0.030	0.175	0.713
Week 6	78	-15.2	68	-25.9	68	-25.8	66	-22.1	0.015*	0.018*	0.125
Week 8	75	-17.2	68	-29.0	64	-32.4	60	-27.0	0.012*	0.002*	0.047
Week 12	68	-17.8	66	-32.5	55	-33.6	54	-30.2	0.006*	0.004*	0.034

*Dunnet's test, maintaining overall alpha =0.05 (p<0.019)

Appendix 7.2.3

Study 454: Number and Percentage of Patients with CGI Global Improvement Score of 1 or 2 - LOCF Analysis

Time-point	Placebo		Paroxetine 20 mg		Paroxetine 40 mg		Paroxetine 60 mg		Pl v. 20 mg	Pl v. 40 mg	Pl v. 60 mg
	N	%	N	%	N	%	N	%	p	p	p
Week 1	1/92	1.1	0/87	0.0	3/88	3.4	2/91	2.2	-	-	-
Week 2	5/92	5.4	6/89	6.7	7/88	8.0	6/91	6.6	0.71	0.50	0.74
Week 3	13/92	14.1	10/89	11.2	13/88	14.8	14/91	15.4	0.56	0.90	0.81
Week 4	18/92	19.6	17/89	19.1	20/88	22.7	21/91	23.1	0.94	0.60	0.56
Week 6	22/92	23.9	29/89	32.6	36/88	40.9	31/91	34.1	0.20	0.02*	0.13
Week 8	28/92	30.4	36/89	40.4	38/88	43.2	33/91	36.3	0.16	0.08	0.40
Week 12	26/92	28.3	40/89	44.9	41/88	46.6	39/91	42.9	0.02	0.01*	0.04

*Significant from placebo using Dunnett's Test to maintain overall alpha=0.05(p<0.019)

Study 454: Number and Percentage of Patients with CGI Global Improvement Score of 1 or 2 - Observed Cases Analysis

Time-point	Placebo		Paroxetine 20 mg		Paroxetine 40 mg		Paroxetine 60 mg		Pl v. 20 mg	Pl v. 40 mg	Pl v. 60 mg
	N	%	N	%	N	%	N	%	p	p	p
Week 1	1/92	1.1	0/87	7.5	3/88	3.4	2/91	2.2	-	-	-
Week 2	5/85	5.9	6/80	7.5	6/72	8.3	5/80	6.3	0.68	0.55	0.92
Week 3	12/77	15.6	10/73	13.7	12/71	16.9	12/73	16.4	0.74	0.83	0.89
Week 4	17/81	21.0	17/70	24.3	19/68	27.9	18/71	25.4	0.63	0.32	0.52
Week 6	21/78	26.9	29/68	42.6	34/68	50.0	28/66	42.4	0.05	0.01*	0.05
Week 8	26/75	34.7	36/68	52.9	34/64	53.1	30/60	50.0	0.03	0.03	0.07
Week 12	22/68	32.4	38/66	57.6	35/55	63.6	34/54	63.0	0.004*	<0.001*	<0.001*

*Significant from placebo using Dunnett's Test to maintain overall alpha=0.05(p<0.019)

Appendix 8.1

Appendix 8.1.2.1: Line Listing of Non-Fatal Serious Adverse Events					
PAROXETINE					
Patient ID	**Age**	**Sex**	**Dose at onset (mg/d)**	**Exposure before Onset (days)[1]**	**Serious Event(s)**
454.001.00039	29	M	60	31 31 32	Brain edema (Car accident) Trauma Headache
502.003.05511	20	M	50	70	Emotional lability/intentional OD of paracetamol & aspirin
502.010.05344	46	M	0	84 (+6)	Cerebrovascular disorder
502.012.05304	40	F	50	44	Cachexia
502.033.05427	53	F	30	19	Trauma (Smoke inhalation)
502.045.05135	40	F	0	84 (+2) 84 (+2) 84 (+4)	Uterine neoplasm Pain (post-operative) Infection (post-operative)
011.00134	46	M	40	135	Paranoia, agitation
009.00076	54	M	60	84	Unintentional overdose
PLACEBO					
502.045.05077	34	M	0	5	Emotional lability
502.045.05132	32	M	0	50 50 50	Dehydration Headache Palpitation
008.00125	24	F	0	84	Unintentional 'overdose'

[1]For events occurring post-treatment, + = number of days after treatment discontinuation at event onset.

Appendix 8.1.4.2.1: Treatment Emergent Adverse Events Occurring in ≥ 1% of Paroxetine Patients (Studies 502, 382, 454)[1]		
Body System/Adverse Event	**Paroxetine** (n=522)	**Placebo** (n=339)
Body as a Whole		
Asthenia	22%	14%
Fever	1%	<1%
Headache	22%	22%
Pain[2]	2%	1%
Trauma[3]	3%	1%
Cardiovascular System		
Migraine	1%	<1%
Vasodilatation[4]	1%	<1%
Digestive System		
Bruxism	1%	0%
Constipation	6%	2%
Appetite decreased	8%	1%
Diarrhea	9%	6%
Dry mouth	9%	3%
Dyspepsia	4%	2%
Dysphagia	1%	0%
Flatulence	4%	2%
Appetite increased	2%	2%

Appendix 8.1.4.2.1 (continued)		
Nausea	24%	6%
Vomiting	3%	<1%
Metabolic/Nutritional Disorders		
Weight gain	1%	<1%
Musculoskeletal System		
Myalgia	4%	3%
Nervous System		
Abnormal dreams	2%	1%
Agitation	2%	1%
Anxiety	4%	4%
Concentration impaired	3%	<1%
Emotional lability	2%	1%
Dizziness	11%	7%
Hyperkinesia	1%	0%
Insomnia	23%	16%
Libido decreased	11%	<1%
Myoclonus	3%	<1%
Nervousness	9%	6%
Paresthesia	2%	1%
Somnolence	23%	5%
Tremor	10%	1%
Respiratory System		
Cough increased	1%	<1%
Pharyngitis	3%	2%
Sinusitis	2%	2%
Yawn	7%	<1%
Skin and Appendages		
Rash	1%	<1%
Sweating	10%	2%
Special Senses		
Abnormal vision[5]	3%	<1%
Taste perversion	1%	<1%
Urogenital System		
Abnormal ejaculation[6,7]	32%	1%
Female genital disorders[6,8]	8%	<1%
Impotence[6]	6%	1%
Urinary frequency	2%	2%
Urination impaired	2%	0%

[1]Events for which paroxetine reporting incidence was ≤ the placebo incidence are not included. These events are: abdominal pain, allergic reaction, back pain, infection, palpitation, confusion, depression, respiratory disorder, rhinitis, and dysmenorrhea.
[2]A variety of injuries with no obvious pattern
[3]Pain in a variety of locations with no obvious pattern
[4]Usually flushing.
[5]Mostly blurred vision.
[6]Percentage corrected for gender.
[7]Mostly anorgasmia or delayed ejaculation.
[8]Mostly anorgasmia or delayed orgasm.

Appendix 8.1.4.2.2: Common (≥5%) and Probably Drug-Related Adverse Events (≥twice placebo rate) (Studies 502, 382, 454)		
	Paroxetine (n=522)	Placebo (n=339)
Constipation	6%	2%
Decreased appetite	8%	1%
Dry mouth	9%	3%
Nausea	24%	6%
Libido decreased	11%	1%
Somnolence	23%	5%
Tremor	10%	1%
Yawning	7%	<1%
Sweating	10%	2%
Abnormal ejaculation[1,2]	32%	1%
Female genital disorders[3,4]	8%	<1%
Impotence	6%	1%

[1]Based on the number of male patients
[2]Mostly anorgasmia or delayed orgasm
[3]Based on the number of female patients
[4]Mostly anorgasmia or delayed orgasm

Appendix 8.1.4.5: Other Events Observed During Premarketing Social Phobia Studies[1,2,3]
Body as a Whole
Abdomen enlarged, chest pain, chills, flu syndrome, malaise, neoplasm
Cardiovascular System
Angina, arrhythmia, bradycardia, cerebrovascular disorder, ECG abnormal, extrasystoles, hypertension, hypotension, peripheral vascular disease, syncope, tachycardia*, vascular disorder
Digestive System
Fecal incontinence, gastroenteritis, gastrointestinal disorder, gingivitis, hepatitis, liver function tests abnormal, oropharynx disorder, rectal disorder, stomatitis, tooth caries, tooth disoder,
Endocrine System
Fertility decreased female, hypothyroidism
Hemic and Lymphatic System
Anemia, leukocytosis, lymphadenopathy, monocytosis, purpura, thrombocytopenia, leukopenia
Metabolic/Nutritional Disorders
Cachexia, dehydration, edema, hyperglycemia, hypoglycemia, LFTs increased, thirst, weight loss
Musculoskeletal System
Arthralgia, bone disorder, myasthenia, myositis
Nervous System
Alcohol abuse, amnesia, ataxia, brain edema, depersonalization, drug dependence, dystonia, euphoria, hallucinations, hostility, hypertonia, hypesthesia, hypokinesia, incoordination, lack of emotion, libido increased, neurosis, paralysis, thinking abnormal, vertigo, vestibular disorder, withdrawal syndrome
Respiratory System
Asthma, bronchitis, dyspnea, hiccup, hyperventilation, larynx disorder, pleura disorder
Skin and Appendages
Acne, contact dermatitis, eczema, herpes, nail disorder, photosensitivity, pruritis, skin discoloration, skin disorder, urticaria
Special Senses
Conjunctivitis, ear disorder, ear pain, glaucoma, keratoconjunctivitis, mydriasis, otitis media, photophobia, taste loss, tinnitus
Urogenital System
Albuminuria, breast pain, cystitis, dysuria, fibrocystic breast, kidney pain, leukorrhea, menstrual disorder, nephritis, nocturia, prostate disorder, pyuria, spermatogenesis arrest, unintended pregnancy, urinary incontinence, urinary retention, UTI, urine abnormality, uterine neoplasm, vaginal moniliasis, vaginitis

[1]Events listed in table 8.1.4.2.1 and 8.1.4.2.2 are excluded.
[2]All events reported in this table were reported at a frequency between 1/100 and 1/1000 within the pool of studies (n=578), except for those marked with an asterisk (*), indicating a frequency of $\geq$1/100.
[3]Gender-specific event rates have been corrected for the number of males and females.

Appendix 8.1.5.3.1.1: Criteria for Identification of Laboratory Values of Potential Clinical Concern

PARAMETER		VALUE	UNITS
Hematology			
White Blood Cells		≤2.8, ≥16.0	10^9/L
Basophils		≥1.6	10^9/L
Eosinophils		≥1.6	10^9/L
Lymphocytes		≥12	10^9/L
Monocytes		≥2.4	10^9/L
Segmented Neutrophils		≤2.4	10^9/L
Neutrophils Bands		>1.6	10^9/L
Platelets		≤75, ≥700	10^9/L
Red Blood Cells	Male	≥8	10^12/L
	Female	≥10	10^12/L
Hematocrit	Male	≤37	%
	Female	≤32	%
Hemoglobin	Male	≤115	g/L
	Female	≤95	g/L
Blood Chemistry			
ALT/SGPT		≥165	IU/L
Alkaline Phosphatase		≥390	IU/L
AST/SGOT		≥150	IU/L
Blood Urea Nitrogen		≥10.71	mmol/L
Serum Creatinine		≥176.8	mcmol/L
Total Bilirubin		≥34.2	mcmol/L
Calcium		≤2.1, ≥3.0	mmol/L
Chloride		≤90, ≥118	mmol L
Potassium		≤3.0, ≥6.0	mmol/L
Sodium		≤126, ≥156	mmol/L
Total T3		≤1.3, ≥2.84	nmol/L
Total T4		≤57.9, ≥160.9	nmol/L
TSH		≥10	mU/L
Urinalysis			
Red Blood Cells	Male	>8	/hpf
	Female	>10	/hpf
White Blood Cells		>10	/hpf
Protein Dipstick		>10 or 4+	0-4+
Glucose		4+	0-4+

Appendix 8.1.5.3.1.2: Proportions of Patients Experiencing Potentially Clinically Significant Changes in Laboratory Values (Studies 454 and 502)				
	Paroxetine (n=428)		Placebo (n=246)	
	Abnormal		Abnormal	
	#	%	#	%
↑ ALT	1	<1	0	0
↑ Bilirubin	3	<1	2	<1
↑ Potassium	2	<1	1	<1
↑ TSH	1	<1	0	0
↑ T3	2	<1	1	<1
↓ T3*	9	2	1	<1
↓ T4	4	1	1	<1
↑ Eosinophils	10	2	2	<1
↑ Monocytes	1	<1	0	0
↑ WBC	1	<1	0	0
↑ Urine protein	1	<1	0	0

*No patients had T3 values < the laboratory reference range of normal (0.92 mmol/L), i.e. the criteria was mistakenly set too high.

Appendix 8.1.5.3.2.1: Criteria for Vital Signs Values of Potential Clinical Significance	
Systolic BP	Normal range = 90-180 mmHg Increase of ≥40, decrease of ≥30 mmHg
Diastolic BP	Normal range = 50-105 mmHg Increase of ≥30, decrease of ≥20 mmHg
Pulse	Normal range = 50-120 bpm Increase or decrease of ≥30 bpm
Weight	No normal range defined Increase or decrease of ≥7%

Appendix 8.1.5.3.2.2: Proportions of Patients with Potentially Clinically Significant Changes in Vital Signs Measures (Studies 454, 502, 382)				
	Paroxetine (n=522)		Placebo (n=339)	
	N	%	N	%
Systolic BP[1] (mmHg) - H	1	<1	2	<1
Diastolic BP[1] (mmHg) - L	2	<1	0	0
Pulse (bpm) [1] - L	2	<1	1	<1
Weight (kg) - H	17	3	10	3
Weight (kg) - L	9	2	3	1

[1]These readings were taken sitting.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020031/S023

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA:	NDA 20-031, Supplement
Applicant:	SmithKline Beecham
Name of Drug:	Paxil (paroxetine hydrochloride) Tablets
Indication:	Social Phobia
Statistical Reviewer:	Kun Jin, DBI/OB, HFD-710
Medical Reviewers:	Susan Molchan, M.M., ODE I, HFD-120

1. Introduction

The sponsor submitted this efficacy supplement in support of paroxetine in treating social phobia. The submission consists of three acute 12 week double-blind, randomized, placebo-controlled efficacy trials, Studies 502, 382 and 454. A long term efficacy trial, Study 470, was an extension to Study 382 in which patients could have been treated for up to a total of 52 weeks. There were 290 patients randomized in Study 502, 187 patients in Study 382 and 384 patients in Study 454. A total of 98 patients also entered the long term study. Studies 502, 382 and 454 will be reviewed in this report.

Two of the acute studies, Studies 502 and 382, were methodologically similar and employed a flexible-dosage design with paroxetine administered in the range of 20 to 50 mg once daily. Study 502 was conducted at multiple centers in Europe and South Africa, and Study 382 was conducted at multiple centers in North America. Study 454, also conducted at multiple centers in North America, employed a fixed-dosage design with paroxetine administered at dosages of 20, 40 and 60 mg once daily.

The primary efficacy variables in the acute studies were the mean change from baseline in the Liebowitz Social Anxiety Scale (LSAS) total score and the proportion of patients responding to treatment as determined by a Clinical Global Impressions (CGI) Global Improvement Item score of 1 (very much improved) or 2 (much improved) relative to baseline.

2. The Sponsor's Results

2.1 Patient Disposition and Demographics

Demographically, the study patients were essentially comparable not only within and between the studies. Across the three acute studies, the treatment group mean age ranged from 35 to 39 years, the percentage of females ranged from 34% to 54%, and the percentage of Caucasians ranged from 76% to 90%. Table 1 presents a summary of the demographic characteristics of patients in the ITT populations of Studies 502, 382 and 454. The treatment groups within and between studies were comparable with regard to the distribution of age and mean ages and the relative distribution of Caucasians and non-Caucasians. In the North American Studies 382 and 454, patients on average weighed approximately 77 kg (169 lbs). This was approximately 7 kg (15 lbs) higher than patients in Study 502, conducted in Europe and South Africa, and most likely reflects underlying population cultural differences. Similarly, the North American studies enrolled a slightly higher percentage of males than females, while Study 502 enrolled a slightly higher percentage of females.

Table 1 Demographic Characteristics of the Acute Studies Samples
ITT Population, Studies 502, 382, and 454

			Study 502		Study 382		Study 454			
			plac.	parox.	plac.	parox.	plac.	parox.		
								20 mg	40 mg	60 mg
Age	<18	n	0	0	0	0	0	0	0	0
		%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	18-24	n	19	25	14	10	18	10	11	13
		%	12.6	18.0	15.1	10.6	18.9	10.3	11.6	13.4
	25-34	n	50	51	35	38	27	18	23	31
		%	33.1	36.7	37.6	40.4	28.4	18.6	24.2	32.0
	35-44	n	50	35	23	27	36	41	40	30
		%	33.1	25.2	24.7	28.7	37.9	42.3	42.1	30.9
	45-54	n	18	19	11	15	10	23	16	22
		%	11.9	13.7	11.8	16.0	10.5	23.7	16.8	22.7
	55-64	n	10	8	5	4	3	3	5	1
		%	6.6	5.8	5.4	4.3	3.2	3.1	5.3	1.0
	³65	n	4	1	5	0	1	2	0	0
		%	2.6	0.7	5.4	0.0	1.1	2.1	0.0	0.0
	All	n	151	139	93	94	95	97	95	97
		mean	37.3	34.7	36.7	35.9	34.7	39.2	37.9	36.0
		SD	11.44	11.56	13.2	10.1	10.41	10.17	9.88	9.70
Weight	(kg)	N	150	137	89	94	95	97	94	96
		mean	69.8	70.0	74.6	77.0	74.2	76.8	76.8	79.1
		SD	16.08	14.25	15.32	19.25	17.25	16.06	13.14	16.30
Gender	Female	n	82	75	37	44	40	46	32	41
		%	54.3	54.0	39.8	46.8	42.1	47.4	33.7	42.3
	Male	n	69	64	56	50	55	51	63	56
		%	45.7	46.0	60.2	53.2	57.9	52.6	66.3	57.7
Race	Caucasian									
		n	136	123	80	71	79	79	77	78
		%	90.1	88.5	86.0	75.5	83.2	81.4	81.1	80.4
	Black	n	4	8	8	15	10	9	8	8
		%	2.6	5.8	8.6	16.0	10.5	9.3	8.4	8.2
	Asian	n	1	1	1	3	1	2	2	2
		%	0.7	0.7	1.1	3.2	1.1	2.1	2.1	2.1
	Other	n	10	7	4	5	5	7	8	9
		%	6.6	5.0	4.3	5.3	5.3	7.2	8.4	9.3

The number of patients who completed or prematurely withdrew from the acute studies is presented in Table 2 below. Overall, nearly 70% of the patients completed 12 weeks of treatment in the three studies: 73% in Study 502, 72% in Study 382, and 64% in Study 454. The primary reason for premature withdrawal from the placebo group was lack of efficacy, while the

primary reason for premature withdrawal from the paroxetine group was adverse experience.

Table 2. Disposition of the Acute-Treatment Population

	Study 502				Study 382				Study 454			
	Placebo		Paroxetine		Placebo		Paroxetine		Placebo		Paroxetine	
Total Randomized	N = 151		N = 139		N = 94		N = 93		N = 95		N = 289	
	n	%	n	%	n	%	n	%	n	%	n	%
LOE	19	12.6	1	0.7	10	10.8	0	0.0	10	10.5	8	2.8
AE	6	4.0	10	7.2	3	3.2	14	14.9	4	4.2	60	20.8
PV	5	3.3	7	5.0	3	3.2	4	4.3	0	0.0	11	3.8
Lost to F/U	8	5.3	9	6.5	5	5.4	12	12.8	8	8.4	22	7.6
Other	4	2.6	8	5.8	0	0.0	2	2.1	5	5.3	9	3.1
Comp.	109	72.2	103	74.1	72	77.4	62	66.0	68	71.6	179	61.9

LOE = lack of efficacy; AE = adverse experience; PV = protocol violation; F/U = follow-up

2.2 Comparison of Baseline

Table 3 presents a summary of the mean baseline scores on the primary and some secondary efficacy measures employed in two of the studies. The CGI Severity of Illness Item scores indicate that, on average, patients in Studies 502 and 454 were rated by the investigators, considering their clinical experience with patients with social anxiety disorder, to be moderately to markedly ill. Although the CGI Severity of Illness Item was not employed in Study 382, the baseline mean LSAS total scores are comparable to those in Study 502, suggesting a similar level of severity of illness at baseline in Study 382. The treatment group baseline mean LSAS total scores and Social Avoidance and Distress (SAD) Scale scores were comparable within studies, and between Studies 502 and 382; they were lower in Study 454, suggesting that patients in Study 454 were somewhat less severely ill. Mean treatment group HAM-D total scores were comparable both within and between treatments.

Table 3. Baseline Measures Scores of the Acute Studies Samples
ITT Population, Studies 502 and 382 (All Centers), and 454 (Excluding Center 005)

		502		382		454			
		plac.	parox.	plac.	parox.	plac.	parox. 20 mg	40 mg	60 mg
LSAS	N	145	136	92	90	92	89	88	91
Total	mean	86.1	87.6	83.5	78.0	73.3	79.8	77.5	76.9
	SE	2.24	2.33	2.31	2.33	2.41	2.42	2.45	2.41
CGI	N	137	129	§		92	90	88	91
Severity	mean	4.3	4.3			4.4	4.4	4.4	4.3
	SE	0.06	0.06			0.06	0.06	0.06	0.06
SAD	N	144	137	92	90	92	89	88	90
Scale	mean	22.6	22.9	22.4	22.6	20.8	22.6	21.2	21.7
Total	SE	0.44	0.46	0.53	0.53	0.55	0.56	0.56	0.55

HAM-D								
	N	151	138	§	95	97	95	97
Total	mean	6.7	6.2		5.6	6.2	5.5	5.3
	SD	3.64	3.63		3.46	3.60	3.76	3.42

§ Data not collected

2.3 Primary Efficacy Results

LSAS Total Score

The mean change from baseline in LSAS total score was analyzed by analysis of variance using the general linear models procedure (GLM) of SAS. When comparing individual dose groups against the placebo group, Dunnett's multiple comparison procedure was used to maintain an overall alpha level of 0.05. The adjusted level of significance was 0.019.

The efficacy of paroxetine in reducing social anxiety was in each of the three acute studies by the mean change from baseline in the LSAS total score. Summaries of the mean baseline and mean change from baseline in the LSAS total scores by treatment group in both the extender and visit-wise datasets for the flexible dosage Studies 502 and 382 are presented in Table 4, and for the fixed dosage Study 454 in Table 5. Efficacy was demonstrated both in the dosage range of 20 to 50 mg daily and at the fixed dosage of 20 mg daily at the protocol-specified timepoint of interest, Week 12 in the both LOCF and OC dataset. The paroxetine within-treatment effect at these dosages at this timepoint was consistent, ranging from a mean improvement of -29.4 points in Study 502 to a mean improvement of -31.4 points in Study 454. Similarly, the paroxetine-placebo between-treatment effect at these dosages at this timepoint was quite consistent, with approximately one-half of the within-treatment effect ranging from -13.8 points in Study 502 to -16.4 points in Study 454. In addition, efficacy was strongly suggested at Week 12 in the extender dataset at the 60 mg fixed dosage in Study 454, as the difference between the greater mean improvement in the paroxetine 60 mg group and that in the placebo group was nearly statistically significant.

Table 4 Studies 502 and 382 LSAS Total Score Mean Baseline and Mean Change from Baseline at Week 12
ITT Population

	Placebo			Paroxetine			
	N	mean §	SE	N	mean	SE	p-values
Study 502							
Baseline	145	86.1	2.24	136	87.6	2.33	0.607
LOCF	145	-15.6	2.72	136	-29.4	2.82	<0.001 *
OC	109	-20.5	3.24	108	-35.3	3.24	<0.001 *
Study 382							
Baseline	92	83.5	2.31	90	78.0	2.33	0.099
LOCF	92	-14.5	2.63	90	-30.5	2.66	<0.001 *
OC	73	-18.1	2.86	64	-37.2	3.07	<0.001 *

* Significant from placebo for alpha = 0.05

Table 5 Study 454 LSAS Total Score Mean Baseline and Mean Change from Baseline at Week 12

ITT Population (Excluding Center 005)

	Placebo			Paroxetine 20 mg			Paroxetine 40 mg			Paroxetine 60 mg		
	N	mean §	SE	N	mean	SE	N	mean	SE	N	mean	SE
Baseline	92	73.3	2.41	89	79.8	2.42	88	77.5	2.45	91	76.9	2.41
LOCF	92	-15.0	3.24	89	-31.4	3.13	88	-24.5	3.23	91	-25.2	3.14
P-values		NA		Pl v 20 mg = 0.001 *			Pl v 40 mg = 0.039			Pl v 60 mg = 0.024		
OC	68	-17.8	3.58	66	-32.5	3.88	55	-33.6	4.14	54	-30.2	4.53
P-values		NA		Pl v 20 mg = 0.006 *			Pl v 40 mg = 0.004 *			Pl v 60 mg =0.034		

§ Mean baseline or mean change from baseline

* Significant from placebo using Dunnett's test to maintain an overall alpha = 0.05 ($p<0.019$)

CGI Global Improvement Responders

The binary response variable of CGI Global Improvement Item Score of 1 or 2 was analyzed by logistic analysis using the categorical modeling procedure (CATMOD) of the Statistical Analysis System (SAS). When comparing individual dose groups against the placebo group, Dunnett's multiple comparison procedure was used to maintain an overall alpha level of 0.05. The adjusted level of significance was 0.019

The efficacy of paroxetine in improving the overall clinical condition of patients with social phobia was also consistently demonstrated in each of the three acute studies by the proportion of CGI Global Improvement Item responders, those rated as either very much improved or much improved relative to baseline (score of either 1 or 2). Summaries of the percentage of CGI Global Improvement Item responders by treatment group in both the LOCF and OC datasets for the flexible dosage Studies 502 and 382 are presented in Table 6 and for the fixed dosage Study 454 in Table 7. Efficacy was demonstrated both in the dosage range of 20 mg to 50 mg daily and at the fixed dosage of 40 mg daily at the protocol-specified timepoint of interest, Week 12 in the both LOCF and OC datasets. In addition efficacy was demonstrated at Week 12 in the OC dataset at the 20 mg and 60 mg fixed dosage in Study 454.

Table 6 Studies 502 and 382 Percentage of Responders with CGI Global Improvement Score of 1 or 2 at Week 12
ITT Population

	Placebo			Paroxetine			
	N	n	%	N	n	%	p-values
Study 502							
LOCF	145	47	32.4	137	90	65.7	<0.001 *
OC	110	46	41.8	110	85	77.3	<0.001 *
Study 382							
LOCF	92	22	23.9	91	50	54.9	<0.001 *
OC	73	21	28.8	64	44	68.8	<0.001 *

* Significant from placebo for alpha = 0.05

Table 7 Study 454 Percentage of Responders with CGI Global Improvement Score of 1 or 2 at Week 12
ITT Population (Excluding Center 005)

	Placebo			Paroxetine 20 mg			Paroxetine 40 mg			Paroxetine 60 mg		
	N	n	%	N	n	%	N	n	%	N	n	%
LOCF	92	26	28.3	89	40	44.9	88	41	46.6	91	39	42.9
P-values		NA		Pl v 20 mg = 0.021			Pl v 40 mg = 0.012 *			Pl v 60 mg = 0.040		
OC	68	22	32.4	66	38	57.6	55	35	63.6	54	34	63.0
P-values		NA		Pl v 20 mg = 0.004 *			Pl v 40 mg = <0.001 *			Pl v 60 mg = <0.001 *		

* Significant from placebo using Dunnett's Test to maintain overall alpha = 0.05 ($p<0.019$)

2.4 Excluding Center 005 in Study 454

The sponsor excluded the data from Center 005 in the primary analyses. The sponsor stated that it had been determined that data generated by this center in studies of three other indications, dysthymia, major depression and panic disorder, had yielded statistically significant treatment-by-center interactions in analyses of efficacy variables. They were only 4 patients, one in each treatment arm, in this center. (*This reviewer has confirmed that the efficacy results with or without center 005 are essentially the same.*)

3. The Reviewer's Comments

This reviewer has reanalyzed the datasets the sponsor submitted to the agency. The results in Section 2.3 were generally confirmed by this reviewer.

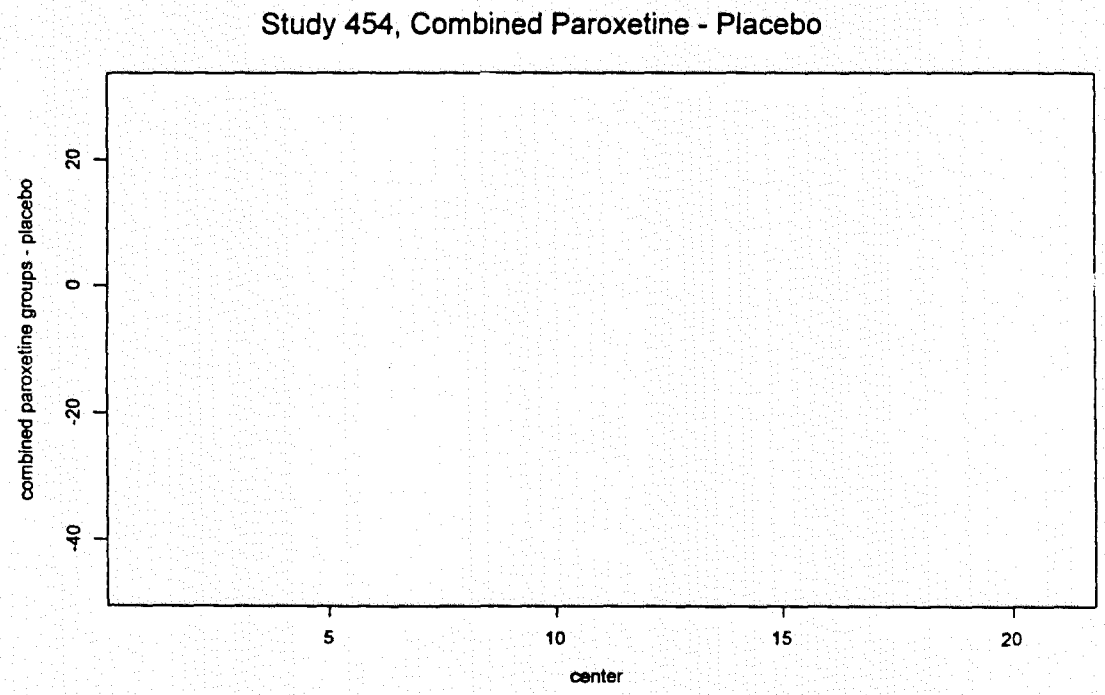
LSAS Total Score in Study 454

The mean changes from baseline in the LSAS total scores in the paroxetine 20 mg and 60 mg groups in the OC dataset of Study 454 are numerically different from the sponsor's, see the bold cases in Table 8. These discrepancies, however, do not affect the relevant p-values.

Table 8 Study 454 LSAS Total Score Mean Change from Baseline at Week 12
ITT-OC DataSet (Excluding Center 005)

	Placebo			Paroxetine 20 mg			Paroxetine 40 mg			Paroxetine 60 mg		
	N	mean §	SE	N	mean	SE	N	mean	SE	N	mean	SE
Sponsor	68	-17.8	3.58	66	-32.5	3.88	55	-33.6	4.14	54	-30.2	4.53
Reviewer	67	-16.0	2.84	66	**-36.0**	3.96	55	-32.8	2.72	55	**-34.2**	3.82

This reviewer confirmed the sponsor's report that the treatment-by-center interaction was found to be significant. To see whether one or two centers were the cause of the interaction, this reviewer calculated the difference of the mean changes from baseline in LSAS total score of combined paroxetine groups and placebo group for each individual center in the ITT-LOCF dataset. The result, which is plotted in the following graph, does not reveal any center to be a possible cause of the interaction.



CGI Global Improvement Responders

The CGI global improvement consists of 7 scores, 1-very much improved, 2-much improved, 3-minimally improved, 4-no change, 5-minimally worse, 6-much worse, and 7-very much worse. The responder analysis was done by looking at the proportion of "improved" patients, i.e. patients with scores 1 or 2. Although the responder analysis showed that paroxetine was favorable over placebo. It is necessary to see whether there were "reversed shifts," namely more patients with scores 5, 6, and 7, in paroxetine groups comparing with placebo. This reviewer calculated the distributions of CGI global improvement scores for all three studies. The results are in the following tables. It can be seen that there were no "reversed shifts" in all the studies.

Table 9. Distributions of CGI global improvement scores of Studies 502, 383 and 454, ITT-LOCF datasets

CGI Score	Study 502				Study 382			
	LOCF		OC		LOCF		OC	
	Placebo	Paroxetine	Placebo	Paroxetine	Placebo	Paroxetine	Placebo	Paroxetine
1	13	36	13	33	8	24	7	21
2	35	55	33	47	14	26	14	22
3	38	21	33	13	30	16	23	9
4	43	19	27	8	38	23	27	9
5	13	5	3	2	2	2	1	1
6	5	0	0	0	0	0	0	0
7	0	1	0	0	0	0	0	0

CGI Score	Study 454							
	LOCF				OC			
	Placebo	20 mg	40 mg	60 mg	Placebo	20 mg	40 mg	60 mg
1	7	17	19	21	7	16	18	21
2	19	25	22	19	15	23	18	15
3	23	23	21	18	21	18	14	11

4	40	26	26	34	24	10	6	9
5	2	0	2	1	1	0	0	0
6	0	1	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0

Conculusion

The results of the three acute studies demonstrate the effectiveness of paroxetine in the treatment of social phobia based on the protocol specified primary endpoints.

/S/

Kun Jin, Ph.D
Team Leader, OBI

APPEARS THIS WAY
ON ORIGINAL

Concur /S/
George Chi, ~~Ph.D.~~
Division ~~Director, OBI~~

cc:
Arch. NDA 20-031, Supplement
HFD-120
HFD-120/Dr. Katz
HFD-120/Dr. Laughren
HFD-120/Dr. Molchan
HFD-120/Ms. Homonnay
HFD-344/Dr. Lisook
HFD-710/Dr. Chi
HFD-710/Dr. Jin
HFD-710/Chron

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020031/S023

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

RECEIVED JUN 1 8 1998

JUN 2 1998

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-031
Paxil® (Paroxetine hydrochloride)
(10, 20, 30 and 40 mg Tablets)

Type of submission: Efficacy Supplement (S-023)
Submission Date: May 6, 1998

Sponsor: Smithkline Beecham

INDICATION: Social Phobia

REVIEWER: Rae Yuan, Ph.D.

This is a efficacy supplement for paxil tablets for the treatment of social anxiety disorder/social phobia. The submission consists of 4 phase III clinical efficacy studies: three short-term clinical efficacy studies (studies #385, 502 and 454) and one long term study (study 470). There is no clinical pharmacology study in the submission. However, because two of the four clinical studies utilized the over-encapsulated products of the approved tablets, dissolution comparisons of these clinical trial capsules to the approved products are submitted.

The dissolution comparisons of the over-encapsulated product (in clinical study #502 and 454) vs. the approved products are provided in the attachment III (The other two clinical studies, i.e. study 385 and 470 utilized the commercial products, therefore, their dissolutions are not provided). It was demonstrated that at equivalent dosage strengths, all the clinical trial capsules meet the dissolution specifications set for the approved products. For the 15 mg capsule strength used in study 502, there is no commercial equivalent and therefore a direct comparison on dissolution could not be made. However, it is bracketed by the other three comparative dissolution profiles for capsule strengths at 10, 20 and 30 mg, it is therefore considered equivalent to the tablets at the same tablet strength. The sponsor has also calculated the similarity factor (f_2) according to SUPAC-IR. All f_2 values comparing over encapsule formulations with the commercial tablet formulations are in the range of . indicating that the formulations are equivalent.

Recommendation:

Based on similar dissolution profiles for the encapsulated tablets and approved tablets, the products used in the four clinical trials are acceptable.

Primary Reviewer: Rae Yuan, Ph.D. /S/

Team Leader: Chandra Sahajwalla /S/

Date of Signature: 6/2/98

Office of Clinical Pharmacology and Biopharmaceutics/Division I

CC list: HFD-120; CSO; HFD-860 (Yuan, Sahajwalla, Malinowski); CDR (Barbara Murphy)

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020031/S023

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

exclusivity checklist Section 3 G

Exclusivity Checklist

NDA: 20-031/S-023				
Trade Name: Paxil Tablets				
Generic Name: Paroxetine Hydrochloride Tablets				
Applicant Name: Smith Kline Beecham Pharmaceuticals				
Division: HFD-120				
Project Manager: Anna M. Homonnay-Weikel				
Approval Date:				
PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?				
1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" t one or more of the following questions about the submission.				
a. Is it an original NDA?	Yes		No	✓
b. Is it an effectiveness supplement?	Yes	✓	No	
c. If yes, what type? (SE1, SE2, etc.)	SE1			
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	Yes	✓	No	
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including you reasons for disagreeing with any arguments made by the applicant that the study was not simpl a bioavailability study.				
Explanation:				
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:				
Explanation:				
d. Did the applicant request exclusivity?	Yes		No	✓
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?				
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously bee approved by FDA for the same use?	Yes		No	✓

exclusivity checklist Section 3 G

If yes, NDA #				
Drug Name:				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes		No	✓
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).				
PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES				
(Answer either #1 or #2, as appropriate)				
1. Single active ingredient product.	Yes		No	
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an alread approved active moiety.	Yes		No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
2. Combination product.	Yes		No	
If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing <u>any one</u> of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed unde an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes		No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				

exclusivity checklist Section 3 G

NDA #	
Drug Product	
NDA #	

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed onl if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (Th Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes	✓	No	

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is n essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical tria such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from so other source, including the published literature) necessary to support approval of the application or supplement?	Yes	✓	No	

If "no," state the basis for your conclusion that a clinical trial is not necessary for approva **AND GO DIRECTLY TO SIGNATURE BLOCKS.**

Basis for conclusion:

b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?	Yes		No	✓
1) If the answer to 2 b) is "yes," do you personally know of an reason to disagree with the applicant's conclusion? If not applicable, answer NO.	Yes		No	

exclusivity checklist Section 3 G

If yes, explain:				
2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?	Yes		No	✓
If yes, explain:				
c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:				
Investigation #1, Study #: 382				
Investigation #2, Study #: 502				
Investigation #3, Study #: 454				
3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been reli on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by th agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approv application.				
a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")				
Investigation #1 382	Yes		No	✓
Investigation #2 502	Yes		No	✓
Investigation #3 454	Yes		No	✓
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?				
Investigation #1 382	Yes		No	✓
Investigation #2 502	Yes		No	✓
Investigation #3 454	Yes		No	✓
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application				

exclusivity checklist Section 3 G

or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any th are not "new"):					
Investigation #1	382				
Investigation #2	502				
Investigation #3	454				
4. To be eligible for exclusivity, a new investigation that is essential to approval must also hav been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.					
a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?					
Investigation #1	Yes	✓	No		
IND#:					
Explain:					
Investigation #2	Yes	✓	No		
IND#:					
Explain:					
Investigation #3	Yes	✓	No		
IND#:					
Explain:					
b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interes provided substantial support for the study?					
Investigation #1	Yes		No		
IND#:					
Explain:					
Investigation #2	Yes		No		
IND#:					
Explain:					
Investigation #3	Yes		No		
IND#:					

exclusivity checklist Section 3 G

Explain:				
c. Notwithstanding an answer of "yes" to (a) or (b), are there othe reasons to believe that the applicant should not be credited with havin "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)	Yes		No	✓
If yes, explain:				

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/S/

Signature of PM/CSO

Date: 4/30/99

/S/

Signature of Division Directo

Date: 5/11/99

cc:

Original NDA

Division File

HFD-93 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

BACK TO TOP

Paxil® (paroxetine hydrochloride) Tablets

ITEM 13/14 - PATENT INFORMATION

The following patent information is being submitted pursuant to 21 C.F.R. 314.53.

Patent No.	Expiry Date	Type of Patent	Patent owner
4 721 723	December 29, 2006 The patent expiration date shown above was calculated in accordance with the U.S. Patent and Trademark Office's Federal Register notice of March 27, 1995. SB believes, however, that the correct expiration date, as properly calculated in accordance with the law and in particular with Section 532 of the Uruguay Round Agreements Act, P.L. 103-564, is September 24, 2008. SB reserves the right to modify the patent data in the future. SB also reserves the right to assert this position against persons or parties who may seek to make, use, offer for sale, import, or sell the approved drug prior to September 24, 2008.	Drug	Beecham Group p.l.c. Brentford, England

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 20031 **Trade Name:** PAXIL (PAROXETINE HCL) TABLETS
Supplement Number: 23 **Generic Name:** PAROXETINE HCL
Supplement Type: SE1 **Dosage Form:**
Regulatory Action: AE **Proposed Indication:** Social Phobia

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? NO

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Status -
Formulation Status -
Studies Needed -
Study Status -

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? YES

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, ANNA MARIE HOMONNAY-WEIKEL

Signature /S/ Date 2/26/99

APPEARS THIS WAY
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represents differing degrees of improvement for each level of the covariate in the pooled. The treatment effect p-value in the analysis of Study 454 data is greater than 0.05 (0.07), which reflects the low response in the very small cells in the low LSAS group for the paroxetine patients (N's of 2, 9, and 3). This overly influences the overall treatment comparison, as the covariate groups are considered equally, regardless of sample size, in the this analysis. A significant covariate did not result from analysis of the CGI Global Improvement responders.

Similarly, when baseline LSAS total score was fitted as a continuous variable, it was found to have a significant linear relationship to the endpoint LSAS total score in the pooled dataset from Studies 502 and 382 and in Study 454. Although the baseline LSAS total score-by-treatment interaction was also found to be significant in the analyses of both the LSAS total score change from baseline and the percentage of CGI Global Improvement Item responders in Study 454 when the covariate was fitted as a continuous variable (LSAS total score), the interaction was not found to be significant when the covariate was fitted as a categorical variable (LSAS total score group).

In the analyses of the pooled dataset from Studies 502 and 382,ongoing psychotherapy at the time of entry into the study was fitted as a categorical covariate, yes or no. No analysis was conducted using psychotherapy for Study 454 because of the small number of patients in some cells (n=11 placebo patients, 10 paroxetine patients receiving psychotherapy). Ongoing psychotherapy in these studies was not found to have a significant effect on either of the primary efficacy variables and there were no significant psychotherapy-by-treatment interactions.

Though there was no interaction detected, the number of patients with ongoing psychotherapy were less than 5% of the total sample.

In both of the analyses of Studies 502 and 454, the mean change from baseline to study endpoint in the HAM-D total score was fitted as a continuous covariate; the HAM-D was not employed in Study 382. The change from baseline in the HAM-D total score was found to have a significant linear relationship with the change from baseline in the LSAS total score and was found to be a significant predictor of response based on the CGI Global Improvement. However, there were no significant changes in HAM-D-by-treatment interactions for either variable in either study,

and the magnitude of the treatment effect p-values remains unchanged with the use of this covariate.

In the analyses of the pooled dataset from Studies 502 and 382 and of Study 454, current comorbidity of interest (depression, OCD, panic disorder, and generalized anxiety disorder) was fitted as a categorical covariate, yes or no. This analysis is limited by the low number of patients with comorbidities, 37 of 463 (8.0%) in the pooled analysis of Studies 382 and 502 and 18 of 360 (5.0%) in Study 454. A significant treatment-by-covariate interaction was found for the pooled analysis for both the change from baseline in the LSAS total and the percentage of CGI responders. In both cases the placebo-paroxetine differences were small in the group of patients who had comorbid diagnoses. The sample sizes within this subgroup are too small to allow a conclusion of no efficacy; the 95% confidence interval around the treatment differences are (-14.2, 22.6) for the LSAS total and (-29.0, 35.0) for the CGI, demonstrating the low level of precision available within this subgroup.

Efficacy was, however, evident in the subgroup without comorbidity; the 95% confidence interval around the treatment differences are (-21.0, -10.2) for the LSAS total and (25.0, 43.0) for the CGI. The treatment comparison for the LSAS total change from baseline (p=0.25) is made weighing each level of the covariate equally, thereby allowing the small comorbid group to overly influence the overall comparison. The interpretation of this p-value is suspect given this level of extreme imbalance between the covariate groups. The numbers of patients in each of the paroxetine groups of Study 454 (3, 3, and 4) are too small to draw any meaningful conclusions about the relative efficacy of patients with comorbid conditions.

In summary, covariate analyses on the primary efficacy measures suggested that patients do not differ in their responsiveness to treatment according to age or concurrent psychotherapy. Although patients with greater baseline LSAS total scores on average achieved greater improvement on this measure with treatment, this improvement did not differ according to whether patients were treated with paroxetine or with placebo. Similarly, patients with greater improvement in depressive signs and symptoms as measured by the change in their HAM-D total scores demonstrated greater improvement on the LSAS and response on the CGI Global Improvement Item, but these beneficial effects occurred irrespective of treatment group assignment.

There was evidence that patients responded better to treatment with paroxetine than with placebo irrespective of their gender

or race, but other suggestions with regard to covariate-by-treatment interactions were inconsistent.

Results also suggested that patients with current psychiatric comorbidities that are likely to be responsive to paroxetine treatment are no more likely to improve or respond with paroxetine treatment than patients without such comorbidities.

7.3.2 Size of Treatment Effect

Treatment effect size was examined in terms of the difference between paroxetine and placebo with respect to the least-squares adjusted mean change from baseline to endpoint in LSAS total score (LOCF) for the three 12-week studies. Results are displayed in Table 7.3.2 below.

Table 7.3.2: Treatment Effect Size as Expressed by the LS Mean Change from Baseline to Endpoint in the LSAS Total Score (LOCF)

Study	Paroxetine	Placebo	Difference
502	-29.4	-15.6	13.8
382	-30.5	-14.5	16.0
454 (20 mg)	-31.4	-15.0	16.4
454 (40 mg)	-24.5		9.5
454 (60 mg)	-25.2		10.2

Drug/placebo differences were statistically significant for studies 502, 382, and for the 20 mg dose of study 454. There was a trend towards significance for the other two doses. These reductions in LSAS score are comparable to those achieved in trials of MAOIs which have been demonstarted to be efficacious in 64-80% of patients with social phobia.

Although at the study endpoints, patients continued to have LSAS scores in the 50s on average, the decrease in scores was statistically significant in all three studies. Taken together with the data from the CGI Global Improvement scores, the effect appears to be clinically significant in 47-66% of patients. These results lend support for the efficacy of paroxetine in the treatment of social phobia. Based on the results from study 454, there does not appear to be a dose-response relationship.

7.3.3 Choice of Dose

All three 12 week studies provide support for the approval of paroxetine for the treatment of social phobia. Studies 502 and 382 utilized a flexible dose range of 20-50 mg daily and were

positive on both primary efficacy measures in both the LOCF and the OC datasets. Mean doses at endpoint for completers were 35 and 41 mg. In the fixed dose study, 454, superiority over placebo was demonstrated using the LSAS total at 20 mg, with trends towards significance at the 40 and 60 mg doses. Statistical significance over placebo was shown at 40 mg for the percentage of patients with a CGI Global Improvement score of 1 or 2. There were statistical trends towards significance at the other two doses.

The sponsor proposes an initial daily dosage of 20 mg. For those not responding, dose increases in 10 mg increments, in intervals of a least one week, are recommended, up to a maximum of 50 mg daily. These recommendations are appropriate given the study results obtained.

In the elderly and those with severe renal or hepatic impairment, the initial recommended dose is 10 mg daily, with a maximum recommended dose of 40 mg.

To explore the possible relationship between dose and efficacy, the sponsor performed a linear regression analysis between the mean change from baseline in LSAS total score and the mean daily dose for completers. A similar analysis was done using the percentage of patients achieving a 1 or 2 on the CGI Global Improvement item. No statistically significant linear trend was seen for the LSAS in the LOCF data set, though significance was reached in the OC dataset at weeks 8 and 12 ($p=0.04$). For the CGI measure, statistical significance was achieved at week 12 in the LOCF dataset ($p=0.04$) and at weeks 6 and 12 for the OC dataset ($p=0.04$ and <0.001, respectively).

Since statistical significance was achieved in the LOCF dataset only at 20 mg for the LSAS and only at 40 mg for the CGI measure, and the linear trend was not statistically significant for the LSAS in the LOCF analysis, the bulk of the evidence goes against there being a significant dose-response relationship demonstrated.

7.3.4 Duration of Treatment

The long-term treatment study, 470, ended with lower than projected enrollment and did not have the statistical power to detect a significant difference in incidence of relapse. The number of patients who entered the double-blind phase of the study was 55 (half on paroxetine and half on placebo), 98 were

estimated as needed. Approximately twice as many placebo as paroxetine patients dropped out of the double-blind phase.

7.4 Conclusions Regarding Efficacy

The sponsor provided data from three short-term (12 week), adequate, well-controlled trials supporting the effectiveness of paroxetine in the treatment of social phobia. The two flexible dose studies (502 and 382) were positive on both primary efficacy measures in both the LOCF and the OC datasets. In the fixed dose study, 454, LCOF analysis showed superiority over placebo using the LSAS total at 20 mg, with trends towards significance at the 40 and 60 mg doses. Statistical significance over placebo was shown at 40 mg for the percentage of patients with a CGI Global Improvement score of 1 or 2. There were statistical trends towards significance at the other two doses.

As noted above the dose ranges proposed by the sponsor are appropriate.

As noted above the relapse prevention study that was completed was inadequate and a commitment for performance of a relapse prevention study is recommended.

The sponsor appropriately notes in the proposed labeling that the efficacy of Paxil has not been demonstrated beyond 12 weeks.

8.0 Integrated Review of Safety

8.1 Background and Methodology for Safety Review

The same formulation of paroxetine chloride tablets has been approved for depression, panic disorder, and OCD, in doses similar to those proposed for the current indication of social phobia, so there is extensive pre- and post-marketing experience with the drug. This safety review therefore, will be relatively limited in scope.

This review will focus on the safety data (adverse events, vital signs, and laboratory) from the three acute 12-week studies and one extended use study of paroxetine in patients with social phobia.

8.1.1 Deaths

One death occurred in the four studies of patients with social phobia. Monitoring was done through 30 days after the last dose of study medication.

The death was a suicide in study 502: Patient 502.037.05146 was a 23 year old male with a 3 year history of social anxiety disorder. Approximately 5 weeks after beginning paroxetine treatment, his mother reported that he had stolen and overdosed on his grandmother's medication (bisoprolol, isosorbide dinitrate, nitrazepam). Autopsy had been refused. The investigator felt that the event was probably unrelated to paroxetine.

8.1.2 Other Serious Adverse Events

A serious non-fatal adverse event (SAE) was defined as any event that was life-threatening, permanently or temporarily disabling or incapacitating or resulted in hospitalization, prolonged a hospital stay or was associated with congenital abnormality, cancer or overdose. In addition, it included any experience that the Investigator regarded as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug.

The sponsor reported all SAEs occurring through 30 days after the last dose of study medication.

Among the 3 acute studies, there were 14 SAEs reported by 8 patients. Six (6/522 or 1.1%) of these were on paroxetine and two (2/339 or 0.6%) on placebo. None were felt to be 'Related' to the study medication by the Investigator. In the extension study, two patients experienced SAEs while on paroxetine and one while on placebo. None were felt to be 'Related' to the study medication by the Investigator.

Data for these SAEs are summarized in a patient line listing in Appendix 8.1.2.1.

The patient in the extension study who became paranoid and agitated was found to have used PCP and the unintentional overdose was asymptomatic; the patient had taken the wrong dose (60 mg) during the first two weeks of the extension.

Narrative summaries for all paroxetine-treated patients with SAEs were reviewed to verify the characterization of events listed.

8.1.3 Dropouts

8.1.3.1 Overall Pattern of Dropouts

Table 8.1.3.1.1 displays the numbers (percentages) of patients who completed the three acute studies and dropouts; Table 8.1.3.1.2 shows this information for the extension study.

Table 8.1.3.1.1: Enumeration (Percentages of Randomized) of Premature Terminations by Reason (Studies 502, 382, 454)

	Paroxetine	Placebo
Randomized	522	339
Completed	345 (66%)	249 (73%)
Dropout due to:		
Adverse Event	84 (16%)	13 (4%)
Lack of Efficacy	9 (2%)	39 (11%)
Protocol Deviation	22 (4%)	8 (2%)
Lost to F/U	43 (8%)	21 (6%)
Other	19 (4%)	9 (3%)

Table 8.1.3.1.2: Enumeration (Percentages of Randomized) of Premature Terminations by Reason (Study 470)

	Open-label	Double-Blind	
		Paroxetine	Placebo
Randomized	98	27	28
Completed	64 (65%)	21 (78%)	15 (54%)
Dropout due to:			
Adverse Event	19 (19%)	2 (7%)	4 (14%)
Lack of Efficacy	8 (8%)	2 (7%)	3 (11%)
Protocol Deviation	7 (7%)	2 (7%)	2 (7%)
Lost to F/U	4 (4%)	0 (0%)	2 (7%)
Other	5 (5%)	0 (0%)	2 (7%)

In the pool of the three acute 12-week studies, 66% of the paroxetine and 73% of placebo patients randomized completed the studies. As expected, more active drug patients than placebo patients dropped out for adverse events, the opposite being true for lack of efficacy. A substantial number of patients (6-8%) were lost to follow-up.

In the extension study (470), patients had completed study 382 and enrolled in an open-label phase, with re-randomization to a double-blind phase if they chose to continue, so by the end of the double-blind phase, more patients had dropped out due to adverse events and lack of efficacy in the placebo group. 19% dropped out during the open-label phase due to an adverse event, the majority of these had been on placebo in study 382.

8.1.3.2 Dropouts Due to Adverse Events

Tables 8.1.3.2.1 and 8.1.3.2.2 show the proportions of patients who dropped out due to adverse events in at least 1% of the paroxetine patients. Since the numbers of patients in the extension study was relatively few, only those events are included that occurred in more than one individual while on either open-label or double-blind paroxetine.

Table 8.1.3.2.1: Adverse Events Leading to Dropout in at least 1% of Paroxetine Patients (Studies 502, 382, 454)

Body System/Event	**Paroxetine** (n=522)	**Placebo** (n=339)
Body as a Whole		
Asthenia	2%	<1%
Sweating	1%	0%
Headache	2%	1%
Digestive		
Flatulence	1%	<1%
Nausea	4%	<1%
Vomiting	1%	0%
Nervous		
Anxiety	1%	0%
Dizziness	2%	0%
Insomnia	3%	0%
Libido decreased	1%	0%
Somnolence	3%	<1%
Tremor	2%	0%
Urogenital		
Ejaculation abnormal*	5%	<1%

*Percentage corrected for gender.

Table 8.1.3.2.2: Adverse Events Leading to Dropout in at least 1% of Paroxetine Patients (Study 470)

Body System/Event	**Open-label** (n=98)	**Double-Blind**	
Body as a whole		**Paroxetine** (n=27)	**Placebo** (n=28)
Asthenia	5%	0%	0%
Headache	1%	4%	4%
Nervous			
Depression	0%	7%	0%
Insomnia	1%	4%	0%
Libido decreased	1%	4%	0%
Nervousness	0%	7%	7%
Somnolence	4%	0%	0%
Urogenital*			
Ejaculation abnormal	8%	0%	0%
Female genital disorder	5%	0%	0%
Impotence	3%	0%	0%

*Percentages corrected for gender.

These observations are typical for SSRIs and similar to those observed with paroxetine for its other psychiatric indications.

A review of all listings and narratives of adverse events leading to dropout among paroxetine subjects in the entire safety database. The only one unexpected from prior experience was increased intraocular pressure in one patient in study 382. This was mild, began 4 days after beginning drug, and resolved after discontinuation.

8.1.4 Adverse Events

8.1.4.1 Establishing Appropriateness of Adverse Event Categorization and Preferred Terms

Adverse experiences were coded using the WHO disease codelist and were then classified by the Adverse Drug Event Coding System (ADECS) (COSTART based) to give the body system and preferred term.

The thesaurus used to encode verbatim AE terms to preferred terms was examined to assess the accuracy and usefulness of this coding process. Coding appeared to be reasonable.

8.1.4.2 Common, Drug-Related Adverse Events

Treatment emergent AEs were those events reported for the first time on or after the first day of double-blind medication and up to the last dose in the treatment phase, i.e., prior to taper. This definition also encompasses non-serious AEs during this phase that were rated as more severe relative to baseline.

Appendix 8.1.4.2.1 presents the proportions of paroxetine and placebo patients who experienced TEAEs for those events occurring in at least 1% of patients within the pool of the three acute 12-week studies.

AEs that were common and probably drug-related (i.e., occurring in at least 5% of the paroxetine patients and at an incidence at least twice that in the placebo group) are summarized in Appendix 8.1.4.2.2.

The extension study (470) included patients who had completed study 382 and contained a relatively small number of patients. Adverse events and their incidence were similar to those shown in the Tables for the acute studies.

8.1.4.3 Effects of Age, Gender, and Race on Adverse Event Reporting Incidence

The sponsor explored the effect of demographics on AE incidence by comparing the incidence of AEs that occurred in ≥5% of the paroxetine patients in the three acute studies between gender subgroups, race subgroups (white vs. non-white), and age subgroups (18-34 years, 35-59 years, ≥60 years). Statistical testing of the odds ratios and relative risk were done on TEAEs occurring in ≥5% of paroxetine patients with an incidence at least twice that of placebo for all variable except age, as there were only 13 patients ≥65 years old (3 on paroxetine, 10 on placebo). Results of these analyses revealed that females are at greater risk for constipation and dry mouth than males. Otherwise, AE incidence was not significantly affected by these demographic variables.

8.1.4.4 Dose-Relatedness

The potential relationship between AE incidence and dose was examined separately in the fixed dose study (454) and the two flexible dose studies by the sponsor. The results from the fixed dose study will be considered here, as it has a good number of subjects in each group (about 100 in the ITT population) and a fixed dose study is most appropriately considered for this type of analysis.

In study 454, dose dependency of adverse events was evaluated by determining which commonly reported events (≥ 5% in any treatment group) occurred with at least a 50% greater incidence in the 40 and/or 60 mg groups as compared to the 20 mg and placebo groups. Events meeting this criteria included abnormal ejaculation, yawn, tremor, sweating, constipation, impotence, vomiting, myoclonus, paresthesia, increased apetite, taste perversion, and urination impaired.

8.1.4.5 Other Events Observed During Premarketing Studies of Social Phobia

Events other than those listed in Appendices 8.1.4.2.1 or 8.1.4.2.2 that were reported during all four studies are depicted in Appendix 8.1.4.5 by body system and preferred term.

8.1.5 Laboratory, Vital Sign and ECG Data

8.1.5.1 Laboratory, Vital Sign, and ECG Assessments

Table 8.1.5.1.1 below summarizes the timing of lab and vital signs assessments. For dropouts, lab and vital sign assessments were done at the time of termination. Lab testing in the three acute studies included: hematology (H/H, WBC/diff, platelets), chemistry (electrolytes, BUN, creatinine, ALT, AST, alkaline phosphatase, bilirubin, calcium), thyroid panel, and urinalysis (dipstick for protein, glucose, rbc & wbc count). Vital signs measurements included sitting blood pressure and pulse rate.

Table 8.1.5.1.1: Timing of Laboratory, Vital Sign, and ECG Assessments

	Study 502	Study 382	Study 454	Study 470
Laboratory tests	Screening, week 12	Screening, week 12	Screening, Week 12	Baseline, weeks 24, 40
Vital signs	Screening, baseline, weeks 1-4, 6, 8, 12	Screening, baseline, weeks 1-4, 6, 8, 12	Screening, baseline, weeks 1-4, 6, 8, 12	Baseline, weeks 1-4, 8, 12, 16, 24-28, 30, 32, 36, 40
12-lead ECG	Screening	Screening	Screening	None

8.1.5.2 Analyses of Laboratory, Vital Sign, and ECG Data

For the ISS analyses, the sponsor pooled the data from the two larger acute studies (454 and 502). The sponsor states that lab results for studies 382 and 470 were not routinely reported to the sponsor, nor were they entered into a formal database for analysis. Any abnormality in those studies deemed to be clinically significant by the investigator was recorded in the Case Report Form as an AE and included in the formal analyses of AE incidence. For the pool of studies 454 and 502, acute study 382, and the extension study (470), this review will focus on an analysis of outliers as well as dropouts due to lab or vital signs abnormalities. Any dropouts or AEs associated with ECG abnormalities will be noted.

8.1.5.3 Results of Analyses

8.1.5.3.1 Laboratory Data

Appendix 8.1.5.3.1.1 displays criteria for lab values of potential clinical concern. Appendix 8.1.5.3.1.2 displays proportions of patients in the paroxetine and placebo groups who experienced a laboratory value of PCS (post-baseline up to 14 days after drug discontinuation) for studies 454 and 502. Only those variables for which at least one paroxetine patient had a

flagged value and for which the drug incidence is higher than the placebo incidence are presented. Narratives were reviewed for all laboratory values of PCS.

No statistical analyses were done to compare the fractions of patients with lab values of PCS on paroxetine vs. placebo. None of the abnormalities were serious, most were not clinically significant. The number of abnormalities was also small (<1%) with the exception of eosinophils. None of the increased eosinophil counts in the paroxetine group were considered to be clinically significant by investigators; none were associated with AEs. The patient with an increased ALT had a level of 206 IU/L at week 12; no corrective action was taken and he declined to return for follow-up evaluation. One patient with increased bilirubin had elevated levels on entry; while on drug increases did not exceed 0.5 mg/dl; none of these increases were considered clinically significant. There were no associated AEs.

No patient dropped out due to a laboratory abnormality.

In study 382, laboratory abnormalities that were reported as AEs were: ALT and AST increased slightly in one patient (none on placebo). There were no dropouts due to laboratory abnormalities.

In the extended study 470, there were no dropouts due to laboratory abnormalities and no clinically significant laboratory abnormalities. Abnormalties reported were: hyperthyroidism (1), AST increased (1), ALT increased (1), and hematuria (1).

Regarding LFTs, for the pooled studies 454 and 503, mean changes of $\geq$5% as compared with baseline were found for ALT (+11%), AST (+9%), and total bilirubin (-7%), while on paroxetine and on placebo, these were, respectively, 1%, 3%, and 0%. Despite these increases, mean values at endpoint were all within the normal reference ranges.

In sum, the data in this NDA provide no evidence that paroxetine is associated with any clinically significant laboratory abnormalities.

8.1.5.3.2 Vital Sign Data

Appendix 8.1.5.3.2.1 displays the criteria for vital signs values of PCS. Appendix 8.1.5.3.2.2 displays the proportions of patients in the paroxetine and placebo groups who experienced a

vital signs reading of PCS post-baseline in the pool of the acute studies: 454, 502, and 382. Data is included only when at least one patient on paroxetine had an abnormality.

No SAEs were associated with any of these vital signs changes; concurrent AEs included nocturnal sweating in one patient with decreased DBP and somnolence in the patient with increased SBP. In the extended study (470), the only PCS value reported was decreased pulse; concurrent AEs were transient tremor and dizziness.

No patient withdrew from a study due to an abnormal vital sign parameter. No significant mean changes in vital signs parameters were seen in the pool of the three acute studies.

8.1.5.3.3 ECG Data

No paroxetine patient dropped out due to an abnormal ECG finding. As noted above, ECGs were done as per the protocols only at screening.

8.2 Adequacy of Patient Exposure and Safety Assessments

The same formulation of paroxetine HCl tablets has been approved for three indications, so its safety has been extensively reviewed in the past and there has been a considerable post-marketing database collected. No new safety concerns have been raised in these studies in patients with social phobia, though the database is relatively limited in terms of number of patients tested (578 on paroxetine) and safety assessments, such as the lack of ECG data collection while on drug. In view of the considerable experience with the drug, it is felt that the submitted database is sufficient to reasonably assess the safety of the drug in this population.

8.3 Safety Findings From Post-Marketing Reports and the Literature

As noted in sections 5.2.2 and 5.2.3 above, there were 4 reports of adverse events associated with paroxetine in which social phobia was the reported indication and three literature reports. None of the post-marketing AEs were serious; all are adequately covered by the proposed labeling. They included: panic attack (post-treatment), furuncles and itching, inability to pass urine, and delayed orgasm.

In the literature reports, reported AEs were generally the common ones included in labeling and none were serious.

8.4 Conclusions Regarding Safety

This safety review revealed no major safety concerns that would preclude approval or warrant substantial modification of labeling as it now exists for Paxil. Based on the pool of the three acute studies, the common AE profile seen in patients with social phobia is very similar to that seen for the other indications.

9.0 Labeling

The revised labeling, submitted with this NDA supplement was reviewed. Only sections of the labeling to which information was added are commented on below.

Clinical Trials

In giving the percentage of CGI Global Improvement Item responders, the percentages from the observed cases analysis is used. It would be more legitimate to use the percentages from the LOCF analysis.

A statement defining who is considered a responder (CGI Global Improvement Item score of 1 [very much improved] or 2 [much improved] relative to baseline) should be added to labeling.

In the sentence: "In addition to the significant difference in the LSAS Total Score at week 2, …" the '2' should be '12'-I assume this is a typo.

The information on positive response to the secondary efficacy measures listed may be excluded.

In the paragraph on Study 3, which is fixed dose study 454, the statement: "Paroxetine dosages of 20 and 40 mg/day were demonstrated to be significantly superior to placebo on the LSAS Total Score or the CGI Global Improvement Item Score" is literally correct. It may be a little misleading though, in that on the LOCF analysis of the LSAS the 20 mg and not the 40 mg dose was statistically significant (though both were significant using the OC analysis). Similarly, for the CGI Improvement Item on the LOCF, the 40 mg and not the 20 mg dose came out as statistically significant, though both were significant on the OC analysis. It would be a bit wordy to get into those points

for labeling and I don't think they are clinically significant. I would probably let their statement stand.

Also on Study 3, the statement about "a suggestion of a possible dose response relationship for effectiveness.." is not very definitive and neither is the data on dose-response (section 7.3.1 of the review). I would delete it.

As for the flexible dose studies, for fixed dose Study 3 in labeling the percentages of CGI responders given are from the OC analysis. The LOCF analysis numbers should be used.

The statement on subgroup analyses would be more accurate if it added that there were "no clinically significant" differences in treatment outcomes. A few probably clinically insignificant and inconsistent differences were found for race as discussed in section 7.3.1.

A statement on the range of ages of patients in the trials could be added.

Indications and Usage

This section is adequate as written.

Adverse Reactions

The data in this section is accurate; the section is adequate as written.

Dose Dependency of Adverse Events

The statement here is accurate and adequate as written.

Other Events Observed During the Premarketing Evaluation of Paxil

This section is accurate and adequate as written.

Dosage and Administration

This section is adequate as written.

10.0 Conclusions

The evidence presented is sufficient to support the claim of efficacy of Paxil in the treatment of social phobia in doses of 20-50 mg daily, for up to 12 weeks.

As for the previously approved indications for Paxil, there is adequate evidence of reasonable safety under the conditions of use in the proposed labeling.

11.0 Recommendations

From a clinical standpoint, it is recommended that Paxil be approved for the treatment of social phobia.

It is recommended that the sponsor be requested to conduct a well-controlled relapse prevention study of Paxil in social phobia.

/S/

Susan Molchan, M.D.
January 11, 1999

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3-5-99

I agree that this supplement is approvable. See memo to file for more detailed comments.

/S/
TL, PDP

cc: NDA 20-031
HFD-120
HFD-120/TLaughren
/SMolchan
/AHomonnay

Appendix 5.1.1.1: Patient Enumeration by Study Type		
Completed Phase 3 Studies	Treatment Groups	
Study Type	Paroxetine	Placebo
12-Week Placebo Control		
Flexible Dose	233	244
Fixed Dose	289	95
Subtotal	522	339
Extension Study		
Flexible Dose Open label	98[1]	
Fixed Dose Placebo-Control	27	28
Total unique patients	578	339

[1]Of these 98, 56 had been on placebo & 42 on paroxetine in study 382.

Appendix 5.1.1.2	**Table of All Studies**			
Study #/country	**Design**	**Dose**	**N,parox**	**N, pbo**
Placebo-Controlled, 12-Week				
502 Belgium, Spain, France, Germany, Ireland, UK, S. Africa	Double-blind, randomized, flexible-dose	20-50 mg	139	151
382 USA, Canada	Double-blind, randomized, flexible-dose	20-50 mg	94	93
454 USA, Canada	Double-blind, randomized, fixed-dose	20, 40, 60 mg	289	95
Extension Study (after study 382)				
470 USA	Open-label, flexible-dose x 24 weeks, to double-blind, randomized, pbo-controlled x 16 weeks	20-50 mg	98[1]	28

[1]27 of the 98 went on to paroxetine in the placebo-controlled phase.

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Appendix 5.1.2.1 Demographic Characteristics for Patients in Three 12-Week Studies (ITT)		
	Paroxetine (n=522)	**Placebo** (n=339)
Age (years)		
Mean	37	36
Range	18-70	18-85
Age Groups		
<35	230 (44%)	163 (48%)
35-64	289 (55%)	166 (49%)
>64	3 (0.6%)	10 (2.9%)
Sex		
Female	238 (46%)	159 (47%)
Male	284 (54%)	180 (53%)
Race		
Caucasian	428 (82%)	295 (87%)
Black	48 (9%)	22 (6%)
Oriental	10 (2%)	3 (1%)
Other	36 (7%)	19 (6%)
Weight (kg)		
Mean	75	73
Range	38-155	42-159

Appendix 5.1.3.1 Number of All Patients Receiving Paroxetine: Mean Daily Dose/Duration							
Duration (days)	Mean Paroxetine Dose (mg/day)					Total N	(%)
	20	**21-30**	**31-40**	**41-50**	**51-60**		
1-7	46	0	0	0	0	46	(8)
8-14	17	11	0	0	0	28	(5)
15-28	9	14	13	3	0	39	(7)
29-42	6	2	10	4	1	23	(4)
43-56	4	4	8	1	0	17	(3)
57-70	2	2	13	5	4	26	(4)
71-84	12	3	13	5	6	39	(7)
85-168	93	37	106	19	47	302	(52)
169-252	1	5	5	3	0	14	(2)
253-336	3	7	18	6	0	34	(6)
337-365	0	2	6	2	0	10	(2)
Total	193	87	192	48	58	578	(100)
(%)	(34)	(15)	(33)	(8)	(10)	(100)	

Appendix 5.1.3.2 Person-Time Exposure to Paroxetine and Placebo		
Treatment	**N**	**Patient-Years**
Paroxetine	578	151
Placebo	339	84

Appendix 7.2.1

Study 502: Principal Investigators

Investigators	Ctr	Location
Frank O'Donoghue	001	St Patricks Hospital, Dublin, Ireland
John Lynch	002	St Luke's Hospital, Clonmel, Ireland
David Nutt	003	Bristol Royal Infirmary, Bristol, U.K.
Shashank Chattree	004	Queen's Park Hospital, Blackburn, U.K.
David Baldwin	005	Royal South Hants Hosp, Southampton, U.K.
Jafer Qureshi	008	Newcross Hospital, Wolverhampton, U.K.
John Cookson	010	Royal London Hospital, London, U.K.
David Wheatley	048	Royal Masonic Hospital, London, U.K.
Isaac Marks	049	Maudsley Hospital, London, U.K.
Michel Faure	011	187 Rue Victor Hugo, Tours, France
Joel Gailledreau	012	8 Boulevard Richerand, Villecresnes, France
Christophe Baggot	012	8 Boulevard Richerand, Villecresnes, France
Philippe Leclercq	013	16 Avenue Robert Schuman, Mulhouse, France
Marie-France Moles-Durand	014	26 Rue Du Languedoc, Toulouse, France
Pierre Le Goubey	015	88 Rue Emmanuel Liasis, Cherbough, France
Didier Deroche	016	57 Rue Gamard, Joue Les Tours, France
J Horenstein	017	Centre Mgen, Paris, France
Manuel De Mondragon	018	17 Rue Du Roi Albert, Nantes, France
Laurent Chneiwiss	019	5 Rue Keppler, Paris, France
Christophe Andre	20	Hopital Sainte Anne, 1 Rue Cabanis, Paris, France
Andre De Nayer	021	Clinique Sainte Theresa, Montigny-Sur-Sambre, Belgium
France Bartholome	022	Clinique Sainte-Joseph, Fleron-Retinne, Belgium
Remi Spiers	034	Keistraat 83, De Pinte, Belgium
Koen Demyttenaere	035	University Hospital Gasthuisberg, Leuven, Belgium
C Van Heeringen	036	University Hospital, Zaandam, Belgium
Eugeen De Bleeker	037	Psychiatrische Kliniek St Lucia, St Niklaas, Belgium
Jamie De La Torre	023	Hospital De La Cruz Roja, Barcelona, Spain
Jose Soria	024	Hospital De La Princesa, Madrid, Spain
Pedro Gonzalez-Quiros	025	Hospital Central De Asturias, Oviedo, Spain
Iver Hand	026	Uniuversitaetskrankenhaus Eppendorf, Hamburg, Germany
Fritz Henn	027	Zentralinstitut Fur Seelische Desundheit, Mannheim
Gerhard Buchkremer	029	Klinikum De Eberhard-Karls-Universitat, Tubingen
Gismar Ziegler	030	Institut F. Psychosomat Forschug, Stuttgart, Germany

Appendix 7.2.1

Study 502

Ingebore Scharwachter	033	Burgestrasse 114, Remscheid, Germany
Dan Stein	038	U. of Stellenbosch, Cape Town, S. Africa
Paul Strong	039	Libertas Med Centre, Cape Town, S. Africa
Michael Berk	040	Wits Medical School, Parktown, S. Africa
Jose Gonzalez De Rivera	041	Avda Reyes Catolicos, Madrid, S. Africa
Charl Els	042	125 President Rietz Ave, Bloemfontein, S. Africa
Jeremy Royds	043	Knighten Surgery, Cape Town, S. Africa
Donald Wilson	044	Groote Schuur Hosp., Cape Town, S. Africa
Leon Gittleson	045	38 Cheviot Place, Wigtown Rd.,Cape Town, S. Africa
Graham Futter	046	Suite 7, Highway Medical Centre, Durban, S. Africa
Farouk Randerre	047	1303 Durdoc Centre, Durban, S. Africa

Study 502: Baseline Demographic Characteristics

Treatment	N	Age (yrs)		Sex [N(%)]		Race [N(%)]	
		Mean	Range	Male	Female	White	Non-White
Paroxetine	139	34.7	18-67	64	75	123	16
Placebo	151	37.3	18-85	69	82	136	15

STUDY 502: COMPLETERS BY VISIT

Treatment	ITT	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 12
Paroxetine	139	131 (94%)	129 (93%)	126 (91%)	121 (87%)	118 (85%)	112 (81%)	104 (75%)
Placebo	151	141 (93%)	139 (92%)	134 (89%)	129 (85%)	119 (79%)	110 (73%)	109 (72%)

Study 502: Mean Dose (mg/day) By Visit

Treatment	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 12
Paroxetine	20	35	30	34	35	36	35

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Appendix 7.2.1

Study 502: LS Mean Change From Baseline In LSAS Total Score-LCOF Analysis					
Timepoint	Paroxetine		Placebo		P*
	N	Mean	N	Mean	
Baseline	136	87.6	145	86.1	0.607
Week 1	131	0.3	139	-2.2	0.158
Week 2	136	-2.5	145	-3.6	0.639
Week 3	136	-8.9	145	-5.4	0.160
Week 4	136	-14.3	145	-7.2	0.011
Week 6	136	-20.3	145	-10.2	0.002
Week 8	136	-23.4	145	-12.1	0.001
Week 12	136	-29.4	145	-15.6	<0.001

*2-sided p-values for pairwise comparisons

Study 502: LS Mean Change From Baseline In LSAS Total Score-Observed Cases Analysis					
Timepoint	Paroxetine		Placebo		P*
	N	Mean	N	Mean	
Baseline	136	87.6	145	86.1	0.607
Week 1	131	0.3	139	-2.2	0.158
Week 2	124	-2.7	134	-4.4	0.480
Week 3	120	-9.6	135	-6.4	0.218
Week 4	120	-15.3	131	-8.0	0.016
Week 6	115	-22.4	125	-11.0	0.002
Week 8	115	-26.3	116	-14.8	0.004
Week 12	108	-35.3	109	-20.5	<0.001

*2-sided p-values for pairwise comparisons

Appendix 7.2.1

Study 502: Proportion of Patients Responding with a CGI Global Improvement Score of 1 or 2 - LOCF Analysis				
Timepoint	Paroxetine		Placebo	
	N	%	N	%
Week 1	7/132	5.3	2/140	1.4
Week 2	18/137	13.1	16/145	11.0
Week 3	31/137	22.6	24/145	16.6
Week 4	52/137	38.0*	26/145	17.9
Week 6	70/137	51.1*	31/145	21.4
Week 8	70/137	51.1*	41/145	28.3
Week 12	90/137	65.7*	47/145	32.4

*$p<0.001$ paroxetine compared to placebo.

Study 502: Proportion of Patients Responding with a CGI Global Improvement Score of 1 or 2 - Observed Cases Analysis				
Timepoint	Paroxetine		Placebo	
	N	%	N	%
Week 1	7/132	5.3	2/140	1.4
Week 2	17/125	13.6	16/134	11.9
Week 3	30/121	24.8	24/135	17.8
Week 4	50/121	41.3*	26/132	19.7
Week 6	66/116	56.9*	30/126	23.8
Week 8	67/116	57.8*	40/116	34.5
Week 12	85/110	77.3*	46/110	41.8

*$p<0.001$ paroxetine compared to placebo.

APPEARS THIS WAY
ON ORIGINAL

Appendix 7.2.2

Study 382: Principal Investigators

Investigators	Center	Location
Bijan Bastani, M.D.	Comprehensive Psychiatric Services	Beachwood, OH
Cathryn Clary, M.D.	Clary Research Associates	New Castle, DE
Larry Davis, M.D.	The Davis Clinic	Indianapolis, IN
Eugene DuBoff, M.D.	Center for Behavior Medicine	Denver, CO
Robert DuPont, M.D.	Institute for Behavior and Health	Rockville, MD
James Ferguson, M.D.	Pharmacology Research Corp.	Salt Lake City, UT
James Jefferson, M.D.	Dean Found. for Health Res./Educ.	Madison, WI
Richard Kavoussi, M.D.	Eastern Penn. Psych. Institute	Phil., PA
Michael Liebowitz, M.D.	New York State Psych. Institute	New York, NY
R. Bruce Lydiard, M.D.	Medical U. of South Carolina	Charleston, SC
Robin Reesal, M.D.	W. Canada Behavioural Res. Centre	Calgary, Alberta
Edward Schweizer, M.D.	University of Pennsylvania	Phil., PA
Murray Stein, M.D.	UC San Diego Medical Center	La Jolla, CA

Study 382: Baseline Demographic Characteristics

Treatment	N	Age (yrs)		Sex [N(%)]		Race [N(%)]	
		Mean	Range	Male	Female	White	Non-White
Paroxetine	94	35.9	18-59	50	44	71	23
Placebo	93	36.7	18-76	56	37	80	13

STUDY 382: COMPLETERS BY VISIT

Treatment	ITT	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 12
Paroxetine	94	85 (90%)	82 (87%)	77 (82%)	73 (78%)	71 (75%)	64 (68%)	62 (66%)
Placebo	93	93 (100%)	91 (98%)	89 (96%)	87 (93%)	81 (87%)	75 (81%)	72 (77%)

Study 382: Mean Dose (mg/day) By Visit

Treatment	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 12
Paroxetine	20	23	29	34	38	41	41

APPEARS THIS WAY
ON ORIGINAL

Appendix 7.2.2

Study 382: LS Mean Change From Baseline In LSAS Total Score-LCOF Analysis					
Timepoint	Paroxetine		Placebo		P*
	N	Mean	N	Mean	
Baseline	90	78.0	92	83.5	0.100
Week 1	86	-4.1	90	-2.6	0.385
Week 2	90	-10.6	92	-4.1	0.007
Week 3	90	-14.4	92	-7.5	0.010
Week 4	90	-19.0	92	-9.8	0.001
Week 6	90	-22.9	92	-13.9	0.007
Week 8	90	-25.6	92	-14.6	0.002
Week 12	90	-30.5	92	-14.5	<0.001

*ANOVA model including effects for treatment and investigator

Study 382: LS Mean Change From Baseline In LSAS Total Score-Observed Cases Analysis					
Timepoint	Paroxetine		Placebo		P*
	N	Mean	N	Mean	
Baseline	90	78.0	92	83.5	0.100
Week 1	86	-4.1	90	-2.6	0.385
Week 2	80	-10.9	87	-3.9	0.008
Week 3	73	-15.1	84	-8.7	0.033
Week 4	74	-21.7	88	-10.0	<0.001
Week 6	71	-25.3	83	-13.9	0.002
Week 8	67	-30.0	81	-16.1	<0.001
Week 12	64	-37.1	73	-18.1	<0.001

*ANOVA model including effects for treatment and investigator

Appendix 7.2.2

Study 382: Proportion of Patients Responding with a CGI Global Improvement Score of 1 or 2 - LOCF Analysis				
Timepoint	Paroxetine		Placebo	
	N	%	N	%
Week 1	0/87	0.0	3/90	3.3
Week 2	7/91	7.7	5/92	5.4
Week 3	17/91	18.7	9/92	9.8
Week 4	29/91	31.9*	13/92	14.1
Week 6	39/91	42.9*	20/92	21.7
Week 8	46/91	50.5**	25/92	27.2
Week 12	50/91	54.9**	22/92	23.9

*$p \leq 0.005$, **$p \leq 0.001$ paroxetine compared to placebo.

Study 382: Proportion of Patients Responding with a CGI Global Improvement Score of 1 or 2 - Observed Cases Analysis				
Timepoint	Paroxetine		Placebo	
	N	%	N	%
Week 1	0/87	0.0	3/90	3.3
Week 2	7/80	8.8	4/87	4.6
Week 3	15/74	20.3	9/84	10.7
Week 4	28/74	37.8*	13/88	14.8
Week 6	36/71	50.7*	17/83	20.5
Week 8	42/67	62.7*	24/81	29.6
Week 12	44/64	68.8*	21/73	28.8

*$p \leq 0.001$ paroxetine compared to placebo.

APPEARS THIS WAY
ON ORIGINAL

Appendix 7.2.3

Study 454: Principal Investigators

Investigators	Center	Location
Bastani, Bijan MD	N.E. Ohio Health Services	Beachwood, OH
Bielski, Robert MD	Institute for Health Studies	Okemos, MI
Bryer, J, MD	Clary Research Associates	New Castle, DE
Davidson, Jonathan MD	Duke University Medical Ctr	Durham, NC
Davis, Larry MD	Davis Psychiatric Clinic, Inc	Indianapolis, IN
DuBoff, Eugene MD	Center for Behavioral Medicine	Denver, CO
DuPont, Robert MD	Institute for Behavior and Health	Rockville, MD
Ferguson, J, MD; Rasmusen, L, MD	Pharmacology Research Corp.	Salt Lake City UT
Jefferson, James MD	University of Wisconsin	Madison, WI
Kavoussi, Richard MD	Allegheny University	Philadelphia, PA
Liebowitz, Michael MD	NY State Psychiatric Institute	New York, NY
Lydiard, Bruce MD	Medical College of S Carolina	Charleston, SC
Miller, Kevin MD; Gall, Jeff PhD; Busner, Joan PhD	St. Louis University	St. Louis, MO
Munjack, Dennis MD; Murphy, John, MD	Southwestern Research Institute	Beverly Hills, CA
Schweizer, Ed MD	Univ. of Pennsylvania	Philadelphia, PA
Shear, M. Katherine MD	Western Psychiatric Institute	Pittsburgh, PA
Smith, Ward MD	Pacific NW Clinical Research	Portland, OR
Stein, Murray MD	Univ. of California San Diego	La Jolla, CA
Stewart, Rege MD	Univ. of Texas SW Med Center	Dallas, TX
Tancer, Manuel MD	Detroit VA Medical Center	Detroit, MI
Weihs, Karen MD	GW Univ. Medical Center	Washington, DC
Bennet, Vern MD	Royal University	Saskatchewan, Can

Study 454: Baseline Demographic Characteristics

Treatment	N	Age (yrs)		Sex [N(%)]		Race [N(%)]	
		Mean	Range	Male	Female	White	Non-White
Parox 20 mg	97	39.2	20-70	51	46	79	18
Parox 40 mg	95	37.9	20-61	63	32	77	18
Parox 60 mg	97	36.0	20-60	56	41	78	19
Placebo	95	34.7	18-65	55	40	79	16

STUDY 454: COMPLETERS BY VISIT

Treatment	ITT	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 12
Paroxetine 20 mg	97	81 (84%)	75 (77%)	74 (76%)	71 (73%)	69 (71%)	68 (70%)	67 (69%)
Paroxetine 40 mg	95	80 (84%)	75 (79%)	72 (76%)	71 (75%)	66 (69%)	58 (61%)	56 (59%)
Paroxetine 60 mg	97	84 (87%)	78 (80%)	75 (77%)	69 (71%)	64 (66%)	57 (59%)	56 (58%)
Placebo	95	89 (94%)	86 (91%)	86 (91%)	82 (86%)	78 (82%)	69 (73%)	68 (72%)

Appendix 7.2.3

Study 454: Mean Dose (mg/day) By Visit							
Treatment	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 12
Parox 20 mg	20	20	20	20	20	20	20
Parox 40 mg	37	40	40	40	40	40	40
Parox 60 mg	38	59	60	60	60	60	60

Study 454: LS Mean Change From Baseline In LSAS Total Score-LOCF Analysis											
Time-point	Placebo		Paroxetine 20 mg		Paroxetine 40 mg		Paroxetine 60 mg		Pl v. 20 mg	Pl v. 40 mg	Pl v. 60 mg
	N	Mean	N	Mean	N	Mean	N	Mean	p	p	p
Baseline	92	73.3	89	79.8	88	77.5	91	76.9	0.047	0.202	0.261
Week 1	92	-2.8	87	-4.4	88	-3.3	91	-4.0	0.461	0.819	0.571
Week 2	92	-6.8	89	-8.5	88	-4.5	91	-5.6	0.519	0.390	0.665
Week 3	92	-9.2	89	-12.5	88	-9.4	91	-11.0	0.293	0.936	0.560
Week 4	92	-11.8	89	-18.0	88	-13.7	91	-15.3	0.077	0.592	0.316
Week 6	92	-12.9	89	-22.1	88	-19.2	91	-21.5	0.022	0.122	0.031
Week 8	92	-14.2	89	-27.5	88	-24.2	91	-23.6	0.002*	0.022	0.029
Week 12	92	-15.0	89	-31.4	88	-24.5	91	-25.2	<0.001*	0.039	0.024

*Dunnet's test, maintaining overall alpha =0.05 (p<0.019)

Study 454: LS Mean Change From Baseline In LSAS Total Score-Observed Cases Analysis											
Time-point	Placebo		Paroxetine 20 mg		Paroxetine 40 mg		Paroxetine 60 mg		Pl v. 20 mg	Pl v. 40 mg	Pl v. 60 mg
	N	Mean	N	Mean	N	Mean	N	Mean	p	p	p
Baseline	92	73.3	89	79.8	88	77.5	91	76.9	0.047	0.202	0.261
Week 1	92	-2.9	87	-5.8	88	-3.9	91	-4.7	0.160	0.646	0.360
Week 2	86	-7.2	80	-11.3	72	-5.6	80	-4.6	0.115	0.580	0.332
Week 3	77	-8.7	73	-16.0	71	-13.8	73	-12.3	0.027	0.132	0.277
Week 4	81	-13.1	70	-21.5	68	-18.4	71	-14.5	0.030	0.175	0.713
Week 6	78	-15.2	68	-25.9	68	-25.8	66	-22.1	0.015*	0.018*	0.125
Week 8	75	-17.2	68	-29.0	64	-32.4	60	-27.0	0.012*	0.002*	0.047
Week 12	68	-17.8	66	-32.5	55	-33.6	54	-30.2	0.006*	0.004*	0.034

*Dunnet's test, maintaining overall alpha =0.05 (p<0.019)

Appendix 7.2.3

Study 454: Number and Percentage of Patients with CGI Global Improvement Score of 1 or 2 - LOCF Analysis

Time-point	Placebo		Paroxetine 20 mg		Paroxetine 40 mg		Paroxetine 60 mg		Pl v. 20 mg	Pl v. 40 mg	Pl v. 60 mg
	N	%	N	%	N	%	N	%	p	p	p
Week 1	1/92	1.1	0/87	0.0	3/88	3.4	2/91	2.2	-	-	-
Week 2	5/92	5.4	6/89	6.7	7/88	8.0	6/91	6.6	0.71	0.50	0.74
Week 3	13/92	14.1	10/89	11.2	13/88	14.8	14/91	15.4	0.56	0.90	0.81
Week 4	18/92	19.6	17/89	19.1	20/88	22.7	21/91	23.1	0.94	0.60	0.56
Week 6	22/92	23.9	29/89	32.6	36/88	40.9	31/91	34.1	0.20	0.02*	0.13
Week 8	28/92	30.4	36/89	40.4	38/88	43.2	33/91	36.3	0.16	0.08	0.40
Week 12	26/92	28.3	40/89	44.9	41/88	46.6	39/91	42.9	0.02	0.01*	0.04

*Significant from placebo using Dunnett's Test to maintain overall alpha=0.05(p<0.019)

Study 454: Number and Percentage of Patients with CGI Global Improvement Score of 1 or 2 - Observed Cases Analysis

Time-point	Placebo		Paroxetine 20 mg		Paroxetine 40 mg		Paroxetine 60 mg		Pl v. 20 mg	Pl v. 40 mg	Pl v. 60 mg
	N	%	N	%	N	%	N	%	p	p	p
Week 1	1/92	1.1	0/87	7.5	3/88	3.4	2/91	2.2	-	-	-
Week 2	5/85	5.9	6/80	7.5	6/72	8.3	5/80	6.3	0.68	0.55	0.92
Week 3	12/77	15.6	10/73	13.7	12/71	16.9	12/73	16.4	0.74	0.83	0.89
Week 4	17/81	21.0	17/70	24.3	19/68	27.9	18/71	25.4	0.63	0.32	0.52
Week 6	21/78	26.9	29/68	42.6	34/68	50.0	28/66	42.4	0.05	0.01*	0.05
Week 8	26/75	34.7	36/68	52.9	34/64	53.1	30/60	50.0	0.03	0.03	0.07
Week 12	22/68	32.4	38/66	57.6	35/55	63.6	34/54	63.0	0.004*	<0.001*	<0.001*

*Significant from placebo using Dunnett's Test to maintain overall alpha=0.05(p<0.019)

Appendix 8.1

Appendix 8.1.2.1: Line Listing of Non-Fatal Serious Adverse Events					
PAROXETINE					
Patient ID	**Age**	**Sex**	**Dose at onset (mg/d)**	**Exposure before Onset (days)[1]**	**Serious Event(s)**
454.001.00039	29	M	60	31 31 32	Brain edema (Car accident) Trauma Headache
502.003.05511	20	M	50	70	Emotional lability/intentional OD of paracetamol & aspirin
502.010.05344	46	M	0	84 (+6)	Cerebrovascular disorder
502.012.05304	40	F	50	44	Cachexia
502.033.05427	53	F	30	19	Trauma (Smoke inhalation)
502.045.05135	40	F	0	84 (+2) 84 (+2) 84 (+4)	Uterine neoplasm Pain (post-operative) Infection (post-operative)
011.00134	46	M	40	135	Paranoia, agitation
009.00076	54	M	60	84	Unintentional overdose
PLACEBO					
502.045.05077	34	M	0	5	Emotional lability
502.045.05132	32	M	0	50 50 50	Dehydration Headache Palpitation
008.00125	24	F	0	84	Unintentional 'overdose'

[1]For events occurring post-treatment, + = number of days after treatment discontinuation at event onset.

Appendix 8.1.4.2.1: Treatment Emergent Adverse Events Occurring in ≥ 1% of Paroxetine Patients (Studies 502, 382, 454)[1]		
Body System/Adverse Event	**Paroxetine** (n=522)	**Placebo** (n=339)
Body as a Whole		
Asthenia	22%	14%
Fever	1%	<1%
Headache	22%	22%
Pain[2]	2%	1%
Trauma[3]	3%	1%
Cardiovascular System		
Migraine	1%	<1%
Vasodilatation[4]	1%	<1%
Digestive System		
Bruxism	1%	0%
Constipation	6%	2%
Appetite decreased	8%	1%
Diarrhea	9%	6%
Dry mouth	9%	3%
Dyspepsia	4%	2%
Dysphagia	1%	0%
Flatulence	4%	2%
Appetite increased	2%	2%

Appendix 8.1.4.2.1 (continued)		
Nausea	24%	6%
Vomiting	3%	<1%
Metabolic/Nutritional Disorders		
Weight gain	1%	<1%
Musculoskeletal System		
Myalgia	4%	3%
Nervous System		
Abnormal dreams	2%	1%
Agitation	2%	1%
Anxiety	4%	4%
Concentration impaired	3%	<1%
Emotional lability	2%	1%
Dizziness	11%	7%
Hyperkinesia	1%	0%
Insomnia	23%	16%
Libido decreased	11%	<1%
Myoclonus	3%	<1%
Nervousness	9%	6%
Paresthesia	2%	1%
Somnolence	23%	5%
Tremor	10%	1%
Respiratory System		
Cough increased	1%	<1%
Pharyngitis	3%	2%
Sinusitis	2%	2%
Yawn	7%	<1%
Skin and Appendages		
Rash	1%	<1%
Sweating	10%	2%
Special Senses		
Abnormal vision[5]	3%	<1%
Taste perversion	1%	<1%
Urogenital System		
Abnormal ejaculation[6,7]	32%	1%
Female genital disorders[6,8]	8%	<1%
Impotence[6]	6%	1%
Urinary frequency	2%	2%
Urination impaired	2%	0%

[1]Events for which paroxetine reporting incidence was ≤ the placebo incidence are not included. These events are: abdominal pain, allergic reaction, back pain, infection, palpitation, confusion, depression, respiratory disorder, rhinitis, and dysmenorrhea.
[2]A variety of injuries with no obvious pattern
[3]Pain in a variety of locations with no obvious pattern
[4]Usually flushing.
[5]Mostly blurred vision.
[6]Percentage corrected for gender.
[7]Mostly anorgasmia or delayed ejaculation.
[8]Mostly anorgasmia or delayed orgasm.

Appendix 8.1.4.2.2: Common (≥5%) and Probably Drug-Related Adverse Events (≥twice placebo rate) (Studies 502, 382, 454)		
	Paroxetine (n=522)	Placebo (n=339)
Constipation	6%	2%
Decreased appetite	8%	1%
Dry mouth	9%	3%
Nausea	24%	6%
Libido decreased	11%	1%
Somnolence	23%	5%
Tremor	10%	1%
Yawning	7%	<1%
Sweating	10%	2%
Abnormal ejaculation[1,2]	32%	1%
Female genital disorders[3,4]	8%	<1%
Impotence	6%	1%

[1]Based on the number of male patients
[2]Mostly anorgasmia or delayed orgasm
[3]Based on the number of female patients
[4]Mostly anorgasmia or delayed orgasm

Appendix 8.1.4.5: Other Events Observed During Premarketing Social Phobia Studies[1,2,3]
Body as a Whole
Abdomen enlarged, chest pain, chills, flu syndrome, malaise, neoplasm
Cardiovascular System
Angina, arrhythmia, bradycardia, cerebrovascular disorder, ECG abnormal, extrasystoles, hypertension, hypotension, peripheral vascular disease, syncope, tachycardia*, vascular disorder
Digestive System
Fecal incontinence, gastroenteritis, gastrointestinal disorder, gingivitis, hepatitis, liver function tests abnormal, oropharynx disorder, rectal disorder, stomatitis, tooth caries, tooth disoder,
Endocrine System
Fertility decreased female, hypothyroidism
Hemic and Lymphatic System
Anemia, leukocytosis, lymphadenopathy, monocytosis, purpura, thrombocytopenia, leukopenia
Metabolic/Nutritional Disorders
Cachexia, dehydration, edema, hyperglycemia, hypoglycemia, LFTs increased, thirst, weight loss
Musculoskeletal System
Arthralgia, bone disorder, myasthenia, myositis
Nervous System
Alcohol abuse, amnesia, ataxia, brain edema, depersonalization, drug dependence, dystonia, euphoria, hallucinations, hostility, hypertonia, hypesthesia, hypokinesia, incoordination, lack of emotion, libido increased, neurosis, paralysis, thinking abnormal, vertigo, vestibular disorder, withdrawal syndrome
Respiratory System
Asthma, bronchitis, dyspnea, hiccup, hyperventilation, larynx disorder, pleura disorder
Skin and Appendages
Acne, contact dermatitis, eczema, herpes, nail disorder, photosensitivity, pruritis, skin discoloration, skin disorder, urticaria
Special Senses
Conjunctivitis, ear disorder, ear pain, glaucoma, keratoconjunctivitis, mydriasis, otitis media, photophobia, taste loss, tinnitus
Urogenital System
Albuminuria, breast pain, cystitis, dysuria, fibrocystic breast, kidney pain, leukorrhea, menstrual disorder, nephritis, nocturia, prostate disorder, pyuria, spermatogenesis arrest, unintended pregnancy, urinary incontinence, urinary retention, UTI, urine abnormality, uterine neoplasm, vaginal moniliasis, vaginitis

[1]Events listed in table 8.1.4.2.1 and 8.1.4.2.2 are excluded.
[2]All events reported in this table were reported at a frequency between 1/100 and 1/1000 within the pool of studies (n=578), except for those marked with an asterisk (*), indicating a frequency of ≥1/100.
[3]Gender-specific event rates have been corrected for the number of males and females.

Appendix 8.1.5.3.1.1: Criteria for Identification of Laboratory Values of Potential Clinical Concern

PARAMETER		VALUE	UNITS
Hematology			
White Blood Cells		≤2.8, ≥16.0	10^9/L
Basophils		≥1.6	10^9/L
Eosinophils		≥1.6	10^9/L
Lymphocytes		≥12	10^9/L
Monocytes		≥2.4	10^9/L
Segmented Neutrophils		≤2.4	10^9/L
Neutrophils Bands		>1.6	10^9/L
Platelets		≤75, ≥700	10^9/L
Red Blood Cells	Male	≥8	10^12/L
	Female	≥10	10^12/L
Hematocrit	Male	≤37	%
	Female	≤32	%
Hemoglobin	Male	≤115	g/L
	Female	≤95	g/L
Blood Chemistry			
ALT/SGPT		≥165	IU/L
Alkaline Phosphatase		≥390	IU/L
AST/SGOT		≥150	IU/L
Blood Urea Nitrogen		≥10.71	mmol/L
Serum Creatinine		≥176.8	mcmol/L
Total Bilirubin		≥34.2	mcmol/L
Calcium		≤2.1, ≥3.0	mmol/L
Chloride		≤90, ≥118	mmol L
Potassium		≤3.0, ≥6.0	mmol/L
Sodium		≤126, ≥156	mmol/L
Total T3		≤1.3, ≥2.84	nmol/L
Total T4		≤57.9, ≥160.9	nmol/L
TSH		≥10	mU/L
Urinalysis			
Red Blood Cells	Male	>8	/hpf
	Female	>10	/hpf
White Blood Cells		>10	/hpf
Protein Dipstick		>10 or 4+	0-4+
Glucose		4+	0-4+

Appendix 8.1.5.3.1.2: Proportions of Patients Experiencing Potentially Clinically Significant Changes in Laboratory Values (Studies 454 and 502)				
	Paroxetine (n=428)		Placebo (n=246)	
	Abnormal		Abnormal	
	#	%	#	%
↑ ALT	1	<1	0	0
↑ Bilirubin	3	<1	2	<1
↑ Potassium	2	<1	1	<1
↑ TSH	1	<1	0	0
↑ T3	2	<1	1	<1
↓ T3*	9	2	1	<1
↓ T4	4	1	1	<1
↑ Eosinophils	10	2	2	<1
↑ Monocytes	1	<1	0	0
↑ WBC	1	<1	0	0
↑ Urine protein	1	<1	0	0

*No patients had T3 values < the laboratory reference range of normal (0.92 mmol/L), i.e. the criteria was mistakenly set too high.

Appendix 8.1.5.3.2.1: Criteria for Vital Signs Values of Potential Clinical Significance	
Systolic BP	Normal range = 90-180 mmHg Increase of ≥40, decrease of ≥30 mmHg
Diastolic BP	Normal range = 50-105 mmHg Increase of ≥30, decrease of ≥20 mmHg
Pulse	Normal range = 50-120 bpm Increase or decrease of ≥30 bpm
Weight	No normal range defined Increase or decrease of ≥7%

Appendix 8.1.5.3.2.2: Proportions of Patients with Potentially Clinically Significant Changes in Vital Signs Measures (Studies 454, 502, 382)				
	Paroxetine (n=522)		Placebo (n=339)	
	N	%	N	%
Systolic BP[1] (mmHg) - H	1	<1	2	<1
Diastolic BP[1] (mmHg) - L	2	<1	0	0
Pulse (bpm) [1] - L	2	<1	1	<1
Weight (kg) - H	17	3	10	3
Weight (kg) - L	9	2	3	1

[1]These readings were taken sitting.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020031/S023

STATISTICAL REVIEW(S)

COMPLETED FEB 2 6 1999

Statistical Review and Evaluation

FEB 2 6 1999

NDA:	NDA 20-031, Supplement
Applicant:	SmithKline Beecham
Name of Drug:	Paxil (paroxetine hydrochloride) Tablets
Indication:	Social Phobia
Statistical Reviewer:	Kun Jin, DBI/OB, HFD-710
Medical Reviewers:	Susan Molchan, M.M., ODE I, HFD-120

1. Introduction

The sponsor submitted this efficacy supplement in support of paroxetine in treating social phobia. The submission consists of three acute 12 week double-blind, randomized, placebo-controlled efficacy trials, Studies 502, 382 and 454. A long term efficacy trial, Study 470, was an extension to Study 382 in which patients could have been treated for up to a total of 52 weeks. There were 290 patients randomized in Study 502, 187 patients in Study 382 and 384 patients in Study 454. A total of 98 patients also entered the long term study. Studies 502, 382 and 454 will be reviewed in this report.

Two of the acute studies, Studies 502 and 382, were methodologically similar and employed a flexible-dosage design with paroxetine administered in the range of 20 to 50 mg once daily. Study 502 was conducted at multiple centers in Europe and South Africa, and Study 382 was conducted at multiple centers in North America. Study 454, also conducted at multiple centers in North America, employed a fixed-dosage design with paroxetine administered at dosages of 20, 40 and 60 mg once daily.

The primary efficacy variables in the acute studies were the mean change from baseline in the Liebowitz Social Anxiety Scale (LSAS) total score and the proportion of patients responding to treatment as determined by a Clinical Global Impressions (CGI) Global Improvement Item score of 1 (very much improved) or 2 (much improved) relative to baseline.

2. The Sponsor's Results

2.1 Patient Disposition and Demographics

Demographically, the study patients were essentially comparable not only within and between the studies. Across the three acute studies, the treatment group mean age ranged from 35 to 39 years, the percentage of females ranged from 34% to 54%, and the percentage of Caucasians ranged from 76% to 90%. Table 1 presents a summary of the demographic characteristics of patients in the ITT populations of Studies 502, 382 and 454. The treatment groups within and between studies were comparable with regard to the distribution of age and mean ages and the relative distribution of Caucasians and non-Caucasians. In the North American Studies 382 and 454, patients on average weighed approximately 77 kg (169 lbs). This was approximately 7 kg (15 lbs) higher than patients in Study 502, conducted in Europe and South Africa, and most likely reflects underlying population cultural differences. Similarly, the North American studies enrolled a slightly higher percentage of males than females, while Study 502 enrolled a slightly higher percentage of females.

Table 1 Demographic Characteristics of the Acute Studies Samples
ITT Population, Studies 502, 382, and 454

			Study 502		Study 382		Study 454			
			plac.	parox.	plac.	parox.	plac.	parox. 20 mg	40 mg	60 mg
Age	<18	n	0	0	0	0	0	0	0	0
		%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	18-24	n	19	25	14	10	18	10	11	13
		%	12.6	18.0	15.1	10.6	18.9	10.3	11.6	13.4
	25-34	n	50	51	35	38	27	18	23	31
		%	33.1	36.7	37.6	40.4	28.4	18.6	24.2	32.0
	35-44	n	50	35	23	27	36	41	40	30
		%	33.1	25.2	24.7	28.7	37.9	42.3	42.1	30.9
	45-54	n	18	19	11	15	10	23	16	22
		%	11.9	13.7	11.8	16.0	10.5	23.7	16.8	22.7
	55-64	n	10	8	5	4	3	3	5	1
		%	6.6	5.8	5.4	4.3	3.2	3.1	5.3	1.0
	³65	n	4	1	5	0	1	2	0	0
		%	2.6	0.7	5.4	0.0	1.1	2.1	0.0	0.0
	All	n	151	139	93	94	95	97	95	97
		mean	37.3	34.7	36.7	35.9	34.7	39.2	37.9	36.0
		SD	11.44	11.56	13.2	10.1	10.41	10.17	9.88	9.70
Weight	(kg)	N	150	137	89	94	95	97	94	96
		mean	69.8	70.0	74.6	77.0	74.2	76.8	76.8	79.1
		SD	16.08	14.25	15.32	19.25	17.25	16.06	13.14	16.30
Gender	Female	n	82	75	37	44	40	46	32	41
		%	54.3	54.0	39.8	46.8	42.1	47.4	33.7	42.3
	Male	n	69	64	56	50	55	51	63	56
		%	45.7	46.0	60.2	53.2	57.9	52.6	66.3	57.7
Race	Caucasian									
		n	136	123	80	71	79	79	77	78
		%	90.1	88.5	86.0	75.5	83.2	81.4	81.1	80.4
	Black	n	4	8	8	15	10	9	8	8
		%	2.6	5.8	8.6	16.0	10.5	9.3	8.4	8.2
	Asian	n	1	1	1	3	1	2	2	2
		%	0.7	0.7	1.1	3.2	1.1	2.1	2.1	2.1
	Other	n	10	7	4	5	5	7	8	9
		%	6.6	5.0	4.3	5.3	5.3	7.2	8.4	9.3

The number of patients who completed or prematurely withdrew from the acute studies is presented in Table 2 below. Overall, nearly 70% of the patients completed 12 weeks of treatment in the three studies: 73% in Study 502, 72% in Study 382, and 64% in Study 454. The primary reason for premature withdrawal from the placebo group was lack of efficacy, while the

primary reason for premature withdrawal from the paroxetine group was adverse experience.

Table 2. Disposition of the Acute-Treatment Population

	Study 502				Study 382				Study 454			
	Placebo		Paroxetine		Placebo		Paroxetine		Placebo		Paroxetine	
Total Randomized	N = 151		N = 139		N = 94		N = 93		N = 95		N = 289	
	n	%	n	%	n	%	n	%	n	%	n	%
LOE	19	12.6	1	0.7	10	10.8	0	0.0	10	10.5	8	2.8
AE	6	4.0	10	7.2	3	3.2	14	14.9	4	4.2	60	20.8
PV	5	3.3	7	5.0	3	3.2	4	4.3	0	0.0	11	3.8
Lost to F/U	8	5.3	9	6.5	5	5.4	12	12.8	8	8.4	22	7.6
Other	4	2.6	8	5.8	0	0.0	2	2.1	5	5.3	9	3.1
Comp.	109	72.2	103	74.1	72	77.4	62	66.0	68	71.6	179	61.9

LOE = lack of efficacy; AE = adverse experience; PV = protocol violation; F/U = follow-up

2.2 Comparison of Baseline

Table 3 presents a summary of the mean baseline scores on the primary and some secondary efficacy measures employed in two of the studies. The CGI Severity of Illness Item scores indicate that, on average, patients in Studies 502 and 454 were rated by the investigators, considering their clinical experience with patients with social anxiety disorder, to be moderately to markedly ill. Although the CGI Severity of Illness Item was not employed in Study 382, the baseline mean LSAS total scores are comparable to those in Study 502, suggesting a similar level of severity of illness at baseline in Study 382. The treatment group baseline mean LSAS total scores and Social Avoidance and Distress (SAD) Scale scores were comparable within studies, and between Studies 502 and 382; they were lower in Study 454, suggesting that patients in Study 454 were somewhat less severely ill. Mean treatment group HAM-D total scores were comparable both within and between treatments.

Table 3. Baseline Measures Scores of the Acute Studies Samples
ITT Population, Studies 502 and 382 (All Centers), and 454 (Excluding Center 005)

		502		382		454			
		plac.	parox.	plac.	parox.	plac.	parox. 20 mg	40 mg	60 mg
LSAS	N	145	136	92	90	92	89	88	91
Total	mean	86.1	87.6	83.5	78.0	73.3	79.8	77.5	76.9
	SE	2.24	2.33	2.31	2.33	2.41	2.42	2.45	2.41
CGI	N	137	129	§		92	90	88	91
Severity	mean	4.3	4.3			4.4	4.4	4.4	4.3
	SE	0.06	0.06			0.06	0.06	0.06	0.06
SAD	N	144	137	92	90	92	89	88	90
Scale	mean	22.6	22.9	22.4	22.6	20.8	22.6	21.2	21.7
Total	SE	0.44	0.46	0.53	0.53	0.55	0.56	0.56	0.55

HAM-D								
	N	151	138	§	95	97	95	97
Total	mean	6.7	6.2		5.6	6.2	5.5	5.3
	SD	3.64	3.63		3.46	3.60	3.76	3.42

§ Data not collected

2.3 Primary Efficacy Results

LSAS Total Score

The mean change from baseline in LSAS total score was analyzed by analysis of variance using the general linear models procedure (GLM) of SAS. When comparing individual dose groups against the placebo group, Dunnett's multiple comparison procedure was used to maintain an overall alpha level of 0.05. The adjusted level of significance was 0.019.

The efficacy of paroxetine in reducing social anxiety was in each of the three acute studies by the mean change from baseline in the LSAS total score. Summaries of the mean baseline and mean change from baseline in the LSAS total scores by treatment group in both the extender and visit-wise datasets for the flexible dosage Studies 502 and 382 are presented in Table 4, and for the fixed dosage Study 454 in Table 5. Efficacy was demonstrated both in the dosage range of 20 to 50 mg daily and at the fixed dosage of 20 mg daily at the protocol-specified timepoint of interest, Week 12 in the both LOCF and OC dataset. The paroxetine within-treatment effect at these dosages at this timepoint was consistent, ranging from a mean improvement of -29.4 points in Study 502 to a mean improvement of -31.4 points in Study 454. Similarly, the paroxetine-placebo between-treatment effect at these dosages at this timepoint was quite consistent, with approximately one-half of the within-treatment effect ranging from -13.8 points in Study 502 to -16.4 points in Study 454. In addition, efficacy was strongly suggested at Week 12 in the extender dataset at the 60 mg fixed dosage in Study 454, as the difference between the greater mean improvement in the paroxetine 60 mg group and that in the placebo group was nearly statistically significant.

Table 4 Studies 502 and 382 LSAS Total Score Mean Baseline and Mean Change from Baseline at Week 12

ITT Population

	Placebo			Paroxetine			
	N	mean §	SE	N	mean	SE	p-values
Study 502							
Baseline	145	86.1	2.24	136	87.6	2.33	0.607
LOCF	145	-15.6	2.72	136	-29.4	2.82	<0.001 *
OC	109	-20.5	3.24	108	-35.3	3.24	<0.001 *
Study 382							
Baseline	92	83.5	2.31	90	78.0	2.33	0.099
LOCF	92	-14.5	2.63	90	-30.5	2.66	<0.001 *
OC	73	-18.1	2.86	64	-37.2	3.07	<0.001 *

* Significant from placebo for alpha = 0.05

Table 5 Study 454 LSAS Total Score Mean Baseline and Mean Change from Baseline at Week 12

ITT Population (Excluding Center 005)

	Placebo			Paroxetine 20 mg			Paroxetine 40 mg			Paroxetine 60 mg		
	N	mean §	SE	N	mean	SE	N	mean	SE	N	mean	SE
Baseline	92	73.3	2.41	89	79.8	2.42	88	77.5	2.45	91	76.9	2.41
LOCF	92	-15.0	3.24	89	-31.4	3.13	88	-24.5	3.23	91	-25.2	3.14
P-values		NA		Pl v 20 mg = 0.001 *			Pl v 40 mg = 0.039			Pl v 60 mg = 0.024		
OC	68	-17.8	3.58	66	-32.5	3.88	55	-33.6	4.14	54	-30.2	4.53
P-values		NA		Pl v 20 mg = 0.006 *			Pl v 40 mg = 0.004 *			Pl v 60 mg =0.034		

§ Mean baseline or mean change from baseline

* Significant from placebo using Dunnett's test to maintain an overall alpha = 0.05 ($p<0.019$)

CGI Global Improvement Responders

The binary response variable of CGI Global Improvement Item Score of 1 or 2 was analyzed by logistic analysis using the categorical modeling procedure (CATMOD) of the Statistical Analysis System (SAS). When comparing individual dose groups against the placebo group, Dunnett's multiple comparison procedure was used to maintain an overall alpha level of 0.05. The adjusted level of significance was 0.019

The efficacy of paroxetine in improving the overall clinical condition of patients with social phobia was also consistently demonstrated in each of the three acute studies by the proportion of CGI Global Improvement Item responders, those rated as either very much improved or much improved relative to baseline (score of either 1 or 2). Summaries of the percentage of CGI Global Improvement Item responders by treatment group in both the LOCF and OC datasets for the flexible dosage Studies 502 and 382 are presented in Table 6 and for the fixed dosage Study 454 in Table 7. Efficacy was demonstrated both in the dosage range of 20 mg to 50 mg daily and at the fixed dosage of 40 mg daily at the protocol-specified timepoint of interest, Week 12 in the both LOCF and OC datasets. In addition efficacy was demonstrated at Week 12 in the OC dataset at the 20 mg and 60 mg fixed dosage in Study 454.

Table 6 Studies 502 and 382 Percentage of Responders with CGI Global Improvement Score of 1 or 2 at Week 12
ITT Population

	Placebo			Paroxetine			
	N	n	%	N	n	%	p-values
Study 502							
LOCF	145	47	32.4	137	90	65.7	<0.001 *
OC	110	46	41.8	110	85	77.3	<0.001 *
Study 382							
LOCF	92	22	23.9	91	50	54.9	<0.001 *
OC	73	21	28.8	64	44	68.8	<0.001 *

* Significant from placebo for alpha = 0.05

Table 7 Study 454 Percentage of Responders with CGI Global Improvement Score of 1 or 2 at Week 12
ITT Population (Excluding Center 005)

	Placebo			Paroxetine 20 mg			Paroxetine 40 mg			Paroxetine 60 mg		
	N	n	%	N	n	%	N	n	%	N	n	%
LOCF	92	26	28.3	89	40	44.9	88	41	46.6	91	39	42.9
P-values		NA		Pl v 20 mg = 0.021			Pl v 40 mg = 0.012 *			Pl v 60 mg = 0.040		
OC	68	22	32.4	66	38	57.6	55	35	63.6	54	34	63.0
P-values		NA		Pl v 20 mg = 0.004 *			Pl v 40 mg = <0.001 *			Pl v 60 mg = <0.001 *		

* Significant from placebo using Dunnett's Test to maintain overall alpha = 0.05 (p<0.019)

2.4 Excluding Center 005 in Study 454

The sponsor excluded the data from Center 005 in the primary analyses. The sponsor stated that it had been determined that data generated by this center in studies of three other indications, dysthymia, major depression and panic disorder, had yielded statistically significant treatment-by-center interactions in analyses of efficacy variables. They were only 4 patients, one in each treatment arm, in this center. (*This reviewer has confirmed that the efficacy results with or without center 005 are essentially the same.*)

3. The Reviewer's Comments

This reviewer has reanalyzed the datasets the sponsor submitted to the agency. The results in Section 2.3 were generally confirmed by this reviewer.

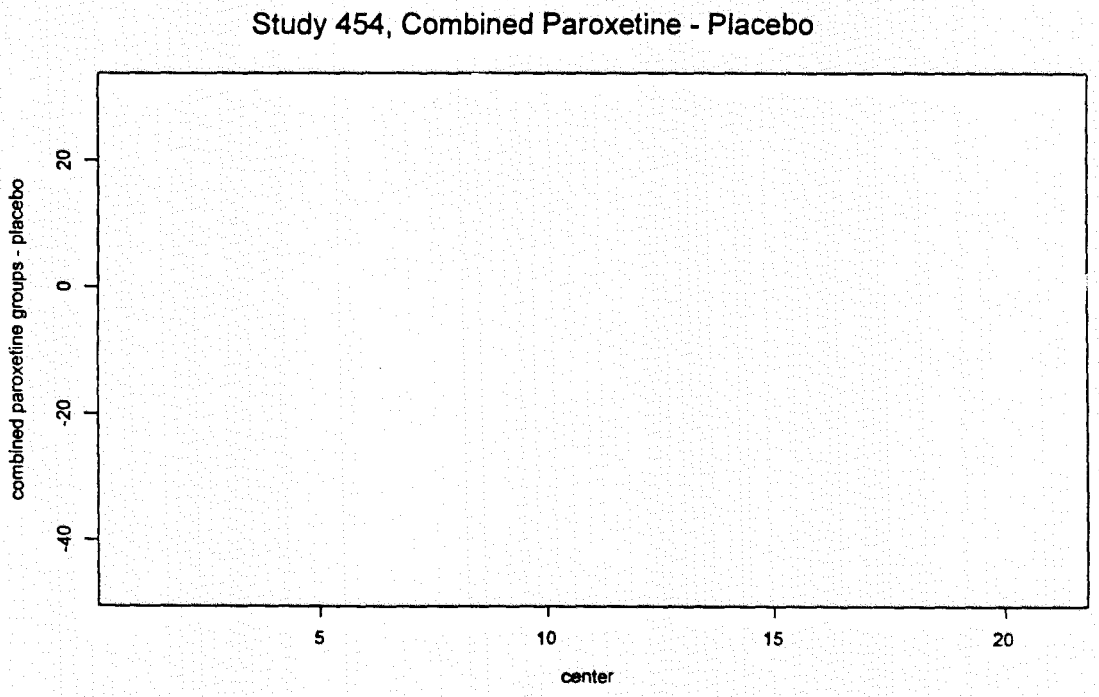
LSAS Total Score in Study 454

The mean changes from baseline in the LSAS total scores in the paroxetine 20 mg and 60 mg groups in the OC dataset of Study 454 are numerically different from the sponsor's, see the bold cases in Table 8. These discrepancies, however, do not affect the relevant p-values.

Table 8 Study 454 LSAS Total Score Mean Change from Baseline at Week 12
ITT-OC DataSet (Excluding Center 005)

	Placebo			Paroxetine 20 mg			Paroxetine 40 mg			Paroxetine 60 mg		
	N	mean §	SE	N	mean	SE	N	mean	SE	N	mean	SE
Sponsor	68	-17.8	3.58	66	-32.5	3.88	55	-33.6	4.14	54	-30.2	4.53
Reviewer	67	-16.0	2.84	66	**-36.0**	3.96	55	-32.8	2.72	55	**-34.2**	3.82

This reviewer confirmed the sponsor's report that the treatment-by-center interaction was found to be significant. To see whether one or two centers were the cause of the interaction, this reviewer calculated the difference of the mean changes from baseline in LSAS total score of combined paroxetine groups and placebo group for each individual center in the ITT-LOCF dataset. The result, which is plotted in the following graph, does not reveal any center to be a possible cause of the interaction.



CGI Global Improvement Responders

The CGI global improvement consists of 7 scores, 1-very much improved, 2-much improved, 3-minimally improved, 4-no change, 5-minimally worse, 6-much worse, and 7-very much worse. The responder analysis was done by looking at the proportion of "improved" patients, i.e. patients with scores 1 or 2. Although the responder analysis showed that paroxetine was favorable over placebo. It is necessary to see whether there were "reversed shifts," namely more patients with scores 5, 6, and 7, in paroxetine groups comparing with placebo. This reviewer calculated the distributions of CGI global improvement scores for all three studies. The results are in the following tables. It can be seen that there were no "reversed shifts" in all the studies.

Table 9. Distributions of CGI global improvement scores of Studies 502, 383 and 454, ITT-LOCF datasets

CGI Score	Study 502				Study 382			
	LOCF		OC		LOCF		OC	
	Placebo	Paroxetine	Placebo	Paroxetine	Placebo	Paroxetine	Placebo	Paroxetine
1	13	36	13	33	8	24	7	21
2	35	55	33	47	14	26	14	22
3	38	21	33	13	30	16	23	9
4	43	19	27	8	38	23	27	9
5	13	5	3	2	2	2	1	1
6	5	0	0	0	0	0	0	0
7	0	1	0	0	0	0	0	0

CGI Score	Study 454							
	LOCF				OC			
	Placebo	20 mg	40 mg	60 mg	Placebo	20 mg	40 mg	60 mg
1	7	17	19	21	7	16	18	21
2	19	25	22	19	15	23	18	15
3	23	23	21	18	21	18	14	11

4	40	26	26	34	24	10	6	9
5	2	0	2	1	1	0	0	0
6	0	1	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0

Conculusion

The results of the three acute studies demonstrate the effectiveness of paroxetine in the treatment of social phobia based on the protocol specified primary endpoints.

/S/

Kun Jin, Ph.D
Team Leader, OBI

APPEARS THIS WAY
ON ORIGINAL

Concur /S/
George Chi, ~~Ph.D.~~
Division ~~Director, OBI~~

cc:
Arch. NDA 20-031, Supplement
HFD-120
HFD-120/Dr. Katz
HFD-120/Dr. Laughren
HFD-120/Dr. Molchan
HFD-120/Ms. Homonnay
HFD-344/Dr. Lisook
HFD-710/Dr. Chi
HFD-710/Dr. Jin
HFD-710/Chron

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020031/S023

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

RECEIVED JUN 1 8 1998

JUN 2 1998

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-031
Paxil® (Paroxetine hydrochloride)
(10, 20, 30 and 40 mg Tablets)

Type of submission: Efficacy Supplement (S-023)
Submission Date: May 6, 1998

Sponsor: Smithkline Beecham

INDICATION: Social Phobia

REVIEWER: Rae Yuan, Ph.D.

This is a efficacy supplement for paxil tablets for the treatment of social anxiety disorder/social phobia. The submission consists of 4 phase III clinical efficacy studies: three short-term clinical efficacy studies (studies #385, 502 and 454) and one long term study (study 470). There is no clinical pharmacology study in the submission. However, because two of the four clinical studies utilized the over-encapsulated products of the approved tablets, dissolution comparisons of these clinical trial capsules to the approved products are submitted.

The dissolution comparisons of the over-encapsulated product (in clinical study #502 and 454) vs. the approved products are provided in the attachment III (The other two clinical studies, i.e. study 385 and 470 utilized the commercial products, therefore, their dissolutions are not provided). It was demonstrated that at equivalent dosage strengths, all the clinical trial capsules meet the dissolution specifications set for the approved products. For the 15 mg capsule strength used in study 502, there is no commercial equivalent and therefore a direct comparison on dissolution could not be made. However, it is bracketed by the other three comparative dissolution profiles for capsule strengths at 10, 20 and 30 mg, it is therefore considered equivalent to the tablets at the same tablet strength. The sponsor has also calculated the similarity factor (f_2) according to SUPAC-IR. All f_2 values comparing over encapsule formulations with the commercial tablet formulations are in the range of , indicating that the formulations are equivalent.

Recommendation:

Based on similar dissolution profiles for the encapsulated tablets and approved tablets, the products used in the four clinical trials are acceptable.

Primary Reviewer: Rae Yuan, Ph.D. /S/

Team Leader: Chandra Sahajwalla /S/

Date of Signature: 6/2/98

Office of Clinical Pharmacology and Biopharmaceutics/Division I

CC list: HFD-120; CSO; HFD-860 (Yuan, Sahajwalla, Malinowski); CDR (Barbara Murphy)

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12 pages

TRADE Secret/

Confidential

Commercial

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020031/S023

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

exclusivity checklist Section 3 G

Exclusivity Checklist

NDA: 20-031/S-023				
Trade Name: Paxil Tablets				
Generic Name: Paroxetine Hydrochloride Tablets				
Applicant Name: SmithKline Beecham Pharmaceuticals				
Division: HFD-120				
Project Manager: Anna M. Homonnay-Weikel				
Approval Date:				
PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?				
1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" t one or more of the following questions about the submission.				
a. Is it an original NDA?	Yes		No	✓
b. Is it an effectiveness supplement?	Yes	✓	No	
c. If yes, what type? (SE1, SE2, etc.)	SE1			
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	Yes	✓	No	
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including you reasons for disagreeing with any arguments made by the applicant that the study was not simpl a bioavailability study.				
Explanation:				
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:				
Explanation:				
d. Did the applicant request exclusivity?	Yes		No	✓
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?				
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously bee approved by FDA for the same use?	Yes		No	✓

exclusivity checklist Section 3 G

If yes, NDA #				
Drug Name:				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes		No	✓
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).				
PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES				
(Answer either #1 or #2, as appropriate)				
1. Single active ingredient product.	Yes		No	
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an alread approved active moiety.	Yes		No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
2. Combination product.	Yes		No	
If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing <u>any one</u> of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed unde an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes		No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				

exclusivity checklist Section 3 G

NDA #	
Drug Product	
NDA #	

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed onl if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (Th Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes	✓	No	

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is n essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical tria such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from so other source, including the published literature) necessary to support approval of the application or supplement?	Yes	✓	No	

If "no," state the basis for your conclusion that a clinical trial is not necessary for approva **AND GO DIRECTLY TO SIGNATURE BLOCKS.**

Basis for conclusion:

b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?	Yes		No	✓
1) If the answer to 2 b) is "yes," do you personally know of an reason to disagree with the applicant's conclusion? If not applicable, answer NO.	Yes		No	

exclusivity checklist Section 3 G

If yes, explain:				
2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?	Yes		No	✓
If yes, explain:				
c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:				
Investigation #1, Study #: 382				
Investigation #2, Study #: 502				
Investigation #3, Study #: 454				
3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been reli on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by th agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approv application.				
a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")				
Investigation #1 382	Yes		No	✓
Investigation #2 502	Yes		No	✓
Investigation #3 454	Yes		No	✓
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?				
Investigation #1 382	Yes		No	✓
Investigation #2 502	Yes		No	✓
Investigation #3 454	Yes		No	✓
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application				

exclusivity checklist Section 3 G

or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any th are not "new"):				
Investigation #1	382			
Investigation #2	502			
Investigation #3	454			
4. To be eligible for exclusivity, a new investigation that is essential to approval must also hav been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.				
a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?				
Investigation #1	Yes	✓	No	
IND#:				
Explain:				
Investigation #2	Yes	✓	No	
IND#:				
Explain:				
Investigation #3	Yes	✓	No	
IND#:				
Explain:				
b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interes provided substantial support for the study?				
Investigation #1	Yes		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				

exclusivity checklist Section 3 G

Explain:				
c. Notwithstanding an answer of "yes" to (a) or (b), are there othe reasons to believe that the applicant should not be credited with havin "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)	Yes		No	✓
If yes, explain:				

BACK TO TOP

/S/

Signature of PM/CSO

Date: 4/30/99

/S/

Signature of Division Directo

Date: 5/11/99

cc:

Original NDA

Division File

HFD-93 Mary Ann Holovac

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BACK TO TOP

Paxil® (paroxetine hydrochloride) Tablets

ITEM 13/14 - PATENT INFORMATION

The following patent information is being submitted pursuant to 21 C.F.R. 314.53.

Patent No.	Expiry Date	Type of Patent	Patent owner
4 721 723	December 29, 2006 The patent expiration date shown above was calculated in accordance with the U.S. Patent and Trademark Office's Federal Register notice of March 27, 1995. SB believes, however, that the correct expiration date, as properly calculated in accordance with the law and in particular with Section 532 of the Uruguay Round Agreements Act, P.L. 103-564, is September 24, 2008. SB reserves the right to modify the patent data in the future. SB also reserves the right to assert this position against persons or parties who may seek to make, use, offer for sale, import, or sell the approved drug prior to September 24, 2008.	Drug	Beecham Group p.l.c. Brentford, England

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 20031 **Trade Name:** PAXIL (PAROXETINE HCL) TABLETS
Supplement Number: 23 **Generic Name:** PAROXETINE HCL
Supplement Type: SE1 **Dosage Form:**
Regulatory Action: AE **Proposed Indication:** Social Phobia

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? NO

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Status -
Formulation Status -
Studies Needed -
Study Status -

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? YES

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, ANNA MARIE HOMONNAY-WEIKEL

/S/ 2/26/99
Signature Date

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SmithKline Beecham
Pharmaceuticals

June 5, 1998

Anna M. Homonnay-Weikel
Project Manager

Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
Woodmont II, 4th Floor
1451 Rockville Pike
Rockville, Maryland 20852

Agency Request for Information

Dear Anna,

Reference is made to the Supplemental Application to NDA 20-031, Paxil (paroxetine hydrochloride) Tablets for the treatment of Social Anxiety Disorder / Social Phobia.

Submitted herein, in duplicate, is a list of investigators pertaining to the aforementioned application. As we discussed on the phone, a duplicate copy of this submission has also been sent to:

Dr. Robert Young
Food and Drug Administration
7520 Standish Place
Route 125
Rockville, Maryland 20855

Please do not hesitate to contact me at (610) 917-5970 should you have any questions or need any additional information.

Sincerely,

Thomas F. Kline
Manager
US Regulatory Affairs

1250 S. Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989 Telephone (610) 917-7000 Fax (610) 917-7565

Paxil (paroxetine hydrochloride) Tablets

Social Anxiety Disorder/Social Phobia

sNDA 20-031

List of Investigators (with number of patients): Alphanumeric by Protocol

For clinical studies 382, 454, 470, and 502

NAME	COUNTRY	PROTOCOL/ CENTER NUMBER	Number of Paxil Patients	Number of Placebo Patients	Total Number of Patients
Study 382					
Bastani, Bijan, M.D. Comprehensive Psychiatric Services 24075 Commerce Park Road Beachwood, OH 44122	United States	382/001	5	6	11
Clary, Cathryn, M.D. Clary Research Associates, P.A. 575 S. duPont Highway New Castle, DE 19720	United States	382/002	6	5	11

NAME	COUNTRY	PROTOCOL/ CENTER NUMBER	Number of Paxil Patients	Number of Placebo Patients	Total Number of Patients
Davis, Larry, M.D. Broad Ripple MedCheck 1091 Broad Ripple Avenue Indianapolis, IN 46220 and Davis, Larry, M.D. Davis Clinic, P.C. 1441 North Delaware Street Indianapolis, IN 46234	United States	382/003	8	8	16
DuPont, Robert L., M.D. Institute for Behavior and Health, Inc. 6191 Executive Blvd. Rockville, MD 20852	United States	382/004	8	8	16
Ferguson, James, M.D. Pharmacology Research Corporation 448 E. 6400 South, Suite 350 Salt Lake City, UT 84107	United States	382/005	8	8	16
Jefferson, James, M.D. Dean Foundation for Health, Research & Education 8000 Excelsior Drive, Suite 302 Madison, WI 53717-1914	United States	382/006	8	8	16
Kavoussi, Richard, M.D. Clinical Neuroscience Research Unit Eastern Pennsylvania Psychiatric Institute 3200 Henry Avenue Philadelphia, PA 19129	United States	382/007	8	8	16

NAME	COUNTRY	PROTOCOL/ CENTER NUMBER	Number of Paxil Patients	Number of Placebo Patients	Total Number of Patients
Liebowitz, Michael R., M.D. New York State Psychiatric Institute 722 West 168th Street New York, NY 10032 and Freedom From Fear 308 Seaview Drive Staten Island, NY 10305	United States	382/008	8	8	16
Lydiard, R. Bruce, M.D., Ph.D. Department of Psychiatry and Behavioural Sciences Medical University of South Carolina 171 Ashley Avenue Charleston, SC 29425 *(Co-Investigator with James C. Ballenger, M.D* Ballenger, James C., M.D. Department of Psychiatry and Behavioural Sciences Medical University of South Carolina 171 Ashley Avenue Charleston, SC 29425 *(Co-Investigator with Bruce R. Lydiard, M.D., Ph.D.).)*	United States	382/009	8	8	16
Stein, Murray B., M.D. UCSD Medical Center UCSD Psychopharmacology Research Program 8950 Villa La Jolla Drive, Suite 2243 La Jolla, CA 92037	United States	382/010	8	8	16

NAME	COUNTRY	PROTOCOL/ CENTER NUMBER	Number of Paxil Patients	Number of Placebo Patients	Total Number of Patients
Schweizer, Edward, M.D. Psychopharmacology Research & Treatment Unit University of Pennsylvania 3600 Market Street, Room 872 Philadelphia, PA 19104	United States	382/011	8	8	16
DuBoff, Eugene, M.D. Center for Behavioral Medicine 4704 Harlan, Suite 430 Denver, CO 80212	United States	382/012	8	8	16
Reesal, Robin, M.D. Western Canada Behavior Research Center Suite 210, 320 23 Avenue S.W. Calgary, Alberta	Canada	382/013	3	2	5

NAME	COUNTRY	PROTOCOL/ CENTER NUMBER	Number of Paxil Patients	Number of Placebo Patients	Total Number of Patients
Study 454					
Bastani, Bijan, M.D. North East Ohio Health Services One Commerce Park Square 23200 Chagrin Blvd Suite 400 Beachwood, OH 44122 and Portage Path CMHC 340 S. Broadway Street Akron, OH 44308	United States	454/001	5	2	7
Bielski, Robert J., M.D. Institute for Health Studies 26105 Orchard Lake Rd Suite 301 Farmington Hills, MI 48334 and Institute for Health Studies 825 Parchment Dr., SE Grand Rapids, MI 49546 and Institute for Health Studies 4084 Okemos Road, Suite C Okemos, MI 48864	United States	454/002	21	7	28

NAME	COUNTRY	PROTOCOL/ CENTER NUMBER	Number of Paxil Patients	Number of Placebo Patients	Total Number of Patients
Bryer, Joseph, M.D. Clary Research Associates, P.A. 575 S. duPont Highway New Castle, DE 19720 *(Co-Investigator with Laura A. Mandos, Pharm.D.)* Mandos, Laura A., Pharm.D. Clary Research Associates, P.A. 575 S. duPont Highway New Castle, DE 19720 *(Co-Investigator with Joseph Bryer, M.D.)*	United States	454/003	6	2	8
Davidson, Jonathan, M.D. Duke University Medical Center Department of Psychiatry Durham, NC 27710 *(Co-Investigator with Richard Weisler, M.D.)* and 900 Ridgefield Drive Suite 320 Raleigh, NC 27609 *(Co-Investigator with Richard Weisler, M.D.)*	United States	454/004	22	8	30
Davis, Larry, M.D. Broad Ripple MedCheck 1001 Broad Ripple Ave. Indianapolis, IN 46220 and Davis Clinic, P.C. 1431 North Delaware Street Indianapolis, IN 46202	United States	454/005	3	1	4

NAME	COUNTRY	PROTOCOL/ CENTER NUMBER	Number of Paxil Patients	Number of Placebo Patients	Total Number of Patients
DuBoff, Eugene, M.D. Center for Behavioral Medicine 4704 Harlan Street, Suite 430 Denver, CO 80212	United States	454/006	16	6	22
DuPont, Robert L., M.D. Institute for Behavior and Health, Inc. 6191 Executive Blvd. Rockville, MD 20852	United States	454/007	20	6	26
Ferguson, James, M.D. Pharmacology Research Corporation Commerce Park 448 E. 6400 South, Suite 350 Salt Lake City, UT 84107 *(Co-Investigator with Lee Rasmusen, M.D.)*	United States	454/008	24	8	32
Jefferson, James, M.D. Dean Foundation for Health, Research & Education 2711 Allen Blvd Middleton, WI 53562	United States	454/009	8	3	11
Kavoussi, Richard, M.D. Allegheny University EPPI Room 250 A 3200 Henry Avenue Philadelphia, PA 19129	United States	454/010	8	3	11

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NAME	COUNTRY	PROTOCOL/ CENTER NUMBER	Number of Paxil Patients	Number of Placebo Patients	Total Number of Patients
Schweizer, Edward, M.D. Psychopharmacology Research and Technology Unit University of Pennsylvania 3600 Market Street, Suite 800 Philadelphia, PA 19104-2649	United States	454/015	6	2	8
Shear, M. Katherine, M.D. Western Psychiatric Institute and Clinic 100 North Bellefield, 7th floor Pittsburgh, PA 15213	United States	454/016	6	2	8
Smith, Ward T., M.D. Pacific NW Clinical Research Center 1849 NW Kearney, Suite 201 Portland, OR 97209 and Pacific NW Clinical Research Center 9495 SW Locust, Suite E Portland, OR 97223	United States	454/017	17	5	22
Stein, Murray B., M.D. UCSD Department of Psychiatry 8950 Villa La Jolla Drive, Suite 2243 La Jolla, CA 92037	United States	454/018	18	6	24
Stewart, Rege, M.D. University of Texas Southwestern Medical Center St. Paul Profesional Bldg I, Suite 520 5959 Harry Hines Blvd Dallas, TX 75235-9101	United States	454/019	24	7	31

NAME	COUNTRY	PROTOCOL/ CENTER NUMBER	Number of Paxil Patients	Number of Placebo Patients	Total Number of Patients
Tancer, Manuel, M.D. University Psychiatry Center - Warren 28800 Ryan Road, Suite 300 Warren, MI 48092	United States	454/020	8	2	10
Weihs, Karen, M.D. George Washington University Medical Center Clinical Psychiatric Research Center 2300 Eye Street, NW Ross Hall, Room 730 Washington, DC 20037	United States	454/021	6	2	8
Bennett, Vern, M.D. Department of Psychiatry Royal University Hospital 103 Hospital Drive Saskatoon, SK S7N 0W8	Canada	454/022	8	2	10

NAME	COUNTRY	PROTOCOL/ CENTER NUMBER	Number of Paxil Patients	Number of Placebo Patients	Total Number of Patients
Study 470					
Bastani, Bijan, M.D. Portage Path Community Mental Health Center 340 S. Broadway Street Akron, OH 44308 and Comprehensive Psychiatric Services 24075 Commerce Park Road Beachwood, OH 44122	United States	470/001	8 (open phase) 2 (double-blind)	2 (double-blind)	8
Clary, Cathryn, M.D. Clary Research Associates, P.A. 575 S. DuPont Highway New Castle, DE 19720	United States	470/002	6 (open phase) 2 (double-blind)	2 (double-blind)	6
Davis, Larry, M.D. Davis Clinic, P.C. 1441 North Delaware Street Indianapolis, IN 46202 and Broad Ripple MedCheck 1091 Broad Ripple Ave. Indianapolis, IN 46220	United States	470/003	12 (open phase) 4 (double-blind)	4 (double-blind)	12

NAME	COUNTRY	PROTOCOL/ CENTER NUMBER	Number of Paxil Patients	Number of Placebo Patients	Total Number of Patients
DuPont, Robert L., M.D. Institute for Behavior and Health 6191 Executive Blvd. Rockville, MD 20852	United States	470/004	6 (open phase) 2 (double-blind)	3 (double-blind)	6
Ferguson, James, M.D. Pharmacology Research Corporation 448 E. 6400 South, Suite 350 Salt Lake City, UT 84107	United States	470/005	7 (open phase) 2 (double-blind)	2 (double-blind)	7
Jefferson, James, M.D. Dean Foundation for Health, Research & Education 8000 Excelsior Drive, Suite 302 Madison, WI 53717-1914	United States	470/006	9 (open phase) 2 (double-blind)	3 (double-blind)	9
Kavoussi, Richard, M.D. Clinical Neuroscience Research Unit Eastern Pennsylvania Psychiatric Institute 3200 Henry Avenue Philadelphia, PA 19129	United States	470/007	8 (open phase) 1(double-blind)	1 (double-blind)	8
Liebowitz, Michael R., M.D. Staten Island Research Clinic located at Freedom From Fear 308 Seaview Avenue Staten Island, NY 10305 and New York State Psychiatric Institute 722 West 168th Street New York, NY 10032	United States	470/008	9 (open phase) 2 (double-blind)	2 (double-blind)	9

NAME	COUNTRY	PROTOCOL/ CENTER NUMBER	Number of Paxil Patients	Number of Placebo Patients	Total Number of Patients
Lydiard, R. Bruce, Ph.D.,M.D. Medical College of South Carolina Department of Psychiatry 171 Ashley Avenue Charleston, SC 29425	United States	470/009	7 (open phase) 1 (double-blind)	1 (double-blind)	7
Stein, Murray B., M.D. UCSD Medical Center UCSD Psychopharmacology Research Program 8950 Villa La Jolla Drive, Suite 2243 La Jolla, CA 92037	United States	470/010	11 (open phase) 4 (double-blind)	3 (double-blind)	11
Schweizer, Edward, M.D. Psychopharmacology Research and Treatment Unit University of Pennsylvania 3600 Market Street, Suite 872 Philadelphia, PA 19104	United States	470/011	7 (open phase) 2 (double-blind)	2 (double-blind)	7

NAME	COUNTRY	PROTOCOL/ CENTER NUMBER	Number of Paxil Patients	Number of Placebo Patients	Total Number of Patients
DuBoff, Eugene, M.D. Center for Behavioral Medicine 4704 Harlan, Suite 430 Denver, CO 80212	United States	470/012	8 (open phase) 3 (double-blind)	 3 (double-blind)	8

NAME	COUNTRY	PROTOCOL/ CENTER NUMBER	Number of Paxil Patients	Number of Placebo Patients	Total Number of Patients
Study 502					
O'Donoghue, Frank St. Patrick's Hospital PO Box No 136 James Street Dublin, Ireland	United Kingdom	502/001	2	1	3
Lynch, John St. Luke's Hospital Clonmel County Tipperary, Ireland	United Kingdom	502/002	5	4	9
Nutt, David Bristol Royal Infirmary Marlborough Street Bristol, UK	United Kingdom	502/003	4	5	9
Chattree, Shashank Queen's Park Hospital Haslingdon Road Blackburn, UK	United Kingdom	502/004	2	3	5
Baldwin, David Royal South Hants Hospital Graham Road Southampton, UK	United Kingdom	502/005	3	4	7

NAME	COUNTRY	PROTOCOL/ CENTER NUMBER	Number of Paxil Patients	Number of Placebo Patients	Total Number of Patients
Qureshi, Jafer Newcross Hospital Wolverhampton, UK	United Kingdom	502/008	0	0	0
Cookson, John Psychiatry Dept John Denham Bldg. Royal London Hospital, St. Clement's 2a Bow Road London, UK	United Kingdom	502/010	2	4	6
Faure, Michel 187 Rue Victor Hugo Tours, France	France	502/011	11	10	21
Gailledreau, Joel 8 Boulevard Richerand Villecresnes, France *(Co-Investigator with Christophe Bagot)*	France	502/012	7	7	14
Leclercq, Philippe 16 Avenue Robert Schuman Mulhouse, France	France	502/013	0	2	2
Moles, Marie-France 26 Rue Du Languedoc Toulouse, France	France	502/014	2	3	5
Le Goubey, Pierre 88 Rue Emmanuel Liasis Cherbough, France	France	502/015	1	1	2

NAME	COUNTRY	PROTOCOL/ CENTER NUMBER	Number of Paxil Patients	Number of Placebo Patients	Total Number of Patients
Deroche, Didier 57 Rue Gamard Joue Les Tours	France	502/016	2	2	4
Horenstein, J. Centre Mgen 152 Avenue De Wagram Paris, France	France	502/017	2	2	4
De Mondragon, Manuel 17 Rue Du Roi Albert Nantes, France	France	502/018	6	6	12
Chneiweiss, Laurent 5 Rue Keppler Paris, France	France	502/019	1	0	1
Andre, Christophe Hopital Sainte Anne 1 Rue Cabanis Paris, France	France	502/020	0	0	0
De Nayer, Andre Clinique Sainte Theresa Rue Trieu Kaisin 13 Montigny-Sur-Sambre, Belgium	Belgium	502/021	3	3	6
Bartholome, France Clinique Sainte-Joseph 23 Avenue Laurent Gilys Fleron-Retinne, Belgium	Belgium	502/022	0	1	1

NAME	COUNTRY	PROTOCOL/ CENTER NUMBER	Number of Paxil Patients	Number of Placebo Patients	Total Number of Patients
De La Torre Hernandez, Jamie Hospital De La Cruz Roja C./Dos De Mayo, 301 Barcelona, Spain	Spain	502/023	4	3	7
Soria, Jose Hospital De La Princesa C./Diego De Leon, 62 Madrid, Spain	Spain	502/024	4	6	10
Gonzalez-Quiros, Pedro Hospital Central De Asturias C/Julien Claveria S/N Oviedo, Spain	Spain	502/025	4	5	9
Hand, Iver Uniuversitaetskrankenhaus Eppendorf Psychiatrische Und Nervenklinik Martinstrasse 52 Hamburg, Germany	Germany	502/026	3	2	5
Henn, Fritz Zentralinstitut Fur Seelische Desundheit Psychiatrische Klinik Postfach 122120 Mannheim, Germany	Germany	502/027	0	2	2

NAME	COUNTRY	PROTOCOL/ CENTER NUMBER	Number of Paxil Patients	Number of Placebo Patients	Total Number of Patients
Buchkremer, Gerhard Klinikum De Eberhard-Karls-Universitat Tubingen Klinik Fur Psychiatrie Und Psychotherapies Osiaderstrasse 22 Tubingen, Germany	Germany	502/029	0	1	1
Ziegler, Gismar Institut F. Psychomat Forschug Herbsthalde 11 Stuttgart, Germany	Germany	502/030	2	2	4
Scharwachter, Ingeborg Burgestrasse 114 Remschcid, Germany	Germany	502/033	6	6	12
Spiers, Remi Keistraat 83 9849 De Pinte De Pinte, Belgium	Belgium	502/034	1	2	3
Demyttenaere, Koen University Hospital Gasthuisberg Department of Psychiatry Hercstraat 49 Leuven, Belgium	Belgium	502/035	0	0	0
Van Heeringen, C. Department of Psychiatry University Hospital Zaandam, Belgium	Belgium	502/036	0	0	0

NAME	COUNTRY	PROTOCOL/ CENTER NUMBER	Number of Paxil Patients	Number of Placebo Patients	Total Number of Patients
De Bleeker, Eugeen Psychiatrische Kliniek St. Lucia Ankerstraat 91 St. Niklaas, Belgium	Belgium	502/037	2	2	4
Stein, Dan University of Stellenbosch Fansle Van Zyl Drive Tygerberg Cape Town, South Africa	South Africa	502/038	6	6	12
Strong, Paull Libertas Medical Centre Voortrekker Street Goodwood Cape Town, South Africa	South Africa	502/039	4	3	7
Berk, Michael Department of Psychiatry 3t16 Wits Medical School 7 York Road Parktown, South Africa	South Africa	502/040	8	8	16
Gonzalez De Rivera, Jose Avda Reyes Catolicos, 2 Madrid, Spain	Spain	502/041	2	1	3
Els, Charl 125 President Rietz Ave Westdene Bloemfontein, South Africa	South Africa	502/042	4	5	9

NAME	COUNTRY	PROTOCOL/ CENTER NUMBER	Number of Paxil Patients	Number of Placebo Patients	Total Number of Patients
Royds, Jeremy Knighten Surgery 6 Kenilworth Street Kenilworth Cape Town, South Africa	South Africa	502/043	3	4	7
Wilson, Donald Department of Psychiatry Groote Schuur Hospital Block J2, Main Road Observatory Cape Town, South Africa	South Africa	502/044	3	3	6
Gittleson, Leon 38 Cheviot Place Wigtown Road Geen Point Cape Town, South Africa	South Africa	502/045	13	12	25
Futter, Graham Suite 7, Highway Medical Centre Box 467 Spine Road Westville Durban, South Africa	South Africa	502/046	2	3	5
Randerre, Farouk 1303 Durdoc Centre 460 Smith Street Durban, South Africa	South Africa	502/047	2	4	6

NAME	COUNTRY	PROTOCOL/ CENTER NUMBER	Number of Paxil Patients	Number of Placebo Patients	Total Number of Patients
Wheatley, David Royal Masonic Hospital Ravenscourt Park London, UK	United Kingdom	502/048	12	11	23
Marks, Isaac Maudsley Hospital Denmark Hill London, UK	United Kingdom	502/049	1	2	3

DEBARRMENT STATEMENT

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, SmithKline Beecham hereby certifies that, to the best of its knowledge and belief, we did not and will not use in any capacity, in connection with this application, the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act.

Ms. Hammerschmidt

NDA 20-031/S-023

MAR 29 1999

SmithKline Beecham Pharmaceuticals
Attention: Thomas F. Kline
Manager, U.S. Regulatory Affairs
1250 South Collegeville Road, P.O. Box 5089
Collegeville, Pennsylvania 19426

Dear Mr. Kline:

Please refer to your supplemental new drug application dated May 6, 1998, received May 6, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paxil® (paroxetine hydrochloride) Tablets.

This supplement provides for the use of Paxil® for the treatment of social phobia as a new indication.

We acknowledge receipt of your amendments dated July 29, 1998; and February 10, 1999 (revised draft labeling).

The User Fee goal date for this application is May 6, 1999.

We have completed the review of this application, as submitted with the draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to respond to the following clinical issues:

1. Labeling

   Accompanying this letter (attachment) is the Agency's proposal for the labeling of Paxil® for social phobia. We believe it presents a fair summary of the information available on the benefits and risks of Paxil®.

   We have proposed a number of changes to the draft labeling submitted in your February 10, 1999, submission. We will be happy to discuss these proposed changes in detail, and to discuss any disagreements you might have with any part of the proposed labeling format or content.

2. Safety Update

Our assessment of the safety of Paxil® in the treatment of social phobia is based on our review of all safety information provided in your original submissions.
Under 21 CFR 314.50(d)(5)(vi)(b), we request that you provide a final safety update. If, as is likely, the amount of additional safety information available, either from new patients or additional visits from ongoing patients, is small relative to what we already have, the safety update can focus on identifying any important new adverse events not previously reported. Consequently, rather than completely redoing the integrated safety summary, it may be preferable for you to submit a safety update of more limited scope, e.g., it might include a line listing of any patients meeting the following criteria and not previously reported in the original NDA: any deaths; any patients dropping out for adverse events; and any patients experiencing serious events (according to the definition used for classifying such patients in your original submission). Narrative summaries should be provided for patients who died, who had a serious event or who had an unexpected cause of dropout. In selected cases, we may ask for copies of case report forms. The Division will be happy to discuss with you more specifically what will be needed in the safety update.

3. Regulatory Status Update

Please provide any new information on the regulatory status of Paxil® for the treatment of social phobia worldwide. We require a review of the status of all actions with regard to this drug for this indication, either taken or pending before foreign regulatory authorities. Approval actions can be noted, but we ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. In addition, we ask that you provide us any current foreign labeling for Paxil® for the treatment of social phobia, if appropriate, along with English translations when needed. It is only necessary to provide information that is more recent than that provided in your original May 6, 1998, submission.

4. World Literature Update

Prior to the approval of Paxil® for social phobia, we require an updated report on the world's archival literature pertaining to the safety of Paxil® in the treatment of social phobia. This report should include only literature not covered in your previous submissions. We need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of Paxil® in the treatment of social phobia. The report should also detail how the literature search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of articles. The report should emphasize clinical data, but new findings in preclinical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

5. Long-Term Efficacy Data

Since social phobia is often a chronic disorder requiring long-term treatment, we ask that you commit to conducting, subsequent to approval, a relapse prevention trial of Paxil® in this disorder.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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 this supplemental application.

If you have any questions, contact Anna Marie Homonnay-Weikel, R.Ph., Project Manager, at (301) 594-5535.

Sincerely yours,

/S/ 3/29/94

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

attachment

MEMORANDUM

To: Division file for NDA 20-031

From: Bob Seevers, Chemistry Team Leader /S/ 5/21/98

Date: May 21, 1998

Re: Supplement SE1-023

The sponsor has requested a categorical exclusion for an environmental assessment for this application per 21 CFR 25.31 (b), stating that estimated aqueous introduction concentration will be and that no extraordinary circumstances (per 21 CFR 25.21) are associated with this action.

I have reviewed this submission and conclude that a categorical exemption may be granted. The supplemental application may be approved from a chemistry standpoint.

APPEARS THIS WAY
ON ORIGINAL