20-031/S-029

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NDA 20-031/S-029
PAXIL®
(PAROXETINE HYDROCHLORIDE) TABLETS

GlaxoSmithKline

POST-TRAUMATIC STRESS DISORDER
1 VOLUME

PDUFA DUE DATE: 12/27/01

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HOMONNAY

NDA 20-031/S-029

GlaxoSmithKline
Attention: Thomas F. Kline
Assistant Director, U.S. Regulatory Affairs
1250 S. Collegeville Rd.
P.O. Box 5089
Collegeville, PA 19426

Dear Mr. Kline:

Please refer to your supplemental new drug application dated July 21, 2000, received July 21, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paxil® (paroxetine hydrochloride) Tablets.

We acknowledge receipt of your amendment dated June 26, 2001 (revised draft labeling).

Your submission of June 26, 2001 constituted a complete response to our May 16, 2001 action letter.

This supplemental new drug application provides for the use of Paxil® (paroxetine hydrochloride) Tablets for the treatment of posttraumatic stress disorder as a new indication.

We also refer to the November 29, 2001, telephone conversation where you indicated agreement with our proposed labeling which we provided by facsimile on November 29, 2001.

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.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no 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-029."

Approval of this submission by FDA is not required before the labeling is used.

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. 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. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

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" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

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-42
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 Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

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

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

If you should have any questions, please call Ms. Anna Marie Homonnay, R.Ph., Regulatory Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
12/14/01 08:10:13 AM

Attachment to FDA Approval Letter
NDA 20-031/S-029

PX:LXX

PRESCRIBING INFORMATION

PAXIL®
brand of
paroxetine hydrochloride tablets and oral suspension

DESCRIPTION

Paxil (paroxetine hydrochloride) is an orally administered psychotropic drug. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-*trans*-4*R*-(4'-fluorophenyl)-3*S*-[(3',4'-methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate and has the empirical formula of $C_{19}H_{20}FNO_3 \cdot HCl \cdot 1/2H_2O$. The molecular weight is 374.8 (329.4 as free base). The structural formula 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 (scored); 20 mg-pink (scored); 30 mg-blue, 40 mg-green. Inactive ingredients consist of dibasic calcium phosphate dihydrate, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycols, polysorbate 80, sodium starch glycolate, titanium dioxide and one or more of the following: D&C Red No. 30, D&C Yellow No. 10, FD&C Blue No. 2, FD&C Yellow No. 6.

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

CLINICAL PHARMACOLOGY

Pharmacodynamics

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

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

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

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

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

Major Depressive Disorder

The efficacy of Paxil (paroxetine hydrochloride) as a treatment for major depressive disorder has been established in 6 placebo-controlled studies of patients with major depressive disorder (ages 18 to 73). In these studies Paxil (paroxetine hydrochloride) was shown to be significantly more effective than placebo in treating major depressive disorder by at least 2 of the following measures: Hamilton Depression Rating Scale (HDRS), the Hamilton depressed mood item, and the Clinical Global Impression (CGI)-Severity of Illness. Paxil (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 outpatients with major depressive disorder who had responded to *Paxil* (HDRS total score <8) during an initial 8-week open-treatment phase and were then randomized to continuation on *Paxil* or placebo for 1 year demonstrated a significantly lower relapse rate for patients taking *Paxil* (15%) compared to those on placebo (39%). Effectiveness was similar for male and female patients.

Obsessive Compulsive Disorder

The effectiveness of *Paxil* in the treatment of obsessive compulsive disorder (OCD) was demonstrated in two 12-week multicenter placebo-controlled studies of adult outpatients (Studies 1 and 2). Patients in all studies had moderate to severe OCD (DSM-IIIR) with mean baseline ratings on the Yale Brown Obsessive Compulsive Scale (YBOCS) total score ranging from 23 to 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.

Generalized Anxiety Disorder

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

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

Study 2 was a flexible-dose study comparing paroxetine (20 mg to 50 mg daily) and placebo. *Paxil* demonstrated statistically significant superiority over placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score.

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

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

Posttraumatic Stress Disorder

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

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

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

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

The majority of patients in these trials were women (68% women: 377 out of 551 subjects in Study 1 and 66% women: 202 out of 303 subjects in Study 2). Subgroup analyses did not

indicate differences in treatment outcomes as a function of gender. There were an insufficient number of patients who were 65 years and older or were non-Caucasian to conduct subgroup analyses on the basis of age or race, respectively.

INDICATIONS AND USAGE

Major Depressive Disorder

Paxil (paroxetine hydrochloride) is indicated for the treatment of major depressive disorder.

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

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

The efficacy of *Paxil* in maintaining a response in major depressive disorder for up to 1 year was demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY). 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).

Generalized Anxiety Disorder

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

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

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

The effectiveness of Paxil in the long-term treatment of GAD, that is, for more than 8 weeks, has not been systematically evaluated in controlled trials. The physician who elects to use Paxil for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see "DOSAGE AND ADMINISTRATION").

Posttraumatic Stress Disorder

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

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

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

the symptoms are present for at least a month and that they cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

The efficacy of Paxil in longer-term treatment of PTSD, i.e., for more than 12-weeks, has not been systemically evaluated in placebo-controlled trials. Therefore, the physician who elects to prescribe Paxil for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

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

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

WARNINGS

Potential for Interaction with Monoamine Oxidase Inhibitors

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

Potential Interaction with Thioridazine

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

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

PRECAUTIONS

General

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

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

Suicide: The possibility of a suicide attempt is inherent in major depressive disorder 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.

Because of well-established comorbidity between major depressive disorder and other psychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric disorders.

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

With this regimen in those studies,the following adverse events were reported at an incidence of 2% or greater for *Paxil* and were at least twice that reported for placebo: abnormal dreams (2.3% vs 0.5%), paresthesia (2.0% vs 0.4%), and dizziness (7.1% vs 1.5%). In the majority of patients, these events were mild to moderate and were self-limiting and did not require medical intervention.

During *Paxil* marketing, there have been spontaneous reports of similar adverse events, which may have no causal relationship to the drug, upon the discontinuation of *Paxil* (particularly when abrupt), including the following: dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), agitation, anxiety, nausea, and sweating. These events are generally self-limiting. Similar events have been reported for other selective serotonin reuptake inhibitors.

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

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.

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

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

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

Information for Patients

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

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

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

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

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

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

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

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

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

Monoamine Oxidase Inhibitors: See CONTRAINDICATIONS and WARNINGS.

Thioridazine: See CONTRAINDICATIONS and WARNINGS.

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

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

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

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

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

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

Drugs Metabolized by Cytochrome $P_{450}IID_6$: Many drugs, including most drugs effective in the treatment of major depressive disorder (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 drugs effective in the treatment of major depressive disorder (e.g.,

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

However, due to the risk of serious ventricular arrythmias and sudden death potentially associated with elevated plasma levels of thioridazine, paroxetine and thioridazine should not be co-administered (see CONTRAINDICATIONS and WARNINGS).
At steady state, when the $P_{450}IID_6$ pathway is essentially saturated, paroxetine clearance is governed by alternative P_{450} isozymes which, unlike $P_{450}IID_6$, show no evidence of saturation (see PRECAUTIONS-Tricyclic Antidepressants).

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

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

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

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

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

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

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

Procyclidine: Daily oral dosing of *Paxil* (30 mg q.d.) 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 major depressive disorder, social anxiety disorder, GAD and PTSD on a mg/m^2 basis. Because the MRHD for major depressive disorder 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 major depressive disorder, social anxiety disorder, GAD and PTSD 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 major depressive disorder, social anxiety disorder and GAD; 8.2 and 4.1 times the MRHD for OCD and PD on a mg/m^2 basis).

Pregnancy

Teratogenic Effects - Pregnancy Category C

Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are equivalent to 9.7 (rat) and 2.2 (rabbit) times the maximum recommended human dose (MRHD) for major depressive disorder, social anxiety disorder, GAD and PTSD (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 major depressive disorder, social anxiety disorder, GAD and PTSD, 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 major depressive disorder and 16.1% (84/522), 11.8% (64/542), 9.4% (44/469) 10.7% (79/735) and 11.7% (79/676) of *Paxil* patients in worldwide trials in social anxiety disorder, OCD, panic disorder, GAD and PTSD respectively, discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate approximately twice or greater for *Paxil* compared to placebo) included the following:

	Major Depressive Disorder		OCD		Panic Disorder		Social Anxiety Disorder		Generalized Anxiety Disorder		PTSD	
	Paxil	Placebo	*Paxil*	Placebo	*Paxil*	Placebo	*Paxil*	Placebo	*Paxil*	Placebo	*Paxil*	Placebo
NS												
)mnolence	2.3%	0.7%	-		1.9%	0.3%	3.4%	0.3%	2.0%	0.2%	2.8%	0.6%
ısomnia	-	-	1.7%	0%	1.3%	0.3%	3.1%	0%			-	-
gitation	1.1%	0.5%	-								-	-
remor	1.1%	0.3%	-				1.7%	0%			1.0%	0.2%
nxiety	-	-	-				1.1%	0%			-	-
izziness	-	-	1.5%	0%			1.9%	0%	1.0%	0.2%	-	-
astrointestinal											-	-
onstipation	-		1.1%	0%							-	-
ausea	3.2%	1.1%	1.9%	0%	3.2%	1.2%	4.0%	0.3%	2.0%	0.2%	2.2%	0.6%
iarrhea	1.0%	0.3%	-									
ry mouth	1.0%	0.3%	-								-	-
omiting	1.0%	0.3%	-				1.0%	0%			-	-
latulence							1.0%	0.3%			-	-
ther											-	-
sthenia	1.6%	0.4%	1.9%	0.4%			2.5%	0.6%	1.8%	0.2%	1.6%	0.2%
bnormal jaculation[1]	1.6%	0%	2.1%	0%			4.9%	0.6%	2.5%	0.5%	-	-
weating	1.0%	0.3%	-				1.1%	0%	1.1%	0.2%	-	-
npotence[1]	-		1.5%	0%							-	-
ibido 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
Major Depressive Disorder

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

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

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

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

Generalized Anxiety Disorder
The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for *Paxil* at least twice that for placebo, derived from Table 3 below) were: asthenia, infection, constipation, decreased appetite, dry mouth, nausea, libido decreased, somnolence, tremor, sweating, abnormal ejaculation.

Posttraumatic Stress Disorder
The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for Paxil at least twice that for placebo, derived from Table 3 below) were: asthenia, sweating, nausea, dry mouth, diarrhea, decreased appetite, somnolence, libido decreased, abnormal ejaculation, female genital disorders, and impotence.

Incidence in Controlled Clinical Trials
The prescriber should be aware that the figures in the tables following cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those 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.

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

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

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

1. Events reported by at least 1% of patients treated with Paxil (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.

Generalized Anxiety Disorder and Postraumatic Stress Disorder

Table 3 enumerates adverse events that occurred at a frequency of 2% or more among GAD patients on *Paxil* who participated in placebo-controlled trials of 8 weeks duration in which patients were dosed in a range of 10 mg/day to 50 mg/day or among PTSD patients on *Paxil* who participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a range of 20 mg/day to 50 mg/day.

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

		Generalized Anxiety Disorder		Posttraumatic Stress Disorder	
		Paxil	Placebo	Paxil	Placebo
Body System	**Preferred Term**	**(n=735)**	**(n=529)**	**(n=676)**	**(n=504)**
Body as a Whole	Asthenia	14%	6%	12%	4%
	Headache	17%	14%	-	-
	Infection	6%	3%	5%	4%
	Abdominal Pain			4%	3%
	Trauma			6%	5%
Cardiovascular	Vasodilation	3%	1%	2%	1%
Dermatologic	Sweating	6%	2%	5%	1%
Gastrointestinal	Nausea	20%	5%	19%	8%
	Dry Mouth	11%	5%	10%	5%
	Constipation	10%	2%	5 6%	3%
	Diarrhea	9%	7%	11%	5%
	Decreased Appetite	5%	1%	6%	3%
	Vomiting	3%	2%	3%	2%
	Dyspepsia	-	-	5%	3%
Nervous System	Insomnia	11%	8%	12%	11%
	Somnolence	15%	5%	16%	5%
	Dizziness	6%	5%	6%	5%
	Tremor	5%	1%	4%	1%
	Nervousness	4%	3%	-	-
	Libido Decreased	9%	2%	5%	2%
	Abnormal Dreams			3%	2%
Respiratory System	Respiratory Disorder	7%	5%	-	-
	Sinusitis	4%	3%	-	-
	Yawn	4%	-	2%	<1%
Special Senses	Abnormal Vision	2%	1%	3%	1%
Urogenital System	Abnormal Ejaculation[2]	25%	2%	13%	2%
	Female Genital Disorder[2]	4%	1%	5%	1%
	Impotence[2]	4%	3%	9%	1%

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

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

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

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

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

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

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

***Male and Female Sexual Dysfunction with SSRIs*:** Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (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 3,200 patients, the ranges for the reported incidence of sexual side effects in males and females with major depressive disorder, OCD, panic disorder, social anxiety disorder, GAD and PTSD are displayed in Table 5 below.

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

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

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

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

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

Weight and Vital Sign Changes: Significant weight loss may be an undesirable result of treatment with *Paxil* for some patients but, on average, patients in controlled trials had minimal (about 1 pound) weight loss 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 major depressive disorder, multiple doses of *Paxil* were administered to 6,145 patients in phase 2 and 3 studies. The conditions and duration of exposure to *Paxil* varied greatly and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose and titration studies. During premarketing clinical trials in OCD, panic disorder, social anxiety disorder, generalized anxiety disorder and posttraumatic stress disorder, 542, 469, 522, 735 and 676 patients, respectively, received multiple doses of *Paxil*. Untoward events associated with this exposure were

recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 9,089 patients exposed to multiple doses of *Paxil* (paroxetine hydrochloride) who experienced an event of the type cited on at least one occasion while receiving *Paxil*. All reported events are included except those already listed in Tables 1 – 3 , those reported in terms so general as to be uninformative and those events where a drug cause was remote. It is important to emphasize that although the events reported occurred during treatment with paroxetine, they were not necessarily caused by it.
Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in the PRECAUTIONS section.

Body as a Whole:; *infrequent:* allergic reaction, chills, face edema, malaise, , neck pain; *rare:* adrenergic syndrome, cellulitis, moniliasis, neck rigidity, pelvic pain, peritonitis, sepsis, ulcer.
Cardiovascular System: *frequent:* hypertension, tachycardia; *infrequent:* bradycardia, hematoma, hypotension, migraine, syncope; *rare:* angina pectoris, arrhythmia nodal, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, heart block, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, varicose vein, vascular headache, ventricular extrasystoles.
Digestive System: *infrequent:* bruxism, colitis, dysphagia, eructation, gastritis, gastroenteritis, gingivitis, glossitis, increased salivation, liver function tests abnormal, rectal hemorrhage, ulcerative stomatitis; *rare:* aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, intestinal obstruction, jaundice, melena, mouth ulceration, peptic ulcer, salivary gland enlargement, sialadenitis, stomach ulcer, stomatitis, tongue discoloration, tongue edema, tooth caries.
Endocrine System: *rare:* diabetes mellitus, goiter, hyperthyroidism, hypothyroidism, thyroiditis.
Hemic and Lymphatic Systems: *infrequent:* anemia, , leukopenia, lymphadenopathy, purpura; *rare:* abnormal erythrocytes, basophilia, bleeding time increased, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia, thrombocytopenia.
Metabolic and Nutritional: *frequent:* weight gain,; *infrequent:* , edema, peripheral edema, SGOT increased, SGPT increased, thirst; weight loss *rare:* alkaline phosphatase increased, bilirubinemia, BUN increased, creatinine phosphokinase increased, dehydration, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, hyperglycemia, hyperkalemia, hyperphosphatemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased.
Musculoskeletal System: *frequent:* arthralgia; *infrequent:* arthritis, arthrosis; *rare:* bursitis, myositis, osteoporosis, generalized spasm, tenosynovitis, tetany.

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

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

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

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

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

Postmarketing Reports

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

There has been a case report of an elevated phenytoin level after 4 weeks of *Paxil* and phenytoin co-administration. There has been a case report of severe hypotension when *Paxil* was added to chronic metoprolol treatment.

DRUG ABUSE AND DEPENDENCE

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

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

OVERDOSAGE

Human Experience

Since the introduction of Paxil in the U.S., 342 spontaneous cases of deliberate or accidental overdosage during paroxetine treatment have been reported worldwide (circa 1999). These include overdoses with paroxetine alone and in combination with other substances. Of these, 48 cases were fatal and, of the fatalities, 17 appeared to involve paroxetine alone. Eight fatal cases which documented the amount of paroxetine ingested were generally confounded by the ingestion of other drugs or alcohol or the presence of significant comorbid conditions. Of 145 non-fatal cases with known outcome, most recovered without sequelae. The largest known ingestion involved 2,000mg of paroxetine (33 times the maximum recommended daily dose) in a patient who recovered.

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

Overdosage Management:

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

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

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

A specific caution involves patients who are taking or have recently taken paroxetine who might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (see 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

Major Depressive 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 initial dose is 20 mg/day. Patients were dosed in a range of 20 to 50 mg/day in the clinical trials demonstrating the effectiveness of *Paxil* in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, the full effect may be delayed. Some patients not responding to a 20 mg dose may benefit from dose increases, in 10 mg/day increments, up to a maximum of 50 mg/day. Dose changes should occur at intervals of at least 1 week.

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

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

Obsessive Compulsive Disorder

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

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

Panic Disorder

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

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

Social Anxiety Disorder

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

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

Generalized Anxiety Disorder

Usual Initial Dosage: *Paxil* should be administered as a single daily dose with or without food, usually in the morning. In clinical trials the effectiveness of *Paxil* was demonstrated in patients dosed in a range of 20 to 50 mg/day. The recommended starting dosage and the established effective dosage is 20 mg/day. There is not sufficient evidence to suggest a greater benefit to doses higher than 20 mg/day. Dose changes should occur in 10 mg/day increments and at intervals of at least 1 week.

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

Posttraumatic Stress Disorder
Usual Initial Dosage: Paxil should be administered as a single daily dose with or without food., usually in the morning. The recommended starting dosage and the established effective dosage is 20 mg/day. In one clinical trial, the effectiveness of Paxil was demonstrated in patients dosed in a range of 20 to 50 mg/day. However, in a fixed dose study, there was not sufficient evidence to suggest a greater benefit for a dose of 40 mg/day compared to 20 mg/day. Dose changes, if indicated, should occur in 10 mg/day increments and at intervals of at least 1 week.

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

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.

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

NOTE: SHAKE SUSPENSION WELL BEFORE USING.

HOW SUPPLIED

Tablets: Film-coated, modified-oval as follows:
10 mg yellow, scored tablets engraved on the front with PAXIL and on the back with 10.
NDC 0029-3210-13 Bottles of 30

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

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

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

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

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

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

DATE OF ISSUANCE xxxxx

GlaxoSmithKline
Research Triangle Park, NC 27709

Rx only

PX:Lx

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Doc

S029FDApropap1lab2.doc

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/s/

Russell Katz
12/14/01 08:10:13 AM

PAXIL[R] TABLETS
(PAROXETINE HYDROCHLORIDE)
NDA 20-031/S-029
PTSD INDICATION

TABLE OF CONTENTS

85 page(s) of revised draft labeling has been redacted from this portion of the review.

EXCLUSIVITY SUMMARY for NDA # 20-031 SUPPL # S-029

Trade Name Paxil Tablets **Generic Name** paroxetine HCl

Applicant Name GlaxoSmithKline **HFD-** 120

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" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X_/

   b) Is it an effectiveness supplement? YES /_X_/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE1

   c) 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 /_X_/ 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 your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      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:

      _____

      _____

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Three years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /__/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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.

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 already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-031 _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

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 any one 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 under 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).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. 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 only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The 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 /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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 not 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 trials, 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), or 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 some other source, including the published literature) necessary to support approval of the application or supplement?

YES /__X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(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 /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

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 /_X_/

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 # Study 651

Investigation #2, Study # Study 648

Investigation #3, Study # _____

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 relied 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 the 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 approved 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 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X/

Investigation #3 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:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(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 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # Study 651

Investigation #__, Study # Study 648

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have 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	
IND # 23,280 YES /_X_/	NO /___/ Explain: _____
	_____
	_____
Investigation #2	
IND # 23,280 YES /_X_/	NO /___/ 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 interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "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 /_X/

If yes, explain: _____

_____

_____

_____ _____

Signature of Preparer Date

Title: _____

_____ /S/ _____ 12/14/01

Signature of Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: March 21, 2001

TO: Anna Marie Homonnay-Weikel, R. Ph., Regulatory Project Manager
Karen Brugge, M.D., Clinical Reviewer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Antoine El-Hage, Ph.D., Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

FROM: Constance Lewin, M.D.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 20-031/SE1-029

APPLICANT: SmithKline Beecham Pharmaceuticals

DRUG: Paxil (paroxetine hydrochloride)

CHEMICAL CLASSIFICATION: 6

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of post-traumatic stress disorder

CONSULTATION REQUEST DATE: September 27, 2000

ACTION GOAL DATE: May 21, 2001

I. BACKGROUND:

Routine clinical inspections were conducted in support of the above-noted application and focused on protocols #29060/651 and #29060/648. Goals of the inspections included validation of the primary efficacy endpoint data and subject safety parameters at the sites noted below, along with an analysis of the adequacy of informed consent.

II. RESULTS (by protocol/site):

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
Robinson/Warren	Portland	Oregon	December 6, 2000	January 22, 2001	VAI
Westin	Tucson	Arizona	December 6, 2000	March 9, 2001	VAI

A. Protocol #29060/651

Site: Michael Robinson, M.D., and Ricks Warren, Ph.D. – Portland, Oregon

Thirty-five (35) subjects were enrolled, twenty-three (23) of whom completed the study. Twelve (12) subjects discontinued, for the following reasons: Consent withdrawal (3), protocol violation (2), lost to follow-up (2), and non-serious adverse event (5).

Records for all subjects were reviewed. A Form FDA 483 was not issued. However, there were a couple of significant items discussed during the inspection. One subject had an abnormal ECG, which was not reviewed prior to enrollment and which ultimately resulted in the subject's withdrawal from the study. In addition, there were no screening ECGs available for three subjects. None of these issues adversely affect data acceptability.

Data acceptable

B. Protocol #29060/648

Site: Dennis C. Westin, M.D. – Tucson, Arizona

Twenty-three (23) subjects were screened, eighteen (18) of whom were randomized. Eleven (11) subjects completed the study. Seven (7) subjects discontinued, for the following reasons: adverse events (1 serious – tachycardia; 2 non-serious), lost to follow-up (2), protocol violation (1), and consent withdrawal (1).

Records were reviewed for ten subjects. A Form FDA 483 was issued for recordkeeping inadequacies, none of which adversely affect data acceptability.

Data acceptable

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Observations noted during the routine clinical inspections of Michael Robinson, M.D., and Ricks Warren, Ph.D.; and Dennis C. Westin, M.D., do not adversely affect the acceptability of the data generated by these clinical investigators and submitted in support of pending NDA #20-031/SE1-029. It is therefore recommended that the data submitted by Drs. Robinson, Warren, and Westin may be used in support of the pending application.

Key to Classification:

NAI = No deviation from regulations. Data acceptable
VAI = Minor deviation(s) from regulations. Data acceptable
VAI-r = Deviation(s) from regulations, response requested. Data acceptable
OAI = Significant deviations from regulations. Data unreliable

/S/

Constance Lewin, M.D.
Pharmacologist
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

/S/

Antoine El-Hage, Ph.D., Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

DISTRIBUTION:
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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: December 3, 2001

FROM: Thomas P. Laughren, M.D. /S/
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 posttraumatic stress disorder (PTSD)

TO: File NDA 20-031/S-029
[**Note:** This overview should be filed with the 6-26-01 response to our 5-16-01 approvable letter.]

GSK's 6-26-01 response to our 5-16-01 approvable letter represented a complete response to all the issues raised in our letter. Dr. Karen Brugge reviewed the responses to clinical issues in a 7-27-01 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 PTSD in 18 nonUS countries and applications are pending in 25 other nonUS countries.

Labeling:

There were several labeling issues, including the addition of langauge to labeling pertinent to the new claim for PTSD, and also the addition of language previously agreed to for the GAD claim, a shift in the depression indication to major depressive disorder, and several minor changes. These issues were easily resolved. The one issue that required negotiations over several months was the addition of new language regarding the emergence of discontinuation emergent symptoms. Since data suggesting such findings were now available from controlled trials, we sought to add stronger language to a Precautions statement, and we ultimately obtained agreement on such language. We held a telcon with GSK regarding this topic on 10-4-01, and we finally reached agreement on labeling on 11-29-01.

Pediatric Rule:

We do not have a policy as yet regarding what would be needed in a pediatric program for PTSD, however, we have asked GSK to either propose a development plan or provide justification for a waiver, under the Pediatric Rule.

Conclusions/Recommendations:

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

cc:
Orig NDA 20-031/S-029 (Paxil)
HFD-120/Div File
HFD-120/TLaughren/RKatz/KBrugge/AMHomonnay

DOC: MMPXPTSD.AP1

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 20, 2001

151

FROM: Thomas P. Laughren, M.D.
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 posttraumatic stress disorder (PTSD)

TO: File NDA 20-031/S-029
[**Note:** This overview should be filed with the 7-21-00
original submission.]

1.0 BACKGROUND

Paroxetine is a selective serotonin reuptake inhibitor currently approved and marketed for depression, OCD, panic disorder, and social anxiety disorder in an immediate release tablet, i.e., Paxil (NDA 20-031, originally approved for depression in December, 1992). Supplement S-026, for Paxil in generalized anxiety disorder (GAD) has been issued an approvable letter. S-029 provides data in support of a new claim for this same Paxil tablet in the treatment of posttraumatic stress disorder (PTSD) in a dose range of 20-50 mg/day.

It should be noted that, at the current time, there is only one other drug specifically approved for the treatment of PTSD, i.e., another SSRI, Zoloft (sertraline). Given the symptom overlap in patients with depression and PTSD, one of the concerns identified early in the development of this new indication for Zoloft was how this overlap would be sorted out in making a judgement regarding the specific benefit of this product in PTSD. During the review of the Zoloft application for PTSD, we were persuaded that there was an effect of this drug specific to PTSD that would justify this specific claim.

We held an end-of-phase 2 meeting with SKB on 9-3-98 to discuss the sponsor's development program for Paxil in PTSD. We generally endorsed the planned program, but did indicate that they would need to address the question of specificity of response to PTSD, e.g., by showing an effect on symptoms considered specific to PTSD, or by showing an effect on PTSD outcomes regardless of level of depressive symptoms at baseline. We also indicated that, if they persisted with the plan

for two primary outcomes in their trials, they would need to make it on both at p = 0.05. We provided additional statistical comments in letters dated 4-16-99 and 6-29-99. There was no preNDA meeting.

Since the proposal is to use the currently approved Paxil immediate release tablets for this expanded population, there was no need for chemistry, pharmacology, or biopharmaceutical reviews of this supplement. The focus was on clinical data. The primary review of the efficacy and safety data was done by Karen Brugge, M.D., from the clinical group. Lu Cui, Ph.D., from the Division of Biometrics, also reviewed the efficacy data.

The studies supporting this supplement were conducted under IND 23,280. The original supplement for this expanded indication (S-029) was submitted 7-21-00.

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.

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.

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 (651, 648, and 627) in adult outpatients meeting DSM-IV criteria for posttraumatic stress disorder (PTSD).

-Patients could not have other primary Axis I disorders, in particular, major depression and dysthymic disorder, however, they could have these and other axis I disorders as "non-predominant secondary psychiatric" conditions.
-The protocol specified primary outcomes for these studies were: (1) mean change from baseline in CAPS-2; and, (2) the proportion of responders on CGI-I, in the LOCF analyses at the week 12 endpoint. "Responders" on the CGI-I were defined as those having a score of 1 (very much improved) or 2 (much improved). The CAPS-2 has a total of 30 items (rated by clinicians), with each item being rated on a scale of 0 to 4 for both frequency and intensity. However, for the purpose of assessing change in treatment trials, the focus is on the first 17 items that map directly to the 17 items in the DSM-IV criteria for PTSD. That was the case for SKB's PTSD program as well, so the CAPS-2 total scores for these 17 items, again with frequency and intensity rated separately, ranges from 0 to 136. The CGI-I ranges from 1-7.
-There were several secondary outcome measures in these trials, including, among others: CAPS-2 clusters (re-experiencing; avoidance and numbing; hyperarousal); CGI-S; Davidson Trauma Scale; MADRS; and Sheehan Disability Scale.
-ANOVA was used for continuous variables and logistic regression for categorical variables. Hochberg's method was used for adusting for the 2 dose groups.

5.1.2 Summary of Studies Pertinent to Efficacy Claims

5.1.2.1 Study 651

This was a randomized, double-blind, parallel group, 12-week, fixed-dose study (58 US and Canadian sites) comparing paroxetine immediate release tablets (20 or 40 mg/day, taken as a single am dose) and placebo in adult outpatients meeting DSM-IV criteria for PTSD. About 45% of patients had secondary MDD and 30% had secondary GAD. Patients were started at 20 mg, and doses were increased at 10 mg weekly increments until the assigned dose was reached. There were 182-186 patients per group in the sample analyzed (n=551), with the % completing to 12 weeks ranging from 62-67%.

Overall, the CAPS-2 total score results from this study consistently favored paroxetine over placebo for both dose groups at weeks 4, 8, and 12, for both LOCF and OC analyses. The p-values (vs placebo) were < 0.001 at all these time points, for both doses, and for both LOCF and OC analyses. For CGI-I, 71% of paroxetine 40 mg completers and 76% of paroxetine 20 mg completers met the response criterion (score of 1 or 2) compared to 48% for placebo ($p < 0.001$ for both dose groups vs placebo). For the CAPS-2 total score, the difference between paroxetine and placebo in mean change from baseline for both the LOCF and OC analyses at 12 weeks, for both 20 and 40 mg, was roughly 14 units. The secondary outcomes, including the re-experiencing cluster from CAPS-2, were similarly positive for both dose groups vs placebo.

In addition, subgroup analyses were performed looking at patients either with or without comorbid secondary MDD, or various other anxiety disorders, and regardless of the subgroupings, the results favored both dose groups vs placebo on the CAPS-2. In another exploratory analysis, the MADRS

baseline scores were used as a covariate for the CAPS-2 outcome, and there was no indication that severity of depression at baseline predicted greater improvement on the CAPS-2.

5.1.2.2 Study 648

This was a randomized, double-blind, parallel group, 12-week, flexible-dose study (37 US and Canadian 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 PTSD. About 35% of patients had secondary MDD and 15% had secondary GAD. Patients were started at 20 mg and were titrated in biweekly increments of 10 mg. There were roughly 150 patients per group in the sample analyzed (n=307), with the % completing to 12 weeks ranging from 60-62%. The mean week 12 paroxetine dose for completers was 36.

Overall, the CAPS-2 total score results from this study consistently favored paroxetine over placebo at weeks 4, 8, and 12, for both LOCF and OC analyses. The p-values (vs placebo) were < 0.001 at the 12 week time point, for both LOCF and OC analyses. For CGI-I, 76% of paroxetine completers met the response criterion (score of 1 or 2) compared to 50% for placebo ($p < 0.001$). For the CAPS-2 total score, the difference between paroxetine and placebo in mean change from baseline at 12 weeks was roughly 11 units for the LOCF and 14 units for the OC analysis. The secondary outcomes, including the re-experiencing cluster from CAPS-2, were similarly positive for paroxetine vs placebo.

In addition, subgroup analyses were performed looking at patients either with or without comorbid secondary MDD, or various other anxiety disorders, and regardless of the subgroupings, the results generally favored paroxetine vs placebo on the CAPS-2. In another exploratory analysis, the MADRS baseline scores were used to subgroup patients (< 21 or ≥ 21), and there was no indication that severity of depression at baseline predicted greater improvement on the CAPS-2.

5.1.2.2 Study 627

This was a randomized, double-blind, parallel group, 12-week, flexible-dose study (44 sites in Europe, South Africa, Israel, and Canada) 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 PTSD. About 49% of patients had secondary MDD and 20% had secondary GAD. Patients were started at 20 mg and were titrated in biweekly increments of 10 mg. There were roughly 160 patients per group in the sample analyzed (n=322), with the % completing to 12 weeks ranging from 65-69%. The mean week 12 paroxetine dose for completers was 34.

Overall, the CAPS-2 total score results from this study did not as consistently favor paroxetine over placebo as in studies 651 and 648. The p-values (vs placebo) were 0.047 at the 12 week time point for the LOCF analysis and 0.071 at the 12 week time point for the OC analysis. For CGI-I, 60% of paroxetine completers met the response criterion (score of 1 or 2) compared to 52% for placebo (not statistically significant). For the CAPS-2 total score, the difference between paroxetine and placebo

in mean change from baseline at 12 weeks was roughly 6 units for both the LOCF and OC analyses. Results for the secondary outcomes were similarly inconsistent, although paroxetine was generally at least numerically favored over placebo.

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 (648 & 627), and thus, provided no evidence pertinent to the issue of dose response. The mean doses for completers to 8 weeks in these two studies were 36 and 34 mg/day, respectively, but these findings are not interpretable regarding dose response since patients in such trials are often pushed to the higher end of the permitted dose range, regardless of need. Study 651 was most informative regarding dose response, and this study suggested no advantage at a dose of 40 mg compared to 20 mg/day. Thus labeling must be clear in noting that the only pertinent evidence suggests no benefit in doses above 20 mg/day.

Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis of gender. There was no indication of differences in response based on gender.

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. CAPS-2 total scores were roughly 74 for the 2 positive studies at baseline, and in the LOCF analyses, there were decreases of roughly 35-40 units at the week 12 endpoint for patients assigned to paroxetine, representing a roughly 14 unit greater effect for drug compared to placebo. 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, these changes are consistent with those seen for other drugs believed to be effective for PTSD, so I am inclined to consider this a clinically relevant treatment effect.

Duration of Treatment

There were no data presented in this supplement pertinent to the question of the long-term efficacy of Paxil for PTSD.

Specificity of Response for PTSD

The exploratory analyses to assess for independence of the PTSD response from an antidepressant or general anxiolytic response were generally supportive of such independence, including a response

on the re-experiencing cluster of the CAPS-2, which is generally considered unique to PTSD. Thus, I consider this a reasonable demonstration of a specific response to paroxetine in patients with PTSD.

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 PTSD. Studies 651 and 648 are both positive, both on the primary outcomes and most secondary outcomes, and study 627 is at least supportive. The sponsor is currently conducting a relapse prevention trial. Since PTSD is also a disorder found in the pediatric population and, once approved for this indication, Paxil will likely be used in pediatric patients, we will require adequate and well-controlled trials of Paxil for PTSD in this population as well.

5.2 Safety Data

Dr. Brugge's safety review of S-029 was based on an integrated database consisting of a pooling of safety data for the three 12-week studies. There was no safety update.

Overall, 676 patients were exposed to Paxil in the sponsor's development program for posttraumatic stress disorder (PTSD). This represented an exposure time on paroxetine of approximately 136 patient years. Patients in this integrated database were roughly 2/3 female and predominantly white. The mean age of patients was roughly 41. Most of the exposure was in the 20-40 mg/day range, with fewer than 5-10% having doses of 50 mg/day.

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 PTSD population.

5.2.1 Overview of Adverse Event Profile for Paxil Tablets in PTSD

Overall, the adverse events profile for Paxil tablets in PTSD was comparable to that observed in patients with depression, OCD, panic disorder, and social anxiety disorder receiving this drug. Dr. Brugge summarized data from the taper and followup phases for these studies for patients who had completed to 12 weeks, and these data suggested a slightly greater risk for certain withdrawal emergent symptoms for paroxetine treated patients compared to those on placebo, in particular, dizziness, nervousness, paresthesias and vertigo. These findings are similar to those reported in the literature suggesting a potential for a mild withdrawal syndrome for paroxetine, and Dr. Brugge feels they are sufficient, along with the supportive literature, to justify a stronger labeling statement regarding this risk. Currently, this risk is only mentioned in the Postmarketing Reports subsection. I agree that labeling needs a stronger statement regarding this risk.

5.2.2 Conclusions Regarding Safety of Paxil in PTSD

There were no new safety findings to suggest a substantially different safety profile for Paxil tablets in PTSD compared to that observed for the other 4 approved indications, and no basis for substantial changes in the labeling for Paxil from the standpoint of safety. However, I agree with Dr.Brugge's suggestion for a stronger statement regarding the risk of withdrawal symptoms and the need for tapering.

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

SKB reported finding no published reports pertinent to the safety of Paxil in the treatment of PTSD, thus, there was no literature review for Dr. Brugge to review.

7.0 FOREIGN REGULATORY ACTIONS

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

To my knowledge, no inspections were conducted for this supplement.

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 7-21-00.

10.2 Foreign Labeling

Paxil is not approved for PTSD anywhere at this time.

10.3 Approvable Letter

The approvable letter includes draft labeling and requests for a literature update and a regulatory status update. We will request pediatric studies in the approval letter.

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 PTSD. 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-029
HFD-120
HFD-120/TLaughren/RKatz/KBrugge/PAndreason/AMHomonnay

DOC: MMPXPTSD.AE1

Review and Evaluation of Clinical Data
sNDA#20-031 SE1-029 AZ

NDA:	20-031 SE1-029 AZ
Sponsor:	SmithKline Beecham Pharmaceuticals
Drug:	Paroxetine Hydrochloride (Paxil®)
Indication:	Post Traumatic Stress Disorder (PTSD)
Material Submitted:	Response to Approvable Letter dated 5/16/01
Correspondence Date:	June 26, 2001
Date Received:	June 27, 2001
Related INDs	

The purpose of this review is to assist the Team Leader and Director of the Division of Neuropharmacological Drug Products in the regulatory processing of this supplemental NDA 20-031 SE1-029.

I. Sponsor's Response to 5/16/01 Approvable Letter

Safety Update.
Study 650 was a study that was ongoing at the time of this supplemental NDA. The safety update describes safety results regarding any deaths, serious adverse events (SAEs) and adverse dropouts (ADOs) that occurred during this study which was completed on 2/24/01. The results, as described by the sponsor, did not reveal any new or unexpected events, or events that were not likely to be attributed to non-drug related, underlying or pre-existing condition(s).

One ADO was reported as an endocrine disorder in a paroxetine patient during the single blind phase of Study 650. According to the narrative, the subject (650.302.05710) was a 32 year old white female with PTSD and an unremarkable medical history and was receiving reproductive hormones concomitantly during the study. On Day 35 of single blind paroxetine treatment she "experienced moderate endocrine disorder" resulting in discontinuation of study drug. No corrective therapy was given to this patient. No other relevant information was provided in the narrative. While this non-serious event could be drug related various endocrine events are described in the current labeling for Paxil®.

Postmarketing events found in the sponsor's Worldwide Clinical Safety database between the dates of 5/5/00 and 5/16/01 were also summarized in which 6 events met regulatory criteria for being classified as serious reports. None of these serious reports were unexpected, not already described in labeling or could not be attributed to a possible underlying or preexisting condition. According to the sponsor, the remaining 19 non-serious events were not new or unexpected.

Regulatory Status Update
The sponsor reports that applications for the marketing of paroxetine HCl for the indication of PTSD were submitted to 43 countries with approvals granted by 18 regulatory authorities. The review of the remaining 25 applications is still pending. This drug has not been withdrawn from the market in any country because of safety reasons.

World Literature
Various databases were employed by the sponsor to conduct a literature search regarding paroxetine treatment for PTSD covering the period since the time of the sNDA submission to the time of the present submission. No new safety information or adverse event data were revealed by the search, according to that described in the submission.

Labeling.
The sponsor provides proposed labeling changes pertaining to PTSD that incorporate the recently approved labeling changes for Generalized Anxiety Disorder (GAD) supplement (S-026). This review is restricted only to the PTSD related labeling changes compared to our draft labeling sent with our 5/15/01 Approvable Letter for S-029. The sponsor is in agreement on most PTSD labeling changes that we provided in our 5/15/01 draft with some exceptions. The sponsor included requested tabular data, while incorporating data from that of the approved labeling changes for GAD. The sponsor also made minor editorial changes. This reviewer has the following comments: (New Table #3)

- A typographical error appears to exist under the PTSD subsection in the "Clinical Trials" section located in that the fourth paragraph of this section which begins with "A third study, also a flexible study...". The sponsor has the term "CAPS-s total score" which should be CAPS-**2** total score.
- In the PTSD subsection under "Indications and Usage" section, the second sentence ("The efficacy of Paxil in the treatment of PTSD was established in two 12-week

[redacted]

Otherwise the sponsor may simply consider using "adults with PTSD" rather than adult patients with PTSD, which is consistent with the language used for the other approved indications in the labeling for Paxil®.

- The most prominent change made by the sponsor was regarding the newly added Discontinuation subsection under the "Dosage and Administration" section of labeling. The following draft labeling shows the proposed changes (strikeouts are used for deletions by the sponsor compared to that which we proposed and double-underlined sections indicate that which was added by the sponsor):

DRAFT

DRAFT

The proposed changes in the last three sentences (counting the deleted sentence) of the above subsection appear to enhance clarity and appear to be acceptable changes. However, other changes are not consistent with that described in the Clinical review of S-029. As described in the review, trials showed adverse events during the taper phase of the trials in which the dose was tapered to 20 mg/day followed by cessation (as described). The following adverse events occurred with at least twice the incidence of that observed in placebo (0.2- 2.9% of paroxetine subjects compared to 0-0.8% of placebo subjects): abnormal dreams, agitation, nervousness, paresthesia, vertigo and trauma (trauma appears to be incidental). Consequently, these events, except trauma, should be described in the labeling similar to the draft sent with the 5/16/01 Approvable Letter. Finally, proposed changes are not consistent with reported cases in the literature and with that reported in a review of clinical data by Dr. Andrew Mosholder (Lilly's NDA 18-936 ——— submission). The clinical data reviewed by Dr. Mosholder were from studies comparing fluoxetine to paroxetine and other drugs of this class on incidences of adverse events associated with treatment interruption.

II. Conclusions and Recommendations

There were not any new or unexpected safety findings reported in the submission. The sponsor's proposed labeling appears acceptable except for the bulleted items in the Labeling section of this review. In summary it is recommended that the sponsor:

- Change CAPS-s to CAPS-2, where indicated above, since this appears to be a typographical error.
- Change language to describe the patient population as either *adults with PTSD or*

"Indications and Usage" section of labeling (as above). The reasons for the recommendation are provided in the labeling section of this review.

- Adopt the draft labeling changes, as recommended under the "Labeling" section of this review.

Karen Brugge, M.D., Date 7/27/01
Medical Reviewer,
FDA CDER ODE1 DNDP HFD 120

cc: IND
HFD 120
HFD 120/P Andreason/K Brugge/A Homonnay/T Laughren

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eed an AP1LABL.DOC created from our AE1LABL.DOC so we can begin to otiate final labeling; we also need to incorporate language re: th ange to MDD from depression.--TPL

REVIEW AND EVALUATION OF CLINICAL DATA

NDA:	20-031 SE1-029
Sponsor:	SmithKline Beecham Pharmaceuticals
Drug:	Paroxetine Hydrochloride
Indication:	Post Traumatic Stress Disorder
Dates of Submission:	July 21, 2000
Materials Reviewed:	Efficacy supplement SE1-029 Inclusion of efficacy results from three 12-week double-blind, randomized trials on a total of 1,180 randomly assigned patients (studies 651, 648 and 627) comparing paroxetine (676 total patients) and placebo (504 total patients) for efficacy and safety for the treatment of Post Traumatic Stress disorder.
Clinical Reviewer:	Karen L. Brugge, M.D.
Review Completion Date:	2/16/01

1.0 Material Utilized in Review

1.1 Materials from NDA/IND

The following items were examined during the course of this clinical review:

Documents Utilized in Clinical Review	
DATE	DESCRIPTION
July 21, 2000	NDA Efficacy Supplement 20-031 SE1-029, 26 volumes on CD-ROM and hard copy version. Case Report Tabulations are provided as SAS transport files on CD-ROM.

1.2 Related Reviews

Please refer to NDA 20-031, in which Paxil® was approved for the indications of treating Depression, Obsessive Compulsive Disorder, and Panic Disorder. Also see the "Administrative History" section below.

2.0 Background

This review is to assist the Team Leader and Director of the Division of Neuropharmacological Drug Products in the regulatory processing of this supplemental NDA 20-031 SE1-029.

2.1 Indication

Indication of Paxil® for treatment of Depression: the antidepressant efficacy of Paxil® was demonstrated in placebo controlled studies of patients with "depression" that "corresponded closely to the DSM-III criteria for major depressive disorder". Studies showed significantly greater efficacy with Paxil® treatment than with placebo on the Hamilton Rating Scale, the Hamilton depressed mood item and the Clinical Global Impression-Severity of Illness. When patients responding to 8 weeks of open-label treatment with Paxil were continued on Paxil for one year, they showed a relapse rate of 15% compared to 39% of patients randomized to placebo treatment for the year. These results support the claim for long-term maintenance efficacy of Paxil® for up to one year.

Indication of Paxil® for treatment of Obsessive Compulsive Disorder: Two 12-week placebo controlled multicenter studies of patients with moderate to severe Obsessive Compulsive Disorder (DSM-IIIR) were reported to show efficacy when using the Yale Brown Obsessive Compulsive Scale.

Indication of Paxil® for treatment of Panic Disorder: efficacy was reported in three 10 to 12 week multicenter, placebo controlled studies in patients with panic disorder (DSM-IIIR) with or without agoraphobia.

Indication of Paxil® for treatment of Social Anxiety Disorder: this indication was based on three 12-week multicenter, placebo controlled studies of adults with social anxiety disorder (DSMIV). These studies showed a significant effect of Paxil® compared to placebo on response

rate using criteria based on scores from the Liebowitz-Social Anxiety Scale and the Clinical Global Impression score or subscores.

2.2 Related INDs and NDAs

INDs:
IND 23,280 – Paroxetine Hydrochloride Tablets
IND 51, 171 – Paroxetine Hydrochloride Modified/Controlled-Release Tablets

NDAs:
NDA 20-031 – Paxil (paroxetine hydrochloride) Tablets
NDA 20-710 - Paxil (paroxetine hydrochloride) Oral Suspension
NDA 20-885 - Paxil (paroxetine hydrochloride) Capsules
NDA 20-936 - Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets
NDA 20-982 - Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets

2.3 Administrative History
Paroxetine hydrochloride is a selective serotonin reuptake inhibitor. The NDA for this drug was approved for the treatment of the following: Depression on 12/29/92, Obsessive Compulsive Disorder on 5/7/96, and Panic Disorder in 1996. On May 6, 1998 a supplemental NDA 20-031/S-023 was submitted requesting approval for the addition of a new indication, Social Anxiety Disorder which was approved on May 11, 1999. Paxil Oral Suspension (NDA 20-710) and Paxil Capsules (NDA 20-885) are also approved for the market. A controlled release formulation Paxil CR (IND 51,171) was approved on 2/16/99 for treatment of "depression" (NDA 20-936) and an NDA for the treatment of panic disorder (NDA 20-982) currently under an "approvable" status. NDA 20-031 SE1-026, which was submitted on April 28, 2000, is currently under review for the proposed efficacy in the treatment of Generalized Anxiety Disorder.

2.4 Directions for Use

Depression: the recommended starting dose is 20 mg single oral daily a.m. dose (with or without food) which can be increased by increments of 10 mg/day at intervals of at least one week, up to a maximum daily dose of 50 mg. The dose range in clinical trials was 20 to 50 mg daily.

Obsessive Compulsive Disorder: the recommendations regarding the starting dose and the regimen for increasing the dose is the same as for depression. However, the recommended daily dose for treatment of Obsessive Compulsive Disorder is 40 mg with a dose range of 20-60 mg/day employed in clinical trials. The dose is not to exceed a maximum of 60 mg/day.

Panic Disorder: the recommended starting dose is 10 mg/day that may be increased by 10 mg/day at intervals of at least one week to a target dose of 40 mg/day. The dose range employed in clinical trials was 10 to 60 mg/day. The maximum daily dose is recommended to be no greater than 60 mg.

Social Anxiety Disorder: the initial recommended dose is 20 mg/day. Although the safety of the drug has been assessed for a dose of up to 60 mg/day in patients with this disorder, "available information does not suggest any additional benefit for doses above 20 mg/day".

Elderly or Debilitated patients, and patients with Severe Hepatic or Renal Impairment: the recommended initial dose is 10 mg/day and the maximum dose is recommended to be no greater than 40 mg/day.

3.0 Chemistry

There are no chemistry issues to review in this submission.

4.0 Animal Pharmacology

There are no animal pharmacology/toxicology issues to review in this submission.

5.0 Description of Clinical Data Sources

5.1 Primary Development Program

5.1.1 Study Design and Patient Enumeration

Three studies examining the efficacy of Paxil® in the treatment of Post Traumatic Stress Disorder (PTSD) were reviewed employing a multi-center, randomized, double blind, placebo controlled parallel group design as shown in the table below.

Clinical Studies Reviewed from this Submission			
Protocol No	**Study Design**	**Treatment**	**N (ITT Pop.) per Treatment group**
651 Fixed Dose Study	Fixed dose Conducted in the US	12 weeks of daily oral doses of: Paxil® 20 mg/day Paxil® 40 mg/day Placebo	 183 182 186
648 Flexible Dose Study	Flexible dose design Conducted in the US and Canada	12 weeks of daily oral doses of: Paxil® 20-50 mg* Placebo	 151 156
627 Flexible Dose Study	Flexible dose design Non-US Multi-national	12 weeks of daily oral doses of: Paxil® 20-50 mg* Placebo	 160 162

* Starting dose is 20 mg/day and after 2 weeks the dose is increased (depending on tolerability and response, as judged by the investigator) by 10/mg/day every 2 weeks to a maximum of 50 mg/day.

5.1.2 Demographic Characteristics

The table below (as provided by the sponsor) shows that the ITT population of the 3 studies (Studies 651, 648 and 627) consisted primarily of women (approximately 64%), under 65 years old (98%) who were primarily Caucasian (87%) with a mean age of 41±12 years. Paroxetine subjects (Ss) were similar to Placebo Ss on these and other various demographic features (mean age, height and weight and in distribution of Ss by age group, race and gender, as below). See each study description in sections below for demographic features of the ITT population of each individual study.

Summary of Patient Demographic Data - Studies 651, 648 and 627 (ITT Population)

	Placebo N= 504		Paroxetine N= 676		Total N= 1180	
AGE (years)	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
18 - 34	170	(33.7)	207	(30.6)	377	(31.9)
35 - 64	322	(63.9)	456	(67.5)	778	(65.9)
65	12	(2.4)	13	(1.9)	25	(2.1)
Mean (S. D.)	40.1 (11.9)		41.3 (11.5)		40.8 (11.7)	
Minimum						
Maximum						
GENDER						
Female	314	(62.3)	438	(64.8)	752	(63.7)
Male	190	(37.7)	238	(35.2)	428	(36.3)
RACE						
Caucasian	437	(86.7)	589	(87.1)	1026	(86.9)
Non-Caucasian	67	(13.3)	87	(12.9)	154	(13.1)
HEIGHT (cm)						
	N = 501		**N = 673**		**N = 1174**	
Mean (S. D.)	168.6 (9.8)		168.6 (9.6)		168.6 (9.7)	
Minimum						
Maximum						
WEIGHT (kg)						
	N = 499		**N = 671**		**N = 1170**	
Mean (S. D.)	77.8 (19.5)		78.9 (20.6)		78.5 (20.1)	
Minimum						
Maximum						

5.1.3 Extent of Exposure

An estimate of person time for paroxetine and placebo Ss of the ITT population of the 3 studies (Studies 651, 648 and 627) is provided below.

Summary of Overall Patient Exposure in Years of the ITT Population		
Treatment	**N**	**Exposure* (patient years)**
Paroxetine	676	136.2
Placebo	504	103.2
*Exposure= # days between 1st and last dose of study drug including the taper phase divided by 365.25		

The treatment phase of each of the three studies was 12 weeks (84 days). The percentage of Ss exposed to study drug for various durations exceeding 70 days during the treatment phase were as follows:

Exposure duration of >70 to 84 days: 68% (456/676 Ss) of paroxetine Ss
66% (332/504 Ss) of placebo Ss

Exposure duration of >84 days: 31% (210/676) of paroxetine Ss
29.4% (148/504) of placebo Ss

The following table summarizes exposure by total daily dose and duration of exposure, as provided in the submission.

Summary of Exposure to Paroxetine Total Daily Dose (mg) Excluding Taper Phase - Studies 651, 648 and 627 (ITT Population)

	Paroxetine N = 676 Total Daily Dose			
	20 mg n (%)	30 mg n (%)	40 mg n (%)	50 mg n (%)
>/= 1 Day	676 (100. 0)	367 (54.3)	275 (40.7)	55 (8. 1)
> 7 Days	514 (76.0)	237 (35.1)	270 (39.9)	52 (7. 7)
> 14 Days	357 (52.8)	115 (17.0)	227 (33.6)	51 (7. 5)
> 28 Days	261 (38.6)	56 (8. 3)	171 (25.3)	36 (5. 3)
> 42 Days	217 (32.1)	40 (5. 9)	145 (21.4)	13 (1. 9)
> 56 Days	203 (30.0)	20 (3. 0)	122 (18.0)	0 (0.0)
> 70 Days	180 (26.6)	6 (0.9)	58 (8. 6)	0 (0.0)
> 84 Days	83 (12.3)	0 (0.0)	1 (0.1)	0 (0.0)

The mean (median) daily dose of study drug in paroxetine ITT Ss of all 3 studies combined was 32±11 mg (30 mg) on the week 12 visit (N=472) and 30±11 mg (30 mg) at treatment endpoint (N=676). Overall, the mean daily dose during the treatment phase (patient mean) was 27.2±8 mg/day (N=676).

The mean (median) daily dose of paroxetine during the treatment phase of paroxetine ITT Ss in the flexible dose study, Study 648 was 36±11 mg/day (40 mg/day) on the week 12 visit (N=99) and 33±11 mg/day (30 mg/day) at treatment endpoint (N=151). In the flexible dose study, Study 627 the mean (median) daily paroxetine dose in paroxetine Ss was 34±11 mg/day (30 mg/day) on week 12 and 31±11mg/day (30 mg/day) at treatment endpoint.

5.2 Secondary Sources of Clinical Data

5.2.1 Post-Marketing Experience

As of July 1, 2000 there were no submissions for authorization of marketing paroxetine for the treatment of PTSD to any foreign country. However, submissions were anticipated simultaneously or soon after the submission of the US sNDA. According to the sponsor, paroxetine hydrochloride has not been withdrawn from the market at any time in any country for any reason related to safety or efficacy.

5.2.2 Literature Review

The submission indicates that a literature search "with a particular focus on clinical trials that evaluated the use of paroxetine in the treatment of PTSD" (exact method of the search was not specified) failed to reveal any reports of adverse event data in PTSD patients treated with paroxetine.

5.3 Adequacy of Clinical Experience

The sponsor makes their claim for the efficacy of Paxil® in the treatment of PTSD on the basis of three multicenter, placebo controlled studies involving approximately 1100 Ss. This is adequate data to review.

5.4 Data Quality and Completeness

This section describes various comparisons made between listings, tables, Case Report Forms, and/or narratives. The results of these comparisons are also described and generally appeared to be accurate, consistent and contain adequate information. Based on these observations, the quality and completeness of the data described in the submission appears to be adequate.

The following listings and tables were compared for internal consistency for Study 648 (selection of Study 648 was arbitrary): listings of Case Report Forms (CRF's), "Index of Patient CRF's by Study and Patient Number", narratives, Summary tables; Tables 44 and 46 in the study report. These listing and tables were generally consistent with some exceptions. While the summary tables 44 and 46 appears to list all Ss, the index table "Index of Patient CRF's...." failed to identify dropouts among those Ss with adverse events (AE's) under the column, "Withdrawal due to –AE". Despite the absence of these dropouts in the "Index of Patient CRF's ..." listing, these Ss were listed in the summary Table 46 for withdrawals due to AE's. However, the Index listings for the other two studies did identify Ss with both SAE and an AE leading to withdraw, under both corresponding columns.

Comparisons between the Preferred Term and Verbatim Text were made for line listings of Serious Adverse Events of paroxetine Ss for all three studies and were generally consistent. Comparisons between these Preferred Terms and Verbatim Text with those listed in narratives were also made for approximately 10 arbitrarily selected Ss and were generally consistent or appeared to be adequate.

Comparisons between narratives for Ss with serious adverse events and CRF's were made for 6 arbitrarily selected Ss from the 3 studies. These comparisons showed that narratives were generally consistent with the CRF's regarding main aspects pertaining to the serious adverse events.

Other minor discrepancies included the report of 61 investigation sites employed in Study 651, yet the listing of investigation sites provided in the submission listed only 60 sites. Results on the enumeration of males with gender specific taper phase emergent adverse events could not be found in the submission. The following appeared in the Summary Tables 7.2.2 and 7.3.2 in Section 22 of the Integrated Summary of Safety part of the submission regarding gender specific Taper Phase emergent adverse event results: "no data available for this report."

Although some discrepancies were noted, the overall conclusion is that based on the above comparisons the quality and completeness of the data in the submission appears to be adequate.

6.0 Human Pharmacokinetics

There are no human pharmacokinetic issues to review with this submission.

7.0 Review of Studies for Which Efficacy Claims Are Made

All three studies employed a 12-week treatment phase to determine efficacy of Paxil® in the treatment of PTSD. Study 651 employed a fixed dose design with placebo, 20 mg and 40 mg Paxil® treatment groups. Studies 648 and 627 generally employed identical methods and used a flexible dose design in which treatment groups were a placebo group and a 20-50 mg flexible dose Paxil® g[illegible]p. Each study is described in detail below.

7.1 Study 651. A 12-Week Randomized, Double-blind, Placebo Controlled, Multi-Center Fixed Dosage Trial to Evaluate the Efficacy and Tolerability of 20 and 40 mg/day Paroxetine in Patients with PTSD; 29060/651.

7.1 A. Investigators and Sites

See Table 7.1.1A in the appendix (as provided by the sponsor) for a listing of the sixty investigative centers (the text of the submission indicates 61 total sites) located in the United States and Canada participated in the study. A total of 58 sites had at least one randomized subject (see Table 7.1.1 A).

7.1 B. Study 651: Objectives

- The primary objective of the study was to determine the efficacy of paroxetine (20 mg and 40 mg) treatment compared to placebo treatment in patients with PTSD.
- The secondary objective was to evaluate safety and tolerability of paroxetine (20 and 40 mg) compared to placebo treatment in patients with PTSD.

7.1 C. Study 651: Study Population

The study population consisted of 551 Ss (the randomized and the ITT population), at least 18 years old, meeting DSM-IV criteria for PTSD as assessed by psychiatric interview employing Clinician Administered PTSD Scale for DSM-IV (CAPS-1) and the Mini International Neuropsychiatric Interview (MINI). A minimum CAPS Part 2 (CAPS-2) score of 50 was also required at the baseline visit, which occurred after a one-week run-in phase. Ss over 65 years old "must have been able to tolerate a paroxetine starting dose of at least 20 mg daily and be without renal or hepatic impairment (laboratory tests results at screening were to be within twice the upper limit of normal)". A compliance rate within 80 to 120% was also required during the run-in phase of the study, for eligibility to enter the treatment phase. Some additional exclusionary criteria included the presence of any of the following conditions or circumstances, in that patients with any of these conditions were excluded from the study:

- Receiving disability payments, or is litigating for compensation for psychiatric illness were excluded.
- "Unresolved" clinical findings at baseline.
- A "current" major depressive episode preceding the diagnosis of PTSD.
- Concomitant Axis I disorders as the "primary diagnosis", such as major depression, dysthymic disorder, simple phobia, OC or panic disorder "as a primary diagnosis" or substance abuse/dependence within 6 months of study entry. According to the submission (page 000075 in volume 015 of Study 651), "patients with non-predominant, secondary psychiatric conditions were eligible".
- ECT within 3 months of study entry.
- "a current homicidal or suicidal risk or unable to comply with the study protocol" per the investigator's judgement.

Permitted concomitant medications during the study were:

- Oral contraceptive agents anytime during the study.
- Chloral hydrate of up to 1000 mg for a maximum of 3 nights/week only during the first two weeks of the study.

Prohibited agents during the study (some also required discontinuation for a specified period prior to study entry) were:

- Various specified psychotropic agents.
- Specific sedative/hypnotic agents.
- Agents listed in the drug interaction section of Paxil® labeling.

7.1 D. Study 651: Design

This double blind randomized, placebo controlled, multi-center, fixed dose, parallel group study involved a 12-week treatment phase. Ss were randomized to one of three treatment groups (1:1:1 ratio): 20 mg or 40mg of paroxetine or placebo. Placebo or paroxetine were administered daily in the morning as a single tablet (over-encapsulated for blinding purposes).

Study assessments were scheduled at screening and/or baseline, on weeks 1, 2, 4, 6, 8 and 12, as described in a separate section below. Safety assessments were also conducted on the Taper End or Early Termination Visit, and on a 14-day Follow-up Visit (14 days after the last dose). If a S had an adverse event on the 14-Day Follow-up Visit, an additional follow-up visit was required within a 28 day period.

A single blind one-week placebo run-in phase was employed to "identify potential placebo responders and to assess compliance" (a compliance within 80 to 120% was required before randomization and entry into the treatment phase). Criteria for "placebo responders" were not specified. However Ss were required to have a CAPS-2 score of ≥50 on the baseline visit, which occurred after the run-in phase. A two-week taper phase was also employed.

The table below outlines the daily dose regimen for the three treatment groups during the treatment and taper phases of the study, as provided by the sponsor. No dose reductions were permitted during the study, except for a single dose interruption, not to exceed 2 days, for management of adverse events.

Medication Strength per Capsule (Daily Oral Dose):

		Treatment Phase		Taper Phase	
Treatment Group	**Week 1**	**Week 2**	**Week 3- 12**	**Week 13**	**Week 14**
Paroxetine 20mg	20 mg	20mg	20mg	Placebo	Placebo
Paroxetine 40mg	20 mg	30mg	40mg	30mg	20mg
Placebo	Placebo	Placebo	Placebo	Placebo	Placebo

Screening (Day –7) for entry into the run-in phase of the study consisted of the following:
A history, psychiatric and physical exam.

- Clinical laboratory evaluation (CBC with differential, platelet count, liver function tests, test dipstick urinalysis, creatinine, blood urea nitrogen, sodium, potassium, and thyroid function tests). Thyroid function tests were only conducted at screening.
- Electrocardiogram (ECG).
- Clinician Administered PTSD Scale for DSM-IV (CAPS-I).
- The Mini International Neuropsychiatric Interview (MINI).

A baseline visit occurred at the end of the run-in phase to assess eligibility of Ss for randomization into the treatment phase of the study. Efficacy and safety assessments were conducted at baseline. Some of these assessments were the following:

- Laboratory and/or physical examination as required for abnormal findings at screening.

- Vital signs (blood pressure, pulse and weight)
- CAPS-2
- Clinical Global Impression-Severity of Illness Item (CGI-S).
- Treatment Outcome PTSD Scale (TOP8)
- Montgomery Asberg Depression Scale (MADRS).
- Various pharmacoeconomic measures such as the Sheehan Disability Scale (SDS)

Anxiety rating scales and a laboratory urine or blood screen for benzodiazepines or other substances with abuse potential were not included.

7.1 E Study 651: Assessments Employed

See the schedule of assessments, as provided by the sponsor, in Table 7.1.2 in the appendix.

Primary efficacy assessments were as follows:

- CAPS-II
- Clinical Global Impression-Global Improvement Item (CGI-I)

Secondary efficacy measures were:

- Cluster subscores of the CAPS-II
- Treatment Outcome PTSD Scale (TOP 8)
- CGI-S
- Davidson Trauma Scale (DTS)
- MADRS
- Items from the Sheehan Disability Scale (SDS)
- "Quality of life and Employment status" measures included the EuroQol, and job attendance questionnaire (to determine total number of missed work days)

Safety assessments obtained at screening and on week 12 of the treatment phase of the study were:

- Vital signs (not including height and weight) and physical examination
- ECG
- Laboratory parameters (except for thyroid function tests)

7.1 F Study 651: Analysis Plan

Primary Efficacy Variable

There were two primary efficacy variables, as follows:

- The mean change from baseline to treatment endpoint (week 12 LOCF endpoint) on the CAPS-2 total score. The baseline measure was defined as the measure on the baseline visit, which occurred on Days –4 to 0, with Day 1 being defined as the first day of treatment.
- The "proportion of responders" on week 12 (LOCF endpoint). Responders were defined as Ss having a score of 1 (very much improved) or 2 (much improved) on the CGI-I score (a non-responder was defined as the endpoint score of ≥3).

Secondary Efficacy Variables

The secondary efficacy variables included the following:

- The mean change (from baseline to treatment LOCF week 12 endpoint) on additional scales or subscales: the DTS score and individual symptom clusters, SDS (work, social life, and family life), CGI-S, TOP-8, the MADRS and the Re-experiencing, Avoidance and Numbing, and the Hyperarousal clusters of the CAPS-2.
- The percentage of Ss with a TOP-8 score of <8 at treatment endpoint (week 12 LOCF endpoint).

The Dataset Analyzed

Statistical analysis was performed on data from the last observation carried forward (LOCF) ITT efficacy dataset from which the sponsor made their "primary inference". The ITT efficacy population was defined as Ss having at least one dose of the study drug and with at least one valid post-baseline efficacy assessment or adverse event. A confirmatory analysis of data from the Per Protocol Population (PPP) was also performed for only the primary efficacy variable. The PPP was defined as Ss with the following:

- At least 2 weeks of exposure to the randomized study drug.
- No major protocol violation was committed regarding inclusion/exclusion criteria at screening/baseline.
- No major protocol violation was committed during the treatment phase.
- Compliant to study medication (no treatment interruption of 3 or more consecutive days or remained within a 80-120% compliance) during the treatment phase.

Additional "confirmatory" analyses were conducted on the LOCF dataset using the last time point when at least 70% of the Ss remained in the study (70% LOCF) and on an observed cases dataset (OC) at the 12 week endpoint. The endpoint measure occurred on week 12, more specifically defined as the measure obtained on days 71-91 of treatment.

Methods of the Statistical Analysis

The sponsor employed two-tailed comparisons of each Paxil® group to placebo with a $p<0.05$ as significant, in which primary efficacy variables were adjusted for multiple comparisons using Hochberg's method. Comparisons were not made between the low and high dose Paxil® groups. Interaction effects were considered significant at $p<0.10$ level. The sponsor estimated 95% confidence intervals for the differences between each treatment group on the primary efficacy variables, while making adjustments for multiple comparisons. These 95% confidence intervals are provided in the summary tables of the results provided in the submission. The level of significance on the primary endpoints was not adjusted for multiple comparisons.

The "primary inference" was to be based on results of an analysis of the main effects of treatment group, center and baseline score (of the efficacy variable being analyzed) and interaction effects. The following covariates were entered into the final model:

- Gender
- Baseline score for the efficacy variable being analyzed
- Trauma type (due to small sample size of the natural disaster category, this category was pooled with "other")
- Time since trauma
- Baseline MADRS score.

Two analyses were conducted: one for the effect of center and treatment and the second for the effect of center, treatment, and with the above covariates. Treatment by covariate interaction effects were examined by using a model building approach (level of significance for interaction effects was $p< 0.10$).

An analysis of variance was employed for continuous efficacy variables, while logistic regression analysis was employed for categorical variables. Treatment, center and covariates were included in the logistic regression model. The "primary inference" was based on the treatment effect from the covariate-adjusted model. Odds ratios (the odds of being classified as a responder) were also determined when employing the specified CGI or the TOP8 cut-off scores for classifying responders and non-responders. 95% confidence intervals were then determined. The Wilcoxon rank sum test was employed for the change from baseline on the CGI-S variable without adjustment for center or covariates.

7.1 G Study 651: Patient Disposition

840 patients were screened. A total of 551 of screened Ss met criteria for entry into the run-in phase, successfully completed the run-in phase, and subsequently met criteria at the baseline visit for randomization into the treatment phase of the study. The remaining 289 screened Ss were either screening or run-in failures due the following reasons (the number of Ss that failed the run-in phase could not be found in the submission): did not meet inclusion/exclusion criteria (185 Ss), were lost to follow-up (50 Ss), had an adverse event (1 S) or for "other" reasons (45 Ss).

The ITT population consisted of 551 Ss. Note that this number is the same as the number of randomized Ss. The table below summarizes the disposition of these Ss.

Reasons for Patient Withdrawal

Reason for Study Conclusion	Placebo		Paroxetine 20 mg		Paroxetine 40 mg		Total	
	(N =186)		(N=183)		(N=182)		(N= 551)	
	n	%	n	%	n	%	n	%
Total Completed*	120	64.5	122	66.7	113	62.1	355	64.4
Adverse experience**	18	9. 7	21	11.5	28	15.4	67	12.2
Lack of efficacy	12	6. 5	6	3. 3	2	1. 1	20	3. 6
Deviation from protocol (including non- compliance)	7	3. 8	7	3. 8	8	4. 4	22	4. 0
Lost to Follow- up	24	12.9	21	11.5	18	9. 9	63	11.4
Other reasons	5	2. 7	6	3. 3	13	7.1	24	4. 4
Total Withdrawn	66	35.5	61	33.3	69	37.9	196	35.6

* Completers were patients who completed 12 weeks of participation in study

** Includes one patient in the placebo group (651.028.07310) and 2 patients in the paroxetine 40mg group 651.046.07017 and 651.055.07711) listed as withdrawn due to AEs which began after study medication was discontinued. Also included in this category is one patient in the paroxetine 20mg group (651.038.08268) who was listed as withdrawn due to an AE which began prior to randomization.

176 (31.9%) of the randomized Ss were considered protocol violators (21 out of 188 in the 20 mg paroxetine group, and 19 out of 197 in the 40 mg paroxetine group). The majority of protocol violators had either less than 2 weeks of the study medication (10.2% of the 551 randomized Ss), or were non-compliant (compliance rate of < 80% or > 120%, consisting of 19.8% of randomized Ss), or had violated "excluded medication" (8.9%). The remaining 7 out

of the 176 Ss that were committed protocol violators had made other violations such as not meeting criteria regarding the CAPS-2, or CAPS-1 score, receiving disability compensation or not meeting the DSM-IV criteria for PTSD.

The distribution of the 176 protocol violators across treatment groups were as follows: 28% of the 551 randomized Ss were in the placebo group, 31% in the 20 mg Paxil® group and 37% in the 40 mg Paxil® group. A similar increasing trend over these treatment groups (placebo, low dose and high dose Paxil® groups) was observed for each of the major subcategories of violators that are described above (less than 2 weeks of study medication, treatment non-compliance, "excluded medication").

7.1 H. Study 651. Baseline Demographics/Medical/Psychiatric Comorbidity and Baseline Efficacy Measures

Baseline Demographics. The treatment groups were similar on various demographic variables including mean age, age-group distribution, gender, mean weight, and racial distribution and showed a predominance of Caucasians (91 to 93% in each group), women (67-70%) and Ss under 65 years old (97-98%). The mean ages and standard deviations (SD) of the paroxetine and placebo groups were 42±12 years in each group. The mean weight ±SD, and the mean height ± SD of each group was approximately 82±22 kg in each group, and 168±9 cm or 169±10 cm in each group, respectively. The racial distribution was as follows:

- 91-93% Caucasians,
- 4-7% African American
- 0-1% Asian
- 1-2% "other".

Medical Comorbidity. Treatment groups were generally similar with respect to the percentage of Ss with each category of current/active or past medical diseases or conditions (based upon visual inspection of results provided in the submission). The most common current "active conditions" were as follows with the range of percentages of affected Ss among the groups indicated in parentheses (psychiatric conditions are provided in the next section):

- Headache (20-30%)
- Allergic rhinitis (22-23%)
- Hypertension (10-15%)
- Migraine (11-12%)
- Genital female disorder, other (10%)
- Adverse effect/analgesic (9-11%)

Hypothyroidism was an active condition in approximately 4-7% of Ss among the groups. Other conditions occurring in at least 5% but occurred in less than 10% of Ss in any treatment group included (note that psychiatric conditions are not included here, as they are described in the next section): adverse effect/antibiotic, asthma, esophagitis, insomnia, back pain, "inflam skin/subcut", elevated clolesterol/triglyceride, menopausal states, arthorpathy, adverse effect/anti-infective, and dyspepsia.

Psychiatric Comorbidity Baseline Scores of Efficacy Rating Scales.

The following psychiatric conditions are those indicated in the submission as "active medical conditions" reported in at least 5% of Ss in any treatment group:

- Stress reaction (100%)
- Depression (24-27%)
- Neuroses (14-20%)
- Anxiety (8-9%)
- Psychoses, Affective (3-7%)

Regarding the incidence of "non-predominant secondary psychiatric conditions", as determined by MINI at screening, the majority of Ss (approximately 45%/group) had Major Depressive disorder. The second most predominant psychiatric disorder was generalized anxiety disorder in approximately 30% in each group. The table below (as provided by the sponsor) shows the incidence of Ss with each psychiatric disorder that was found in at least 5% of Ss in a given treatment group, in descending order of frequency. In addition to the disorders listed in the table, obsessive compulsive disorder was in approximately 4% of Ss /group and alcohol dependence/abuse was in 2 to 4% of Ss/group. Less than 3% of Ss/group had psychotic disorders of bulimia.

The Number (percentage) of Subjects with a "Secondary" Psychiatric Disorder Determined by the MINI at Screening.

Psychiatric Disorder	Placebo (N = 186) N (%)	Paroxetine 20 mg (N =183) N (%)	Paroxetine 40 mg (N =182) N (%)
Major Depressive Disorder	82 (44.1)	82 (44.8)	84 (46.2)
Generalized Anxiety Disorder	55 (29.6)	60 (32.8)	51 (28.0)
Agoraphobia	40 (21.5)	38 (20.8)	45 (24.7)
Suicidality	41 (22. 0)	29 (15. 8)	28 (15. 4)
Panic Disorder	32 (17.2)	25 (13.7)	27 (14.8)
Social Phobia	21 (11.3)	26 (14.2)	26 (14.3)
Dysthymia	22 (11.8)	17 (9. 3)	17 (9. 3)
(Hypo) Manic Episode	11 (5. 9)	13 (7. 1)	10 (5. 5)

The mean duration of PTSD symptoms for Ss of this study combined with Study 648 was approximately 13 years (this information for only Study 651 could not be found in the study report). The treatment groups of Study 651 were generally similar in mean CAPS-2, DTS, SDS, TOP-8 and MADRS total scores at baseline and in the median score on CGI-S at baseline, as shown in Table 7.1.3 in the appendix (as provided by the sponsor). The treatment groups were also similar on the mean (approximately 16 or 15±15 mean years), median (approximately 10 median years) and range (<1 year to approximately 55 years) of years since the trauma. The majority of the Ss in each group had a history of physical or sexual assault (approximately 50% in each group), while approximately 18% in each group had witnessed the trauma. The table below summarizes the number and percentage of Ss with a given type of trauma in each group (as provided by the sponsor).

The Number (percentage) of Subjects by Type of Trauma in Each Group

Type of Trauma	Placebo (N = 186) N (%)	Paroxetine 20 mg (N =183) N (%)	Paroxetine 40 mg (N =182) N (%)
Physical or Sexual Assault	101 (54.3)	87 (47.5)	93 (51.1)
Seeing someone hurt or die	31 (16.7)	33 (18.0)	33 (18.1)
Serious accident/ fire/ injury	11 (5. 9)	20 (10. 9)	22 (12. 1)
Being in a war or combat	14 (7. 5)	11 (6. 0)	9 (4. 9)
Natural disaster	2 (1. 1)	3 (1. 6)	0 (0. 0)
Other	27 (14.5)	28 (15.3)	25 (13.7)

7.1 I. Study 651. Concomitant Medications

The number (percentage) of Ss reporting concomitant medication during the treatment phase of the study were similar among the treatment groups in which the percentages ranged from 83 to 86% across the three groups. Furthermore, the groups do not appear to show substantial differences in either the pattern of use, or in the total use of concomitant medication based on visual inspection of the descriptive data provided in the submission. An exception was the use of vitamins reported in 21% of placebo Ss compared to 13% and 15% in the 20 mg and 40 mg paroxetine groups, respectively.

Vitamins and analgesics were the most common concomitant medications. Analgesic use was reported in 13% to 32% of Ss for a given type of analgesic (paracetamol, acetylsalicylic acid and ibuprofen) across the treatment groups. Estrogen-like medications were third most common type of medication in which approximately 9% of Ss/group were taking conjugated estrogens and approximately 8% were taking ethynylestradiol. Medroxyprogesterone acetate was reported in 4 to 8% of Ss of each group. Loratadine was reported in 5 to 8% of Ss among the groups. Levothyroxine Na was reported in approximately 5% of Ss/group. Pseudophedrine was reported in 7 to 9% of Ss/group.

7.1 J. Study 651. Efficacy Results

Primary Efficacy Variables.

1. **The mean change from baseline to treatment endpoint (in adjusted least square means) on the CAPS-2 total score.**

The following results are the least square means adjusted for treatment, center and the covariates: gender, baseline total Caps-2 score, trauma type, time since last trauma and MADRS score at baseline. Each paroxetine group (-39.6±2.0, N=166 in the 20 mg group, -37.9±2.3, N=156 in the 40 mg group) showed significantly greater improvement ($p<0.001$ for each comparison) on the CAPS-2 total score than the controls (-25.3±2.0, N=167) for the LOCF dataset. Similar results were obtained for the OC dataset and for the PPP in both LOCF and OC datasets (LOCF of the PPP: mean change of –27.0±2.3, N=126 in the placebo group, -40.2±2.3, N=124 with $p<0.001$, in the 20 mg paroxetine group, -40.91±2.6, N=111 with $p<0.001$ in the 40 mg group; OC of the PPP: $p<0.01$ to 0.015 for each pair-wise comparison). Table 7.1.4 (as provided by the sponsor) in the appendix shows the mean change from baseline of the CAPS-2 total score at each week for each treatment group of the ITT efficacy population for the LOCF and OC datasets.

2. **The proportion of Responders on the CGI-I (responders are those with a week 12 endpoint CGI-I score of 1 or 2; very much improved or much improved, respectively).**

Significantly more responders (ITT LOCF dataset) were observed in each paroxetine group (63% in the 20 mg group and 57% in the 40 mg group) compared to the placebo group (37%) reflected by the odds ratio (adjusted for treatment, center and covariates) of responders with paroxetine versus placebo treatment using a 95% confidence interval ($p<0.001$ for each comparison). The percentage of responders provided for each group is adjusted for treatment, center and covariates using a logistic regression analysis, as previously described. Refer to Table 7.1.5 (as provided by the sponsor) in the appendix, which shows results for the LOCF and OC datasets for the ITT population. Similar results were obtained when analyzing the LOCF and OC datasets of the PPP in which each paroxetine to placebo group comparison yielded a p value of less than 0.001.

Covariate by treatment interaction effects on the primary efficacy variables. The sponsor reports no covariate (gender, baseline total score of the primary efficacy variable being analyzed, trauma type, time since last trauma and MADRS score at baseline) by treatment interaction effects on both primary efficacy variables.

Examination of Gender Effects. As previously described, gender by treatment interaction effects on each of the primary efficacy variables were not revealed by the sponsor when gender was considered a covariate in the analyses. However, the sample sizes were insufficient for the analyses to include 5 covariates, as employed by the sponsor, whereby a Type II error is likely to occur. Gender by treatment interaction effects were observed in clinical trials examining Zoloft™ in PTSD patients, as described in the labeling for Zoloft™. Therefore, the statistical reviewer (Dr. Lu Cui) was asked to conduct a more conservative statistical analysis of the sponsor's data (ITT LOCF dataset) for each of the 3 studies (651, 648 and 627) to determine if treatment group by gender interaction effects could be revealed. Such an analyses was conducted employing a treatment group by gender analysis of variance on the change of CAPS-2 total score and using Chi square analyses for CGI-I responders (refer to the Statistic Review of this submission). The analyses revealed no gender by treatment interaction effects.

Secondary Efficacy Variables.

The following were the secondary efficacy variables, which yielded similar results to those of the primary efficacy variables in which each paroxetine group were reported to show greater improvement compared to the placebo group:

- The mean change (from baseline to treatment LOCF week 12 endpoint) on additional scales or subscales: the DTS (self-rating scale) score and individual symptom clusters, SDS (work, social life, and family life), CGI-S, TOP-8, the MADRS and the Re-experiencing, Avoidance and Numbing, and the Hyperarousal clusters of the CAPS-2.
- The percentage of Ss with a TOP-8 score of <8 at treatment endpoint (week 12 LOCF endpoint).

Comparison of each paroxetine group to the placebo group on each secondary efficacy variable for the LOCF dataset generally yielded a p value of less than 0.001. The Hyperarousal symptom cluster on the DTS Scale and Individual Item Scores on the SDS showed trends for greater improvement in the paroxetine group compared to placebo ($p<0.02$ to 0.03). However, the sponsor did not correct for multiple comparisons.

Additional Subgroup Analysis Requested from the Sponsor on the Primary Efficacy Variables.

Given that the observed treatment effects on the primary efficacy variables may be reflecting nonspecific underlying antidepressant and/or non-PTSD anxiolytic effects of paroxetine, the sponsor was asked to conduct a subgroup analysis of the LOCF dataset. One reason for considering a potential for nonspecificity of paroxetine in the observed treatment effects, is that a fairly large proportion of the Ss had concomitant active major depressive disorder (approximately 45%/group) and/or non-PTSD anxiety disorders (approximately 20-30%/group with generalized anxiety disorder or other specific anxiety disorders) based on a MINI interview. Consequently, this reviewer, (with input from the Statistical Reviewer, Dr. Lu Cui) asked the sponsor to subgroup the LOCF ITT dataset into specific subgroups (Major Depressive Disorder positive and negative subgroups, non-PTSD anxiety disorder positive and negative groups, and other subgroups), as outlined below. The sponsor was asked to conduct an analyses for subgroup by treatment main effects and interaction effect on the primary efficacy variables for each of the subgroups. A subgroup by treatment and interaction effect ANOVA was performed for the change in the total CAPS-2 score and logistic regression for treatment by subgroup main and interaction effects and treatment by subgroup Chi square analyses were performed on the percentage of CGI-I responders.

Subgroups analyzed by the sponsor (ITT efficacy LOCF dataset):

1. Subgroup by presence versus absence of concomitant Major Depressive Disorder (referred as MDD + and MDD – subgroups, respectively).
2. Subgroup by the presence (non-PTSD AD + group) versus absence (non-PTSD AD - group) of the following concomitant disorders: Panic disorder, Agoraphobia, Social Phobia, Obsessive Compulsive Disorder and Generalized Anxiety Disorder. Subjects with at least one of these disorders are classified as non-PTSD Anxiety Disorder positive subjects and subjects without any of these disorders is classified as non-PTSD Anxiety disorder negative subjects.
3. Subgroup by the presence or absence of the following concomitant disorders: Major Depressive disorder and any of the anxiety disorders listed under time 2 above (Panic disorder, Agoraphobia, Social Phobia, Obsessive Compulsive Disorder and Generalized Anxiety Disorder). Subjects with at least one of these disorders are classified as Depression/non-PTSD Anxiety disorder positive subjects (non-PTSD AD and/or MDD + subgroup) and subjects without any of these disorders is classified as Depression/non-PTSD Anxiety Disorder negative subjects (non-PTSD AD and/or MDD - subgroup).
4. Subgroup by subjects with a baseline MADRS score of < 21 (low MADRS scorers) and subjects with a baseline MADRS score of ≥ 21 (high MADRS scorers). Using SAS, this reviewer revealed that a MADRS score of 21 is the median, as well as the mean score in the ITT LOCF population in the study.

Results of the Subgroup Analyses. The above analyses revealed that there were no significant subgroup main effects or subgroup by interaction effects on the primary efficacy variables (p values generally ranged from 0.1 to 0.8). Furthermore, the difference between placebo and paroxetine groups in each subgroup on the mean change from baseline to treatment endpoint on the total CAPS-2 score (CAPS-2 delta, adjusted for covariates: gender, baseline MADRS, time since trauma, trauma type, country group, the subgroup main effect and subgroup

by treatment interaction) was generally highly significant (using 95% confidence intervals, p values generally ranged from 0.02 to 0.001). The mean treatment group differences on the adjusted CAPS-2 deltas ranged from –7 to –20 score points. Similar results were observed for the change from baseline on the percentage of CGI-I responders. Refer to the Statistical Review conducted by Dr. Lu Cui which also describes these results.

7.1 K Study 651. Conclusions

This 12-week clinical trial shows significantly greater improvement in paroxetine-treated patients than placebo-treated patients with PTSD on both of the primary efficacy measures. The two primary efficacy variables were the adjusted least squares mean change from baseline to week-12 (treatment endpoint) in the total CAPS-2 score, and in the odds ratio for responders using a CGI-I cut-off score. However, the observed effects do not appear to be dose dependent when comparing the 20 mg daily paroxetine group to the 40 mg treatment group on each of the primary efficacy variables.

A potential caveat to the interpretation of the results of this study, as well as those the other two studies (Studies 648 and 627) is that an observed treatment effect in the PTSD patients may be secondary to an underlying or primary treatment effect on a concomitant psychiatric disorder of major depressive disorder or of another anxiety disorders (e.g. generalized anxiety disorder or panic disorder). A large proportion of Ss had these psychiatric disorders co-existing with their primary disorder of PTSD. Furthermore, a strong correlation between a change (from baseline to treatment endpoint) on the CAPS-2 total score and a change on the MADRS total score was observed (Kendalls Tau of 0.6, 0.4 and 0.5 in the placebo and 20 and 40 mg paroxetine groups, respectively with $p<0.001$). Although this observation is difficult to interpret, it suggests that improvement of PTSD and depressive symptoms are inter-related. However, a significant correlation was also observed among the placebo group, such that this relationship appears to be independent of active drug treatment. Another notable finding was that the baseline MADRS score failed to show significant covariance with treatment effects on the primary efficacy variables (based on results of a covariate analyses). These results suggest that the severity of depressive symptoms at baseline did not appear to influence the observed treatment group effects on the primary efficacy variables. An analysis of data from the re-experiencing symptom cluster on the CAPS-2, which includes several cardinal symptoms of PTSD, showed significantly greater improvement (from baseline to treatment endpoint) in each paroxetine group compared to the placebo group. These results support a conclusion that paroxetine treatment improves some cardinal symptoms believed to be PTSD specific. Nevertheless, whether a direct and independent effect of paroxetine treatment on PTSD specific symptoms exists remains unclear.

The most definitive way to rule out the possibility for an improvement in PTSD symptoms secondarily to the antidepressant effect or non-PTSD specific anxiolytic effects of paroxetine treatment, is to conduct a clinical trial that includes a PTSD population that is free of concomitant mood disorder or other anxiety disorders. However, such a population may not be representative of the PTSD population in general, as suggested by comments by experts on the Advisory Committee during a meeting on PTSD held on 10/8/99. The majority of the PTSD population is reported to have concomitant mood and/or anxiety disorders as observed in other studies of PTSD, including patient populations studied in clinical trials supporting the indication of Zoloft® for treatment of PTSD. Furthermore, PTSD is in itself an anxiety disorder with some symptoms that overlap with other anxiety disorders, as well as with symptoms of major depressive disorder. Therefore, the difficulty in differentiating antidepressant versus anxiolytic

versus anti-PTSD-specific effects of paroxetine treatment in PTSD patients remains a potentially difficult task.

Given the potential for treatment effects reflecting an underlying antidepressant or non-PTSD anxiolytic effect of paroxetine, the sponsor was asked to conduct a subgroup analyses on the primary efficacy variables. The LOCF ITT dataset was subdivided into various subgroups as follows: concomitant major depressive disorder (MDD) positive versus negative subgroups, concomitant non-PTSD Anxiety disorder (AD) positive versus negative subgroups, concomitant MDD and/or AD positive versus MDD and AD negative subgroups, and finally low versus high baseline MADRS scorers. Statistical analyses were performed on each of these subgroups in an attempt to reveal potential subgroup main effects or subgroup by treatment interaction effects on the primary efficacy variables. The analyses generally showed results supporting a conclusion that the observed treatment effects of paroxetine compared to placebo were independent of the presence or absence of no subgroup or interaction effects. Furthermore, significant treatment effects in favor of paroxetine treatment were generally revealed for all subgroups independent of the presence or absence of MDD and/or non-PTSD AD, or of high versus low scores on the baseline MADRS. While these *post-hoc* analyses must be interpreted with caution, these results coupled with those from the sponsor's original analyses using *a priori* methods (also confirmed by an analyses conducted by Statistical reviewer, Dr. Lu Cui, as describe in his review) provide evidence supporting the sponsor's claim that paroxetine treatment is indicated for treatment of PTSD.

Another possible concern regarding the population examined in this study, as well as the other two studies described below, is that drug and alcohol screens were not conducted on Ss. The protocol does require exclusion of Ss with substance abuse/dependence within 6 months of study entry. Since denial is common among patients with this disorder, it is optimal to screen patients for the presence of alcohol and substances during the study. Nevertheless, the possible confound of including Ss with alcohol and/or substance abuse/dependence in the study, unbeknownst to the investigator, would tend to minimize treatment groups differences and the distribution of Ss in each treatment group would be expected to be similar since group assignment was randomized.

Despite, potential caveats, as above, overall the study supports the indication of paroxetine treatment in patients with PTSD.

7.2 Study 648. A 12-Week, Randomized, Double-blind, Placebo Controlled, Parallel Group, Flexible Dosage Trial to Evaluate the Efficacy and Tolerability of 20 to 50 mg/day Paroxetine in Patients with Posttraumatic Stress Disorder; 29060/648.

7.2 A. Study 648. Investigators and Sites

Table 7.1.1 B in the appendix (as provided by the sponsor) shows a listing of the 37 investigative centers that participated in the study. These sites were located in the US and Canada, as in Study 648 described above.

7.2 B. Study 648. Objectives

The objectives of this study are the same as those for Study 651, which are to determine the efficacy, safety and tolerability of paroxetine treatment compared to placebo treatment in patients with PTSD. However, Study 648 employed a flexible daily oral dose range of 20 to 50 mg of paroxetine treatment, rather than two fixed daily oral doses of 20 and 40 mg.

7.2 C. Study 648. Study Population

323 male and female Ss (randomized population) ages 18 years and older, with PTSD (DSM-IV) participated in the study. The screening methods and inclusionary and exclusionary criteria for this study are the same as those employed in Study 651.

7.2 D. Study 648. Design

The design of the Study 648 was generally the same as that employed in Study 651, except for employing a flexible 20-50 mg dose regimen and a 3-week taper-phase, instead of a 2-week taper phase, during which dummy dosing was not employed. Study assessments during the 12-week treatment phase were scheduled for weeks 1, 2, 4, 6, 8 and week 12 or upon early withdrawal, as described in a separate section below. The overall design included the following in the order of occurrence with assessments being similar to those employed in Study 651:

- S screening
- A one-week placebo run-in phase (80-120% compliance is required)
- Baseline visit
- 12-week treatment phase
- 3-week taper phase
- 14±3 day follow-up visit after the last dose
- A second follow-up visit within 28 days, in the case of an ongoing adverse event.

Ss in the paroxetine group were started on 20 mg/day (dose level 1) for two weeks before commencing up-titration of the dose at 10mg increments at intervals of at least two-weeks, per the discretion of the investigator (based on clinical response and tolerability). The maximum daily dose was 50 mg (dose level 4). A single dose reduction (a decrease to the next lowest dose level) was permitted for management of an adverse event, upon discretion of the investigator. This dose reduction could occur no sooner than the week 2 visit, and only in Ss receiving a dose level 2 (30 mg/day) or higher.

A three-week taper phase was employed following the schedule shown in the table below, as provided by the sponsor.

Taper Phase Treatment Schedule

Dose level at the end of treatment	Week 13	Week 14	Week 15
1 (20 mg)	No treatment	No treatment	No treatment
2 (30 mg)	2 caps* daily for 7 days	No treatment	No treatment
3 (40 mg)	3 caps* daily for 7 days	2 caps* daily for 7 days	No treatment
4 (50 mg)	4 caps* daily for 7 days	3 caps* daily for 7 days	2 caps* daily for 7 days

* 10 mg capsules were employed during the taper phase

7.2 E. Study 648. Assessments

Assessments conducted for this study, as well as the time and frequency of each assessment were the same as those employed in Study 651. Refer to (as provided by the sponsor) 7.1.2 in the appendix for the assessment schedule.

7.2 F. Study 648. Analysis Plan

The primary efficacy variables were identical to those in Study 651. The secondary efficacy variables, as well as the statistical methods employed were generally the same as those of Study

651. However, in Study 648, data from Ss with trauma categorized, as "natural disaster" was not pooled with data from Ss categorized with the trauma type of "other". Instead these two categories were considered separately, as the sponsor considered the number of Ss in the former category sufficient to be considered a separate category. Methods for testing for significant treatment group effects were the same as those employed in Study 651, except "Center group" was entered into the model as an additional covariate. Refer to the Statistical Review of this submission by Dr. Cui regarding statistical issues and center grouping effects.

7.2 G. Study 648. Patient Disposition

457 patients were screened and 323 of them met criteria for entry into the run-in phase of the study, successfully completed the run-in phase and subsequently met criteria at the baseline visit for randomization into the treatment phase of the study. The total number of screening and run-in failures was 134 patients. The ITT Efficacy population consisted of 307 Ss. The table below provides descriptive statistics, as provided by the sponsor, regarding the disposition of the 307 Ss of the ITT Safety population.

Reasons for Patient Withdrawal

	Placebo (N= 156)		Paroxetine (N= 151)		Total (N= 307)	
Reason for Study Conclusion	**n**	**%**	**n**	**%**	**n**	**%**
Total Completers*	94	60.3	93	61.6	187	60.9
Adverse experience**	10	6. 4	18	11.9	28	9. 1
Lack of efficacy	8	5. 1	3	2. 0	11	3. 6
Deviation from protocol (including non- compliance)	16	10.3	16	10.6	32	10.4
Lost to Follow- up	17	10.9	16	10.6	33	10.7
Other reasons	11	7.1	5	3.3	16	5. 2
Total Withdrawn	62	39.7	58	38.4	120	39.1

** Includes one patient in the paroxetine group (648.830.01468) and one patient in the placebo group (648.810.00501) that withdrew due to adverse experience that began during the single- blind placebo run- in phase; one patient in the placebo group (648.808.00401) that withdrew due to adverse experience that began after study medication was stopped.

118 out of the 307 (38.7%) randomized Ss were identified as protocol violators (40% of placebo Ss and 36% of paroxetine Ss), as defined by criteria also employed in Study 651 described above. Treatment groups were similar in the incidence of violators for each type of violation. The majority of protocol violations were due to non-compliance during the study (27%), having < 2 weeks on randomized study drug (12%), or use of excluded medication (11%). A few Ss were protocol violators due to receiving disability payments or having an insufficient baseline CAPS-2 score.

7.2 H. Study 648. Baseline Demographics/Severity of Illness

Demographic Characteristics. The treatment groups were similar on various demographic variables including mean age, age-group distribution, gender, mean weight, and racial distribution. There was a predominance of Caucasians (69 to 76% in each group), women (approximately 66%) and Ss under 65 years old (99%) in each treatment group. The mean ages and standard deviations (SD) of the paroxetine and placebo groups were 42±11 years and 40±12 years, respectively. The mean weight ±SD, and the mean height ± SD of each group was

approximately 78±19 or ±21 kg and 168 cm ±9 or 10 SD, respectively. The racial distribution was as follows: 69-76% Caucasians, 12-17% African American, 1% Asian and 15-19% "other".

Medical Comorbidity. Treatment groups were generally similar on the number Ss with active medical disorders/conditions, as well as on the type of conditions. The most common (defined as an incidence of ≥10%) current "active conditions" were as follows with the range of percentages of affected Ss among the groups indicated in parentheses (psychiatric conditions are provided in the next section):

- Headache (13-16%)
- Hypertension (10-12%)
- Allergic rhinitis (10-12%)
- Migraine (8-10%)

Hypothyroidism was an active condition in approximately 3 and 6% of Ss in the paroxetine and placebo groups, respectively. Other conditions occurring in at least 5% but less that 10% of Ss in any treatment group included (psychiatric conditions are not included, but described in the next section): adverse effect/antibiotic, asthma, heartburn, athropathy, back pain, adverse effect/analgesic, genital female disorder/other, visual disturbances, and diabetes mellitus.

Psychiatric Comorbidity and Baseline Scores of Efficacy Rating Scales.
The following lists psychiatric conditions that were indicated in the submission as "active medical conditions" occurring in at least 5% of Ss in any given group:

- Stress reaction (incidence of 90-94% across treatment groups)
- Depression (7%)
- Neuroses (6-5%)
- Psychoses, Affective (3-6%)

Regarding the incidence of "non-predominant secondary psychiatric conditions", as determined by MINI at screening, the majority of Ss (33 and 37% of placebo and paroxetine Ss, respectively) had Major Depressive Disorder. Dysthymia, "Suicidality", and various anxiety disorders were also common, as shown in the table similar to that provided by the sponsor, below.

Number (percentage) of Subjects with a "Secondary" Psychiatric Disorder

Psychiatric Histories* n (%)	Placebo (N= 156)	Paroxetine (N= 151)
Major Depressive Disorder	52 (33.3)	56 (37.1)
Generalized Anxiety Disorder	24 (15.4)	25 (16.6)
Dysthymia	16 (10.3)	25 (16.6)
Suicidality	23 (14.7)	22 (14.6)
Agoraphobia	15 (9. 6)	21 (13.9)
Panic Disorder	18 (11.5)	15 (9. 9)
Social Anxiety Disorder	16 (10.3)	11 (7. 3)
Obsessive Compulsive Disorder	4 (2. 6)	3 (2. 0)
(Hypo) Manic Episode	2 (1. 3)	2 (1. 3)
Alcohol (Dependence/ Abuse)	2 (1. 3)	2 (1. 3)
Substance (Dependence/ Abuse)	1 (0. 6)	1 (0. 7)

*As assessed by the MINI. Patients may have more than one disorder.

The mean duration of PTSD symptoms for Ss of this study pooled with Ss of Study 651 was approximately 13 years, as previously indicated. The treatment groups were generally similar in mean total scores of various efficacy measures at baseline (CAPS-2, DTS, TOP-8, SDS and MADRS total scores) and in the baseline median score on CGI-S, as shown in Table 7.1.3 in the appendix.

The treatment groups were similar on the mean, median and of years since the trauma, as shown in the table below, as provided by the sponsor. The majority of the Ss in each group had a history of physical or sexual assault (approximately 50% in each group), while approximately 18% in each group had witnessed the trauma. The table below summarizes the number and percentage of Ss with a given type of trauma in each group (similar to that provided by the sponsor).

Psychiatric and Psychopharmacologic History (ITT)

PTSD History	Placebo (N= 156)	Paroxetine (N= 151)
Time since trauma (yrs)		
N	154	150
Mean (SD)	15.5 (14.8)	14.2 (12.3)
Median	8.6	11.4
Range	0.3 – 57.30	0.1 – 52.67
Trauma Type n (%)		
Physical or Sexual Assault	79 (50.6)	72 (47.7)
Seeing someone hurt or die	29 (18.6)	29 (19.2)
Serious accident/ fire/ injury	12 (7. 7)	20 (13. 2)
Being in a war or combat	11 (7. 1)	10 (6. 6)
Natural disaster	0 (0. 0)	2 (1. 3)
Other	25 (16.0)	18 (11.9)

7.2 I. Study 648. Concomitant Medications

The number (percentage) of Ss reporting concomitant medications during the treatment phase of the study was 129 (83%) and 120 (80%) of Ss in the placebo and paroxetine groups, respectively. The percentages and distribution of Ss among the more commonly used medications were similar to that observed in Study 651, in which the most commonly reported concomitant medications were analgesics (paracetomol, Ibuprofen, acetylsalicylic acid) and vitamins. Estrogen-like compounds were also among the most commonly reported concomitant medications which included Ethinylestradiol (used in 6% and 10% of placebo and paroxetine Ss, respectively), conjugated estrogens (5% in each group), contraceptive agents (5% in each group), among other less commonly used sex hormonal agents. Caffeine intake was reported in 5 and 6% of paroxetine and placebo Ss, respectively and levothyroxine Na use was reported in 3% and 5% of Ss in the paroxetine and placebo groups, respectively.

7.2 J. Study 648. Efficacy

Primary Efficacy Variables.

1. **The mean change from baseline to treatment endpoint (in adjusted least square means) on the CAPS-2 total score.**

The following results are the least square means adjusted for treatment, center, gender, baseline total Caps-2 score, trauma type, time since last trauma and MADRS score at baseline. The

paroxetine group (-35.5±2.0, N=136) showed significantly greater improvement ($p<0.001$ for each comparison) on the CAPS-2 total score than the controls (-24.7±2.0, N=133 in the placebo group) for the LOCF dataset. Similar results were obtained for the OC dataset and for the PPP in both LOCF and OC datasets (LOCF of the PPP: mean change of –25.4±2.5, N=92 in the placebo group, -37.8±2.0, N=93 in the paroxetine group, $p<0.001$; OC of the PPP: $p<0.001$ for the placebo to paroxetine group pair-wise comparison). Table 7.2.1 A (as provided by the sponsor) in the appendix shows the mean change from baseline of the CAPS-2 total score at each week for each treatment group of the ITT efficacy population for the LOCF and OC datasets.

2. The Proportion of Responders on the CGI-I (responders are those with a week 12 endpoint CGI-I score of 1 or 2; very much improved or much improved, respectively).

The percentage of responders in the paroxetine group was 59% contrasted to 38% of responders in the placebo group (ITT LOCF dataset). The odds ratios representing the odds of responders (adjusted for treatment, center and covariates) with paroxetine relative to the placebo treatment was significantly in favor of paroxetine treatment using a 95% confidence interval ($p<0.001$). The percentage of responders provided for each group is adjusted for treatment, center and covariates using a logistic regression analysis, as previously described. Refer to Table 7.2.1 B (as provided by the sponsor) in the appendix, which shows results for the LOCF and OC datasets for the ITT population. Similar results were obtained when analyzing the LOCF and OC datasets of the PPP in which each paroxetine to placebo group comparison yielded a p value of less than 0.001.

Covariate by treatment interaction effects on the primary efficacy variables.

a. Change from Baseline on CAPS-2 Total Score.

A statistically significant (pre-defined as $p<0.10$) treatment by time since trauma interaction effect was observed ($p=0.037$, week 12 LOCF). To further examine this interaction effect the sponsor subcategorized Ss into three groups based on time since trauma as follows: < 5 years, 5 to < 20 years, ≥ 20 years since the time of the trauma. Each subgroup was analyzed separately to determine which subgroup showed treatment group effects, using the same statistical methods previously employed for this subcategorization of Ss. The group with the longest duration since the trauma (>20 years) showed the most robust and significant improvement in the paroxetine compared to the placebo group on the primary efficacy variable ($p=0.001$ at week 12, $p=0.01$ or 0.02 for weeks 8 and 4, respectively). This effect appeared to increase with increasing duration of treatment. The group with trauma occurring < 5 years ago, failed to show significant treatment effects (p values ranged from 0.5 to 1.0 at weeks 4, 8 and 12), while trends for a treatment effect was found for the subgroup having trauma 5 to<20 years ago (p values ranged from 0.03 to 0.07 at weeks 4, 8 and 12). These results which are of the LOCF ITT dataset, as well as those of other ITT datasets are shown in more detail in Table 7.2.2 in the appendix, which was provided in the submission.

The sponsor notes that a greater percentage of Ss who withdrew from the study who were in the < 5 years since time of trauma subcategory compared to the placebo group of this subcategory and compared to other groups in the other two subcategories, as suggested by that shown in the table below (provided in the submission).

Percentage of data carried forward in the week 12 CAPS- 2 Analysis by Time Since Trauma
(Intent- to- Treat population)

Treatment group:	Paroxetine			Placebo		
Time Since Trauma Subgroups:	< 5 years	5 to < 20 years	≥ 20 years	< 5 years	5 to < 20 years	≥ 20 years
% of CAPS- 2 data carried forward from earlier visits in the week 12 LOCF dataset:	48.9%	32%	26.8%	29.8%	30.6%	32.7%

The sponsor concludes that the "effect of the withdrawals, combined with the LOCF methodology, contributed to" differential treatment effects observed among the time-since-trauma subcategories. The submission does address other potential confounding variables (i.e. type of trauma) that might vary among the time-since trauma subgroups to explain the time-since-trauma by treatment interaction effect. However, in the original analysis of the dataset prior to subcategorization by time since trauma, type of trauma, among other covariates were not found to show a significant interaction effect with treatment on the primary efficacy variable.

A treatment by center interaction effect was observed (p=0.09, week 12 LOCF). Four of the 18 study site groups showed greater improvement in placebo Ss compared to paroxetine Ss. The submission does not provide an explanation for this observation and the data was reanalyzed considering center and treatment by center interaction effects as random, while other covariates were considered fixed effects. When the LOCF ITT dataset was reanalyzed with this assumption and using a model that weighted treatment effects to account for the observed heterogeneity, the resulting adjusted mean difference between paroxetine and placebo was –10.4 points at week 12 (95%CI of -16.9 to –3.9, p=0.003).

b. Proportion of Responders on the CGI-I.

A significant treatment by type of trauma interaction effect was observed (p=0.019, week 12 LOCF ITT). The "seeing someone hurt or die" category showed a robust and highly significant (p<0.001) treatment effects reflected by the odd ratio of 15.8 (the odds of a response in paroxetine relative to that of placebo treatment). Other categories only showed trends for an odds ratio favoring paroxetine over placebo treatment. Most of the Ss (making up the Week 12 LOCF ITT dataset) were in the "seeing someone hurt or die" (N=23) or "physical assault" (N=36) categories. All other categories were small ranging from 6 to 11 Ss, in each category whereby a Type II error of accepting the null hypothesis is more likely to occur. These other categories, as well as the physical assault category showed odds ratios ranging from 0.7 to 2.5 (p values ranging from 0.5 to 0.08) which included the following categories: physical assault (N=36), serious accident/fire/injury (N=11), being in combat, (N=6) other which included natural disaster (N=11).

A significant study site by treatment interaction effect was reported on the percentage of CGI-I responders (p=0.07, Week 12 LOCF ITT dataset). Five of the 18 center groups did not show odds ratios in favor of paroxetine over placebo treatment. Three of these 5 sites were the same as the 4 sites that showed greater improvement on the CAPS-2 total score in placebo compared to paroxetine groups. An explanation for the observed interaction effect was not provided in the submission. When the data was re-analyzed considering the center by treatment and center effects as random effects in which treatment effects were weighted at each site to account for heterogeneity across sites, the odds ratio between paroxetine and placebo was 2.28

(Week 12 LOCF ITT dataset, p=0.005. This analysis was conducted using a generalized linear model fitted by the Schall (1991) method.

c. Examination of Gender Effects. For reasons previously described regarding Study 651, a more conservative statistical analysis was conducted by the statistical reviewer of the sponsor's dataset (ITT, LOCF dataset) to determine if gender by treatment interaction effects could be revealed that were not revealed by the sponsor's analyses considering gender as a covariate. The more conservative analyses revealed no gender by treatment interaction effects on the primary efficacy variables (refer to the Statistical Review of this submission).

Secondary Efficacy Variables.

The following were the secondary efficacy variables, which yielded similar results to those of the primary efficacy variables in which each paroxetine group were reported to show greater improvement compared to the placebo group:

- The mean change (from baseline to treatment LOCF week 12 endpoint) on additional scales or subscales: the DTS (self-rating scale) score and individual symptom clusters, SDS (work, social life, and family life), CGI-S, TOP-8, the MADRS and the Re-experiencing, Avoidance and Numbing, and the Hyperarousal clusters of the CAPS-2.
- The percentage of Ss with a TOP-8 score of <8 at treatment endpoint (week 12 LOCF endpoint).

Comparison of each paroxetine group to the placebo group on each secondary efficacy variable for the LOCF ITT dataset generally yielded a p value of less than 0.01 to 0.001. The SDS Individual scores showed trends for greater improvement in paroxetine compared to placebo groups with the p value generally being approximately less than 0.02. The sponsor did not correct for multiple comparisons.

Additional Subgroup Analysis Requested from the Sponsor on the Primary Variables.

As with Study 651, the potential for nonspecific effects (i.e. antidepressant and non-PTSD anxiolytic effects) of paroxetine treatment on the primary efficacy variables in PTSD Ss needs to be considered. As observed in the study population for Study 652, a number of Ss in the present study had concomitant Major Depressive disorder and/or non-PTSD anxiety disorders. Given these considerations, the sponsor was asked to conduct a subgroup analysis of the LOCF ITT dataset, as described in the results Section 7.1 J 4 for Study 651. This analysis was conducted as an effort to determine if significant treatment effects could be observed, independent of or in the absence of concomitant non-PTSD psychopathology, such as Major Depressive disorder, non-PTSD anxiety disorders or a baseline MADRS score of ≥ 21.

Results of the Subgroup Analysis. Results of the subgroup analysis, as previously described, generally revealed results similar to that observed in Study 651. Significantly greater improvement on each of the primary efficacy variables in the paroxetine group compared to placebo was generally observed, while subgroup main effects (p values of 0.3 to 0.9) or subgroup by treatment interaction effects (p values of 0.1 to 1.0) were absent for each subgroup analyses. Furthermore, when analyzing the data of subgroups that were free of concomitant psychopathology (i.e. non-PTSD Anxiety disorders and/or Major Depressive disorder, or a baseline MADRS score of < 21), significant treatment effects were still observed for each of the primary efficacy variables in favor of paroxetine treatment. The difference between the paroxetine and placebo groups on the mean change (from baseline to treatment endpoint, LOCF

ITT population) in CAPS-2 total score in concomitant psychopathology free subgroups ranged from –7.3 to –11.3 score points (adjusted for various covariates as previously described) which were significant (p values of 0.03 to 0.001). The odds ratio of paroxetine to placebo treatment on the proportion of CGI-I responders ranged from 2.0 to 3.0 which were significant (p values of 0.01 to 0.001). A trend for an interaction effect between the presence versus absence of non-PTSD anxiety disorders and treatment effects was observed for the mean change in CAPS-2 score (p=0.053, F=3.80, df=1) in which it appeared that a more robust treatment effect was observed in the subgroup with concomitant non-PTSD anxiety disorders compared to the subgroup free of non-PTSD anxiety disorder. These results are provided in a table below, as provided by the sponsor:

Summary of the Change from Baseline in CAPS- 2 Analyses of Subgroups With or Without Concomitant Non-PTSD Anxiety Disorder (non-PTSD AD presence or absence, respectively)*

non- PTSD AD Subgroup	Treatment	N	Unadjusted Mean	Std Error	Treatment difference	95% confidence interval	P- value
Presence	Paroxetine	37	-41.16	3.88	-20.04	[- 31.09, -9.00]	<0.001
	Placebo	33	-22.48	4.07			
Absence	Paroxetine	99	-33.41	2.24	-7.32	[- 13.82, -0.81]	0.028
	Placebo	100	-25.39	2.33			

these analyses, as described in the text above, are based on a week 12 LOCF endpoint and are adjusted for gender, baseline MADRS, time since trauma, trauma type, country group, non- PTSD AD and non- PTSD AD treatment interaction (also see text above)

Refer to the Statistical Reviewer's (Dr. Lu Cui) review regarding these results.

7.2. K. Study 648. Conclusions

The study showed significant treatment effects in favor of paroxetine treatment compared to placebo on the primary efficacy variables and at least trends for a favorable outcome on various secondary efficacy variables, including the Re-experiencing CAPS-2 symptom cluster, which includes cardinal symptoms of PTSD. Given the potential that known antidepressant or non-PTSD specific anxiolytic effects of paroxetine treatment may underlie the observed treatment effects in Study 648, the sponsor was asked to conduct a subgroup analysis, like that employed for Study 651. The ITT LOCF dataset was analyzed as an attempt to reveal subgroup main effects or subgroup by treatment interaction effects for subgroups with or without concomitant psychopathology (i.e. non-PTSD Anxiety disorders and/or Major Depressive disorder, or a baseline MADRS score of ≥ 21). Although results of these *post hoc* subgroup analyses must be interpreted with caution, the analyses revealed evidence suggesting a treatment effect in favor of paroxetine that appears to be independent of the presence versus absence of concomitant non-PTSD anxiety and/or major depressive disorders. While a trend was observed for a treatment by non-PTSD anxiety disorder (presence versus absence) subgroup effect, a similar analyses of the data from Study 651 failed to reveal even a trend for such an interaction effect. Therefore, the observed interaction effect does not appear to be reproducible and may be a Type I error given that this was a *post-hoc* analyses involving multiple tests and subgroup comparisons. Also refer to Dr. Lu Cui's Statistic Review.

A significant center group by treatment interaction effect was observed on both primary efficacy variables (mean change on CAPS-2 total score and % of CGI-S responders). For results of each primary efficacy variable, 3 or 5 center group sites out of a total of 18, failed to show an outcome favorable to paroxetine treatment over placebo. Some of these sites showed an outcome in the direction opposite to that hypothesized (placebo treatment showed greater improvement than paroxetine treatment). The sponsor was not able provide an explanation for these observations. However, when the data were re-analyzed with the assumption that the center and center by treatment interaction effects were random effects and treatment effects were weighted accordingly, a treatment effect was still observed at level of significance of p less than 0.01. Also refer to Dr. Cui's statistical review.

Time-since-trauma was found to significantly influence treatment effect on the mean change (from baseline to the 12-week treatment endpoint) of the CAPS-2 total score, whereby the most robust and significant treatment effect was observed in the subgroup with the longest time since trauma (≥20 years of time-since-trauma). The subgroup with < 5 years of time-since-trauma showed the least improvement in the paroxetine compared to placebo groups which did not reach a level of significance. The intermediate subgroup (≥5 to 20 years of time-since-trauma) appeared to show an intermediate trend for greater improvement in the paroxetine group relative that that observed in the other two time-since-trauma subgroups. Given the potential bias in post-hoc subgrouping of the study population, coupled with the potential for a sample size effect that may result in a Type II error, these results are difficult to interpret.

A significant type-of-trauma by treatment interaction effect was reported for one of the primary efficacy variables, the percentage of CGI-I responders. The most robust and highly significant treatment effects were observed in the subgroup "seeing someone hurt or die" in contrast to other subgroups. These results are also difficult to interpret for reasons similar to those previously described regarding other interaction effects observed in the study.

Upon consultation with the Statistical Reviewer, Dr. Lu Cui, regarding the above observed interaction effects, it appears that the results are difficult to interpret and may not be reflecting real interaction effects. Sample sizes were small and selection bias is introduced upon an arbitrary subgrouping of the study population. The sample sizes of treatment groups within each center grouping were small, typically with only a few Ss and generally no more that 10 Ss. Most of the other subcatogorizations (subgrouped by time-since-trauma or by type-of-trauma) also resulted sample sizes that were insufficient to allow for clear interpretation of the findings. Consequently a sample size effect may have resulted in the failure to observe significant treatment effects in all subgroups and a selection bias of arbitrary subgroupings may lead to misleading conclusions. Furthermore, Dr. Cui conducted several statistical analyses to explore possible explanations for the observed interaction effects. The results of this analyses suggest that the chance of finding significant site, time-since-trauma, and type of trauma by treatment interaction effects is high and these effects cannot be explained qualitatively. Refer to the statistical review for further details.

A few points regarding the baseline demographic characteristics of the study population of Study 648 contrasted to that of the other two studies, Studies 651 and 627 are noted. The study population for Study 648 had 12-17% of Non-Caucasians, primarily the African American, which shows at least a trend for a greater percentage of African American compared to that observed in the other two studies (4-7% in Study 651 and 3-4% in Study 627). Upon inspection of Table 7.1.3 (shows the mean baseline scores on various efficacy measures), the baseline mean MADRS score shows at least a trend for being less in the study population in Study 648 (mean

total scores of 21 to 22) than that of the other two studies (mean total scores of 24 to 26 in Studies 651 and 627). Despite these small differences the results of the three studies are generally similar, as described in later sections of this review.

Given the above observations, the overall conclusion regarding Study 648 is that results support an overall claim that paroxetine treatment is indicated for the treatment of patients with PTSD.

7.3 Study 627. A 12-Week, Randomized, Double-blind, Placebo Controlled, Flexible Dosage Trial to Evaluate the Efficacy and Tolerability of 20 to 50 mg/day Paroxetine in Patients with PTSD; 29060/627.

7.3 A. Study 627. Investigators and Sites

The multi-center study was conducted in 44 European sites (Belgium, Canada, Netherlands, South Africa, Israel, Switzerland, UK, Ireland, France, Germany, Austria, and Italy). A listing of the sites and investigators is provided in Table 7.1.1 C the appendix, as provided by the sponsor.

7.3 B. Study 627. Objectives

The primary and secondary objectives were the same as those for Studies 651 and 648, which were to examine efficacy and safety/tolerability, respectively, of paroxetine versus placebo in the treatment of PTSD.

7. 3 C. Study 627. Study Population

322 Ss (the randomized population) met eligibility criteria for entry into the treatment phase of the study. The inclusion/exclusion criteria employed were similar to those of Studies 651 and 648. However, some differences are worth noting. One major difference is that patients with other Axis I disorders as the "primary diagnosis" were not excluded in Study 651 (as indicated in the submission and in the CRF form). Instead the criteria regarding other Axis I disorders only specifies the exclusion of Ss with substance abuse/dependence within 6 months of entry. Nevertheless, as later described in this review, the percentages and distribution of Ss with concomitant Axis I psychiatric disorders is similar to that observed in the other two studies. These concomitant psychiatric disorders are specified in the submission as being "non-predominant" Another difference is regarding the required compliance during the treatment phase and the run-in placebo phase in which a maximum permitted cut-off for compliance (i.e. 120%, as employed in the other two studies) was not employed. Another potentially important difference from methods employed in other studies is that patients receiving herbal medications, such as St John's Wort, were excluded in the present study. Nevertheless, the actual number of Ss reporting concomitant or prior use of herbal medications in Study 627 was quite small (only a few Ss).

Another potentially important difference regarding selection of Ss involves the exclusion of Ss with potential or actual secondary gain associated with having the disorder of PTSD. The exclusion criterion employed in Study 627 regarding this issue is specified as follows: "In the opinion of the investigator, were likely to exaggerate or falsify the symptoms of PTSD or other related psychiatric disorders for financial or personal gain". The wording of this exclusion criterion appears vulnerable to investigator differences in making such a judgement.

This is contrasted to the wording of exclusion criteria employed in the other two studies, which were specified as follows:

- "Patients receiving disability payments because of PTSD or any other psychiatric disorder"
- "Patients engaged in compensation litigation whereby personal gain would be achieved from prolonged symptoms of PTSD or any other psychiatric disorder".

The above criteria appear to be more clearly and operationally (objectively) defined, rather than involving "the opinion of the investigator".

7. 3 D. Study 627. Design

The study employed a double-blind, randomized, placebo controlled flexible dosage trial design in which Ss were either randomized into a placebo group or a paroxetine group (daily oral dose of 20 to 50 mg). The methods employed in this study were the same as those employed in Study 648 with a few exceptions. These exceptions included potentially important differences between Study 648 and the other two studies regarding specific exclusion criteria, as already described in this review (see the previous section, Section 7.3 C.). Other exceptions were regarding follow-up of Ss after the treatment phase, and the frequency of several assessments. Regarding frequency of assessments, several efficacy assessments and vital signs were conducted more frequently during the treatment phase of Study 627. Laboratory and ECG assessments were not conducted on the taper end visit. Regarding the follow-up of Ss, the protocol for Study 627 was amended in June of 1998 (study was approved in April 1998) to insert a Taper Phase visit and to more clearly specify the time-frame for the follow-up visit. The time frame was clarified as being required within 14±3 days since the last dose of the study drug, as employed in the other two studies. This amendment did not include Germany and Austria.

Protocol amendments. Several protocol changes were made prior to the study completion dates of July of 1998 at Austria/Belgium/Canadian sites and January of 2000 for other sites. Note that the study was approved on April '98.

The amendments are listed below (date of the amendment are also indicated):

1. The sponsor inserted a taper phase visit and a specified time frame for the follow-up visit to be 14±3 days after last dose in June of 1998.
2. In August of 1998 the sponsor changed the duration of the illness required in a S to be eligible, from 6 months to 3 months, "to align all centers with DSMIV criteria."
3. Nov. 1998: The sponsor changed the duration of the required benzodiazepine washout period from 14 days (as employed in 651 and 648) to 7 days.
4. In Nov. 1998 the sponsor clarified "the investigator judgement required when responding to the exclusion criteria" regarding compensation, litigation and disability payments.

7. 3 E. Study 627. Assessments

Assessments conducted for this study were identical to those employed in Studies 651 and 648, with some exceptions regarding the frequency of some of the assessments and in the follow-up of Ss, as already described. Refer to Table 7.1.2 in the appendix for the assessment schedule, as provided by the sponsor.

7. 3 F. Study 627. Analysis Plan

The primary efficacy variables were the same as those in the other two completed studies (651 and 648). The secondary efficacy variables included those of the other study, along with

additional variables (such as symptom clusters of the DTS) or additional time points between baseline and treatment endpoint (not just the change from baseline to treatment endpoint) that were not employed in the other two studies. The statistical methods employed in study 627 were generally the same as those employed in the other two studies.

7. 3 G. Study 627. Patient Disposition

394 patients were entered into the study, of which 322 of them were randomized into the treatment phase of the study. The table below provides descriptive statistics regarding the disposition of Ss in the ITT population, as provided by the sponsor. Presumably the overall sample size provided in the table for each group is that of randomized Ss rather than that of the ITT population, since the total number shown in the table is 322, which is identical to the number of randomized Ss, as above.

The Number (%) of Randomized Patients who Completed the Study or were Withdrawn by the Reason for Study Withdrawal: ITT Population

	Treatment Group		
	Paroxetine	**Placebo**	**Total**
	(N = 160)	**(N = 162)**	**(N = 322)**
Study Conclusion Reason	**n (%)**	**n (%)**	**n (%)**
Completed Study*	111 (69.4)	106 (65.4)	217 (67.4)
Withdrawal Reason			
Adverse Experience**	16 (10.0)	9 (5.6)	25 (7. 8)
Lack of Efficacy	3 (1.9)	10 (6. 2)	13 (4. 0)
Deviation from Protocol+	15 (9. 4)	20 (12.3)	35 (10.9)
Lost to Follow- up	12 (7. 5)	12 (7. 4)	24 (7. 5)
Other Reason++	3 (1.9)	5 (3.1)	8 (2.5)
Total Withdrawn	49 (30.6)	56 (34.6)	105 (32.6)

*A patient was considered to have completed the study if they completed the active treatment phase of the study, i. e. completed all visits up to the end of week 12
** Including death as an outcome
+Including non- compliance
++ Includes unknown and non- study- related personal reasons

A total of 110 Ss of the ITT population were protocol violators (34% of the paroxetine ITT Ss and 35% of the placebo ITT Ss). The percentage of protocol violators and distribution of Ss across various categories of protocol violations between treatment groups were similar when comparing treatment groups and to that observed in the other two studies (based on visual inspection of the descriptive data provided in the submission). However, some differences between studies should be noted. Ss in Study 627 were not required to have at least 2 weeks of exposure to the randomized study medication to be included in the per protocol population (PPP), unlike that of Ss in the other two studies. Hence, the majority of protocol violators in Study 627 did not include Ss with less than 2 weeks of the study medication, but were primarily Ss who were non-compliant (22% in each group) and due to excluded medication (11 and 12 % in paroxetine and placebo groups, respectively). Secondly, Study 627 did not include a maximum cut-off for compliance of the study medication (i.e. 120%) that in the other two studies was employed. Nevertheless, the percentage of non-compliant Ss in Study 627 (22%/group) was similar to that observed in the other two studies (20 to 27%). A few Ss in each treatment group of Study 627 made other violations such as not meeting criteria regarding the

baseline CAPS-2 score, not meeting CAPS-1 criteria, or were receiving disability compensation. Despite some differences between this study and the other two studies regarding criteria for protocol violators, descriptive statistical results of the these three studies were in general, similar.

7. 3 H. Study 627. Baseline Demographics/Severity of Illness

The treatment groups were similar on various demographic variables including mean age, age-group distribution, gender, mean weight, and racial distribution and showed a predominance of Caucasians (92 to 93% in each group) and Ss under 65 years old (97-99% in each group). However, there were several differences (at least trends for differences) between this study and the other two studies (651 and 648) on several demographic parameters. The number of men and women in each group was almost equal in which the percentages of women in the paroxetine and placebo groups were 53% and 54%, respectively. This is in contrast to the other two studies, which had at least 66% women in each group. The mean age (±SD) was also slightly less (mean ages of 40±12 and 39±12 years of the paroxetine and placebo groups, respectively), but not significantly less, than that of Ss in the other two studies (mean age was approximately 42 years. Finally, the mean weight ±SD of each group in Study 627 was approximately 74±17 kg compared to mean weights of approximately 78±19 kg and 82±22 kg in Studies 648 and 651, respectively. However, the mean height of Ss in each of the three studies was similar (approximately 168±10 cm). The racial distribution in Study 627 was as follows: 92-93% Caucasians, 3-4% African Americans, 1% Asian and 3-4% "other".

Medical Comorbidity

The most common active illness in paroxetine Ss was headache reported in 12% compared to 7% of placebo Ss. Hypertension was reported in 7% of Ss in each group. All other non-psychiatric illnesses were reported in 0 to 4% of Ss/group (see the next section for psychiatric conditions listed as "active conditions" in the submission). These observations are contrasted to those of the other two studies, which appeared to show upon visual inspection of the results, a higher incidence of other active non-psychiatric conditions such as migraine, allergic rhinitis, genital female disorder/other, among others.

Psychiatric Comorbidity and Baseline Scores of Efficacy Rating Scales

The following psychiatric conditions were three most common conditions listed among "active medical conditions" in the submission (percentage of Ss with each condition per treatment group or the range of the percentages of Ss among the groups is provided):

- Stress Reaction (99%)
- Depression 18-21%)
- Neuroses (9-11%)
- Anxiety (6%)

Regarding the incidences of "non-predominant secondary psychiatric conditions", as determined by MINI at screening, treatment groups were generally similar on each psychiatric condition. However, the incidence of agoraphobia showed at least a trend for being greater in paroxetine Ss compared to placebo Ss (24% and 15%, respectively). A similar trend also seems to exist when comparing treatment groups in Study 648 and possibly between the placebo and high dose paroxetine group of Study 651. Since agoraphobia was diagnosed on the basis of the MINI at screening, there is no apparent explanation for this observed distribution of Ss with

agoraphobia among the treatment groups other than it being due to chance alone. The predominant concomitant, "non-predominant" psychiatric disorder among Ss in Study 627 (in descending order in the paroxetine group) was Major Depressive Disorder, followed by agoraphobia, "Suicidality", other various anxiety disorders and Dysthymia, as shown in the table below (the table is similar to that provided by the sponsor).

As previously indicated in this review, the eligibility criteria employed in Study 651 (in the submission and in the CRF form), does not include the exclusion criterion that patients who have another Axis I disorders as their "primary diagnosis" be excluded from the study. This omission is contrasted to the methods employed in the other two studies, which excluded these patients. Nevertheless, upon inspection of the table below, the percentages and distribution of Ss with various Axis I concomitant psychiatric disorders, referred in the submission as "non-predominant secondary" disorders, is generally similar to that observed in the other two studies.

Incidence (Secondary Psychiatric Comorbidity by Treatment group : ITT Population

	Paroxetine (N = 160)	Placebo (N = 162)	Total (N = 322)
Psychiatric Comorbidity*			
Major Episode of Depression	79 (49.4)	79 (48.8)	158 (49.1)
Agoraphobia	38 (23.8)	24 (14.8)	62 (19.3)
Suicidality	33 (20.6)	31 (19.1)	64 (19.9)
Generalized Anxiety Disorder	29 (18.1)	36 (22.2)	65 (20.2)
Panic Disorder	25 (15.6)	27 (16.7)	52 (16.1)
Dysthymia	18 (11.3)	14 (8. 6)	32 (9. 9)
Social Phobia	159. 4)	13 (8. 0)	28 (8. 7)

Patients could have more than one psychiatric comorbidity and could have taken more than one previous psychoactive medication

*As assessed by the MINI. The incidences of Eating disorders, (hypo) Manic Episode, Obsessive Compulsive disorder, somatization disorder, and alcohol abuse/dependence disorder ranged from 0 to 3% in any given group.

The duration of PTSD symptoms in Ss of this study was not recorded and is therefore unknown. The treatment groups were generally similar in mean baseline total scores on various efficacy rating scales (CAPS-2, DTS, SDS, TOP-8 and MADRS total scores) and in the baseline median score on CGI-S, as shown in Table 7.1.3 in the appendix (as provided in the submission). However, upon inspection of Table 7.1.3 the Ss showed at least a trend for higher mean scores on the various efficacy scales, some of which may be significantly higher than in Ss of the other two studies. The magnitude of the difference between mean scores in Study 627 compared to the other studies was small (generally only a few units on a given efficacy measure). Furthermore, the median CGI-S in this study was similar (5 units out of a maximum score of 7 units) to that of the other studies (4-5 units).

The mean and median years since the time of the trauma were similar when comparing the treatment groups. However, when compared to that observed in the other two studies, these parameters were approximately 2 fold (for the mean years) to 5 fold (for the median years) shorter in duration in Study 627. The table below, as provided by the sponsor, shows the various parameters regarding the time since the trauma and the percentage of Ss with each type of trauma. The incidences by type of trauma are generally similar between treatment groups. However, when contrasted to the other two studies the incidence of Ss in the "serious

accident/fire/injury" category is 20-25% among the groups in contrast to the incidence observed in Studies 648 and 651, in which the incidences ranged from 6% to 12%.

Summary of Time Since Trauma and Number (%) of Patients by Trauma Type and by Treatment Group : ITT Population

	Treatment Groups		
	Paroxetine	**Placebo**	**Total**
PTSD History	**(N = 160)**	**(N = 162)**	**(N = 322)**
Time Since Trauma (yrs)			
Mean (SD)	7.6 (11.4)	5.9 (7. 9)	-Median
	2.9	2. 6	-Range
	0. 3 – 56.7	0. 3 – 40.5	-Trauma
Type n (%)			
Physical or sexual assault	70 (43.8)	65 (40.1)	135 (41.9)
Seeing someone hurt or die	25 (15.6)	33 (20.4)	58 (18.0)
Serious accident/ fire/ injury	32 (20.0)	41 (25.3)	73 (22.7)
Being in a war or combat	12 (7. 5)	9 (5.6)	21 (6. 5)
Natural Disaster	3 (1.9)	1 (0.6)	4 (1.2)
Other	18 (11.3)	13 (8. 0)	31 (9. 6)

7. 3 I. Study 627. Concomitant Medications

Only 56% of placebo Ss and 60% of paroxetine Ss used concomitant medication in contrast to 80 to 86% of Ss in the treatment groups in the other two studies (651 and 641). The commonly reported medications were the analgesics, Paracetamol (25% and 29% in placebo and paroxetine Ss, respectively), acetylsalicylic acid (in 7 and 12% of Ss among the groups, respectively), and ibuprofen (7 and 8%, respectively). Codeine phosphate use was reported in 8 and 12% of Ss in each group, respectively. Caffeine was also common, as it's use was reported by 8% and 12% of Ss in each group, respectively. Hormonal agents, ethinylestradiol (7 and 10%, respectively), levonorgestrel (3 and 6%, respectively) were also common concomitant medications.

7. 3 . Study 627. Efficacy Results

Primary Efficacy Variables.

1. **The mean change from baseline to treatment endpoint (in adjusted least square means) on the CAPS-2 total score.**

The following results are the least square means adjusted for treatment, center and the covariates: gender, baseline total Caps-2 score, trauma type, time since last trauma and MADRS score at baseline. The paroxetine group (-30.8±2.1, N=154) showed at least a trend for greater improvement ($p<0.05$) on the CAPS-2 total score than the controls (-26.2±1.9, N=159) for the LOCF ITT dataset. Similar results were obtained for the OC dataset ($p=0.07$) and for the PPP in both LOCF and OC datasets (LOCF of the PPP: -30..0±2.4, N=105 in the placebo group and –35.5±2.6, N=104 in the paroxetine group, $p=0.06$; OC of the PPP: mean change of –32.4±2.7, N=83 in the placebo group, -38.6±2.8, N=88 with $p=0.08$, in the paroxetine group). Table 7.3.1 A (as provided by the sponsor) in the appendix shows the mean change from baseline of the CAPS-2 total score at each week for each treatment group of the ITT efficacy population for the LOCF and OC datasets.

2. **The proportion of Responders on the CGI-I (responders are those with a week 12 endpoint CGI-I score of 1 or 2; very much improved or much improved, respectively).**

50% of paroxetine Ss were CGI-I responders and 44% of placebo Ss were responders (ITT LOCF dataset). The odds ratio (adjusted for treatment, center and covariates) of responders with paroxetine versus placebo treatment was 1.46 (p=0.12, using a 95% confidence interval). The percentages of responders provided for each group are adjusted for treatment, center and covariates using a logistic regression analysis, as previously described. Refer to Table 7.3.1 B (as provided by the sponsor) in the appendix, which shows results for the LOCF and OC datasets for the ITT population. Similar results were observed for the PPP dataset in which the odds ratios were 1.7 and 1.9 for Week 12 of the LOCF and OC datasets, respectively but did not reach a level of significance (OC week 12: p=0.053 and LOCF Week 12: p=0.1.

Covariate or site by treatment interaction effects on the primary efficacy variables. The sponsor reports a significant center by treatment interaction effect on both of the primary efficacy variables (p=0.0001 for the change in CAPS-2 total score, week 12 LOCF and p=0.09 for the odds ratios of the proportion of paroxetine versus placebo CGI-I responders, week 12 LOCF). The site groupings were by country in which some countries were combined when the sample sizes were small. The France center grouping showed an adjusted mean treatment difference of +27.5 (CI:11.9, 43.1) on the change in CAPS-2 score and an odds ratio of 0.2 for CGI responders in favor of placebo over paroxetine treatment while other country groupings generally showed values in the direction of favoring paroxetine treatment.

Interaction effects were not observed for the various covariates. A more conservative analyses was conducted by the statistical reviewer of this submission to determine if gender by treatment interaction effects could be revealed on the primary efficacy variables (ITT LOCF dataset) for reasons already described for Studies 651 and 648. No gender by treatment interaction effects were revealed.

Secondary Efficacy Variables. The following were the secondary efficacy variables, which yielded similar results to those of the primary efficacy variables in which each paroxetine group were reported to show greater improvement compared to the placebo group:

- The mean change (from baseline to treatment LOCF week 12 endpoint) on additional scales or subscales: the DTS (self-rating scale) score and individual symptom clusters, SDS (work, social life, and family life), CGI-S, TOP-8, the MADRS and the Re-experiencing, Avoidance and Numbing, and the Hyperarousal clusters of the CAPS-2.
- The percentage of Ss with a TOP-8 score of <8 at treatment endpoint (week 12 LOCF endpoint).

Trends for greater improvement on various secondary efficacy variables in the paroxetine group compared to the placebo group were generally observed (p ranging from 0.02 to 0.04). However, the treatment group differences on the mean change in the MADRS sore and in the CGI-S score did not approach significance (p values of 0.13 and 0.3, respectively) but the direction of the treatment group differences was in favor of the paroxetine group. Due to insufficient responses on the SDS work item (less than 80% of Ss responded), results of treatment group comparisons on this item and the SDS total score was not provided.

7. 3 K. Study 627. Conclusions

This study showed at least trends for greater improvement in the paroxetine compared to the placebo groups. The level of significance for mean change on the CAPS-2 total score (from baseline to week 12/treatment endpoint) was a p value of less than 0.05. The percentage of CGI-I responders was only 6% greater in the paroxetine compared to the placebo group, which was not significant based on the 95% confidence interval for a difference in the odd ratio estimates for responders in paroxetine relative to placebo groups. Various secondary efficacy variables showed results that were generally consistent with that observed for the primary efficacy variables.

Perhaps failure to show significant or more robust treatment effects is a consequence of potential methodological problems, possibly associated with previously described methodological differences between this study and the other two studies or due to some of the protocol amendments occurring during the study. One of the protocol changes included the need for clarification to investigators of the exclusion criterion regarding Ss with disability, litigation and compensation associated with PTSD. This criterion was worded in such a way as to be based upon the discretion of the investigator. Confusion over this issue may have resulted in the inclusion of Ss receiving compensation or other secondary gain for having PTSD, such that the S feared losing their PTSD-related compensation if they showed a positive response to treatment. Another protocol amendment, was the reduction from 6 to 3 months of the duration of PTSD symptoms required for eligibility for entry into the study. Studies, 651 and 648, which were positive studies on the primary efficacy variables, employed the 3 month duration of symptoms as part of the DSMIV criteria for PTSD in their original protocols. Perhaps, duration of symptoms played a role in failure of Study 627 to show significant treatment effects in contrast to the positive results of the other two studies. A recording of the actual duration of PTSD symptoms in the Ss of Study 627 was not included in the protocol for Study 627. Therefore, it is not clear how studies compared on actual mean or median duration of symptoms.

As in Study 648, significant treatment by site interaction effects on the primary efficacy variables were observed in the present study. However, the grouping of sites by countries appears arbitrary and the rationale for this type of grouping did not appear to be provided in the submission. Only one of the center groupings (France) appeared to deviate on treatment group differences on the primary efficacy variables from that observed at other sites. The reason for this deviation is unclear and is difficult to interpret given the large variance at each site on each efficacy parameter, along with other considerations. These other considerations involve potential sample size effects and the potential for creating a bias with the subcategorization of the study population, as previously described in reference to the interpretation of interaction effects observed in Study 651.

Overall, the results of this study fail to show significant treatment effects on both of the primary efficacy variables. Given potential methodological differences or problems associated with various protocol amendments, together with trends for a treatment effect in favor of paroxetine over placebo observed on most efficacy measures, this study appears to be a "failed" study, rather than a "negative" study. In other words, the failure to show significant efficacy effects on most of the efficacy measures in this study may be more related to methodological issues or potential underlying confounding variables, rather than due to a true absence in a treatment effect of paroxetine in patients with PTSD. Consequently, this study does not appear to provide evidence refuting an overall claim of paroxetine in the treatment of patients with PTSD, but simply fails to provide evidence supporting the claim.

8.0 Integrated Safety Information

The sponsor provides safety information for primarily the completed studies (Study 651, 648, and 627) described in the submission. The submission briefly describes an ongoing long term study being conducted in non-US countries (Study 650). Any deaths and serious adverse events reported to occur during Study 650 were also provided in the submission and are described below.

Safety analyses were conducted on the three completed studies in which the data from the ITT safety population (Ss receiving at least one dose of study drug and one post-dose efficacy assessment or had an adverse experience). This population consisted of at total of 1180 patients in the three 12 week trials in which 676 of them were in a paroxetine group and 504 of them were in a placebo group.

Safety assessments were primarily conducted at Screening, Week 12 of treatment or early termination, and if abnormal, were followed on Follow-up Day 14 (14±3 days after the last dose). If assessments were abnormal at follow-up another follow-up visit was required within 28 days of the 14 Day Follow-up visit. Adverse events were monitored at Baseline, Weeks 1, 2, 4 ,6, 8 and 12 of treatment or on early termination, Taper end visit, and Follow-up Day 14. If a S had an adverse event on this follow-up visit then an additional follow-up visit was required within 28 days.

8.1.1 Deaths

Studies 651, 648, and 627: There were two deaths (Ss 648.822.01061 and 627.605.01012) in the completed studies (Studies 651, 648, 627). One was due to suicide in a placebo S and the other was an "accidental overdose" in a paroxetine S. The paroxetine S (648.822.01061) was found dead in his truck on August 23, 1999, 21 days after cessation of treatment. No external cause of death could be identified. The patient had a history of asthma, left knee pain (torn medial meniscus) and seizure, and as below, a history consistent with alcohol abuse or dependence disorder. His concomitant medications were Albuterol, Vicodin and Motrin. However, the coroner's report indicated the cause of death as an accidental overdose of ethyl alcohol (a "concentration" of 0.37%) and paroxetine (a "concentration" of 0.58 ug/ml, note that Cmax for 30 mg/day after steady state in the labeling is 0.0617 ng/ml). Although the S reported no history of drug or alcohol abuse at screening, the narrative indicates that he had a history of alcohol abuse (he had several "DUI's" resulting in license suspension). This S had his last dose of study drug on Aug. 3, 1999 (week 6 of treatment) and was withdrawn from the study due to drinking and failure to cooperate. Laboratory values on his early withdrawal visit on August 19th were unremarkable except for an elevated SGOT of 95 U/l (16.0-46.0 is within normal limits). The grandmother had reported that the S was "confused and was hallucinating" on the day before he was found dead in his truck. Based on the above information it appears that this patient had an alcohol abuse or dependence disorder. However, since he reported no such history he was included in the study. It is likely that his suicide was related to complications secondary to alcohol abuse/dependence, and possibly related to an underlying PTSD (and possibly an undiagnosed major depressive disorder), in which the patient overdosed on alcohol and paroxetine.

S (627.605.01012) was in the placebo group in Study 627, who committed suicide by a gunshot wound 17 days after cessation of treatment.

Study 650: One other death was reported in Study 650, which is an ongoing and long term study involving an open label 12-week trial, followed by a 24-week double-blind trial. The study employs two flexible dose treatment groups of 20-50 mg paroxetine or placebo. One death out of a total of 269 enrolled Ss is reported in the submission, which was due to suicide using a gun. This death was reported after the first dose of paroxetine and is likely to be due to underlying psychopathology.

8.1.2 Serious Adverse Events

Studies 627, 651, and 648: Out of 1180 Ss of the ITT Safety, 27 out of 676 (4%) paroxetine Ss and 16 out of 504 (3%) placebo Ss were reported to have SAE's, counting the 2 aforementioned fatalities). A listing for these Ss, as provided by the sponsor, is included as Table 8.1.2.1 in the appendix. Narratives were provided for these Ss, except for 627.802.01674 (an "Unintended Pregnancy" which was provided upon request in a supplemental submission dated 10/13/00). The predominant SAE for paroxetine Ss were psychiatric (i.e. "Emotional Lability", "Anxiety", "Depression", etc.) reported in 10 of the 27 SAEs in this population (627 total paroxetine Ss) which primarily occurred while on the study drug. The placebo group showed a similar predominance of psychiatric-like SAE's reported in which 10 out the 16 SAE's of placebo Ss (a total of 504 Ss). It is likely that these events were due to underlying psychiatric morbidity unrelated to the study drug. Other SAE's were either not likely to be drug related (i.e. had a pre-existing condition or had risk factors, etc.), or were not unexpected events reported with this drug (already included in the labeling for Paxil®). One SAE of tachycardia, which is an event included in the labeling for Paxil®, was reported in a paroxetine S, as described below.

S 648.830.014161: This 52 year old female had "went into tachycardia just after taking her a.m. dose" in approximately her third day on paroxetine. The S reported a pulse rate up to 170 beats/min. upon self-examination. The patient rested and reported that her pulse rate normalized by 10 pm that day. The study drug was stopped, due to this event. The event resolved and was considered by the investigator as "a significant hazard, contraindication, side-effect or precaution" that was possibly related to treatment of the study drug. Tachycardia is an event described as "frequent" in the product labeling, occurring in at least 1/100 patients, as observed in the pre-marketing evaluation of Paxil®. Tachycardia can also be associated with anxiety symptoms and may have been associated with the S's underlying psychopathology, such that it is unlikely to have been drug-related. One must also consider other potential underlying pathology in this subject given her age of 52 years, such that the S may have been peri-menopausal or post-menopausal or had undiagnosed cardiac disease.

S 651.063.07416 had an exacerbation of Crohn's disease and began prednisone on July 30, 1999, approximately 8 weeks after starting the treatment phase of 40 mg paroxetine/day. The S had an elevated WBC meeting criteria for being of "Potential Clinical Concern" on her week 8 visit, which was likely secondary to ileitus. On August 7, 1999, approximately one week after starting the prednisone treatment the patient was withdrawn from the study due to ileitus associated with Crohn's disease. Then on August 13, 1999, about one week after cessation of paroxetine treatment, the patient "experienced predinsone-induced behavioral problems" resulting in hospitalization which was reported as "prednisone-induced mania".

The above described events reported in S 651.063.07416 are not likely to be drug-related, as the patient had pre-existing Crohn's disease and mania is a known potential side effect of prednisone treatment. However, one possible consideration is that this patient may have an underlying undiagnosed bipolar disorder in which the patient could have been predisposed to a manic reaction to pharmacological agents, such as prednisone or an antidepressant such as paroxetine. Finally, an interaction effect of paroxetine with prednisone might also be considered. The product labeling also includes "manic reaction" as an "infrequent" AE (reported in 1//00 to 1/1000 patients) and has a section on "Activation of Mania/Hypomania" under "Precautions" regarding patients with unipolar depression or bipolar depression. A possible interaction effect of paroxetine with Crohn's disease might also be considered regarding the episode of ileitus in this S, since diarrhea and rarely enteritis are reported in patients receiving paroxetine, as described in the product labeling.

Ongoing Study 650: SAE's were reported in a total of 9 out of 269 enrolled Ss. A line listing is provided in Table 8.1.2.2 in the appendix, which contains information taken from that provided by the sponsor. This listing includes chest pain and CVA in one S (650.002.05804) and extrasystolic arrhythmia in another S (650.901.05884). The drug received by these Ss is blinded. Nevertheless, these events are not unexpected and are included in various sections of the current labeling for Paxil® in other psychiatric populations. The S (650.002.05804) with chest pain and cerebrovascular accident (CVA) was male and approximately 61 years old at the time of the study. The S is recorded as "recovered" for both events. However, the CVA was recorded as being associated with sequelae, in that the patient was recorded as being "recovered with sequelae" regarding this SAE. Given the patient's age and gender, it is likely that both SAE's were due to underlying atherosclerotic, cardiovascular, and/or cerebrovascular disease.

Some of the other SAE's provided in the line listing are suicide ("shooting"), among other psychiatric SAE's which were likely due to underlying psychopathology. One S had a hysterectomy/"ovarectomy" for some unspecified reason. The labeling includes female genital disorders.

8.1.3 Dropouts due to Adverse Events in Completed Studies (Studies 651, 648 and 627)

A total of 79 paroxetine treated Ss (11.7%) and 34 placebo treated Ss (6.7%) withdrew due to an AE after randomization. The adverse events, as provided below were not unexpected and are included in various sections in the labeling for Paxil® regarding other psychiatric populations.

The table below provides the number and percentages of randomized Ss (ITT Population) withdrawn due to an AE in each treatment group of each study.

The Number (%) of Randomized Subjects (ITT Population) Withdrawn Due to an AE in Each Treatment Group of Each Study

Study	Placebo Group	paroxetine Group
651	18 (9.7%)	**20 mg group:** 21 (11.5%) **40 mg group:** 28 15.5%)
648	10 (6.4%)	18 (11.9%)
627	9 (5.6%)*	15 (9.4%)*

* Does not include gender specific adverse dropouts. Gender specific adverse events were reported in 1 paroxetine subject (a male subject out of a total of 75 male paroxetine subjects). Tabulations for the Studies 651 and 648 include all adverse events leading to withdrawal (gender non-specific and gender specific).

The table below summarizes AEs leading to withdrawal that occurred in at least 1% of Ss in placebo or paroxetine groups with a frequency of at least twice that of placebo, as provided by the sponsor.

Summary of Treatment Phase Emergent Adverse Experiences Leading to Withdrawal (>= 1.0% and Twice Placebo) By Body System and Preferred Term -Studies 637, 641 and 642 (ITT Population)

Body Systems Preferred Terms	n	Placebo N =529 (%)	n	Paroxetine N =735 (%)
Body as a Whole				
Asthenia	1	(0.2)	11	(1.6)
Digestive System				
Nausea	3	(0.6)	15	(2.2)
Nervous System				
Somnolence	3	(0.6)	19	(2.8)
Tremor	1	(0.2)	7	(1.0)

AE's leading to withdrawal of two or more Ss, including those occurring in less than 1% of Ss in each treatment group are shown in Table 8.1.3.1 in the appendix, as provided in the submission. It should be noted that several Ss were reported as having adverse events leading to withdraw when instead these events occurred while off the study drug (after cessation of the study drug or prior to treatment onset), as described in the submission. Hence, these Ss (4 paroxetine and 3 placebo Ss) were not included in the tabulations in specified tables in the submission and in summary tables in this review.

Upon inspection of the incidence of AE's occurring at rate of less than 1% of paroxetine Ss shown in Table 8.1.3.1 (in the appendix) several of these AE's were at least 2-fold greater than the incidence in placebo Ss. However, an important caveat to this observation is that a possible floor effect in these AE's may result in misleading comparisons between placebo and paroxetine Ss, given that the incidence in placebo Ss for a number of these AE's is 0%. Furthermore, the sample size of placebo Ss is smaller than the sample size of the paroxetine Ss (504 placebo Ss compared to 676 paroxetine Ss, respectively). Although these preliminary observations do not warrant changes in the labeling for Paxil®, they are worth noting in this review for future reference if additional findings should arise.

Another important observation is that upon inspection of several line listings for adverse dropouts, events recorded as hot flashes under the "Verbatim Text" column are recorded as vasodilation as the "Preferred Term", and consequently are tabulated as vasodilation in the summary tables. Nevertheless, only 2 paroxetine adverse dropouts were due to vasodilation, as shown in Table 8.1.3.1 in the appendix.

Regarding the potential for a dose-dependent effect on adverse dropouts, none of the AE's associated with drug cessation in the fixed dose study (Study 651 which employed 20 and 40 mg paroxetine groups) occurred at an incidence of 5% or greater in Paroxetine groups, as shown in the table below (showing the incidence of AE's associated with drug cessation that occurred in at least 2 Ss in treatment group for Study 651). These AE's are also included as either treatment

emergent AE's or AE's associated with cessation of the drug in the labeling regarding other psychiatric populations. These findings are similar to that observed for other diagnostic categories approved as indications for Paxil®.

Number (%) of Adverse Experiences Which Lead to Withdrawal During the Treatment Phase Showing at Least a Trend for a Dose-Dependent Effect Between the High and Low Dose Paroxetine Groups in Study 651 (only includes events occurring in at least two patients in any treatment group with an incidence greater than placebo)*

Preferred Term	Placebo (N= 186)		Paroxetine 20 mg (N= 183)		Paroxetine 40 mg (N= 182)	
	n	(%)	n	(%)	N	(%)
Asthenia	0	(0.0)	3	(1.6)	5	(2.7)
Nausea	0	(0.0)	0	(0.0)	5	(2.7)
Confusion	0	(0. 0)	0	(0. 0)	2	(1. 1)
Diarrhea	2	(0.0)	0	(0.0)	2	(1.1)
Emotional Lability	1	(0. 5)	1	(0. 5)	2	(1. 1)
Vomiting	0	(0. 0)	1	(0. 5)	2	(1. 1)

*Results taken from Table 41 of adverse dropouts for Study 651 in the submission from the following sources as indicated in the submission: Data Source Tables 15.1.5.1 and 15.1.5.1.X, Section 13, Patient Listing 15.1.4, Appendix D, and study report section 3.16
Per submission: N. B. AEs leading to withdrawal for Patients 651.028.07310, 651.038.08268, 651.046.07017, 651.055.07711and 651.063.07416 (manic reaction only) have been excluded since these AEs did not occur on therapy during the Treatment phase.

8.1.4 Specific Search Strategies

Taper Phase Emergent AE's.
A total of 256 placebo treated Ss and 345 paroxetine treated Ss among the three completed studies entered the Taper Phase. Table 8.1.4.1 in the appendix (as provided by the sponsor) summarizes results on AE's occurring during the Taper Phase of the combined Studies 651, 648 and 627. This table shows that none of the AE's occurred in 5% or more of the paroxetine Ss. However, dizziness was reported in 4.6% of paroxetine Ss compared to 1.2% of placebo Ss. The following occurred with twice the incidence in paroxetine Ss (incidences ranged from 1.2% to 2.9%) to that of the placebo Ss (incidences of 0 to 0.8%): abnormal dreams, agitation, nervousness, paresthesia, vertigo, and trauma.

The flexible dose studies (648 and 627 using 20-50 mg dose range) involved a three week taper phase of 10mg/day decrements of dose at weekly intervals until reaching 20 mg/day, which was continued for one week before discontinuation. The fixed dose study (Study 651, which had 20 mg and 40 mg paroxetine groups) used a similar taper phase regimen, which occurred over a two-week period. Ss assigned to the 20 mg and placebo groups received placebo during the taper phase.

Most of the Taper Phase (TP) AE's were considered to be mild or moderate in intensity. AE's considered as severe in intensity were reported in 1.2% of the paroxetine group and 1.2% of the placebo group among Ss that entered the Taper Phase. The most common severe TP AE in the paroxetine group was headache in 1.2% of paroxetine Ss.

Follow-up Phase Emergent AE's.
A follow-up visit was required of all Ss on Day 14 following completion of the Taper Phase of the study or following the last dose of treatment (in the case of early withdrawal after the completion of at least 2 weeks of study medication in the treatment phase). The incidence of Follow-up Phase Emergent AE's (FUP AE's) in paroxetine (31.9%; 96 out of a total of 301 Ss) and placebo (25.6%; 64 out of 250 Ss) groups were similar for the three completed studies combined. However, one follow-up phase AE was reported in ≥5% of paroxetine Ss and twice the incidence reported for placebo Ss. This AE was dizziness which was reported in 6.0% of Paroxetine Ss compared to 0.8% of placebo Ss. Those FUP AE's reported in paroxetine Ss with an incidence of twice of that for placebo Ss, as shown in Table 8.1.4.2 in the appendix (as provided in the submission) are as follows: back pain, vasodilatation, dizziness, nervousness, paresthesia, tremor, vertigo, vestibular disorder, and sweating. These events occurred in 1 to1.3% of paroxetine Ss compared to 0% in placebo Ss, except for sweating which occurred in 0.4% of placebo Ss.

Most of the reported FUP AE's were mild to moderate in intensity. 7.3% of paroxetine Ss and 4.8% of placebo Ss reported at least one FUP AE considered as severe. Gender non-specific FUP AE's that occurred in ≥1% of paroxetine Ss were as follows:

- Anxiety (2.0% and 1.6% of paroxetine and placebo Ss, respectively).
- Emotional Lability (1.0% and 1.6% of paroxetine and placebo Ss, respectively).
- Insomnia (1.0% and 0.4% of paroxetine and placebo Ss, respectively).

Dosage Reductions and Interruptions Secondary to AE's.
The flexible dose studies (648 and 627) permitted a reduction in the dose for management of AE(s) in Ss receiving the 30 mg, 40 mg or 50 mg daily dose regimens (dose levels 2, 3, 4 respectively with 20 mg as dose level 1). The dose could be decreased in these Ss to the next lower dose level. Treatment or Taper Phase AE's resulting in a dose reduction that occurred in ≥1% of paroxetine Ss were the following: somnolence, nausea, asthenia, headache, anxiety, dizziness and tremor. These are not unexpected AE's given that described in the labeling for Paxil®.

8.1.5 Adverse Events

At least one treatment phase emergent adverse event (AE) considered to be "gender non-specific", was reported in 80% of paroxetine Ss and in 68% of placebo Ss. The following enumerates commonly (≥5%) reported AE's by Ss in the three completed studies (Studies 651, 648 and 627, combined, as provided by the sponsor). These AE's are similar to those described for other psychiatric populations in the labeling. See Table 8.1.5.1 for treatment phase emergent AE's occurring in ≥2% of paroxetine Ss (as provided in the submission).

Common Treatment Phase Emergent Adverse Experience Associated with Paroxetine Occurring in >/= 5% of Paroxetine Patients and at Least Twice the Incidence of Placebo

Treatment Phase, ITT Population, Studies 651, 648 and 627

Body System	Placebo N = 504		Paroxetine N = 676	
Preferred Term	**N**	**(%)**	**n**	**(%)**
Body as a Whole				
Asthenia	21	(4.2)	80	(11.8)
Digestive System				
Nausea	42	(8.3)	130	(19.2)
Dry Mouth	24	(4.8)	68	(10.1)
Decreased Appetite	13	(2. 6)	40	(5. 9)
Nervous System				
Somnolence	23	(4.6)	108	(16.0)
Libido Decreased	9	(1.8)	35	(5.2)
Urogenital System				
Abnormal Ejaculation*	3	(1.6)	30	(12.6)
Impotence*	1	(0.5)	22	(9.2)

* Percentage corrected for gender

Dose Dependent Relationship of Treatment Emergent Adverse Events. The table below (as provided by the sponsor) shows the incidences of AE's that occurred in at least 5% of paroxetine treated Ss that also appeared to show a dose dependent relationship between the 20 mg and 40 mg paroxetine groups in the fixed dose parallel group study (Study 651).

Incidence of Selected Adverse Events in Study 651 (see above text)

Adverse Event	Placebo Group N=186	20 mg Paroxetine Group N=183	40 mg Paroxetine Group N=182
Somnolence	5.4	15.8	20.3
Abnormal Ejaculation*	1.6	15.8	20.0
Impotence*	0.0	7.0	20.0
Nausea	4.8	15.8	19.2
Constipation	4.3	3.3	7.7
Infection	2.7	3.8	7.1
Decreased Appetite	1.1	5.5	6.6

*percentages adjusted for the gender

When examining incidences of AE's that were considered to be severe only one AE, abnormal ejaculation occurred in at least 5% of Ss in either of the two paroxetine groups (20 and 40 mg/day) in Study 651. The incidence of this AE, considered as severe, was as follows: 5.5% in the high dose group, 1.8% in the low dose group and 0% in the placebo group.

Other AE's occurring with an incidence of ≥1% in either paroxetine group that appear to show at least a trend for a dose relationship between the low and high dose paroxetine groups are shown in the below.

Incidence of Selected Adverse Events Considered as Severe in Study 651 (see above text)

Adverse Event	Placebo Group N=186	20 mg Paroxetine Group N=183	40 mg Paroxetine Group N=182
Abnormal Ejaculation*	0.0	1.8	5.5
Female Genital Disorders	0.0	0.0	2.4
Diarrhea	0.5	0.5	2.2
Asthenia	0.0	0.5	1.1
Decreased Appetite	0.0	0.5	1.1
Infection	0.0	0.5	1.1

*percentages adjusted for the gender

Gender, Age-group and Racial-group Analyses of AE's. Due to insufficient sample size of Ss over 65 years old or non-Caucasian Ss, subgroup analyses for racial-group or age-group by treatment interaction effects would not yield meaningful or interpretable results. However, 35% to 38% of the paroxetine and placebo Ss, respectively were male, such that a summary of gender analyses is provided in this review (see the summary table, Table 8.1.5.2 in the appendix, as provided by the sponsor). When comparing paroxetine treated males to paroxetine treated females on the incidence of common AE's (disregarding abnormal ejaculation and impotence), asthenia was found to be reported twice as often in females than males. However, the incidence of asthenia in female placebo Ss was also over 2-fold greater than that observed in male placebo Ss. Consequently, paroxetine Ss show at least twice the incidence of asthenia compared to that of the placebo Ss in males, as well as females. The paroxetine to placebo relative risk and odds ratio estimates were determined for each gender for each common AE reported in paroxetine Ss. Differences in the odds ratios between male and female Ss on these AE's were not found to be significant.

8.1.6 Laboratory Findings

8.1.6.1 Analysis of Central Tendency

A list of the laboratory tests that were performed may be found in Tables 7.1.2 and 8.1.6.1.1 A in the appendix, as provided by the sponsor. Tables 8.1.6.1.2 and 8.1.6.1.3 in the appendix summarizes results on the mean laboratory values at baseline and the mean change from baseline to endpoint for the 3 completed studies (combined), as provided in the submission. As shown in these summary tables the paroxetine and placebo groups were similar in mean baseline values of the various parameters and were generally similar in mean change of each parameter. The range of these mean changes was 0 to ± a few units and remained within the normal reference range for each parameter. However, the variance or standard deviations for the mean changes are generally several fold to 10 fold larger in magnitude than the value for the mean change for each respective parameter.

The sponsor provides the following observations regarding the mean change in laboratory values when expressed as a percentage (the mean change at endpoint/mean baseline valuex100%). Most parameters showed a mean percent change of 5% or less. Exceptions were total bilirubin (8.9% and 9.7% in the paroxetine and placebo groups, respectively) and aspartate aminotransferase (6.9% and 1.0%, respectively). Alkaline phosphatase was noted to show a mean percent increase of 3.6% in the paroxetine group and 0.9% in the placebo group.

However, as already stated the mean changes of the various parameters were within the normal reference range.

8.1.6.2 Analysis of Outliers

Table 8.1.6.1.1 A in the appendix provides the "potential clinical concern" (PCC) criteria for each laboratory measure monitored (as provided in the submission). The table below summarizes Ss meeting criteria for potential clinical concern (PCC), as provided by the sponsor. With the exceptions of low hematocrit and eosinophilia, the incidence of all other laboratory values meeting PCC criteria within each treatment group was less than 1%.

Clinical Laboratory Values from Studies 651, 648 and 627
Meeting Sponsor- Defined Potential Clinical Concern Criteria

Laboratory Variable	High/ Low	Placebo (N= 504) n (%)	Paroxetine (N= 676) n (%)
Hematology			
Hemoglobin	Low	1 (0.3)	2 (0.5)
Hematocrit	Low	2 (0. 6)	6 (1. 4)
WBC	High	0 (0.0)	3 (0.7)
	Low	1 (0.3)	0 (0.0)
Lymphocytes	High	1 (0. 3)	0 (0. 0)
Monocytes	High	0 (0. 0)	1 (0. 2)
Eosinophils	High	6 (1. 8)	3 (0. 7)
Neutrophils, Segmented	Low	1 (0.3)	0 (0.0)
Liver Function			
Total Bilirubin	High	1 (0. 3)	2 (0. 5)
Renal Function			
Creatinine	High	0 (0. 0)	1 (0. 2)
BUN	High	0 (0.0)	2 (0.5)
Other Tests			
Potassium	High	1 (0.3)	4 (0.9)

Hematological results: A total of 7 paroxetine Ss met PCC criteria for HgB and/or HCT and a total of 8 paroxetine Ss met PCC criteria for WBC and/or the differential among the three completed studies. Three paroxetine Ss had AE's associated with hematological parameters as follows: anemia (627.302.01559 and 651.040.07479) and leukopenia (648.800.00009). There were no reported cases of agranulocytosis. The majority of these Ss had either abnormal values at baseline or a pre-existing condition that was likely to underlie the aberrant hematological parameter(s). Various hematological events, such as anemia, eosinophilia, leukopenia, among others are reported as "infrequent" under the section, "Other Events Observed During the Premarketing Evaluation of Paxil" in the labeling for this drug. Selected Ss are described and further details are provided below.

There were no adverse dropouts or serious adverse events due to laboratory parameters meeting PCC criteria in paroxetine Ss. However, S 651.063.07416, who had an elevated WBC of PCC, had both an SAE ("prednisone induced mania") and an AE ("exacerbation of Crohn's disease") leading to cessation of 40 mg/day of paroxetine. The elevated WBC in this S was likely secondary to the exacerbation of their pre-existing Crohn's disease. This S is described in more detail in the SAE section, above.

Further Details and Descriptions of Selected Outliers or Ss with AE's involving WBC and/or differential:

Among the 3 studies, a total of only 8 paroxetine Ss met PCC criteria for WBC and/or differential counts. All but 1 S (627.607.01610) had abnormal values at baseline and/or had a pre-existing condition associated with the abnormal WBC or differential. According to the narrative, S 627.607.01610 was a 29 year old with a mildly elevated eosinophil count of 13% on week 12 of paroxetine and had reported "headache, nausea and infection during the study". A drug-related eosinophilia cannot be ruled out, but is included as an "infrequent" event in the labeling for Paxil®.

The S reported to have leukopenia as an AE (S 648.800.0009) was a 24 y.o. white female with a medical history of asthma who had slightly abnormal eosinophil, monocyte and neutrophil counts at screening who's monocyte count became slightly elevated (15% compared to 0-12% within normal limits) and the white cell count was decreased to 3.0 x 10^9/L (4.0-11.0x 10^9/L within normal limits) on week 12. There were no clinical symptoms or adverse events reported in the narrative for this patient. The decrease in the white count was mild. The possibility of the decrease white count being drug-related cannot be ruled out, but did not appear to be of clinical significance and is an event included in the labeling for Paxil®.

Further Details and Descriptions of Selected Outliers or Ss with AE's involving HCT and/or HgB parameters:

There were a total of 7 paroxetine patients in Studies 651 and 648 and no paroxetine Ss in Study 627 that met PCC criteria for low HgB and/or HCT. All but one of these outliers (6 out of these 7 Ss) could be accounted for by a pre-existing condition such as anemia or an abnormal value at baseline. The HCT levels were mildly low at approximately 31 to 32% and the narratives do not report clinical sequelea associated with the anemia. The lowest HCT level was 26% (35-46% within normal limits) in S 648.801.00060 who had abnormally low values at baseline. One S (651.041.07308) meeting PCC criteria for HCT at week 8 only had a mildly low level at 30% and had various conditions that could also be attributed to the anemia (such as elderly, history of cancer and radiation of left breast). However, S 648.839.01902 who met PCC criteria for a low HCT level on week 12 of the study was a 39 y.o. female with an unremarkable medical history. Her HCT level was only mildly decreased to 30% and was not associated with any AE's according to the narrative. The reason for her anemia is not clear, such that the possibility of her anemia being drug-related cannot be ruled out.

Ss 627.302.01559 and 651.040.07479 were reported to have anemia as AE's in which the former S did not meet PCC criteria and the latter S had anemia at baseline. Anemia is included as an "infrequent" event in the labeling for Paxil®.

The sponsor provided laboratory transition tables. These summary tables provide results on the number of Ss showing a decrease, increase or no change from baseline to week 8 or study endpoint for each laboratory parameter, in which laboratory values at each time-point are categorized among three categories (low, intermediate, or high) relative to the normal reference range. The Paroxetine and Placebo treatment groups showed similar percentages of Ss (ranging from 2 to 3%) transitioning from a higher category (high or intermediate level) to a lower category (intermediate or low) on various hematological parameters (HgB, HCT, RBC and WBC), as determined from results of the laboratory transition tables. The denominators for these percentages were the total numbers of Ss with transition results provided in each treatment group in the transition tables in the submission. Hence, these results show that treatment groups were

similar in the frequency of Ss that showed a decrease (based on categorical data) in hematological parameters during treatment. Similar results were obtained for platelet counts in each treatment group in which 0.6% or less Ss decreased from baseline to week 8 or study endpoint. An increase in eosinophils (cells/l) was observed in 1.5% and 1.9% of placebo Ss at weeks 8 and study endpoint and in 2.5% and 2.0%, respectively of paroxetine Ss. One of these placebo Ss met PCC criteria, while 4 paroxetine Ss met PCC criteria. The maximum level of eosinophils among these 4 paroxetine Ss was 13% (S 641.118.0085, described above).

Renal Function and Electrolyte Parameters.

Two paroxetine Ss (627.041.01210 and 648.819.00919) and no placebo Ss met PCC criteria for elevated BUN and/or Cr levels. Both Ss had abnormal values or pre-existing conditions at baseline such that these values were not likely drug-related.

Four paroxetine Ss and 1 placebo S met the PCC criterion for elevated potassium levels. The range of the elevated levels among the paroxetine Ss was 6.7 to 7.1 uM (3.5-5.0, within normal limits) of which no symptoms were described concurrently with these elevations. The labeling for Paxil® includes hyperkalemia as a "rare" (an incidence of <1/1000) event reported in the premarketing evaluation of the drug. Selected Ss are described below in the subsection "Description of Individual Ss".

There were no paroxetine Ss reported as having an SAE or as being an adverse dropout due to a renal function or electrolyte parameter meeting PCC criteria. However, two Ss (627.606.01402 and 627.606.01891) met PCC criteria for hyperkalemia who also had SAE's ("fainting" and "depression aggravated and suicide attempt", respectively). The SAE's in these Ss were likely to be related to their pre-existing psychiatric condition, as described below (also described in Section 8.1.2 "Serious Adverse Events", above). Only one S (627.302.01559) had either an abnormal renal or electrolyte parameters reported as an AE. Hyperkalemia, along with anemia (see previous section which includes this S) were the AE's reported in this S. However, there is no narrative provided for this S, as the S was not reported to have a SAE, withdrawal from the study due to an AE, or to have met PCC criteria on any of the safety parameters. Therefore, one cannot rule out the possibility that this S's hyperkalemia was drug-related.

Description of Individual Ss with Aberrant Renal Function or Electrolyte Parameters.

Two of the paroxetine Ss had SAE's (627.606.01402 and 627.606.01891), described under the SAE section), in which the former S fainted after two arguments, was hospitalized and following a diagnostic work-up was found to have no "organic pathology". Approximately 63 days later (Day 86) this 46 y.o. S's potassium level met PCC criteria. The narrative indicated "no further data are available" regarding this abnormal level. With the lack of other information a drug-related effect on the potassium level cannot be eliminated. The latter S meeting PCC criteria for elevated potassium was also reported to have a SAE of "Depression Aggravated and suicide attempt" (suicidal ideation, rather than an actual suicide attempt was indicated in the narrative), for which the treatment included paroxetine among other psychotropic agents. The narrative fails to provide any information regarding her potassium level that met PCC criteria. Hence, without further information, a drug-related effect on potassium levels cannot be eliminated.

A drug-related effect cannot be ruled out regarding the elevated potassium level in S 651.008.07791 who was a 38 y.o. female with current back pain and indigestion. She did not appear to have any underlying pre-existing condition that could account for her mild

hyperkalemia that was of PCC on week 12. However, S 627.606.01706 had an elevated potassium at baseline such this S had a pre-existing hyperkalemia, prior to treatment.

Liver function tests: Only 2 Paroxetine Ss and 1 placebo S had liver function test(s) that met PCC criteria which was an elevated bilirubin level in each of these 3 Ss. The possibility of bilirubinemia being drug-related in one paroxetine S cannot be eliminated (627.001.01184), while Gilbert's disease associated with bilirubinema was reported in the other paroxetine S (627.041.01196). The former S's bilirubin increased from 7.0 uM at screening to 39.0 uM on week 12 and was a 47 y.o. female with history of diabetes. This S also had low HgB, HCT and Cr levels that did not meet PCC criteria on week 12, while at baseline these parameters were within normal limits. According to the narrative, "no further data are available" and "no adverse experiences were reported during the study". The submission does not report any SAE's or adverse dropouts in paroxetine Ss due to a liver function test meeting PCC criteria. Two Ss had AE's reported as having abnormal liver function tests (648.801.000067 and 651.028.07751) which were not listed as meeting criteria. The labeling for Paxil® includes bilirubinemia as a rare event reported in the premarketing evaluation of the drug.

Thyroid Function Tests. Only Study 651 included assessments of thyroid function during treatment, which were conducted on only 2 Ss in the 40 mg group at week 12 of which TSH levels were obtained. It is not clear why only these 2 Ss were tested, as the methods section appears to indicated that all laboratory parameters conducted at screening, including TSH levels, were also conducted at week 12 of the treatment phase. Among these two Ss, one met PCC criteria for high TSH levels. This S (651.030.06972) was a 43 y.o. white male with diabetes (receiving Glyburide), sinusitis and "heartburn" who had a TSH level of 11.9 mU/L (0.4-5.5 mU/L within normal limits) on week 1, according to the narrative. The patient also experienced dry mouth of "severe intensity" and withdrew from the study on May 5, 1999 (first dose of the drug was on April 22, 1999). The S continued to have a "thyroid disorder" (no laboratory values provided subsequent to the week 1 value), while the dry mouth resolved within 15 days. Although, the investigator considered the elevated TSH to be "unrelated to study medication", the possibility of this event being drug-related cannot be ruled out, given the limited information described in the narrative. Hyper- and hypothyroidism are included in the Paxil® product labeling as a "rare" event (occurring at <1/1000) reported during the premarketing evaluation of the drug.

Urinalysis Results of Ss with Positive Urine Dipstick Result for Protein, Blood and/or Glucose. The table below, is composite of a table provided in a fax dated October 4, 2000 (in response to inquiries e-mailed to the sponsor dated 9/21/00) and results described in the submission enumerating Ss who were positive on the urine dipstick test for blood, glucose or protein.

The Incidence (%) of Treatment Emergent Positive Dipstick Results

Urine Dipstick Parameter	Paroxetine Group (N=504)	Placebo Group (N=676)
Protein	2 (0.4)	1 (0.2)
Blood	14 (2.8)	11 (1.6)
Glucose	3 (0.6)	4 (0.6)

None of these abnormal parameters were 5% or greater in incidence of occurrence in a given group. The incidence of these abnormal parameters was no greater than 1.8% in a given group on a given parameter. Four paroxetine Ss had an AE associated with an abnormal urine dipstick parameter in which their urine dipstick results were normal at baseline. The AE's reported in these four Ss were as follows: urinary tract infection (S 648.836.01751), cystitis (651.047.07450), dysmenorrhea (651.018.07517), and metrorrhagia (651.023.07517). It is likely that the urine specimen was contaminated in the latter two Ss, accounting for the abnormal dipstick result. Regarding the AE's in the former two Ss, these AE's are included in various sections in the product labeling for Paxil®.

8.1.7 Vital Signs

8.1.7.1 Analysis of Central Tendency

See Table 8.1.7.1.1 in the appendix, as provided by the sponsor, which shows results on the mean baseline and mean change from baseline to endpoint on vital sign variables and weight for the paroxetine and placebo groups for the three studies combined. Treatment groups were similar in the mean change from baseline to endpoint on each vital sign parameter and on weight. The magnitude in the observed mean changes per treatment group was less than 1 unit for each vital sign parameter, in which mean values were within the normal range. These mean values and mean changes were not clinically significant. Weight was not monitored during treatment or afterwards in any of the three studies.

8.1.7.2 Analysis of Outliers

Criteria for PCC for vital signs are provided in Table 8.1.6.1.1 B in the appendix (as provided in the submission). None of the Ss in the three completed studies met PCC criteria for the vital sign parameters during the treatment or taper phase, as indicated in the submission and in a response to a request for a additional information/clarification from the sponsor dated 9/19/00. The submission specifies that while the Data Source Table 9.1 in section 22 of the submission indicates no outliers, "upon further inspection of the database" two Ss (651.039.07458 and 627.204.01165) were found to have met PCC criteria for elevated diastolic blood pressure during the "post week 12 period". These Ss were not reported to have an AE associated with their elevated blood pressure.

The percentages of Ss with reported AE's involving blood pressure (hypertension, hypotension or syncope) or pulse rate (arrhythmia, bradycardia, palpitations or tachycardia) during the treatment or taper phases were generally less than 1% in each treatment group. The exceptions were palpitation reported in 1.2% of paroxetine Ss and 0.8% of placebo Ss and tachycardia reported in 1.3% and 0.2% of paroxetine and placebo Ss, respectively. Vasodilitation was reported in 2.4% and 1.2% of paroxetine and placebo Ss, respectively. These adverse events are included in the product labeling for Paxil®.

8.1.8 Electrocardiographic Results

An electrocardiogram (ECG) was conducted at screening and/or baseline and week 12 or upon early withdrawal. The investigator classified these ECG's as "abnormal" or "normal". There were no *a priori* PCC criteria proposed for the three completed studies. However, upon request the sponsor provided a summary table enumerating patients with treatment emergent ECG abnormalities at study endpoint (in a fax dated 10/4/00). There were no paroxetine Ss and 2 placebo Ss with treatment emergent ECG out of a total of 676 and 502 paroxetine and placebo

Ss, respectively. The submission indicates that upon inspection of the patient data listing (not provided in the submission) 2 paroxetine Ss and 2 placebo Ss had "abnormal" ECG's during the post week 12 period. There were no SAE's or adverse dropouts due to an abnormal ECG. Given these results, there was no signal for treatment emergent clinically abnormal ECG recordings. Current product labeling includes various cardiac events such as those related to cardiac conduction, rate or rhythm reported during the premarketing evaluation of Paxil®.

9.0 Labeling Review

The major proposed labeling changes regarding efficacy for Paxil® (tablets and oral suspension) include the following:

- [redacted]
- [redacted]
- Under the "Indications and Usage" section of the "*Paxil* (paroxetine hydrochloride) is indicated for the treatment of Posttraumatic Stress Disorder (PTSD) [redacted] "

Based on the sponsor's results described in the submission, Studies 651 and 648 support the efficacy claim of Paxil® for the treatment of patients with PTSD. Study 627 did not show significant treatment effects on at least one primary efficacy variable, such that the results do not support the efficacy claim. However, failure to show significant efficacy effects does not refute the claim for efficacy in treating patients with PTSD, as it appears that Study 627 is a failed study rather than a negative study. The conclusion that Study 627 is a failed study is based on the observed trends for a treatment effect found on most efficacy variables, including various secondary variables. Furthermore, several potential methodological concerns or underlying variables as previously discussed, may have played in a role in failure to reach a level of significance in these observed trends.

Regarding labeling changes related to safety, consideration for recommending a taper phase regimen upon discontinuation of treatment, similar to that employed in most clinical trials conducted by the sponsor, including all studies described in this review, might be considered. A discussion regarding this issue is described in Section 10, below.

10.0 Conclusions

Two of three studies, Studies 651 and 648, revealed significant treatment group effects on both of the primary efficacy variables, based on the results provided in the submission. Gender was not found to influence treatment group effects in any of three studies. Age-group (over 65 years old compared to < 65 years old) or racial-group analyses of efficacy or safety variables would not yield meaningful or interpretable results, due to insufficient numbers of Ss over 65 (only 2-5 Ss/group in each study) or who were non-Caucasian (10-47 Ss/group in each study). These conclusions were confirmed by a statistical review by the Biometrics reviewer Dr. Lu Cui.

Regarding the overall safety of paroxetine treatment in PTSD patients, paroxetine treatment appears to be adequately safe in this population. The safety profile as described in the submission is similar to that observed in other patient populations and that described in the labeling for Paxil®. However, consideration may be given to potential withdrawal effects of paroxetine and other selective serotonin reuptake inhibitors, as suggested by spontaneous reports that discontinuation, particularly upon abrupt cessation, may lead to various adverse events as described in the current labeling for Paxil®. These adverse events described in the "Postmarketing Reports" section of the current labeling for Paxil® include the following: dizziness, sensory disturbances, agitation, anxiety, nausea and/or sweating which are "generally self-limiting." Also refer to Dr. Andrew Mosholder's review of Lilly's NDA18-936 ——— submission regarding results of studies on adverse events associated with treatment interruption of various selective serotonin reuptake inhibitors, including Paxil.®

Most clinical trials of paroxetine hydrochloride conducted for approved indications, including trials described in this review, employed a taper phase such that Ss were gradually tapered off of paroxetine treatment. The typical taper phase regimen was a weekly incremental decrease in the daily dose by 10 mg per week until a daily dose of 20 mg was achieved. The 20 mg/day dose was then continued for one week before terminating treatment. Despite the use of this taper phase regimen in the fixed and flexible dose trials described in this review (doses up to 50 mg/day were employed), some taper phase emergent AE's (Taper Phase AE's) were observed in paroxetine Ss with an incidence that was twice that of placebo Ss. Dizziness was the only common (5% in paroxetine Ss, 1.2% of placebo Ss) Taper Phase AE, considered by definition to be drug-related (defined as showing an incidence of ≥5% and twice that of placebo Ss). Other Taper Phase AE's reported in paroxetine Ss with an incidence of twice that of placebo Ss (1.2% to 2.9% of paroxetine Ss compared to 0 to 0.8% in placebo Ss) were as follows: abnormal dreams, agitation, nervousness, paresthesia, vertigo and trauma. This Taper Phase AE profile, with the possible exception of trauma, is generally similar to that reported in the published literature and/or in current labeling, as above. Some of the Taper Phase AE's were also reported on the 14-Day post-taper phase visit showing an incidence in paroxetine Ss that was twice that of placebo Ss. Among these AE's, dizziness was again found to be a common AE in paroxetine Ss (incidence of 6%) while others occurred in <2% of paroxetine Ss but showed an incidence twice that of placebo Ss. These AE's were nervousness, paresthesia, tremor, vertigo, vestibular disorder, and sweating.

It is difficult to interpret safety results from the Taper Phase and 14-Day post taper phase follow-up visits regarding the potential for withdrawal effects of paroxetine. The trials described in this review and in the submission were not designed to examine or address this issue. Consequently, controlled trials with the primary objective of examining withdrawal AE's upon abrupt and/or gradual discontinuation of treatment are needed. Some studies described in the literature provide evidence suggesting that withdrawal AE's may occur with abrupt cessation of selective serotonin reuptake inhibitors. Also refer to Dr. Mosholders review of NDA18-936 ——— describing results of studies on the issue of adverse events associated with treatment interruption of various selective serotonin reuptake inhibitors. It is recommended that consideration be given to providing advice in the "Dosage and Administration" section of labeling, that when terminating treatment, the dose should be gradually reduced rather than terminated abruptly. A taper phase regimen to be considered might be similar to that employed in the clinical trials described in the current submission, as well as that employed in previous trials supporting the sponsor's claims for other approved indications for Paxil® treatment.

Alternatively, the sponsor may wish to conduct well designed controlled studies that provide evidence that clinically significant withdrawal effects do not occur with abrupt cessation of paroxetine treatment.

11.0 Recommendations

An approvable action is recommended for supplement SE1-029 pending the sponsor's agreement to the Divisions draft labeling modifications.

/S/

Karen L. Brugge, M.D.
Medical Review Officer, DNDP
FDA CDER ODE1 DNDP HFD 120

cc: IND
HFD 120
HFD 120/
P Andreason
K Brugge
A Homonnay
T Laughren

3-20-01

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

/S/

APPENDIX

Table 7.1.1 A. Study 651: Principal Investigators, SB Assigned Center Number, Affiliation, and Study Center Location

		Center Number	Investigator Affiliation	City, State
Adler	Lawrence W.	001	Clinical Insights	Glen Burnie, MD
Apter	Jeffrey T.	002	Princeton Biomedical Research	Princeton, NJ
Baker	Dewleen	003	Cincinnati VA Medical Ctr.	Cincinnati, OH
Balogh	Scott	051	Clinical Discovery Ctr.	Martinez, GA
Bystritsky Pynoos	Alexander/ Robert	004	UCLA Neuropsychiatric Institute Los Angeles, CA and Hospital	
Cruz Margolin	Herbert A./ David	006	Private Practice	Fresno, CA
Delgado	Pedro L.	007	Arizona Health Sciences Ctr., Department of Psychiatry	Tucson, AZ
DePriest	Michael W.	008	Pharmacology Research Clinic	Las Vegas, NV
Dietrich	Anthony	009	Neuropsychiatric Associates	Woodstock, VT
DuBoff	Eugene A.	010	Denver Center for Medical Research	Denver, CO
Dubovsky	Steven L.	011	University of Colorado Health Sciences Ctr.	Denver, CO
Dunner	David L.	012	Center for Anxiety and Depression	Seattle, WA
Fabre	Louis	013	Fabre Research Clinics, Inc.	Houston, TX
Fanelli	Joseph G.	052	Midwest Center for Neurobehavioral Medicine	Oakbrook Terrace, IL
Fieve	Ronald R.	053	Fieve Clinical Services, Inc.	New York, NY
Feighner	John P.	014	Feighner Research Institute	San Diego, CA
Garcia- Ferrer	Eduardo	054	Unity Health Research	St. Louis, MO
Gimeno*	Michael	016	DMI Health Care Group, Inc.	Largo, FL
Ginsberg	Lawrence D.	017	Red Oak Psychiatry Associates	Houston, TX
Gualtieri	C. Thomas	018	North Carolina Neuropsychiatry Clinic, PA	Chapel Hill, NC
Hafez	Hisham	019	Institute for Clinical Research at the Medical Ctr.	Nashua, NH
Hale	Mahlon S.	020	New Britain General Hospital	New Britain, CT
Haykal	Radwan	021	Research Memphis	Memphis, TN
Helfing	Saul H.	062	Oregon Center for Clinical Investigations (OCCI)	Lake Oswego, OR
Holland	Peter	022	Boca Raton Medical Research, Inc.	Boca Raton, FL
Hoopes	Scott P.	055	Private	Boise, ID
Jain	Rakesh	056	R/ D Clinical Research	Lake Jackson, TX
James	Steven P.	023	Clinical Studies, Arizona	Phoenix, AZ
Kablinger	Anita	024	Louisiana State University Medical Ctr.	Shreveport, LA
Kalin	Ned H.	025	Wisconsin Psychiatric Institute and Clinics	Madison, WI
Kaye	Neil S.	061	Private Practice	Wilmington, DE

Investigator		Center Number	Affiliation	City, State
Kyser	James Gregory	057	Clinical Research Associates	Nashville, TN
Khan	Arif	027	Northwest Clinical Research Ctr.	Bellevue, WA
Lindley	Steven E.	028	National Center for PTSD	Menlo Park, CA
Lipkin	John	029	PeaceHealth Medical Group	Eugene, OR
Machado	Julio C.	030	Miami Research Associates, Inc.	Miami, FL
Marshall	Randall	031	New York State Psychiatric Institute	New York, NY
Menza Hamer	Matthew/ Robert	032	Robert Wood Johnson Medical School	Piscataway, NJ
Mortimer	Dale	063	Oregon Center for Clinical Investigations, Inc.	Vancouver, WA
Oldroyd	Julie	033	Irvine Clinical Research Ctr.	Irvine, CA
Phillips	Wayne	035	Alpine Clinical Research Ctr.	Boulder, CO
Pratty	James S.	036	Private Practice	Torrance, CA
Ranjan	Rakesh	037	Rakesh Ranjan, MD and Associates, Inc.	Medina, OH
Reed*	Ronald C.	015	University Hospitals of Cleveland Cleveland, OH	
Reichler	Robert	038	Pacific Institute of Mental Health Seattle, WA	
Richter	Ralph	039	Clinical Pharmaceutical Trials	Tulsa, OK
Robinson Warren	Michael/ Rick	040	Westover Heights Clinic	Portland, OR
Rubin	Steven E.	059	Delta Research Group	Granite Bay, CA
Shrivastava	Ram K.	041	Eastside Comprehensive Medical Services	New York, NY
Simon	Jeffrey S.	042	—	Brown Deer, WI
Stein	Murray Brent	044	University of California at San Diego, Department of Psychiatry	La Jolla, CA
Teicher	Martin H.	045	McLean Hospital/ Harvard Medical School	Belmont, MA
Telew	Nicholas W.	046	Oregon Center for Clinical Investigators, Inc.	Eugene, OR
Thomas	H. Mikel	047	CTT Consultants, LLC	Overland Park, KS
Trivedi	Madhukar H.	060	University of Texas Southwestern Medical Ctr.	Dallas, TX
West	Scott A.	048	Psychiatric Institute of Florida	Orlando, FL
Winokur Ford	Andy/ Julian	049	University of Connecticut Health Ctr.	Farmington, CT
Wolner	Ron	034	Upstate Neurology Consultants, LLP	Albany, NY
Wronski	Craig	043	Affiliated Research Insititute	Santa Ana, CA
Zimmerman*	Mark	050	Rhode Island Hospital	Providence, RI

* Centers which did not randomize at least one patient

Table 7.1.1 B. Study 648: Principal Investigators, SB Assigned Center Number, Affiliation, and Study Center Location

Investigator		Center No.	Affiliation	City, State
Banov	Michael	800	Northwest Behavioral Medicine	Marietta, GA
Barbee	James	837	LSU Medical Center	New Orleans, LA
Bari	Mohammed	801	Synergy Clinical Research Center	Chula Vista, CA
Bastani	Bijan	802	NorthCoast Clinical Trials, Inc	Beachwood, OH
Beck	David A.	803	University of Missouri- Columbia	Columbia, MO
Birnbaum	Robert J.	804	Beth Israel Deaconess Medical Center	Boston, MA
Brady	Kathleen	805	Medical University of South Carolina	Charleston, SC
Bremner	Douglas J.	806	Scirex Clinical Research Unit at Yale	New Haven, CT
Brown	David W.	807	Charter Hospital of Austin	Austin, TX
Casada	John	808	University of Texas Health Science Center	San Antonio, TX
Ciraulo	Domenic A.	809	Boston University School of Medicine	Boston, MA
Extein	Irl L.	810	Health Sciences America	Boca Raton, FL
Ferguson	James	832	Pharmacology Research Corporation	Salt Lake City, UT
Goldstein	David	811	Georgetown University	Washington, DC
Haines	Francis X.	814	ICSL Clinical Studies	Providence, RI
Kang	Jasbir	813	Western Pennsylvania Psychiatric Center	Aliquippa, PA
Kass	Ethan	838	ICSL Clinical Studies	Fort Lauderdale, FL
Landbloom	Ronald	816	Regions Hospital	St. Paul, MN
Levine	Robert H.	812	Neuropsych Research Associates	New York, NY
Liebowitz	Michael	817	The Medical Research Network, LLC	New York, NY
Logan	Michael	831	Advanced Clinical Research	Milwaukee, WI
Londborg	Peter	818	Seattle Clinical Research Center	Seattle, WA
Melchor	Pedro	819	Private Practice	Miami, FL
Merideth	Charles	822	Affiliated Research Institute	San Diego, CA
Miller	Kevin	824	St. Louis University School of Medicine	St. Louis, MO
Murphy	John	821	Southwestern Research Institute	Beverly Hills, CA
Nemeroff	Charles	827	Emory University School of Medicine	Atlanta, GA
Pigott	Teresa	823	University of Texas Medical Center (UTMC) at Galveston	Galveston, TX
Pollack	Mark	828	Massachusetts General Hospital	Boston, MA
Rynn	Moira	825	University of Pennsylvania	Philadelphia, PA
Sheehan	David	826	University of South Florida Psychiatry Center	Tampa, FL
Tucker	Phebe	829	University of Oklahoma	Oklahoma City, OK
Weisler	Richard	839	Private Practice	Raleigh, NC
Westin	Dennis C.	830	Palo Verde Behavioral Health	Tucson, AZ
Wong	Cheryl	833	Bronx Veterans Administration Hospital	Bronx, NY
Munshi	Autar	836	Private Practice	Sydney, NS
Reesal	Robin	835	Western Canada Behavioral Center Calgary, Alberta	

Table 7.1.1 C. Study 627: Principal Investigators, SB Assigned Center Number, Affiliation, and Study Center Location

Investigator	Center No. / Affiliation/ Address
Switzerland	
Antal Kasas	001 Rue H. F. Sandoz 49
Blajo Blajev	002 3a Rue De La Gare
Dominique Baettig	003 Centre medico- psychol pour adultes faubourg des capucins 20 2800 Delemont
Marco Frei	041 plazza Collegiata 7a 6500 Bellinzona
Israel	
Richard Shiffer	051 Lev Hasheron Hospital, Pardessia
Kremer Ilana	053 Haemek Hospital, Afula 18101
The Netherlands	
Heinrich Witte	100 Wilhelminalaan 33, 3701 BE Zeist
Heinrich Witte	101 Wilhelminalaan 33, 3701 BE Zeist
Ilonka Boomsma	102 Centrum voor Vrouwenhulpcerlening Henry Verhagen
Italy	
Marco Grignani	151 Co- ord Struttura Intermedia del CSM ASL no. 3, Viale Ancona 8/ 10, Regione Umbria, 06034 Foligno
Paola Merlo	153 Instituto Humanitas Via Manzoni Rozzano
Giorgio Sandrini	159 Centro Interuniversitario Cefalee Disordini Adattativi, Via Palestro 3, 27100 Pavia
Guiseppe Spinetti	162 Responsabile Del Servizio, Psichiatrico Di Diagnosi E Cura, Ospedale Di Costa Rainera, Via Aurelia, 18100 Imperia
UK	
Michael Isaac	202 Lewisham And Guy'S Mental Health Nhs Trust, Lewisham Hospital, Lewisham High Street, London
Peter Jenkins	203 St. Cadock Hospital, Newport, Gwent
Chris Freeman	204 The Andrew Duncan Clinic, Royal Edinburgh Hospital, Morningside Terrace, Edinburgh
Belgium	
Andre De Nayer	300 Clinique Sainte Therese secretariat De Psychiatrie, Rue Trieu Kaisin 134, Montigny Sur Sambre, 6061
Christine Reynaert	302 Service Psychiatrie, Clinique Universitaire Ucl, Avenue Docteur Therasse, 1, Yvoir, 5530
Grigori Stefos	304 Hopital St. Pierre, Service de Psychiatrie, Rue Haute 322, B- 1000 Brussels
Ireland	
Oscar Daly	400 Department of Psychiatry, Lagan Valley Hospital, Lisburn BT28 1JP
France	
Aurore Seguin	502 79 rue Caulaincourt, 75018 Paris
Jean- Michel Darves- Bornoz	503 Clinique psychiatrique Universitaire, CHU de Tours, Rue du Coq, 37044 Saint Cyr sur Loire
Michel Goudemand	504 Service de Psychiatrie Generale, Clinique Michel Fontan, 6 rue du Professeur Laguesse, 59037 Lille
Joel Gailledreau	505 Centre Medical Claude Bernard, 3 avenue du Mont Cassel, 78990 Elancourt

Investigator	Center No.	Affiliation/ Address
Bernard Vanier	506	45 rue du Marechal Foch, 78000 Versailles
South Africa		
Dan Stein	600	Department of Psychiatry, University of Stellenbosch, Fansie Van Zyl Drive, Tygerborg 7505, Cape Town
Michael Berk	601	58 Forest Road, Bramley, Johannesburg 2090
Charl Els	602	Calmdene, 125 president Reitz Avenue, Westdene, Bloemfontein 9301
Ian Taylor	603	114 Park Medical Center, St Georges Park, Port Elizabeth
Catherine Maud	604	Suite 5 Westville Hospital, Spine Road, Westville 3630
Marius Mathey	605	30 Langwa Crescent, Wapadrand, Pretoria
Clare Hollands	606	Suite 211, Medical Centre, Kenridge Hospital, Eton Road, Parktown
Farouk Randeree	607	1303 Durdoc Centre, 460 Smith Street, Durban 4001
Paull Strong	608	Libertas Medical Centre, Voortrekker Street, Goodwood 7460, Cape Town
Germany		
U Frommberger	700	Klinikum Der Albert- Ludwigs- Universitaet, Hauptstr. 5, Freiburg 79104
Adolf Pietzcker	702	Universitaetsklinikum Benjamin Franklin, Platanenallee 19, Berlin 14050
Austria*		
Siegfried Kasper	703	Department of General Psychiatry, University of Vienna, A- 1090 Vienna, Wahringer Gurtel 18- 20
Canada		
Jean- Pierre Fournier	800	Centre Hospitalier Universitaire de Quebec Pavillon CHUL 2705 boul. Laurier Ste- Foy Quebec
Kevin Kjernisted	801	Anxiety Disorders Clinic, St. Boniface Hospital, M- 1- 409 Tache Bld., Winnipeg, Manitoba, R2H 2A6
Margaret Oakander	802	Department of Psychiatry, Calgary General Hospital, Bow Valley Centre, 841 Centre Avenue, Calgary, Alberta T2E 0A1
Francisco Pinero-Medina	803	Centre Universitaire de Sante De L'Estrie Site Bowen 555 rue Murray Sherbrooke PQ
Nicholas Coupland	804	Department of Psychiatry, University of Alberta, Room 1E7.28 Mackenzie Centre, 8440- 112 Street, Edmonton, Alberta T6G 2B7
Peter Stenn	805	St. Michaels Hospital, 30 Bond Street, Suite 4103M, Toronto, Ontario M5B 1W8
Lee Rasmusen	806	Inova Health Research Inc., 1441 Ellis St., Suite 205, Kelowna, British Columbia, V1Y 2A3

*Centre 703 was run by SB Germany and therefore is listed as a German centre in the Data Source Tables and Listings.

Table 7.1.2 Schedule of Assessments (as provided by the sponsor).

Assessments	Screening (Day -7)	Baseline (Day 0)	Treatment Phase Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12	Taper end Visit	Early termination	14 day follow-up[1]	Safety follow-up
Written informed consent	X											
Patient demography	X											
Pharmacotherapy Assessment	X											
Vital signs	X	X						X	X[1]	X	X[1]	X[1]
ECG	X	X[1]						X	X[1]	X	X[1]	
Medical/surgical history	X											
Physical examination	X	X[1]						X		X	X[1]	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (Serum)	X											
Laboratory evaluation	X	X[1]						X	X[1]	X	X[1]	X[1]
MINI	X											
CAPS-1	X											
Inclusion/exclusion criteria	X	X										
Adverse Experiences		X	X	X	X	X	X	X	X	X	X	X
Patient randomization		X										
CAPS-2		X			X		X	X		X		
Clinical Global Impression (CGI)		X*	X	X	X	X	X	X		X		
Sheehan Disability Scale		X				X		X		X		
MADRS		X						X		X		
TOP 8		X						X		X		
DTS		X			X		X	X		X		
Employment status and earnings		X										
Job Attendance: Days off work		X	X	X	X	X	X	X		X		
EuroQol		X						X		X		
Study Med Record/Compliance	X	X	X	X	X	X	X	X	X	X		

TOP 8 = Treatment Outcome PTSD Scale; DTS = Davidson Trauma Scale; MINI= Mini International Neuropsychiatric Interview; CAPS 1 & 2 = Clinician Administered PTSD Scale for DSM-IV
MADRS = Montgomery and Asberg Depression Rating Scale; *CGI Severity of Illness item only
[1]All patients (including patients who either prematurely terminated or who completed the study with an ongoing adverse experience)
[1]Laboratory evaluations and ECG to be performed only if abnormal values were noted at the Screening / Week 12 or Early Termination evaluations; Physical examination to be performed only if abnormal values were noted at Screening, Week 12 or Early termination evaluations; Vitals to be performed only if abnormal values were noted at Week 12 or Early Termination, taper end or 14 day follow up.

Table 7.1.3 Studies 651, 648 and 627: Mean Baseline Efficacy Scores by Study ITT Population

		Fixed Dosage Study Study 651			Flexible Dosage Studies			
					Study 648		Study 627	
		Paroxetine						
	Scale	placebo	20 mg	40 mg	placebo	paroxetine	placebo	paroxetine
CAPS- 2	n	186	183	182	156	151	161	158
Total	mean	74.4	75.3	74.3	73.2	74.3	78.4	77.4
	SE	1.2	1. 2	1.2	1. 3	1.4	1. 3	1.5
DTS	n	185	181	181	155	150	161	157
Total	mean	75.2	77.4	73.8	73.6	73.1	84.1	81.5
	SE	1.9	1. 8	1.8	1. 8	1.9	1. 9	1.8
CGI	n	186	183	182	156	151	162	159
Severity	median	4.0	5. 0	5.0	5. 0	4.0	5. 0	5.0
TOP- 8	n	185	183	182	156	151	161	157
Total	mean	18.5	18.4	18.4	18.2	18.3	20.1	19.4
	SE	0.3	0. 3	0.4	0. 4	0.4	0. 4	0.4
SDS	n	177	171	170	154	146	147	145
Total	mean	16.6	16.6	16.2	17.3	17.0	20.6	19.4
	SE	0.5	0. 5	0.5	0. 6	0.6	0. 5	0.5
MADRS	n	185	183	182	156	151	161	157
	mean	24. 4	25. 2	24. 9	21. 2	22. 2	26. 3	25. 6
	Se	0.6	0. 6	0.6	0. 7	0.7	0. 7	0.7

Table 7.1.4 Efficacy Results for Study 651

CAPS- 2 Total Score Baseline and Change from Baseline by Week and Treatment Group (ITT Population)									
	Placebo			Paroxetine 20 mg			Paroxetine 40 mg		
	n	Mean	SE	n	Mean	SE	n	Mean	SE
Baseline	186	74.4	1. 2	183	75.3	1. 2	182	74.3	1. 2
LOCF									
Week 4	163	-20.1	1. 8	162	-30.0	1. 7	154	-31.0	2. 1
Week 8	167	-24.3	1. 9	166	-36.7	2. 0	156	-35.9	2. 2
Week 12	167	-25.3	2. 0	166	-39.6	2. 0	156	-37.9	2. 3
OC									
Week 4	158	-20.8	1. 8	152	-31.4	1. 8	140	-32.3	2. 2
Week 8	134	-28.0	2. 0	138	-38.9	2. 1	118	-40.6	2. 4
Week 12	107	-30.0	2. 4	103	-44.2	2. 3	101	-43.6	2. 8

Treatment Difference						
	20 mg vs Placebo			40 mg vs Placebo		
	Difference*	95% CI	p- value	Difference*	95% CI	p- value
LOCF						
Week 4	-9.9	-14.8, -5. 1	<0. 001	-10.7	-15.6, -5. 8	<0. 001
Week 8	-12.5	-17.8, -7. 2	<0. 001	-11.5	-16.9, -6. 1	<0. 001
Week 12	-14.3	-19.7, -8. 8	<0. 001	-12.2	-17.7, -6. 6	<0. 001
OC						
Week 4	-10.6	-15.6, -5. 7	<0. 001	-11.2	-16.2, -6. 1	<0. 001
Week 8	-10.8	-16.5, -5. 0	<0. 001	-11.4	-17.3, -5. 5	<0. 001
Week 12	-13.9	-20.7, -7. 1	<0. 001	-12.1	-18.9, -5. 3	<0. 001

*Adjusted for treatment, center and covariates

Table 7.1.5 Efficacy Results for Study 651

Number (%) of Responders on the Clinical Global Impression, Global Improvement Item by Study Visit (ITT Population)

CGI- I Responders**	Placebo			Paroxetine 20 mg			Paroxetine 40 mg		
	n	%	N	n	%	N	n	%	N
LOCF									
Week 1	13	7. 7	169	11	6.3	176	17	10.1	168
Week 2	27	14.8	183	45	25.0	180	35	20.0	175
Week 4	48	26.2	183	85	47.2	180	76	43.4	175
Week 6	52	28.4	183	99	55.0	180	84	48.0	175
Week 8	63	34.4	183	106	58.9	180	96	54.9	175
Week 12	67	36.6	183	113	62.8	180	99	56.6	175
OC									
Week 1	13	7. 7	169	11	6.3	176	17	10.1	168
Week 2	27	15.4	175	44	25.7	171	35	21.6	162
Week 4	47	29.2	161	83	55.0	151	74	51.7	143
Week 6	48	34.8	138	85	63.4	134	74	59.2	125
Week 8	61	45.5	134	95	67.9	140	85	70.8	120
Week 12	51	48.1	106	78	75.7	103	72	71.3	101

Pairwise Comparisons						
CGI- I Responders**	20 mg vs Placebo			40 mg vs Placebo		
	Odds Ratio*	95% CI	p value	Odds Ratio*	95% CI	p value
LOCF						
Week 1	0. 00	-	-	-	-	-
Week 2	0. 00	-	-	-	-	-
Week 4	2. 82	1. 7, 4.6	<0.001	2.44	1.5, 4.0	<0.001
Week 6	3. 62	2. 2, 5.9	<0.001	2.64	1.6, 4.3	<0.001
Week 8	2. 91	1. 9, 4.6	<0.001	2.45	1.6, 3.9	<0.001
Week 12	3.20	2.0, 5.1	<0.001	2.42	1.5, 3.8	<0.001
OC						
Week 1	0. 80	0. 3, 1.9	0. 603	1.37	0.6, 2.9	0. 426
Week 2	1. 98	1. 2, 3.4	0. 014	1.58	0.9, 2.8	0. 116
Week 4	3. 12	1. 9, 5.1	<0.001	2.95	1.8, 4.9	<0.001
Week 6	3. 30	2. 0, 5.5	<0.001	2.82	1.7, 4.7	<0.001
Week 8	2. 55	1. 5, 4.2	<0.001	2.99	1.8, 5.1	<0.001
Week 12	3.52	1.9, 6.5	<0.001	2.90	1.6, 5.2	<0.001

*The odds ratio represents the odds of improving with paroxetine relative to that with placebo. Adjusted for treatment, center and covariates. The odds ratio could not be calculated for weeks 1 and 2 of the LOCF analysis due to non- convergence of the center effect.

** A responder was defined as a score of 1 (very much improved) or 2 (much improved) on the scale at endpoint

Tables 7.2.1 A and B. Efficacy Results for Study 648

Tables 7.2.1 A. CAPS- 2 Total Score Baseline and Change from Baseline by Week and Treatment Group (ITT)

	Placebo			Paroxetine			Paroxetine vs Placebo		
	n	Mean	SE	N	Mean	SE	Diff.*	95% CI	p value
Baseline	156	73.2	1. 3	151	74.3	1. 4			
LOCF									
Week 4	133	-16.1	1. 6	133	-21.8	1. 8	-5. 7	-10.5, -0. 9	0.019
Week 8	133	-22.6	1. 8	136	-30.4	2. 0	-7. 3	-12.7, -2. 0	0.008
Week 12	133	-24.7	2. 0	136	-35.5	2. 0	-10.6	-16.2, -5. 0	<0. 001
70% LOCF Endpoint	133	-16.1	1. 6	136	-22.1	1. 8	-5. 9	-10.8, -1. 1	0.017
OC									
Week 4	130	-15.7	1. 6	119	-22.4	1. 8	-7. 4	-12.3, -2. 5	0.003
Week 8	111	-24.1	2. 1	101	-32.8	2. 3	-8. 8	-14.8, -2. 8	0.004
Week 12	92	-27.4	2. 5	87	-40.7	2. 2	-14.0	-20.8, -7. 2	<0. 001

*Adjusted for center, gender, baseline total CAPS- 2 score, trauma type, time since trauma and baseline MADRS score.

Tables 7.2.1 B. Number (%) of Responders on the Clinical Global Impression, Global Improvement Item by Study Visit (ITT)

CGI- I	Placebo			Paroxetine			Paroxetine vs Placebo		
Responders**	n	%	N	n	%	N	Odds Ratio*	95% CI	p value
LOCF									
Week 1	7	5.0	141	10	7.0	143	1.9	0. 7, 5.4	0. 231
Week 2	8	5.3	150	33	22.3	148	5.4	2. 4, 12.3	<0.001
Week 4	25	16.7	150	51	34.5	148	2.7	1. 5, 4.7	<0.001
Week 6	41	27.3	150	72	48.6	148	2.9	1. 7, 4.9	<0.001
Week 8	54	36.0	150	77	52.0	148	2.1	1. 3, 3.4	0. 003
Week 12	57	38.0	150	87	58.8	148	2.6	1. 6, 4.3	<0.001
70% LOCF Endpoint	41	27.3	150	72	48.6	148	2.9	1. 7, 4.9	<0.001
OC									
Week 1	7	5.0	141	10	7.0	143	1.9	0. 7, 5.4	0. 231
Week 2	8	5.7	141	32	23.9	134	5.4	2. 3, 12.4	<0.001
Week 4	25	19.2	130	46	37.7	122	2.5	1. 4, 4.5	0. 002
Week 6	38	31.4	121	67	60.4	111	4.0	2. 2, 7.5	<0.001
Week 8	52	46.4	112	64	62.7	102	2.2	1. 2, 3.9	0. 010
Week 12	46	50.0	92	66	75.9	87	4. 0	1.9, 8.3	<0.001

*The odds ratio represents the odds of improving with paroxetine relative to that with placebo. Adjusted for center, gender, trauma type, time since trauma and baseline MADRS score.
** A responder was defined as a score of 1 (very much improved) or 2 (much improved) on the scale at endpoint
Note: Center has been excluded from the model at weeks 1, 2 and 4 due to non- convergence.

Table 7.2.2. Study 648: Change from Baseline in Total CAPS- 2 Score by Time Since Trauma (Intent- to-Treat Population Adjusted for Center Group, Baseline Total Score, Gender, Trauma Type, Time since Trauma, Treatment* Time since Trauma and Baseline MADRS Score)

		Paroxetine			Placebo						
		Mean	s. e.	N.	Mean	s. e.	N	AMD#	Lower 95% CI	Upper 95% CI	p-value
< 5 years	Baseline	74.88	2.54	52	75.33	2.09	54	.	.	.	.
	Week 12 OC	-40.43	3.20	23	-29.94	4.21	33	-13.46	-26.19	-0. 72	0. 039
	Week 12 LOCF	-31.09	3.25	45	-27.87	3.52	47	-3. 58	-13.22	6.05	0.465
	70% LOCF	-18.56	2.85	45	-19.19	2.72	47	0.74	-7. 63	9. 10	0. 862
5 to < 20 years	Baseline	74.09	2.16	54	74.35	2.27	46	.	.	.	.
	Week 12 OC	-42.62	4.10	34	-26.40	4.39	25	-13.05	-25.11	-1. 00	0. 034
	Week 12 LOCF	-39.00	3.33	50	-25.64	3.42	36	-11.34	-21.51	-1. 17	0. 029
	70% LOCF	-24.68	3.10	50	-15.58	3.07	36	-8. 49	-17.31	0.34	0.060
≥ 20 years	Baseline	73.61	2.63	44	70.46	2.19	54	.	.	.	.
	Week 12 OC	-38.77	3.80	30	-25.61	4.41	33	-13.57	-24.93	-2. 21	0. 020
	Week 12 LOCF	-36.15	3.56	41	-20.82	3.49	49	-16.48	-26.47	-6. 49	0. 001
	70% LOCF	-22.98	3.44	41	-13.49	2.47	49	-10.01	-18.69	-1. 33	0. 024

Adjusted Mean Difference, Subgroups may be underpowered to detect statistical significance

Tables 7.3.1 A and B. Efficacy Results for Study 627

Tables 7.3.1 A Summary of the Change on the CAPS- 2 Total Score Relative to Baseline at Each Visit, by Treatment Group : ITT Population

	Paroxetine			Placebo			Paroxetine vs Placebo		
	N	Mean	s. e.	N	Mean	s. e.	Diff+	95% CI	p value
Baseline	158	77.4	1. 5	161	78.4	1. 3	-	-	-LOCF
Wk 1	148	-8. 9	1.1	155	-7. 1	1.0	-1.5	-4.4, 1.3	0. 293
Wk 2	154	-13.8	1. 4	159	-11.6	1. 4	-2. 6	-6. 2, 1.0	0. 161
Wk 4	154	-19.5	1. 6	159	-15.1	1. 6	-4. 5	-8. 8, -0. 2	0.039*
Wk 6	154	-23.0	1. 8	159	-20.2	1. 7	-3. 2	-8. 0, 1.6	0. 189
Wk 8	154	-27.5	1. 9	159	-24.1	1. 8	-3. 8	-8. 8, 1.3	0. 141
Wk 12	154	-30.8	2. 1	159	-26.2	1. 9	-5. 5	-10.9, -0. 1	0.047*
OC									
Wk 1	148	-8. 9	1.1	155	-7. 1	1.0	-1.5	-4.4, 1.3	0. 293
Wk 2	141	-14.7	1. 5	149	-11.8	1. 4	-3. 4	-7. 2, 0.4	0. 082
Wk 4	133	-20.8	1. 7	140	-15.8	1. 8	-4. 9	-9. 6, -0. 2	0.039*
Wk 6	122	-24.4	2. 0	126	-21.2	2. 0	-3. 0	-8. 5, 2.4	0. 269
Wk 8	121	-30.7	2. 2	120	-26.1	2. 1	-3. 6	-9. 4, 2.2	0. 224
Wk 12	109	-36.5	2. 5	103	-30.8	2. 5	-6. 2	-13.0, 0.5	0. 071

*Statistically significant at p< 0. 05, 70% Endpoint was week 6 (LOCF)
+Difference in adjusted least square means (adjusted for centre and covariates: gender, baseline CAPS- 2 score, baseline MADRS, trauma type and duration of trauma)

Tables 7.3.1 B Summary of Responders for CGI Items 1 or 2 (All Countries) at Each Visit : ITT Population

	Treatment Group								
	Paroxetine			Placebo			Paroxetine vs Placebo		
	n	%	N	n	%	N	Odds Ratio+	95% CI	p value
LOCF									
Wk 1	17	11.3	150	12	7.7	156	-	-	-Wk
2	32	20.5	156	25	15.5	161	1.53	0.8, 3. 0	0. 212
Wk 4	55	35.3	156	32	19.9	161	2.47	1.4, 4. 3	0. 001*
Wk 6	65	41.7	156	54	33.5	161	1.51	0.9, 2. 5	0. 102
Wk 8	71	45.5	156	63	39.1	161	1.40	0.9, 2. 3	0. 177
Wk 12	78	50.0	156	70	43.5	161	1.46	0.9, 2. 4	0. 134
OC									
Wk 1	17	11.3	150	12	7.7	156	-	-	-Wk
2	30	21.0	143	25	16.8	149	1.46	0.7, 2. 9	0. 278
Wk 4	51	38.3	133	30	21.3	141	2.62	1.5, 4. 7	0. 001*
Wk 6	57	46.7	122	48	37.8	127	1.55	0.9, 2. 7	0. 118
Wk 8	64	52.5	122	54	44.6	121	1.48	0.9, 2. 6	0. 167
Wk 12	65	59.6	109	54	52.4	103	1.66	0.9, 3. 1	0. 115

*Statistically significant at p< 0. 05
70% Endpoint was week 6 (LOCF)
+The odds ratio represents the odds of improving with paroxetine relative to the odds of improving with placebo. Adjusted for centre and covariates (gender, baseline CGI Items 1 and 2, baseline MADRS, trauma type and duration of trauma)

Table 8.1.2.1 Post- Randomization Phase Emergent Non-Fatal Serious Adverse Experiences in Studies:651, and 627

Patient Number	Age (years)	Sex	Days on Study at Event Onset	Total Days on Dbl-Blind Study Drug	Serious Adverse Experience	Severity	Relationship	Action
Placebo								
651.028.07310	28	F	55	56	Anxiety, Depression, Emotional Lability, Thinking Abnormal, Trauma	Severe	Unrelated	Drug Stopped
651.040.07501	25	F	24	26	Hypertension Intracranial	Severe	Unrelated	Drug Stopped
648.801.00064	39	F	21	14	Emotional Lability	Severe	Unrelated	None
648.808.00401	38	M	7	6	Angina Pectoris	Severe	Unrelated	Drug Stopped
648.821.01008	23	F	45	34	Unintended Pregnancy	Severe	Unrelated	Drug Stopped
648.832.01559	28	F	33	44	Pregnancy and Puerperal Disorder	Severe	Unrelated	Drug Stopped
627.100.01062	25	F	55	80	Agitation	Moderate	Unrelated	None
627.100.01065	22	M	21	84	Anxiety	Severe	Unrelated	None
627.503.01471	29	M	9	15	Convulsion	Severe	Possibly Related	Drug Stopped
627.600.01310	32	F	109	84	Anxiety	Mild	Unrelated	None
627.605.01060	57	F	73	82	Gastrointestinal Disorder,	Moderate	Probably Unrelated	None
					Haematemesis	Mild	Unrelated	None
627.606.01700	34	M	14	6	Alcohol Abuse, Depression, Emotional Lability	Severe	Unrelated	None
627.606.01707	23	F	123	86	Ovary Disorder	Severe	Unrelated	None
627.703.01328	29	F	4	4	Emotional Lability	Severe	Unrelated	Drug Stopped
627.802.01101	45	M	1	1	Depression	Severe	Unrelated	None
Paroxetine								
651.012 07942	50	M	56	86	Skin Benign Neoplasm	Moderate	Unrelated	None
651.013.07013	42	M	45	72	Accidental Overdose	Mild	Related	Drug Stopped
651.019.07653	33	F	20	57	Uterine Neoplasm	Severe	Unrelated	Drug Stopped
651.024.07103	38	F	2	11	Headache	Severe	Possibly Related	Drug Stopped
651.034.07802	27	F	91	83	Anxiety	Severe	Unrelated	None
					Emotional Lability, Hallucinations	Moderate	Unrelated	None

Table 8.1.2.1 continued

Patient Number	Age (years)	Sex	Days on Study at Event Onset	Total Days on Dbl-Blind Study Drug	Serious Adverse Experience	Severity	Relationship	Action
651.052.07095	46	F	26	24	Emotional Lability	Moderate	Probably Unrelated	None
651.055.07711	38	F	16	15	Emotional Lability	Severe	Unrelated	Drug Stopped
651.056.07296	18	F	76	76	Unintended Pregnancy	Mild	Unrelated	Drug Stopped
651.063.07416	30	F	21	55	Rectal Hemorrhage,	Moderate	Probably Unrelated	None
					Ileitis	Severe	Unrelated	Drug Stopped
			69	55	Manic Reaction	Moderate	Unrelated	Drug Stopped
648.800.00019	28	F	68	80	Pneumonia	Severe	Unrelated	None
648.808.00406	47	M	84	84	Alcohol Abuse	Severe	Unrelated	Drug Stopped
648.816.00752	56	F	116	84	Cholecystitis	Severe	Unrelated	None
648.823.01104	22	F	101	85	Dyspnea, Nausea	Severe	Possibly Related	None
					Migraine	Severe	Related	None
648.826.01251	28	F	83	80	Unintended Pregnancy	Severe	Unrelated	None
648.829.01415	59	M	2	84	Skin Carcinoma	Mild	Unrelated	None
648.830.01453	58	F	15	55	Cellulitis	Severe	Probably Unrelated	None
648.830.01461	52	F	3	3	Tachycardia	Severe	Possibly Related	Drug Stopped
831.01503	30	F	77	71	Stillbirth, Unintended Pregnancy	Severe	Unrelated	None
648.836.01754	23	F	1	4	Nausea	Moderate	Related	None
			2	4	Vomiting	Severe	Related	None
627.503.01478	39	F	4	22	Anxiety, Depression	Severe	Unrelated	None
627.505.01121	45	F	36	32	Depression	Severe	Possibly Related	None
627.601.01047	52	F	10	84	Headache	Severe	Possibly Related	None
627.603.01028	27	M	4	4	Depression, Emotional Lability	Severe	Unrelated	Drug Stopped
627.606.01042	46	F	23	85	Syncope	Moderate	Unrelated	None
627.606.01891	41	F	87	81	Depression, Emotional Lability	Severe	Unrelated	None
627.802.01674*	33	F	88	81	Unintended Pregnancy		Unrelated	None
648.838.01857	37	M	23	23	Depression, Emotional Lability	Moderate	Possibly Related	Drug Stopped

*Not captured as an SAE in study 627 report.

Table 8.1.2.2 Line Listings of Subjects with Serious Adverse Events in the Ongoing Study 650					
Identification Number	**Verbatim Term**	**Drug**	**Date of Onset**	**Start/End Date(s) of Study Drug**	**Outcome**
650.002.05804	Chest pain	29060	Oct 29 1999	Aug 12 1999 - - - -	Recovered without sequelae
650.002.05804	Cerbrovascular accident	29060 (blinded)	Nov 17 1999	Nov 9 1999 - - - -	Recovered with sequelae
650.302.05912	Pregnancy	29060	Nov 4 1999	Sep 22 1999/ Oct 6 1999 Oct 6 1999 Oct 16 1999	Not yet recovered
650.305.05761	Attack of Asthma, Pneumopathy	29060 (blinded)	Jun 4 1999	Jun 2 1999 Jun 3 1999	Recovered without sequelae, Recovered without sequelae
650.307.05737	Popliteal Anuerysm	29060	Feb 25 2000	Jan 13 2000 Feb 25 2000	Recovered without sequelae
650.307.06282	Suicide	29060	Mar 30 2000	Mar 23 2000 Mar 30 2000	Death due to AE
650.901.05884	Extrasystolic arrhythmia	29060 (blinded)	Dec 16 1999	Jul 9 1999 - - - -	Not Yet recovered
650.901.05886	Hysterectomy/ ovarectomy	29060	Feb 21 2000	Dec 16 1999 - - - -	Recovered without sequelae, Recovered without sequelae
650.901.05887	Depression Alcohol withdrawal	29060 (blinded)	Jan 21 2000 Jan 21 2000	Apr 28 1999 Jan 14 2000	Recovered without sequelae
650.xxx.xxxx	Back Pain (worsening)	29060 (blinded)	May 3 2000	- - - - - - - -	- - - -

Table 8.1.3.1 Summary of Treatment Phase Emergent Adverse Experiences Leading to Withdrawal of Two or More Patients by Body Systems and Preferred Terms (as provided by the sponsor) - Studies 651, 648 and 627 (ITT Population)

Body Systems		Placebo N =504		Paroxetine N = 676
Preferred Terms	**n**	**(%)**	**n**	**(%)**
Body as a Whole				
Abdominal Pain	1	(0.2)	2	(0.3)
Asthenia	1	(0.2)	11	(1.6)
Chest Pain	2	(0.4)	1	(0.1)
Headache	6	(1.2)	11	(1.6)
Cardiovascular System				
Vasodilation	0	(0. 0)	2	(0. 3)
Digestive System				
Constipation	1	(0. 2)	3	(0. 4)
Decreased Appetite	0	(0. 0)	3	(0. 4)
Diarrhea	0	(0.0)	4	(0.6)
Dry Mouth	0	(0.0)	2	(0.3)
Flatulence	0	(0.0)	2	(0.3)
Nausea	3	(0.6)	15	(2.2)
Vomiting	1	(0.2)	5	(0.7)
Nervous System				
Agitation	5	(1. 0)	1	(0. 1)
Anxiety	3	(0.6)	7	(1.0)
Concentration Impaired	1	(0.2)	2	(0.3)
Confusion	0	(0.0)	2	(0.3)
Depression	6	(1.2)	6	(0.9)
Dizziness	2	(0.4)	6	(0.9)
Emotional Lability	2	(0. 4)	5	(0. 7)
Insomnia	3	(0.6)	4	(0.6)
Nervousness	2	(0.4)	0	(0.0)
Somnolence	3	(0.6)	19	(2.8)
Tremor	1	(0.2)	7	(1.0)
Respiratory System				
Yawn	0	(0.0)	3	(0.4)
Skin and Appendages				
Rash	2	(0.4)	1	(0.1)
Special Senses				
Abnormal Vision	0	(0.0)	3	(0.4)
Urogenital System				
Abnormal Ejaculation*	0	(0.0)	2	(0.8)
Impotence*	0	(0.0)	2	(0.8)
Female Genital Disorders*	0	(0.0)	3	(0.7)
Unintended Pregnancy*	1	(0. 3)	2	(0. 5)

SOURCE: ISS Data Source Table 7.6.3, Section 22

* Percentage corrected for gender

Table 8.1.4.1. A Summary of Results (Incidence) on Taper Phase Emergent Adverse Events

	Placebo N=256	**Paroxetine N=345**
Adverse Event (AE):	**%**	**%**
Gender Non-Specific	19.1	33.6
AE's occurring in Paroxetine subjects at twice the rate of Placebo subjects:		
Dizziness	1.2	4.6
Abnormal Dreams	0.0	1.2
Agitation	0.0	1.2
Nervousness	0.8	2.9
Paresthesia	0.8	2.3
Vertigo	0.4	2.3
Trauma	0.8	1.7
AE's occurring in at least 1% of subjects in a treatment group:		
Asthenia	1.2	1.4
Headache	3.9	4.1
Infection	1.2	1.2
Diarrhea	1.2	1.2
Nausea	2.0	2.3
Anxiety	3.1	4.3
Depression	1.2	1.2
Insomnia	2.7	4.3
Sinusitis	1.2	1.2
Gender Specific* in Females	2.0	0.0
Gender Specific in Males	Not reported	Not reported

*Percentages adjusted for that gender

Data source: Table 27 on page 90 of the ISS of the submission.

Table 8.1.4.2. Incidence of Follow-up Phase Emergent Adverse Events Reported in ≥1% of Paroxetine Subjects

	Placebo N=250	**Paroxetine N=301**
Adverse Event (AE):	**%**	**%**
Gender non-specific	25.6	31.9
AE's occurring in Paroxetine subjects at twice the rate of Placebo subjects:		
Back Pain	0.0	1.0
Vasodilatation	0.0	1.0
Dizziness	0.8	6.0
Nervousness	0.4	1.3
Paresthesia	0.0	1.3
Tremor	0.0	1.3
Vertigo	0.0	1.0
Vestibular Disorder	0.0	1.0
Sweating	0.4	1.0
AE's occurring in at least 1% of subjects in a treatment group:		
Headache	1.6	2.0
Diarrhea	1.6	1.0
Nausea	3.6	3.7
Anxiety	4.0	4.0
Depression	3.2	2.3
Emotional Lability	2.0	2.0
Insomnia	3.2	3.7
Somnolence	2.0	1.3
Respiratory disorder	1.6	1.0
Gender Specific* in Females	1.3	1.0
Gender Specific in Males	3.1	0.0

*Incidence adjusted for that specific gender

Table 8.1.5.1 Treatment Phase Emergent Adverse Experiences Occurring in >/= 2% of Paroxetine Patients

(Treatment Phase, ITT Population, Studies 651, 648 and 627)

	Placebo N =504		Paroxetine N =676	
Preferred Term	**n**	**%**		**(%)**
Nausea	42	(8.3)	130	(19.2)
Headache	97	(19.2)	128	(18.9)
Somnolence	23	(4.6)	108	(16.0)
Abnormal Ejaculation*	3	(1.6)	30	(12.6)
Asthenia	21	(4.2)	80	(11.8)
Insomnia	57	(11.3)	80	(11.8)
Diarrhea	27	(5.4)	71	(10.5)
Dry Mouth	24	(4.8)	68	(10.1)
Impotence*	1	(0.5)	22	(9.2)
Respiratory Disorder	35	(6.9)	44	(6.5)
Dizziness	23	(4.6)	41	(6.1)
Decreased Appetite	13	(2. 6)	40	(5. 9)
Trauma	26	(5.2)	39	(5.8)
Constipation	17	(3. 4)	37	(5. 5)
Libido Decreased	9	(1.8)	35	(5.2)
Infection	19	(3.8)	33	(4.9)
Female Genital Disorders*	2	(0. 6)	21	(4. 8)
Dyspepsia	17	(3.4)	31	(4.6)
Sweating	7	(1.4)	31	(4.6)
Abdominal Pain	16	(3.2)	29	(4.3)
Tremor	7	(1.4)	29	(4.3)
Anxiety	20	(4.0)	26	(3.8)
Sinusitis	22	(4.4)	26	(3.8)
Back Pain	17	(3.4)	23	(3.4)
Abnormal Vision	5	(1.0)	22	(3.3)
Nervousness	22	(4.4)	20	(3.0)
Vomiting	10	(2.0)	20	(3.0)
Abnormal Dreams	8	(1.6)	17	(2.5)
Depression	15	(3.0)	17	(2.5)
Pharyngitis	11	(2.2)	16	(2.4)
Vasodilatation	6	(1. 2)	15	(2. 2)
Yawn	1	(0.2)	14	(2.1)

* Percentage corrected for gender

SOURCE: ISS Data Source Table 7.3.1X, Section 22

Table 8.1.5.2. Summary of Treatment Phase Emergent Adverse Experiences Occurring in 5% or More of the Paroxetine Population by Gender - Studies 651, 648 and 627 (ITT Population)

Gender	Female				Male			
	Placebo		Paroxetine		Placebo		Paroxetine	
Preferred	N =314		N =438		N =190		N =238	
Terms	n	(%)	n	(%)	n	(%)	n	(%)
Nausea	31	(9.9)	90	(20.5)	11	(5.8)	40	(16.8)
Headache	64	(20.4)	96	(21.9)	33	(17.4)	32	(13.4)
Somnolence	12	(3.8)	73	(16.7)	11	(5.8)	35	(14.7)
Abnormal Ejaculation	0	(0.0)	0	(0.0)	3	(1.6)	30	(12.6)
Asthenia	18	(5.7)	65	(14.8)	3	(1.6)	15	(6.3)
Insomnia	29	(9.2)	56	(12.8)	28	(14.7)	24	(10.1)
Diarrhea	21	(6.7)	42	(9.6)	6	(3.2)	29	(12.2)
Dry Mouth	17	(5.4)	47	(10.7)	7	(3.7)	21	(8.8)
Impotence	0	(0.0)	0	(0.0)	1	(0.5)	22	(9.2)
Respiratory Disorder	23	(7.3)	31	(7.1)	12	(6.3)	13	(5.5)
Dizziness	16	(5.1)	28	(6.4)	7	(3.7)	13	(5.5)
Decreased Appetite	7	(2. 2)	27	(6. 2)	6	(3. 2)	13	(5. 5)
Trauma	20	(6.4)	24	(5.5)	6	(3.2)	15	(6.3)
Constipation	10	(3.2)	25	(5.7)	7	(3.7)	12	(5.0)
Libido Decreased	4	(1.3)	20	(4.6)	5	(2.6)	15	(6.3)

Table 8.1.6.1.1 A. Predefined Clinical Laboratory Values of Potential Clinical Concern

PARAMETER	VALUE	UNITS	PARAMETER	VALUE	UNITS
Hematology			Blood Chemistry		
White Blood Cells	<2. 8, >16	10^ 9/ L	ALT/ SGPT	>165	IU/ L
Basophils	10	%	Alkaline Phosphatase	>390	IU/ L
Eosinophils	10	%	AST/ SGOT	>150	IU/ L
Lymphocytes	75	%	Blood Urea Nitrogen	>10.71	mmol/ L
Monocytes	15	%	Serum Creatinine	>176.8	umol/ L
Segmented Neutrophils	15	%	Total Bilirubin	>34.2	umol/ L
Neutrophils Bands	>10	10^ 9/ L	Potassium	<3. 0, >6. 0	mmol/ L
Platelets	<75, >700	10^ 9/ L	Sodium	<126, >156	mmol/ L
Red Blood Cells Male	>8	10^ 12/ L	TSH	>10	mU/ L
Female	>10	10^ 12/ L			
Hematocrit Male	<37	%			
Female	<32	%			
Hemoglobin Male	<115	g/ L			
Female	<95	g/ L			

The above table is Table 29 in the ISS of the submission, Source as indicated in the submission: Study 651 Data Source Table 15. 3. 2, Section 13

Table 8.1.6.1.1 B. Predefined Vital Sign Values of Potential Clinical Concern

Variable	Normal Range		Changes from baseline	
Diastolic Blood Pressure (mmHg)	50- 105	decrease	20, increase	30
Systolic Blood Pressure (mmHg)	90- 180	decrease	30, increase	40
Pulse Rate (bpm)	50- 120	decrease	30, increase	30

Table 8.1.6.1.2 Mean Clinical Lab Value Changes* from Baseline to Endpoint in Hematology Values

	Placebo N= 504			Paroxetine N= 676		
Parameter	**n**	**mean**	**SD**	**n**	**mean**	**SD**
White Blood Cells (10^ 9/ L)						
Baseline	494	7.1	2. 0	668	7.1	2. 1
Δ at Endpoint	317	-0. 1	1.7	413	-0. 0	1.6
Basophils (10^ 9/ L)						
Baseline	492	0.4	0. 4	668	0.4	0. 3
Δ at Endpoint	315	0.0	0. 5	413	0.0	0. 4
Eosinophils (10^ 9/ L)						
Baseline	492	2.8	2. 4	668	2.8	2. 0
Δ at Endpoint	315	-0. 1	2.5	413	-0. 1	1.7
Lymphocytes (10^ 9/ L)						
Baseline	492	30.4	7. 7	668	30.8	7. 9
Δ at Endpoint	315	0.7	7. 8	413	-0. 4	6.6
Monocytes (10^ 9/ L)						
Baseline	492	5.8	2. 4	668	5.6	2. 3
Δ at Endpoint	315	-0. 2	2.4	413	0.2	2. 2
Segmented Neutrophils (10^ 9/ L)						
Baseline	492	60.5	8. 7	668	60.4	8. 6
Δ at Endpoint	315	-0. 5	9.2	413	0.3	7. 3
Platelets (10^ 9/ L)						
Baseline	494	256.3	57.9	668	250.3	58.3
Δ at Endpoint	317	1.4	37.1	413	7.5	37.3
Red Blood Cells (10^ 12/ L)						
Baseline	494	4.6	0. 5	668	4.5	0. 5
Δ at Endpoint	317	-0. 0	0.3	413	-0. 0	0.3
Hematocrit (%)						
Baseline	494	41.9	4. 0	668	41.7	4. 0
Δ at Endpoint	317	-0. 1	2.5	413	-0. 4	2.7
Hemoglobin (g/ L)						
Baseline	494	141.1	14.0	668	140.5	13.7
Δ at Endpoint	317	-0. 7	8.6	413	-1. 4	7.8

*Mean Baseline values and values for mean changes from Baseline to Endpoint were calculated based on Screening values.

This table was provided in the submission, Data Source: ISS Data Source Table 10. 2. 1, Section 22

Table 8.1.6.3 Mean Clinical Lab Value Changes from Baseline to Endpoint in Blood Chemistry Values

	Placebo N= 504			Paroxetine N= 676		
Parameter	**n**	**mean**	**SD**	**n**	**mean**	**SD**
Alanine Aminotransferase (IU/ L)						
Baseline	498	21.8	17.3	671	21.6	15.6
Δ at Endpoint	325	-0. 7	14.2	422	0.7	12.5
Alkaline Phosphatase (IU/ L)						
Baseline	496	70.4	22.3	670	71.4	23.9
Δ at Endpoint	324	-0. 6	9.9	421	2.6	12.7
Aspartate Aminotransferase (IU/ L)						
Baseline	496	19.2	9. 3	670	18.9	8. 1
Δ at Endpoint	324	0.2	7. 7	421	1.3	7. 1
Blood Urea Nitrogen (mmol/ L)						
Baseline	500	4.7	1. 4	672	4.7	1. 5
Δ at Endpoint	330	0.2	1. 1	424	0.2	1. 2
Serum Creatinine (mcmol/ L)						
Baseline	498	71.5	19.6	671	70.8	22.2
Δ at Endpoint	327	2.6	18.9	423	1.0	19.1
Total Bilirubin (mcmol/ L)						
Baseline	498	9.3	7. 3	671	9.0	6. 3
Δ at Endpoint	327	-0. 9	5.6	423	-0. 8	5.1
Potassium (mmol/ L)						
Baseline	496	4.3	0. 5	669	4.3	0. 4
Δ at Endpoint	324	-0. 0	0.5	422	-0. 0	0.5
Sodium (mmol/ L)						
Baseline	500	140.8	2. 3	673	140.9	2. 3
Δ at Endpoint	330	-0. 1	2.7	425	-0. 6	2.6

This table was provided in the submission, Data Source: ISS Data Source Table 10. 2. 1, Section 22

Table 8.1.7.1.1 Population Mean Vital Signs and Mean Changes from Baseline to Endpoint

Treatment Phase, ITT Population, Studies 651, 648 and 627

Parameter	Placebo N= 504			Paroxetine N = 676		
Timepoint	**n**	**Mean**	**S. D.**	**n**	**Mean**	**S. D.**
Systolic BP (sitting)						
Baseline	502	122.19	15.6	676	122.42	15.9
Change at Endpoint	381	-0. 52	13.3	484	-0. 69	12.3
Diastolic BP (sitting)						
Baseline	502	77.33	10.0	676	77.46	10.0
Change at Endpoint	381	-0. 41	8. 1	484	0.16	8.2
Pulse						
Baseline	503	73.98	9.5	676	73.88	9.6
Change at Endpoint	382	0.55	9.0	483	-0. 69	9. 6

SOURCE: ISS Data Source Table 9.2, Section 22

Statistical Review and Evaluation

NDA: 20,031
Applicant: SmithKline Beecham Parmaceuticals
Drug Name: Paxil (paroxetine hydrochloride) tablets
Indication: Posttraumatic Stress Disorder (PTSD)
CDER receiving date: 7/21/2000
Document Reviewed: Electronic submission

This NDA submission is to support the once daily oral administration of paroxetine in treating patients with PTSD In this NDA submission, there are three pivotal studies (Studies 648, 627 and 651) for the efficacy and safety of paroxetine. These studies are the focus of this review.

1. Outline of the studies

Design

Studies 648 and 627 shared a similar design. Both studies were double-blinded, placebo controlled with parallel grouping. The objectives of these studies were to assess the efficacy and safety of paroxetine in treating patients with PTSD. The primary efficacy endpoints for these two studies were mean change from baseline in Clinician Administrated PTSD Scale / Part 2 (CAPS-2) Total Score at endpoint and proportion of responders based on the Clinical Global Impressions global improvement item (CGI), where response was defined as a score of 1 (very much improved) or 2 (much improved) on the scale. Non-response was defined as the score no less than 3. The secondary efficacy variables included change from baseline in the Davidson Trauma Scale, Sheehan Disability Inventory, Treatment Outcome Scale (TOP 8), Montgomery and Asberg Depression Rating Scale (MADRS), Treatment Outcome PTSD Scale. The treatment for these two studies consisted of one week placebo run-in period, followed by a 12 weeks of active treatment phase and a maximum of a three week taper phase after the active treatment period. After the placebo run-in, patients (males and females, ≥18 years, CAPS-2 ≥ 50) were randomized at 1:1 ratio to receive either placebo or paroxetine (20-50mg flexible dose daily) for 12 weeks. The efficacy outcomes for the two treatment groups were to be compared using the intent-to-treat database with LVCF imputation. Continuous variables, including the change from baseline in CAPS-2, were to be analyzed using Analysis of Variance (ANOVA) with treatment and center as terms. Categorical variables, including CGI responders, were to be analyzed using logistic regression with treatment and center as factors. Covariate adjusted analysis was proposed in the protocol. Hypothesis testing was to be performed at 0.05 level (two-sided). The total sample size planned was 250 (125/group) which was sufficient to detect a 10 point difference in the change from baseline in the CAP-2 total score with 90% power. No decision rule on how to reach an efficacy conclusion based on the two primary endpoints was clearly specified in the protocol.

The major difference in trial design between Study 651 and Study 648 or Study 627 was that multiple fixed doses were used in Study 651. In this study, patients were randomized (at 1:1:1 ratio) to receive either placebo, or 20 mg or 40 mg paroxetine once daily. The design of Study 651 in other major aspects were as the same as those in Studies 627 and 648. The planned sample size was 147 subjects per group for Study 651.

2. Sponsor's result

Study 648

This 12-week study involved 37 study centers in the United States and Canada. The first patient was randomized on Feb. 8, 1999 and the last study visit was on Feb 24, 2000. In this study, a total of 323 patients were randomized. The ITT patient population included 307 patients. Out of 16 excluded patients, twelve patients were lost to follow up after baseline visit. The numbers of patients who completed the study were similar in the two treatment groups (94 in placebo and 93 in the paroxetine group).

The following tables summarize the demographic and baseline characteristics and the primary efficacy results for Study 648. The results given in the tables were based ITT patient population and LVCF method unless indicated as for OC or 70% patient populations.

Demographic characteristics / 648

Demographic/baseline Characteristics	Treatment Group	
	Placebo	Paroxetine
	(N=156)	(N=151)
males (n, %)	54 (34.6)	51 (33.8)
Caucasian (n, %)	118 (75.6)	104 (68.9)
Mean higt (cm)	168.2	167.6
Mean weight (kg)	78.0	78.3
Mean age (years)	39.8	41.9

Change from baseline / CAPS-2 / 648

Analysis	Placebo			Paroxetine			Paroxetine vs Placebo		
	N	Mean	SE	N	Mean	SE	Difference*	95% CI	p value
Baseline	156	73.2	1.3	151	74.3	1.4			
% of completers	94			93					
Week 4	133	-16.1	1.6	133	-21.8	1.8	-5.7	-10.5, -0.94	0.019
Week 8	133	-22.6	1.8	136	-30.4	2.0	-7.3	-12.7, -2.0	0.008
Week 12	133	-24.7	2.0	136	-35.5	2.0	-10.6	-16.2, -5.0	<0.001
70% LOCF	133	-16.1	1.6	136	-22.1	1.8	-5.9	-10.8, -1.1	0.017
OC at Week 12	92	-27.4	2.5	87	-40.7	2.2	-14.0	-20.8, -7.2	<0.001

* Adjusted mean

Responders on CGI / 648

Analysis	Placebo (n, %, N)	Paro (n, %, N)	Odds ratio / paro vs. pla (95% CI)	p-value
Week 4	25, 16.7, 150	51, 34.5, 148	2.7 (1.5, 4.7)	<0.001
Week 8	54, 36.0, 150	77, 52.0, 148	2.1 (1.3, 3.4)	0.003
Week 12	57, 38.0, 150	87, 58.8, 148	2.6 (1.6, 4.3)	<0.001
70% LOCF	41, 27.3, 150	72, 48.6, 148	2.9 (1.7, 4.9)	<0.001
OC at Week 12	46, 50.0, 92	66, 75.9, 87	4.0 (1.9, 8.3)	<0.001

The baseline and demographic characteristics between treatment groups appeared comparable. There was a statistically significantly larger reduction in CAPS-2 in the paroxetine group as compared to placebo at Week 12 ($p<0.001$). The percentage of responders with respect to CGI was statistically significantly higher in the paroxetine group as compared to placebo at Week 12 ($p<0.001$). Larger improvement in the paroxetine group with respect to both endpoints was found at different visits too. The sponsor reported a significant quantitative treatment-by-trauma type interactions with respect to CAP-2 and CGI in this study. However, the treatment differences in CAP-2 and CGI were numerically in favor of paroxetine with respect to different trauma catagories.

The sponsor's 70% LOCF and OC analyses (Week 12) on CAPS-2 and CGI, in general, are difficult to interpret because the original randomization may not be preserved after a large percentage of dropoff. Nevertheless the results of these analyses appeared consistent with those based on ITT patient population.

Statistically significant treatment differences in favor of paroxetine were observed for the secondary endpoints such as CAPS-2 symptom clusters change from baseline, DTS total score, TOP8 total score, MADRS total score and others.

Change from baseline / secondary endpoint / 648

Analysis	Placebo (mean, n)		Paroxetine (mean, n)		p-value
	baseline	Week 12	Baseline	Week 12	
CAPS-2/ re-experiencing	20.7 (156)	-7.9 (133)	20.6 (151)	-10.5 (136)	0.007
CAPS-2/ avoidance	30.1 (156)	-10.4 (133)	30.4 (151)	-15.0 (136)	<0.001
CAPS-2/ hyperarousal	22.5 (156)	-6.3 (133)	23.3 (151)	-10.0 (136)	<0.001
DTS total	73.6 (155)	-23.3 (132)	73.1 (150)	-21.0 (134)	<0.001
TOP8 total score	18.2 (156)	-6.3 (106)	18.3 (151)	-9.3 (102)	<0.001
MADRS total score	21.2 (156)	-5.1 (105)	22.2 (151)	-9.6 (102)	0.004

Study 627

This 12-week study involved 44 study centers in nine European countries, South Africa, Israel, and Canada. The first patient was randomized on July. 8, 1998 and the last study visit was on Jan. 21, 2000. In this study, a total of 322 patients were randomized. All randomized patients were included in ITT patient population. The numbers of patients who completed the study were similar in the two treatment groups (106 in placebo and 111 in the paroxetine group). The results of the sponsor's analyses are given below which were based on ITT patient population with LVCF imputation unless indicated otherwise.

The two treatment groups appeared comparable with respect to demographic and baseline characteristics.

Demographic characteristics / 627

Demographic/baseline	Treatment Group (ITT)	
Characteristics	Placebo	Paroxetine
	(N=162)	(N=160)
males (n, %)	74 (45.7)	75 (46.9)
Caucasian (n, %)	150 (92.6)	147 (91.9)
Mean hight (cm)	169.6	169.3
Mean weight (kg)	73.4	74.1
Mean age (years)	38.9	39.5

The primary endpoints, CAPS_2 total score and CGI score were analyzed based on ITT patient population with a last observed value carried forward. The numerical reduction in CAPS_2 score was observed over the time in both placebo and the paroxetine group. The reduction in CAPS_2 for paroxetine appeared larger as compared to placebo. The difference was nominally statistically significant at Week 12 (p=0.047). According to the sponsor, there was a significant treatment-by-country interaction with respect to CAPS_2 total score (p=0.001, Week 12, LOCF). The sponsor believes that this iteraction was due to a large placebo effect in the centers located in France (36 subjects in total). After excluding these patients, the significant treatment difference in CAPS_2 in favor of paroxetine could be seen (treatment difference:-9.7, p<0.001). The treatment difference in CGI between the two treatment groups was not statistically significant.

Change from baseline / CAPS-2 / 627

Analysis	paroxetine		placebo		Trt diff (paro-pla)	
	n	Mean/mean change	n	Mean / mean change	Diff (95% CI	p-value
Baseline	158	77.4	161	78.4		
% of completers	69.4		65.4			
Week 4	154	-19.5	159	-15.0	-4.5 (-8.75,-0.23)	0.039
Week 8	154	-27.5	159	-24.1	-3.8 (-8.79, 1.25)	0.141
Week 12	154	-30.8	159	-26.2	-5.5 (-10.9, -0.08)	0.047
70% LOCF	154	-23.0	159	-20.2	-3.2 (-8.0, 1.6)	0.189
OC at Week 12	109	-36.5	103	-30.8	-6.2 (-13.0, 0.5)	0.071
No France (Wk 12)	135	-32.7	142	-24.0	-9.7 (-15.3, -4.0)	<0.001

Responders on CGI / 627

Analysis	paro (n, %, N)	Pla (n, %, N)	Odds ratio / paro vs. pla (95% CI)	p-value
Week 4	55, 35.3, 156	32, 19.9, 161	2.5 (1.4, 4.3)	0.001
Week 8	71, 45.5, 156	63, 39.1, 161	1.4 (0.9, 2.3)	0.177
Week 12	78, 50.0, 156	70, 43.5, 161	1.5 (0.9, 2.4)	0.134
70% LOCF	65, 41.7, 156	54, 33.5, 161	1.5 (0.9, 2.5)	0.102
OC at Week 12	65, 59.6, 109	54, 52.4, 103	1.7 (0.9, 3.1)	0.115
No France (Wk 12)	70, 51.1, 137	57, 39.9, 143	1.9 (1.1, 3.3)	0.018

The sponsor's 70% LOCF and OC analyses on CAPS-2 and CGI, in general, are difficult to interpret because the original randomization was preserved after a large percentage of dropoff. Nevertheless the results of these analyses appeared numerically consistent with those based on ITT patient population.

The responses with respect to the major secondary endpoints were in favor of paroxetine numerically but may not reach a nominal statistical significance.

Reduction from baseline / secondary endpoint / 627 (ITT)

Endpoint	Placebo (mean, n)		Paroxetine (mean, n)		p-value
	baseline	Week 12	Baseline	Week 12	
CAPS-2/ re-experiencing	21.6 (161)	-8.1 (159)	21.8 (158)	-9.8 (154)	0.038
CAPS-2/ avoidance	32.4 (161)	-12.8 (159)	31.6 (158)	-12.6 (154)	0.058
CAPS-2/ hyperarousal	24.3 (161)	-7.3 (159)	24.0 (158)	-8.4 (154)	0.185
DTS total	84.1 (161)	-26.2 (159)	81.5 (157)	-31.3 (150)	0.022
TOP8 total score	20.1 (161)	-6.6 (129)	19.4 (157)	-8.2 (126)	0.030
MADRS total score	26.3 (161)	-8.1 (159)	25.6 (157)	-9.1 (153)	0.143

Study 651

This 12-week fixed dose (20 and 40 mg daily of paroxetine and placebo) study involved 60 study centers in the United States. The first patient was randomized on Feb. 4, 1999 and the last study visit was on Jan. 14, 2000. In this study, a total of 551 patients were randomized. The ITT patient population included 489 patients. The numbers of patients who completed the study were similar among two treatment groups (120 in placebo, 122 for 20mg paroxetine, and 113 for 40mg paroxetine). Early withdrawals from the trial were mainly due to adverse experience and lack of efficacy and loss to follow up (24 for placebo, 21 for 20mg, and 18 for 40mg). The results of the sponsor's analyses are given below, which were based on ITT patient patient population and LVCF imputation unless indicated otherwise.

The treatment groups appeared comparable with respect to demographic and baseline demographic characteristics.

Demographic characteristics / 651

Demographic/baseline	Treatment		
Characteristics	Placebo	Paroxetine 20mg	Paroxetine 40mg
males (n, %)	62 (33.3)	57 (31.1)	55 (30.2)
Caucasian (n, %)	169 (90.9)	168 (91.8)	170 (93.4)
Mean height (cm)	168	168.9	168.7
Mean weight (kg)	81.5	81.5	80.9
Mean age (years) Mean	41.6	41.5	41.4

Baseline characteristics / 651

Analysis		Placebo			Paroxetine 20 mg			Paroxetine 40 mg	
	n	Mean	SE	n	Mean	SE	n	Mean	SE
CAPS-2 Total	186	74.4	1.2	183	75.3	1.2	182	74.3	1.2
DTS Total	185	75.2	1.9	181	77.4	1.8	181	73.8	1.8
CGI-Severity*	186	4.0	N/A	183	5.0	N/A	182	5.0	N/A
TOP-8 Total	185	18.5	0.3	183	18.4	0.3	182	18.4	0.4
SDS Total	177	16.6	0.5	171	16.6	0.5	170	16.2	0.5
MADRS	185	24.4	0.6	183	25.2	0.6	182	24.9	0.6

Nominally statistically significant difference in reduction in CAPS-2 total score at Week 12 were found for both dosage levels in favor of paroxetine. The adjusted mean reduction in CAPS-2 in the 20mg paroxetine group was 14.3 more than that in placebo ($p<0.001$). The adjusted mean reduction in CAPS-2 in the 40mg paroxetine group was 12.2 more than that in placebo ($p<0.001$). The sponsor's analysis of the difference in the proportion of CGI-I reponders indicated that the odds of CGI response were significantly greater in the two paroxetine treatment groups as compared to placebo.

Change in CAPS-2 from baseline / 651

Analysis	Placebo			Paroxetine 20 mg			Paroxetine 40 mg		
	n	Mean	SE	n	Mean	SE	n	Mean	SE
Baseline	186	74.4	1.2	183	75.3	1.2	182	74.3	1.2
% of completers	64.5			66.7			62.1		
Week 4	163	-20.1	1.8	162	-30.0	1.7	154	-31.0	2.1
Week 8	167	-24.3	1.9	166	-36.7	2.0	156	-35.9	2.2
Week 12	167	-25.3	2.0	166	-39.6	2.0	156	-37.9	2.3
	Treatment Difference								
	20 mg vs Placebo				40 mg vs Placebo				
	Difference*	95% CI		p-value	Difference*	95% CI		p-value	
Week 4	-9.9	-14.8, -5.1		<0.001	-10.7	-15.6, -5.8		<0.001	
Week 8	-12.5	-17.8, -7.2		<0.001	-11.5	-16.9, -6.1		<0.001	
Week 12	-14.3	-19.7, -8.8		<0.001	-12.2	-17.7, -6.6		<0.001	

Responders on CGI /651

Analysis	Placebo			Paroxetine 20 mg			Paroxetine 40 mg		
	n	%	N	n	%	N	n	%	N
Week 4	48	26.2	183	85	47.2	180	76	43.4	175
Week 8	63	34.4	183	106	58.9	180	96	54.9	175
Week 12	67	36.6	183	113	62.8	180	99	56.6	175
Pairwise Comparisons									
	20 mg vs Placebo			40 mg vs Placebo					
	Odds Ratio	95% CI	p value	Odds Ratio	95% CI	p value			
Week 4	2.82	1.7, 4.6	<0.001	2.44	1.5, 4.0	<0.001			
Week 8	2.91	1.9, 4.6	<0.001	2.45	1.6, 3.9	<0.001			
Week 12	3.20	2.0, 5.1	<0.001	2.42	1.5, 3.8	<0.001			

Statistically significant differences in favor of paroxetine were observed for the secondary endpoints such as CAPS-2 symptom clusters change from baseline, DTS total score, TOP8 total score, MADRS total score and others.

Reduction from baseline / secondary endpoint / 651 (ITT)

Analysis	Placebo (mean, n)		Paroxetine, 20mg (mean, n)		Paroxetine, 40ng (mean, n)		p-value 20mg vs. pla	p-value 40mg vs. pla
	baseline	Week 12	Baseline	Week 12	baseline	Week 12		
CAPS-2/ re-experiencing	20.0 (186)	-7.2 (167)	20.4 (183)	-11.6 (166)	20.1 (182)	-11.1 (156)	<0.001	<0.001
CAPS-2/ avoidance	31.1 (186)	-11.1 (167)	31.7(183)	-16.9 (166)	31.6 (182)	-16.7 (156)	<0.001	<0.001
CAPS-2/ hyperarousal	23.4 (186)	-7.0 (167)	23.1 (183)	-11.1 (166)	22.6 (182)	-10.0 (156)	<0.001	<0.001
DTS total	75.2 (185)	-25.1 (166)	77.4 (181)	-38.5 (164)	73.8 (181)	-36.0 (155)	<0.001	<0.001
TOP8 total score	18.5 (185)	-6.3 (130)	18.4 (183)	-9.8 (125)	18.4 (182)	-9.5 (124)	<0.001	<0.001
MADRS total score	24.4 (185)	-5.7 (130)	25.2 (183)	-12.2 (126)	24.9 (182)	-11.3 (126)	<0.001	<0.001

3. Reviewer's analyses and conclusion

In all three studies, there were two primary efficacy endpoints, CAPS-2 and CGI-I scores in the protocols. According to the current position of the Division of Neuropharm Drug Product, both endpoints need to be positive in order to claim the efficacy of paroxetine.

Study 648

This reviewer analyzed submitted efficacy data for Study 648. The demographic and baseline characteristics appeared comparable between the two treatment groups as indicated previously. Overall proportions of dropouts in the two treatment groups appeared similar.

In this reviewer's analysis of CAPS-2 data, analysis of variance with treatment and study center as factors was used This reviewer's analysis focused on ITT patient population with a valid randomization. Last value carrying forward method was used to impute CAPS-2 score for the patients who withdrew from the trial before completion. The result of this reviewer's analysis was very similar to that by the sponsor.

A statistically significantly larger reduction in CAPS-2 in the paroxetine treatment group as compared to placebo was found at Week 12. However, test for interaction indicated a treatment-by-center interaction (p=0.0293). In 10 out of all 35 study centers (29%), group differences in reduction in CAPS-2 from baseline were in the wrong direction (in favor of placebo). This interaction was understandable because of small number of patients in each center and a large variation in CAPS-2 response. In fact, all 35 centers, except one, had fewer than 9 patients per treatment group. Majority of them had fewer than 5 patients per group, More than a half of centers had fewer than 3 patients in at least one treatment group. By this reviewer's calculation, assuming the observed group difference in reduction in CAPS-2 (-10.8) and the population standard deviation (23) as the true corresponding values and using the average number of patients per center (n=8), the probability for treatment difference in the wrong direction in a center is about 25%, in line with the observed 29%. In this reviewer's opinion, because of very small sample size per center, the center effect was inevitably confounded with biases introduced from unbalanced prognostic factors within each center due to small sample size, and therefore difficult to interpret. Without center in the model, the difference in reduction in CAPS-2 was still significant (p<0.001). No treatment by baseline CAPS-2 interaction was found.

Efficacy outcome / CAPS-2 / 648 /LOCF

Analysis	Placebo		Paroxetine		p-value
	N	Mean	N	Mean	
Baseline	133	73.0	136	73.8	
Week 4	133	-16.1	133	-21.8	0.0169
Week 8	133	-22.6	136	-30.4	0.0057
Week 12	133	-24.7	136	-35.5	0.0002
Week 12	133	-24.7	136	-35.5	0.0001*

- Chi-square test without the center factor

This reviewer analyzed CGI response data using both logistic regression with treatment and center as factors and chi-square test (only for Week 12). This reviewer's analysis indicated that the percentage of responders in paroxetine treated patients with respect to CGI was statistically significant higher than that in placebo. Because of the small per-center sample size, which might result in unbalanced baseline across treatment groups and introduce biases to confound the effect of the treatment within a center, Chis-square test was also performed ignoring the center factor for Week 12.

Responders on CGI / 648

Week	Placebo (n, %, N)	Paro (n, %, N)	Odds ratio / parpo vs. pla (95% CI)	p-value
4	25, 16.7, 150	51, 34.5, 148	3.3 (1.8, 6.0)	0.0002
8	54, 36.0, 150	77, 52.0, 148	2.1 (1.2, 3.4)	0.0059
12	57, 38.0, 150	87, 58.8, 148	2.5 (1.5, 4.1)	0.0004
12	57, 38.0, 150	87, 58.8, 148		<0.001*

*Chi-square test

Descriptive statistics with respect to response in CAPS-2 and CGI were obtained for gender and racial subgroups. Since there were only a small number of elderly patients (>64 years), no subgroup analysis was performed by age subgroup.

Responses in CAPS-2 and CGI by gender at Week 12 / 648

subgroup	CAPS-2 (change from baseline)				CGI (improvement)	
	placebo		paroxetine		Placebo (n/N, %)	Paroxetine (n/N,%)
	N, baseline	change	N, baseline	change		
Female	84, 74.3	-30.0	87, 73.9	-36.8	36/98 (36.7)	57/97 (58.8)
Male	49, 70.6	-20.7	49, 73.6	-33.2	21/52 (40.4)	30/51 (58.8)
white	98, 71.5	-24.0	94, 73.8	-35.3	41/113 (36.3)	59/103 (57.3)
Non-white	35, 77.0	-26.7	42, 73.8	-36.0	16/37 (43.3)	28/45 (62.2)

Study 627

This reviewer analyzed submitted efficacy data for Study 627. The demographic and baseline characteristics appeared comparable between the two treatment groups as indicated previously. Overall proportions of dropouts in the two treatment groups appeared similar.

In this reviewer's analysis of CAPS-2 data, analysis of variance with treatment and study center as factors was used. This reviewer's analysis focused on ITT patient population which had a valid trial randomization. Last observation carrying forward method was used to impute CAPS-2 score for the patients who withdrew from the trial before completion. The result of this reviewer's analysis was very similar to that by the sponsor.

Numerically larger reduction in CAPS-2 from baseline in the paroxetine treatment group as compared to placebo was observed at Week 12. The observed difference was nominally statistically significant (p=0.0363 with center as a term). No treatment-by-center or treatment-by-baseline CAPS-2 interaction were found at significance level 0.10.

Change from baseline / CAPS-2 / 627 /LOCF

Analysis	Placebo		Paroxetine		p-value
	N	Mean	N	Mean	
Baseline		78.2	154	77.5	
Week 4	159	-15.1	154	-19.6	0.0211
Week 8	159	-24.1	154	-27.6	0.0857
Week 12	159	-26.2	154	-30.8	0.0363
Week 12	159	-26.2	154	-30.8	0.1075*

* without center factor

Responders on CGI / 627

Week	Paro (n, %, N)	Pla (n, %, N)	Odds ratio / paro vs. pla (95% CI)	p-value
4	56, 35.9, 156	32, 19.9, 161	3.0 (1.6, 5.5)	0.0003
8	72, 46.2, 156	63, 39.1, 161	1.5 (0.9, 2.5)	0.1239
12	78, 50.0, 156	70, 43.5, 161	1.4 (0.9, 2.3)	0.2450*
12	78, 50.0, 156	70, 43.5, 161	1.4 (0.9, 2.3)	0.1654

*chi-square test

Treatment difference in CGI was not statistically significant at α=0.05 for the overall patient population.

This reviewer investigated reported treatment-by-country interaction with respect to CAPS-2 and found that the extreme responses in CAPS-2 occurred in two particular centers (Center 505, n=5 and Center 506, n=12), especially Center 506, in France. The treatment differences in these two centers were 45.3 (Center 505) and 48.6 (Center 506) while the treatment differences for the other centers ranged from -37.2 to 26.5. The mean of center treatment differences without these Centers 505 and 506 was -8.9 with standard deviation 14.8 (without adjustment for the different per-center sample size). The outcomes in Centers 505 and 506 appeared beyond 3 times of standard deviation from the mean treatment difference. The following table gives the change from baseline in CAPS-2 for each patient in Center 506. It could be seen that the patients in placebo in that center uniformly showed a very large reduction in CAPS-2 and the majority of patients in paroxetine group had almost no improvement. The sponsor provided the photocopies of case report forms for these twelve patients in Center 506. It appeared that the submitted data set contained more follow-up information on CAPS-2 for some placebo patients than that in the case report forms.

Change from baseline in CAPS-2 / Center 506 / France / 627

Treatment	Baseline CAPS-2	Change from baseline
Placebo	64	-53
	83	-68
	77	-49
	80	-65
	77	-59
	76	-50
Paroxetine	79	4
	89	-46
	82	8
	74	0
	76	9
	56	-27

The outcome in Center 506 was very influential to the overall outcome. Without this center, the treatment-by-country interaction was insignificant (p=0.3709) and the difference in reduction in CAPS-2 from baseline between the two treatment groups were nominally statistically significant (p=0.0065). This reviewer noted that it might be improper to let the response from Center 506, representing slightly less than 4% overall patient population, determine the overall significance of the treatment difference. However, no conclusion was made based on the restricted patient population excluding Center 506, since the other two studies provide sufficient information on the efficacy of paroxetine. For the same reason, no attempt to determine the cause or confirm the outlier nature of the apparent peculiar responses in Center 506 and Center 505 was made by this reviewer.

Descriptive statistics with respect to response in CAPS-2 and CGI were obtained for gender and racial subgroup. No subgroup analysis was performed by age subgroups.

Responses in CAPS-2 and CGI by gender and race at Week 12 / 627

gender	CAPS-2 (change from baseline)				CGI (improvement)	
	Placebo		paroxetine		Placebo (n/N, %)	Paroxetine (n/N,%)
	N, baseline	Change	N, baseline	change		
Female	85, 76.8	-27.4	82, 73.4	-34.7	45/87 (51.7)	49/82 (59.8)
Male	74, 80.0	-24.8	72, 82.1	-26.5	25/74 (33.8)	29/74 (39.2)
white	147, 78.1	-26.5	142, 76.9	-30.2	65/149 (43.6)	72/143 (50.4)
Non-white	12, 80.8	-22.0	12, 84.8	-38.4	5/12 (41.7)	6/13 (46.2)

Study 651

This reviewer analyzed submitted efficacy data for Study 651. The demographic and baseline characteristics appeared comparable among the three treatment groups as indicated previously. Overall proportions of dropouts in the treatment groups appeared similar.

In this reviewer's analysis of CAPS-2 data, analysis of variance with treatment and study center as factors was used. This reviewer's analysis focused on ITT patient population which preserved the trial randomization. Last observation carrying forward method was used to impute CAPS-2 score for the patients who withdrew from the trial before completion. The result of this reviewer's analysis was very similar to that by the sponsor. Statistically significant differences in reduction of CAPS-2 total score from baseline among treatment groups were observed at Week 12 ($p=0.0001$). Statistically significantly larger reductions in CAPS-2 from baseline in each of active treatment groups was found as compared to placebo (Dunnett test). No treatment-by-center interaction or treatment-by-baseline CAPS-2 score were found at significance level $\alpha=0.10$.

Change from baseline / CAPS-2 / 651

Analysis	Pla		20 mg		40 mg		p-value*	
	n	mean	n	mean	n	mean		
Baseline	167	74.4	166	74.2	156	74.9		
Week 4	163	-20.1	162	-30.0	154	-31.0	0.0001	
Week 8	167	-24.3	166	-36.6	156	-35.9	0.0001	
Week 12	167	-25.3	166	-39.6	156	-37.9	0.0001	
Week 12	167	-25.3	166	-39.6	156	-37.9	0.0001 **	

* p-value for group difference, ** without center as a term

This reviewer analyzed CGI response data using both logistic regression with treatment and center as factors and chi-square test (only for Week 12). This reviewer's analysis indicated that the percentages of responders in CGI in both paroxetine groups were statistically significant larger than that in placebo

CGI responder / 651

Analysis for	Placebo			Paroxetine 20 mg			Paroxetine 40 mg			p-value
	N	%	N	n	%	N	n	%	N	
Week 4	48	26.2	183	84	46.7	180	76	43.4	175	0.001
Week 8	62	33.9	183	106	58.9	180	96	54.9	175	0.001
Week 12	67	36.6	183	113	62.8	180	99	56.6	175	0.001
Pairwise Comparisons										
	20 mg vs Placebo					40 mg vs Placebo				
	Odds Ratio*	95% CI		p value		Odds Ratio*	95% CI		p value	
Week 4	2.9	1.8, 4.8		0.0001		2.6	1.6, 4.3		0.0002	
Week 8	3.3	2.0, 5.3		0.0001		2.5	1.6, 4.1		0.0001	
Week 12	3.4	2.1, 5.5		0.0001		2.4	1.5, 3.9		0.0002	

- logistic regression

Descriptive statistics with respect to response in CAPS-2 and CGI were obtained for gender and racial patient subgroups. Since there were a small number of elderly patients (>64 years), no subgroup analysis was performed by age subgroup.

Responses in CAPS-2 and CGI by gender/race at Week 12 / 651

gender	palcebo	Paroxetine 20	Paroxetine 40
	CAPS-2 (N, baseline, change)		
female	110, 74.5, -27.3	115, 75.3, -42.0	107, 74.5, -39.9
male	57, 74.2, -21.5	51, 71.9, -34.2	49, 75.7, -33.6
white	154, 73.8, -24.7	153, 74.2, -39.0	146, 74.4, -38.3
Non-white	13, 81.8, -32.1	13, 74.9, -46.8	10, 82.3, -32.1
	CGI / global improvement (n/N, %)		
Female	49/122 (40.2)	81/124 (65.3)	68/121 (56.2)
male	18/61 (29.5)	32/56 (57.1)	32/54 (57.4)
white	61/167 (36.5)	103/165 (62.4)	92/164 (56.1)
Non-white	6/16 (37.5)	10/15 (66.7)	7/11 (63.6)

Additional analysis

To address the concern that the primary efficacy measurements CAPS-2 and CGI may not be specific for PTSD, additional analyses were requested by Dr. Brugge, the medical reviewer. The analyses were based on sub-patient populations such as patients with or without major depressive disorder (MDD), non-PTSD anxiety disorder (non-PTSD AD) and MDD or non-PTSD AD. The sponsor's analyses with respect to CAPS-2 and CGI based on the mentioned subgroups indicated apparent numerical consistency of treat effect in favor of paroxetine.

Reviewer's conclusion

The sponsor's Study 648 and Study 651, conducted in North America, demonstrated significant effect of paroxetine in improving CAPS-2 and CGI improvement item. Similar effects on the secondary efficacy variables were observed. Study 627, conducted outside of the United States, failed to demonstrate the efficacy of paroxetine, perhaps due

to peculiar outcomes in two centers in France. However, the numerical trend of the primary outcomes in Study 627 were consistent with those observed in Study 648 and Study 651. In conclusion, this NDA submission demonstrates the effectiveness of paroxetine in improving CAPS-2 and CGI.

Lu Cui /S/
Ph.D., Mathematical Statis
2/20/2001

Concur: Dr. Kun Jin /S/

Dr. George Chi /S/

cc:
NDA #20,031, Paxil
HFD-120
HFD-120 / Ms. Homonnaya
HFD-120 / Dr. Katz
HFD-120 / Dr. Laughren
HFD-120/ Dr. Brugge
HFD-110 / Mr. David
HFD-344 / Dr. Barton
HFD-710 / Dr. Chi
HFD-710 / Dr. Jin
HFD-710 / Dr. Mahjoob
HFD-710 / Dr. Cui
HFD-710 / Chron.
Review/paxi/rpt2.doc

MEMORANDUM OF TELECON

NDA: 20-031/S-029

DRUG: Paxil® (paroxetine HCl) Tablets

SPONSOR: GSK

DATE: 11/29/01

TELEPHONE NUMBER: (610) 917-7665

CONVERSATION WITH: Thomas Kline

CONVERSATION: Tom Kline indicated that GSK is in agreement with the proposed FDA labeling that was faxed on 11/29/01. I told him that we will be issuing an approval letter shortly with the agreed upon language in the labeling.

/S/

Anna Marie Homonnay, R.Ph.
Regulatory Health Project Manager

34 page(s) of revised draft labeling has been redacted from this portion of the review.

Homonnay Weikel, Anna M

From: Homonnay Weikel, Anna M
Sent: Tuesday, November 20, 2001 4:13 PM
To: 'Thomas.F.Kline@sbphrd.com'
Subject: RE: Paxil PTSD Labeling NDA 20-031/S029

is

-----Original Message-----
From: Thomas.F.Kline@sbphrd.com [mailto:Thomas.F.Kline@sbphrd.com]
Sent: Tuesday, November 20, 2001 2:44 PM
To: homonnaya@cder.fda.gov
Subject: Paxil PTSD Labeling NDA 20-031/S029

Anna,
Any word from the reviewers on the Paxil PTSD labeling? I'd appreciate your best guess since I need to provide some idea on timings from my end. If there is ANYTHING I could do to help, please let me know.
Thanks as always,
Tom

Homonnay Weikel, Anna M

From: Laughren, Thomas P
Sent: Saturday, November 17, 2001 8:51 AM
To: Homonnay Weikel, Anna M
Cc: Brugge, Karen
Subject: RE: Paxil NDA 20-031/S-029 PTSD Labeling

Anna Marie,

Karen and I have talked about this response, and we are in agreement with the proposed changes, with the exception of one sentence. That is the following sentence: [redacted] This concept is covered under the more general statement suggesting that there may be no causal relationship; it is unnecessary, and tends to discount the important message. Thus, we want this sentence deleted. There is no room for negotiation on this, at least at my level, so if they accept this change, fine, but if not, I will forward the package to Rusty acknowledging this disagreement. So please let them know our position, and then let me know their response. Once I hear from you, I will write a very brief memo. Please prepare a finalized version of labeling (with their proposed changes, except for that sentence) for the package and a letter.

Thanks,

Tom

-----Original Message-----
From: Homonnay Weikel, Anna M
Sent: Tuesday, November 06, 2001 8:41 AM
To: Brugge, Karen; Laughren, Thomas P
Cc: David, Paul A
Subject: FW: Paxil NDA 20-031/S-029 PTSD Labeling

Please find the response from GSK re: Paxil/PTSD
-----Original Message-----
From: Thomas.F.Kline@sbphrd.com [mailto:Thomas.F.Kline@sbphrd.com]
Sent: Monday, November 05, 2001 4:41 PM
To: HOMONNAYA@cder.fda.gov
Subject: Paxil NDA 20-031/S-029 PTSD Labeling

Anna,
Here is our counter-proposal for labeling regarding the Paxil PTSD supplement, ie NDA 20-031/S-029. For reviewer convenience, we used annotations to show any difference between this version and the Division's recent proposal. Two data tables are also provided to support the list of adverse events cited (ie in the taper and follow-up phase, at 2% or greater incidence and twice the rate of placebo, using the recent GAD and PTSD datasets). I trust our comments [within brackets] are clear but please let me know otherwise. Since much of this may be viewed as rather minor in nature, we are hopeful that an "Approval" letter could be forthcoming shortly, but please let me know your perspective on timings etc. If a brief telecon would be helpful, please let me know.

Proposed labeling:

Referenced data source tables:

Thank you for your assistance,
Tom

Homonnay Weikel, Anna M

From: Thomas.F.Kline@sbphrd.com

Sent: Monday, November 05, 2001 4:41 PM

To: HOMONNAYA@cder.fda.gov

Subject: Paxil NDA 20-031/S-029 PTSD Labeling

Anna,
Here is our counter-proposal for labeling regarding the Paxil PTSD supplement, ie NDA 20-031/S-029. For reviewer convenience, we used annotations to show any difference between this version and the Division's recent proposal. Two data tables are also provided to support the list of adverse events cited (ie in the taper and follow-up phase, at 2% or greater incidence and twice the rate of placebo, using the recent GAD and PTSD datasets). I trust our comments [within brackets] are clear but please let me know otherwise. Since much of this may be viewed as rather minor in nature, we are hopeful that an "Approval" letter could be forthcoming shortly, but please let me know your perspective on timings etc. If a brief telecon would be helpful, please let me know.

Proposed labeling:

Referenced data source tables:

Thank you for your assistance,
Tom

12 page(s) of revised draft labeling has been redacted from this portion of the review.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-031/S-029

Issued 5/16/01

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

Dear Mr. Kline:

Please refer to your supplemental new drug application dated July 21, 2000, received July 21, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paxil® (paroxetine hydrochloride) Tablets.

We also acknowledge receipt of your amendments dated October 13 and 23, 2000; and February 14, 2001.

This supplemental new drug application provides for the use of Paxil® (paroxetine hydrochloride) Tablets for the treatment of posttraumatic stress disorder (PTSD) as a new indication.

We have completed the review of this application, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit the following:

Draft Labeling

Accompanying this letter as an attachment is our proposal for the labeling of Paxil® Tablets for the treatment of posttraumatic stress disorder. Please submit revised draft labeling identical in content to the enclosed labeling (text for the package insert). Explanations for our proposed changes are provided in the bracketed comments embedded within the proposed text. We would be happy to discuss these proposed changes in more detail through a teleconference if you wish.

Safety Update

Under 21 CFR 314.50(d)(vi)(b), we request that you provide a final safety update for Paxil® Tablets for PTSD.

Regulatory Status Update

Please provide any new information on the worldwide regulatory status of Paxil® Tablets for PTSD, including the status of all actions either taken or pending before foreign regulatory authorities.

World Literature Update

Prior to the approval of Paxil® Tablets for PTSD, we will require an updated report on the world archival literature pertaining to the safety of this product for this indication.

In addition, all previous revisions as reflected in the most recently approved labeling must be included, especially, the new changes resulting from the approval of S-026 for the generalized anxiety disorder indication. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

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 should have any questions, please call Anna Marie Homonnay, R.Ph., Regulatory Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

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

Attachment

33 page(s) of revised draft labeling has been redacted from this portion of the review.

10/5/00

To: Mr. Thomas Kline, Assistant Director
US Regulatory Affairs
SmithKline Beecham
Fax: 610/917-7665
Re: NDA20031 S029 Paxil and PTSD
From: Karen Brugge, MD (5)
Paul Andreason, MD (5)
Reviewers
CDER, FDA

Thank you for the requested information you recently faxed to us dated 10/4/00. However, as we discussed during our telephone conversation today, we have not received line listings of subjects meeting criteria for "Potential Clinical Concern" on vital sign parameters. Also, as discussed, we need additional information and/or clarification, as described below. We will be looking forward to receiving this information by October 13th.

Please clarify the following column headings in Table 23 page 000081 of the ISS document: "Days on Study at Event Onset" and "Total Days on Dbl-Blind Study Drug". Note that some subjects show a greater number of days under the former column compared to the number under the latter column, while for other subjects the greater and lesser values are reversed. Additionally, I was not able to match the numbers on this table to those provided in the narrative and was not sure how the number of this table matches up with the numbers on the line listings. Please clarify.

We do not have the narrative for 627.802.01674. Please provide the narrative, since it is listed in the aforementioned table (Table 23) as a serious adverse event.

The Narrative on subject 651.013.07013 is very sparse and the preferred term "Therapeutic Response Increased" is confusing, particularly when juxtaposed with the verbatim term "Overdose (unintentional). Please clarify and provide information regarding events leading up to the incident, a description of the incident, what the patient overdosed on, and when, other clinical features associated and pertinent to this incident, the treatment employed, and the clinical outcome. Any pertinent laboratory data would also be helpful. Also include, if available, plasma levels of drugs/substances obtained due to the overdose. Please note that the narrative only gives some demographic information, the patient's medical history, and concomitant medications, presumably obtained at screening/baseline) and provides no other information, including a description of the event, as requested above.

********** -COMM. JOURNAL- ********** DATE SEP-12-2000 ***** TIME 11:25 *** P.01

MODE = MEMORY TRANSMISSION START=SEP-12 11:21 END=SEP-12 11:25

FILE NO.= 166

STN NO.	COM	ABBR NO.	STATION NAME/TEL.NO.	PAGES	DURATION
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-FDA/DNDP -

********** - - ***** - 3015942859- **********

facsimile
TRANSMITTAL

To: Thomas Kline
Sponsor: Smith Kline Beecham
Fax #: (610) 917-7665
Re: NDA ~~19-839/S-035~~ 20-031/S-029
Date: 9/12/00
Pages: (including cover sheet) 2

CC: NDA 20-031/S-029

From the desk of...

Ms. Anna M. Homonnay-Weikel, R.Ph.
Project Manager
Division of Neuropharmacological Drug Products / HFD-120
Food and Drug Administration
Rockville, Maryland 20857
301-594-5535
Fax: 301-594-2859

Re: NDA 20,0031 SE1-029 Paxil for Treatment of PTSD
To: Tom Kline, US Regulatory Affairs
From: Karen Brugge, MD and Paul Andreason, MD/CDER, FDA

Please provide line listings of each of the following for each completed study:

1)Serious Adverse Events

2)Adverse Event Withdrawals

3)Outliers (subjects meeting criteria for "Clinical Concern") for all safety parameters (laboratory, vital signs, and others). Please provide a separate table of the normal reference range and the corresponding "Clinical Concern" for each safety parameter in the same units as that employed for the values provided for the subjects. (It is preferred that units are converted to those employed in the U.S.)

Electronic Mail Message

Date: 3/19/01 11:52:29 AM
From: Anna Marie Homonnay (HOMONNAYA)
To: Thomas_F_Kline@sbphrd.com
Subject: re: Supplement for Paxil/PTSD

Tom,
Please find attached a request for information.

Thanks,

Anna Marie

FDA Request for Information
NDA 20-031/S-029
Paxil/PTSD
March 19, 2001

Please clarify the definition of (methods for obtaining) the CAPS-2 total score which was used for the primary efficacy variable: change from baseline to endpoint of the CAPS-2 score.

1. Did you use the total (frequency + intensity) scores from the 3 symptom cluster sections B+C+D (a total of 17 items) or was some other method employed to obtain a CAPS-2 total score?

2. Please specifically state the methods for obtaining the CAPS-2 total score for each of the three studies (651, 648 and 627), as we were not able to find an explicit statement in the methods section in the submission.

BRIEF TELECON MINUTES

DATE: October 4, 2001
NDA: 20-031/S-029
LOCATION:
DRUG: Paxil
INDICATION: PTSD
PARTICIPANTS:

GSK:
Dr. Allan Metz
Dr. Murray
Mr. Kline

FDA:
Dr. Laughren
Dr. Brugge
Ms. Homonnay

BACKGROUND: FDA's proposed labeling was faxed to GSK on 9/26/01 for the PTSD indication. Included was the relocation of language about discontinuation symptoms to PRECAUTIONS. GSK requested the teleconference for additional clarification.

DISCUSSION:

- GSK inquired about the criteria the Agency uses to list ADRs in PRECAUTIONS. FDA said that, in general, ADRs are located in PRECAUTIONS or WARNINGS based on their importance to the prescriber and the strength of the evidence for a causal linkage to drug use. We noted that it was our view that the signal for withdrawal emergent symptoms associated with Paxil meets this test, and this is the basis for our placing these findings in PRECAUTIONS.

- GSK objected to the bracketed language on p 12 in the fax referring to this phenomenon as [redacted] ' and preferred the term 'discontinuation symptoms' instead. FDA agreed that this was largely a semantic issue, and it was not intended to suggest that there is evidence for dependency.

- GSK inquired whether FDA is planning to revise the labeling for other drugs in this class. FDA acknowledged that this phenomenon will be looked at for the whole drug class, but we do not view this as a situation requiring class labeling.

- FDA reaffirmed the deletion of the phrase [redacted] since the Agency may not have all the relevant data as yet.

- GSK asked about the data sources in support of the AEs concerned with the discontinuation syndrome and whether possible re-emergence of PTSD anxiety symptoms was considered as an alternative explanation. FDA replied that the data supporting the proposed statement came from a pool of the taper and discontinuation phases of the PTSD trials, but we acknowledged the difficulty in sorting out discontinuation symptoms from re-emergence of the underlying clinical syndrome being treated. Nevertheless, we noted that the appearance of new symptoms, e.g., sensory experiences, does support the view that there may well be a discontinuation phenomenon. We indicated that we would be happy to review any alternative analyses of the data they might wish to undertake.

- Finally, GSK expressed concern about the timing of the changes to PRECAUTIONS and FDA replied that, while we believe the signal is strong enough to justify its addition to PRECAUTIONS , the role of recent public attention cannot be ignored.

Minutes by: _____
Anna Marie Homonnay
Regulatory Health Project Manager

Concurrence:_____
Thomas Laughren, M.D.
Clinical Teamleader, Psychiatric Drugs

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/s/

Anna-Marie Homonnay
11/26/01 05:03:52 PM
CSO

Thomas Laughren
11/27/01 10:21:01 AM
MEDICAL OFFICER

MEETING MINUTES

Date: 9/3/98
IND: 23,280
NDA: 20-031
Location: Woodmont II, Conference Room E
Firm: SmithKline Beecham
Drug: PAXIL (paroxetine hydrochloride) tablets
Indication: PTSD & GAD
Meeting Type: Clinical Development Plan
Participants:
FDA Attendees:

Paul Leber, M.D.	Director
Tom Laughren, M.D.	Teamleader PDP
Greg Dubitsky, M.D.	Medical Reviewer
Susan Molchan, M.D.	Medical Reviewer
Japo Choudhury, Ph.D.	Statistician

SKB Attendees:

Stella Jones, Ph.D.	Vice President, U.S. Regulatory Affairs
Thomas Kline	Manager, U.S. Regulatory Affairs
Rajinder Kumar, M.D.	Group Director, CNS/GI, Clinical Research
John Travers, M.D.	Director, CNS/GI, Clinical Research
Daniel Burnham, Ph.D.	Assistant Director, CNS/GI Clinical Research
Cornelius Pitts, RPh	Assistant Director, CNS/GI Clinical Research
Rosemary Oakes	Senior Statistician

BACKGROUND:
This meeting was requested by SKB in order to obtain guidance for the proposed Phase III clinical development programs for PAXIL in the treatment of Post-traumatic Stress Disorder (PTSD) and Generalized Anxiety Disorder (GAD) for eventual efficacy supplements to the approved NDA for PAXIL.

DISCUSSION:

PTSD

- The Division viewed the proposed trial duration of 12 weeks as acceptable and had no major objection to the proposal that sleep medication would be allowed during the first two weeks of the study. However, the study could be stratified to determine whether sleep medications have any effect. Also, the study may be stratified according to whether patients received psychotherapy treatment.

- The Division recommended conducting at least one dose ranging study to determine whether PAXIL demonstrates a dose response effect as suggested for OCD.

- Disability recipients and litigation patients may be excluded.
- The time since trauma to symptoms onset should be recorded as a covariate.
- It is difficult to define a clinically meaningful treatment effect in quantitative terms.
- We noted that if they identify two outcomes as primary, as they have done, the studies will have to show an effect at the 0.05 level for paroxetine on both to be considered positive.
- The Division stressed that they should be able to detect a unique effect of the drug on the cardinal manifestations of the disease, e.g., decreased frequency and intensity of repetitive instrusive thoughts, and repetitive flashbacks of stressful/traumatic events apart from any effects on comorbid symptoms, i.e.,depression. Since this is a novel indication, there is no definitive instrument established yet.
- The proposed non-parametric statistical tests should be more concretely specified.

GAD

- As for PTSD, they should be able to show a unique effect, e.g., HAM A, items #1 and #2.
- Studies of eight weeks duration are okay for acute efficacy, but do not address long-term efficacy.
- Division recommended stratification by benzodiazepine usage.

/S/

Signature, minutes preparer: [illegible]
Anna M. Homonnay-Weikel
Project Manager

Concurrence Chair: /S/ 11-25-98
Tom Laughren, M.D.
Teamleader, PDP

cc:
Orig IND
Orig NDA
Div Files
HFD-120/PLeber
HFD-120/TLaughren/11.25.98
HFD-120/GDubitsky/10.8.98/SMolchan/10.8.98
HFD-710/JChoudhury
HFD-120/AMHomonnay

draft: ahw/10.7.98
Final: ahw/11.25.98
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MEETING MINUTES