CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-936/S-012

Name:	Paxil CR Controlled-Release Tablets
Generic:	paroxetine hydrochloride
Sponsor:	GlaxoSmithKline
Approval Date:	October 16, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-936/S-012

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-936/S-012

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-936/S-012

GlaxoSmithKline, U.S. Regulatory Affairs
Attention: Matthew Whitman
Associate Director, Regulatory Affairs
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101

Dear Mr. Whitman:

Please refer to your supplemental new drug application dated December 20, 2002, received December 20, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paxil® CR (paroxetine HCl) Controlled-release Tablets.

We also acknowledge receipt of your amendments dated March 31; April 4 and 10; June 6; July 22; August 11, 21, 25; and October 7, 9, and 10, 2003.

This supplemental new drug application provides for the use of Paxil® CR (paroxetine hydrochloride) Controlled-release Tablets for the treatment of social anxiety disorder as a new indication.

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 agreed upon 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 labeling attached to this letter.

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 20-936/S-012." Approval of this submission by FDA is not required before the labeling is used.

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.

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

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
10/16/03 03:49:13 PM

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

Approval Letter

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-936/S-012

FINAL PRINTED LABELING

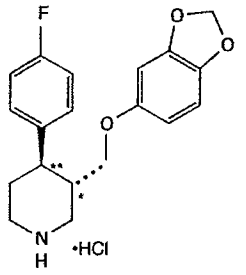
[NDA 20-936/S-012 Final FDA Approved Labeling: Attachment to approval letter for Paxil CR for social anxiety disorder]

PC:LX
PRESCRIBING INFORMATION

PAXIL CR™
(paroxetine hydrochloride) Controlled-Release Tablets

DESCRIPTION

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



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

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

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

CLINICAL PHARMACOLOGY

Pharmacodynamics: The efficacy of paroxetine in the treatment of major depressive disorder, panic disorder, social anxiety disorder, and Premenstrual Dysphoric Disorder (PMDD) is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT). Studies at clinically relevant doses in humans have demonstrated that paroxetine blocks the uptake of serotonin into human platelets. In vitro studies in animals also suggest that paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. In vitro radioligand binding studies indicate that paroxetine has little affinity for muscarinic, $alpha_1$-, $alpha_2$-, beta-adrenergic-, dopamine (D_2)-, 5-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: PAXIL CR tablets contain a degradable polymeric matrix (GEOMATRIX™) designed to control the dissolution rate of paroxetine over a period of approximately 4 to 5 hours. In addition to controlling the rate of drug release in vivo, an enteric coat delays the start of drug release until tablets of PAXIL CR have left the stomach.

Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt. In a study in which normal male and female subjects (n = 23) received single oral doses of PAXIL CR at 4 dosage strengths (12.5 mg, 25 mg, 37.5 mg, and 50 mg), paroxetine C_{max} and $AUC_{0\text{-}inf}$ increased disproportionately with dose (as seen also with immediate-release formulations). Mean C_{max} and $AUC_{0\text{-}inf}$ values at these doses were 2.0, 5.5, 9.0, and 12.5 ng/mL, and 121, 261, 338, and 540 ng.hr./mL, respectively. T_{max} was observed typically between 6 and 10 hours post-dose, reflecting a reduction in absorption rate compared with immediate-release formulations. The mean elimination half-life of paroxetine was 15 to 20 hours throughout this range of single doses of PAXIL CR. The bioavailability of 25 mg PAXIL CR is not affected by food.

During repeated administration of PAXIL CR (25 mg once daily), steady state was reached within 2 weeks (i.e., comparable to immediate-release formulations). In a repeat-dose study in which normal male and female subjects (n = 23) received PAXIL CR (25 mg daily), mean steady state C_{max}, C_{min}, and $AUC_{0\text{-}24}$ values were 30 ng/mL, 20 ng/mL, and 550 ng.hr./mL, respectively.

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

In steady-state dose proportionality studies involving elderly and nonelderly patients, at doses of the immediate-release formulation of 20 mg to 40 mg daily for the elderly and 20 mg to 50 mg daily for the nonelderly, some nonlinearity was observed in both populations, again reflecting a

saturable metabolic pathway. In comparison to C_{min} values after 20 mg daily, values after 40 mg daily were only about 2 to 3 times greater than doubled.

Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic acid and sulfate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 the potency of the parent compound at inhibiting serotonin uptake. The metabolism of paroxetine is accomplished in part by 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 doses of 20, 30, and 40 mg of the immediate-release formulation, C_{min} concentrations were about 70% to 80% greater than the respective C_{min} concentrations in nonelderly subjects. Therefore the initial dosage in the elderly should be reduced (see DOSAGE AND ADMINISTRATION).

Clinical Trials

Major Depressive Disorder: The efficacy of PAXIL CR controlled-release tablets as a treatment for major depressive disorder has been established in two 12-week, flexible-dose, placebo-controlled studies of patients with DSM-IV Major Depressive Disorder. One study included patients in the age range 18 to 65 years, and a second study included elderly patients, ranging in age from 60 to 88. In both studies, PAXIL CR was shown to be significantly more effective than placebo in treating major depressive disorder as measured by the following:

Hamilton Depression Rating Scale (HDRS), the Hamilton depressed mood item, and the Clinical Global Impression (CGI)–Severity of Illness score.

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

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

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

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

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

PAXIL CR demonstrated statistically significant superiority over placebo on both the LSAS total score and the CGI Improvement responder criterion. For patients who completed the trial,

64% of patients treated with PAXIL CR compared to 34.7% of patients treated with placebo were CGI Improvement responders.

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

Premenstrual Dysphoric Disorder: The effectiveness of PAXIL CR for the treatment of Premenstrual Dysphoric Disorder (PMDD) has been established in 2 placebo-controlled trials. Patients in these trials met DSM-IV criteria for Premenstrual Dysphoric Disorder. In a pool of 1030 patients, the mean duration of the PMDD symptoms was approximately 11±7 years. Patients on systemic hormonal contraceptives were excluded from these trials. Therefore, the efficacy of PAXIL CR in combination with systemic (including oral) hormonal contraceptives for the treatment of PMDD is unknown. In both positive studies, patients (N = 672) were treated with PAXIL CR 12.5 mg/day or 25 mg/day or placebo continuously throughout the menstrual cycle for a period of 3 menstrual cycles. The VAS-Total score is a patient-rated instrument that mirrors the diagnostic criteria of PMDD as identified in the DSM-IV, and includes assessments for mood, physical symptoms and other symptoms. PAXIL CR 12.5 mg/day and 25 mg/day were significantly more effective than placebo as measured by change from baseline to the endpoint on the luteal phase VAS-Total score.

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

INDICATIONS AND USAGE

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

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

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

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

PAXIL CR has not been systematically evaluated beyond 12 weeks in controlled clinical trials; however, the effectiveness of immediate-release paroxetine hydrochloride in maintaining a response in major depressive disorder for up to 1 year has been demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY—Clinical Trials). The physician

who elects to use PAXIL CR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

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

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

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

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

Social Anxiety Disorder: PAXIL CR is indicated for the treatment of social anxiety disorder, also known as social phobia, as defined in DSM-IV (300.23). Social anxiety disorder is characterized by a marked and persistent fear of 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 CR as a treatment for social anxiety disorder has been established, in part, on the basis of extrapolation from the established effectiveness of the immediate-release formulation of paroxetine. In addition, the efficacy of PAXIL CR was established in a 12-week trial, in adult outpatients with social anxiety disorder (DSM-IV). PAXIL CR has not been studied in children or adolescents with social phobia (see CLINICAL PHARMACOLOGY—Clinical Trials).

The effectiveness of PAXIL CR in long-term treatment of social anxiety disorder, i.e., for more than 12 weeks, has not been systematically evaluated in adequate and well-controlled trials.

Therefore, the physician who elects to prescribe PAXIL CR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

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

The efficacy of PAXIL CR in the treatment of PMDD was established in 2 placebo-controlled trials (see CLINICAL PHARMACOLOGY—Clinical Trials).

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

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

CONTRAINDICATIONS

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

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

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 an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. While there are no human data showing such an interaction with paroxetine hydrochloride, limited animal data on the effects of combined use of paroxetine and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that PAXIL CR not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. At least 2 weeks should be allowed after stopping PAXIL CR before starting an MAOI.

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

An in vivo study suggests that drugs which inhibit $P_{450}IID_6$, 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 of immediate-release paroxetine hydrochloride, hypomania or mania occurred in approximately 1.0% of paroxetine-treated unipolar patients compared to 1.1% of active-control and 0.3% of placebo-treated unipolar patients. In a subset of patients classified as bipolar, the rate of manic episodes was 2.2% for immediate-release paroxetine and 11.6% for the combined active-control groups. Among 1627 patients with major depressive disorder, panic disorder, social anxiety disorder, or PMDD treated with PAXIL CR in controlled clinical studies, there were no reports of mania or hypomania. As with all drugs effective in the treatment of major depressive disorder, PAXIL CR should be used cautiously in patients with a history of mania.

Seizures: During premarketing testing of immediate-release paroxetine hydrochloride, seizures occurred in 0.1% of paroxetine-treated patients, a rate similar to that associated with other drugs effective in the treatment of major depressive disorder. Among 1627 patients who received PAXIL CR in controlled clinical trials in major depressive disorder, panic disorder, social anxiety disorder, or PMDD, 1 patient (0.1%) experienced a seizure. PAXIL CR should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

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 CR 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 CR: Adverse events while discontinuing therapy with PAXIL CR were not systematically evaluated in most clinical trials; however, in recent placebo-controlled clinical trials utilizing daily doses of PAXIL CR up to 37.5 mg/day, spontaneously reported adverse events while discontinuing therapy with PAXIL CR were evaluated. Patients receiving 37.5 mg/day underwent an incremental decrease in the daily dose by 12.5 mg/day to a dose of 25 mg/day for 1 week before treatment was stopped. For patients receiving 25 mg/day or 12.5 mg/day, treatment was stopped without an incremental decrease in

dose. With this regimen in those studies, the following adverse events were reported at an incidence of 2% or greater for PAXIL CR and were at least twice that reported for placebo: Dizziness (11.9% versus 1.3%), nausea (5.4% versus 2.7%), nervousness (2.4% versus 1.1%), and additional symptoms described by the investigator as associated with tapering or discontinuing PAXIL CR (e.g., emotional lability, headache, agitation, electric shock sensations, fatigue, sleep disturbances) (2.4% versus 0.3%). These events were reported as serious in 0.3% of patients who discontinued therapy with PAXIL CR .

In clinical trials of immediate-release paroxetine which employed a taper phase with an incremental decrease in the daily dose by 10 mg/day to a total daily dose of 20 mg/day, rather abrupt discontinuation, events which met the above criteria were: Abnormal dreams, paresthesia, and dizziness. In the majority of patients, these events were mild to moderate and were self-limiting and did not require medical intervention.

During marketing of immediate-release paroxetine hydrochloride, there have been spontaneous reports of similar adverse events, which may have no causal relationship to the drug, upon the discontinuation of immediate-release paroxetine hydrochloride (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 CR is being prescribed. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION).

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

[We have replaced the previous version of the following statement with a slightly modified version, making only editorial changes.]

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

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

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

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

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

Information for Patients: Physicians are advised to discuss the following issues with patients for whom they prescribe PAXIL CR:

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

Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.): Patients should be cautioned about the concomitant use of PAXIL CR and nonsteroidal anti-inflammatory drugs, aspirin, or other drugs that affect coagulation since combined use of these drug products has been associated with an increased risk of bleeding.

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

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

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

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

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

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

Laboratory Tests: There are no specific laboratory tests recommended.

Drug Interactions: ***Tryptophan:*** As with other serotonin reuptake inhibitors, an interaction between paroxetine and tryptophan may occur when they are coadministered. Adverse experiences, consisting primarily of headache, nausea, sweating, and dizziness, have been reported when tryptophan was administered to patients taking immediate-release paroxetine. Consequently, concomitant use of PAXIL CR with tryptophan is not recommended.

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 CR and warfarin should be undertaken with caution (see *Drugs That Interfere With Hemostasis*).

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

Phenobarbital: Phenobarbital induces many cytochrome P_{450} (oxidative) enzymes. When a single oral 30-mg dose of immediate-release paroxetine was administered at phenobarbital steady state (100 mg once daily for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 25% and 38%, respectively) compared to paroxetine administered alone. The effect of paroxetine on phenobarbital pharmacokinetics was not studied. Since paroxetine exhibits nonlinear pharmacokinetics, the results of this study may not address the case where the 2 drugs

are both being chronically dosed. No initial dosage adjustment with PAXIL CR is considered necessary when coadministered with phenobarbital; any subsequent adjustment should be guided by clinical effect.

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

Drugs Metabolized by 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 paroxetine dosing. In 1 study, daily dosing of immediate-release paroxetine (20 mg once daily) under steady-state conditions increased single-dose desipramine (100 mg) C_{max}, AUC, and $T_{1/2}$ by an average of approximately 2-, 5-, and 3-fold, respectively. Concomitant use of PAXIL CR 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 CR or the other drug.

Therefore, coadministration of PAXIL CR with other drugs that are metabolized by this isozyme, including certain drugs effective in the treatment of major depressive disorder (e.g., nortriptyline, amitriptyline, imipramine, desipramine, and fluoxetine), phenothiazines, and Type 1C antiarrhythmics (e.g., propafenone, flecainide, and encainide), or that inhibit this enzyme (e.g., quinidine), should be approached with caution.

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

At steady state, when the $P_{450}IID_6$ pathway is essentially saturated, paroxetine clearance is governed by alternative P_{450} isozymes that, 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 coadministration under steady-state conditions of paroxetine and terfenadine, a substrate for $P_{450}IIIA_4$, 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 cyclosporine. Based on the

assumption that the relationship between paroxetine's in vitro K_i and its lack of effect on terfenadine's in vivo clearance predicts its effect on other $IIIA_4$ substrates, paroxetine's extent of inhibition of $IIIA_4$ activity is not likely to be of clinical significance.

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

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

[This statement was acceptable as proposed.]

Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.):

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentiated the risk of bleeding.

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

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

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

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

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

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

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

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

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

Impairment of Fertility: A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of 15 mg/kg/day, which is approximately twice the MRHD on a mg/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 (approximately 8 and 4 times the MRHD on a mg/m^2 basis).

Pregnancy: 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 approximately 8 (rat) and 2 (rabbit) times the maximum recommended human dose (MRHD) on an 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 approximately one-sixth of the MRHD on an mg/m^2 basis. 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. 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 CR is administered to a nursing woman.

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

Geriatric Use: In worldwide premarketing clinical trials with immediate-release paroxetine hydrochloride, 17% of paroxetine-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).

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

ADVERSE REACTIONS

The information included under the "Adverse Findings Observed in Short-Term, Placebo-Controlled Trials With PAXIL CR" subsection of ADVERSE REACTIONS is based on data from 10 placebo-controlled clinical trials. Three of these studies were conducted in patients with major depressive disorder, 3 studies were done in patients with panic disorder, 1 study was conducted in patients with social anxiety disorder, and 3 studies were done in female patients with PMDD. Two of the studies in major depressive disorder, which enrolled patients in the age range 18 to 65 years, are pooled. Information from a third study of major depressive disorder, which focused on elderly patients (60 to 88 years), is presented separately as is the information from the panic disorder studies and the information from the PMDD studies. Information on additional adverse events associated with PAXIL CR and the immediate-release formulation of paroxetine hydrochloride is included in a separate subsection (see Other Events).

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

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

	PAXIL CR (n = 212)	Placebo (n = 211)

Nausea	3.7%	0.5%
Asthenia	1.9%	0.5%
Dizziness	1.4%	0.0%
Somnolence	1.4%	0.0%

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

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

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

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

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

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

Premenstrual Dysphoric Disorder: Thirteen percent (88/681) of patients treated with PAXIL CR in PMDD studies discontinued treatment due to an adverse event.

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

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

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

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

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

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

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

Premenstrual Dysphoric Disorder: The most commonly observed adverse events associated with the use of PAXIL CR (incidence of 5% or greater and incidence for PAXIL CR

at least twice that for placebo, derived from Table 5) were: Nausea, asthenia, libido decreased, somnolence, insomnia, female genital disorders, sweating, dizziness, diarrhea, and constipation.

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

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

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

Body System/Adverse Event	% Reporting Event	
	PAXIL CR (n = 212)	Placebo (n = 211)
Body as a Whole		
Headache	27%	20%
Asthenia	14%	9%
Infection[3]	8%	5%
Abdominal Pain	7%	4%
Back Pain	5%	3%
Trauma[4]	5%	1%

Pain[5]	3%	1%
Allergic Reaction[6]	2%	1%
Cardiovascular System		
Tachycardia	1%	0%
Vasodilatation[7]	2%	0%
Digestive System		
Nausea	22%	10%
Diarrhea	18%	7%
Dry Mouth	15%	8%
Constipation	10%	4%
Flatulence	6%	4%
Decreased Appetite	4%	2%
Vomiting	2%	1%
Nervous System		
Somnolence	22%	8%
Insomnia	17%	9%
Dizziness	14%	4%
Libido Decreased	7%	3%
Tremor	7%	1%
Hypertonia	3%	1%
Paresthesia	3%	1%
Agitation	2%	1%
Confusion	1%	0%
Respiratory System		
Yawn	5%	0%
Rhinitis	4%	1%
Cough Increased	2%	1%
Bronchitis	1%	0%
Skin and Appendages		
Sweating	6%	2%
Photosensitivity	2%	0%
Special Senses		
Abnormal Vision[8]	5%	1%
Taste Perversion	2%	0%
Urogenital System		
Abnormal Ejaculation[9,10]	26%	1%
Female Genital Disorder[9,11]	10%	<1%
Impotence[9]	5%	3%
Urinary Tract Infection	3%	1%

Menstrual Disorder[9]	2%	<1%
Vaginitis[9]	2%	0%

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

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

Body System/Adverse Event	**% Reporting Event**	
	PAXIL CR (n = 104)	**Placebo (n = 109)**
Body as a Whole		
Headache	17%	13%
Asthenia	15%	14%
Trauma	8%	5%
Infection	6%	2%
Digestive System		
Dry Mouth	18%	7%
Diarrhea	15%	9%
Constipation	13%	5%
Dyspepsia	13%	10%
Decreased Appetite	12%	5%
Flatulence	8%	7%
Nervous System		
Somnolence	21%	12%

Insomnia	10%	8%
Dizziness	9%	5%
Libido Decreased	8%	<1%
Tremor	7%	0%
Skin and Appendages		
Sweating	10%	<1%
Urogenital System		
Abnormal Ejaculation[3,4]	17%	3%
Impotence[3]	9%	3%

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

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

Body System/Adverse Event	**% Reporting Event**	
	PAXIL CR (n = 444)	**Placebo (n = 445)**
Body as a Whole		
Asthenia	15%	10%
Abdominal Pain	6%	4%
Trauma[3]	5%	4%
Cardiovascular System		
Vasodilation[4]	3%	2%
Digestive System		
Nausea	23%	17%
Dry Mouth	13%	9%
Diarrhea	12%	9%
Constipation	9%	6%
Decreased Appetite	8%	6%
Metabolic/Nutritional Disorders		
Weight Loss	1%	0%
Musculoskeletal System		
Myalgia	5%	3%
Nervous System		

Body System/Adverse Event	% Reporting Event	
	PAXIL CR (n = 444)	Placebo (n = 445)
Insomnia	20%	11%
Somnolence	20%	9%
Libido Decreased	9%	4%
Nervousness	8%	7%
Tremor	8%	2%
Anxiety	5%	4%
Agitation	3%	2%
Hypertonia[5]	2%	<1%
Myoclonus	2%	<1%
Respiratory System		
Sinusitis	8%	5%
Yawn	3%	0%
Skin and Appendages		
Sweating	7%	2%
Special Senses		
Abnormal Vision[6]	3%	<1%
Urogenital System		
Abnormal Ejaculation[7,8]	27%	3%
Impotence[7]	10%	1%
Female Genital Disorders[9,10]	7%	1%
Urinary Frequency	2%	<1%
Urination Impaired	2%	<1%
Vaginitis[9]	1%	<1%

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

8. Mostly anorgasmia or delayed ejaculation.
9. Based on the number of female patients.
10. Mostly anorgasmia or difficulty achieving orgasm.

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

Body System/Adverse Event	% Reporting Event	
	PAXIL CR (n = 186)	**Placebo (n = 184)**
Body as a Whole		
Headache	23%	17%
Asthenia	18%	7%
Abdominal pain	5%	4%
Back pain	4%	1%
Trauma[3]	3%	<1%
Allergic reaction[4]	2%	<1%
Chest pain	1%	<1%
Cardiovascular System		
Hypertension	2%	0%
Migraine	2%	1%
Tachycardia	2%	1%
Digestive System		
Nausea	22%	6%
Diarrhea	9%	8%
Constipation	5%	2%
Dry mouth	3%	2%
Dyspepsia	2%	<1%
Decreased appetite	1%	<1%
Tooth disorder	1%	0%
Metabolic/Nutritional Disorders		
Weight gain	3%	1%
Weight loss	1%	0%
Nervous System		
Insomnia	9%	4%
Somnolence	9%	4%
Libido decreased	8%	1%
Dizziness	7%	4%
Tremor	4%	2%
Anxiety	2%	1%
Concentration impaired	2%	0%
Depression	2%	1%
Myoclonus	1%	<1%
Paresthesia	1%	<1%

Body System/Adverse Event	% Reporting Event	
	PAXIL CR (n = 186)	Placebo (n = 184)
Respiratory System		
Yawn	2%	0%
Skin and Appendages		
Sweating	14%	3%
Eczema	1%	0%
Special Senses		
Abnormal vision[5]	2%	0%
Abnormality of accommodation	2%	0%
Urogenital System		
Abnormal ejaculation[6,7]	15%	1%
Impotence[6]	9%	0%
Female genital disorders[8,9]	3%	0%

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

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

	% Reporting Event	
Body System/Adverse Event	**PAXIL CR (n = 681)**	**Placebo (n = 349)**
Body as a Whole		
Asthenia	17%	6%
Headache	15%	12%
Infection	6%	4%
Cardiovascular System		
Migraine	1%	<1%
Digestive System		
Nausea	17%	7%
Diarrhea	6%	2%
Constipation	5%	1%

	% Reporting Event	
Body System/Adverse Event	**PAXIL CR (n = 681)**	**Placebo (n = 349)**
Dry Mouth	4%	2%
Increased Appetite	3%	<1%
Decreased Appetite	2%	<1%
Dyspepsia	2%	1%
Musculoskeletal System		
Arthralgia	2%	1%
Nervous System		
Libido Decreased	12%	5%
Somnolence	9%	2%
Insomnia	8%	2%
Dizziness	7%	3%
Tremor	4%	<1%
Concentration Impaired	3%	<1%
Nervousness	2%	<1%
Anxiety	2%	1%
Lack of Emotion	2%	<1%
Abnormal Dreams	1%	<1%
Respiratory System		
Yawn	2%	<1%
Cough Increased	1%	<1%
Skin and Appendages		
Sweating	7%	<1%
Urogenital System		
Female Genital Disorders[3]	8%	1%
Menorrhagia	1%	<1%
Vaginal Moniliasis	1%	<1%

1. Adverse events for which the PAXIL CR reporting rate was less than or equal to the placebo rate are not included. These events are: Abdominal pain, back pain, pain, trauma, weight gain, myalgia, pharyngitis, respiratory disorder, rhinitis, sinusitis, pruritus, dysmenorrhea, menstrual disorder, urinary tract infection, vomiting.

2. <1% means greater than zero and less than 1%.

3. Mostly anorgasmia or difficulty achieving orgasm.

Dose Dependency of Adverse Events:

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

Incidence of Common Adverse Events in Placebo, Low and High Dose Paxil CR-Treated Subjects in a Pool of 3 Fixed-Dose PMDD Trials

	PAXIL CR 25 mg (n = 348)	**PAXIL CR 12.5 mg (n = 333)**	**Placebo (n = 349)**

	%	%	%
Common Adverse Event			
Sweating	8.9	4.2	0.9
Tremor	6.0	1.5	0.3
Concentration Impaired	4.3	1.5	0.6
Yawn	3.2	0.9	0.3
Paresthesia	1.4	0.3	0.3
Hyperkinesia	1.1	0.3	0.0
Vaginitis	1.1	0.3	0.3

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Adverse events for which frequencies are provided below occurred in clinical trials with the controlled-release formulation of paroxetine. During its premarketing assessment in major depressive disorder, panic disorder, social anxiety disorder, and PMDD multiple doses of PAXIL CR were administered to 1627 patients in phase 3 double-blind, controlled, outpatient studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a COSTART-based dictionary. The frequencies presented, therefore, represent the proportion of the 1627 patients exposed to PAXIL CR who experienced an event of the type cited on at least 1 occasion while receiving PAXIL CR. All reported events are included except those already listed in Tables 1 through 5 and those events where a drug cause was remote. If the COSTART term for an event was so general as to be uninformative, it was deleted or, when possible, replaced with a more informative term. It is important to emphasize that although the events reported occurred during treatment with paroxetine, they were not necessarily caused by it.

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

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

paroxetine are included. The extent to which these events may be associated with PAXIL CR is unknown.

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

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

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

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

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

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

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

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

Nervous System: Frequent were depression; infrequent were amnesia, convulsion, depersonalization, dystonia, emotional lability, hallucinations, hyperkinesia, hypesthesia, hypokinesia, incoordination, libido increased, neuralgia, neuropathy, nystagmus, paralysis,

vertigo; rare were ataxia, coma, diplopia, dyskinesia, hostility, paranoid reaction, torticollis, withdrawal syndrome; also observed were abnormal gait, akathisia, akinesia, aphasia, choreoathetosis, circumoral paresthesia, delirium, delusions, dysarthria, euphoria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hyperalgesia, irritability, , manic reaction, manic-depressive reaction, meningitis, myelitis, peripheral neuritis, psychosis, psychotic depression, reflexes decreased, reflexes increased, stupor, trismus.

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

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

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

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

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

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

DRUG ABUSE AND DEPENDENCE

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

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

OVERDOSAGE

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

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

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

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

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

A specific caution involves patients taking or recently having taken paroxetine who might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (see PRECAUTIONS—*Drugs Metabolized by Cytochrome $P_{450}IID_6$*).

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

DOSAGE AND ADMINISTRATION

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

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

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

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

Panic Disorder: *Usual Initial Dosage:* PAXIL CR should be administered as a single daily dose, usually in the morning. Patients should be started on 12.5 mg/day. Dose changes should

occur in 12.5 mg/day increments and at intervals of at least 1 week. Patients were dosed in a range of 12.5 to 75 mg/day in the clinical trials demonstrating the effectiveness of PAXIL CR. The maximum dosage should not exceed 75 mg/day.

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

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

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

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

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

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

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

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

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

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

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

HOW SUPPLIED

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

12.5-mg yellow tablets, engraved with Paxil CR and 12.5

NDC 0029-3206-13 Bottles of 30

NDC 0029-3206-20 Bottles of 100

25-mg pink tablets, engraved with Paxil CR and 25

NDC 0029-3207-13 Bottles of 30

NDC 0029-3207-20 Bottles of 100

NDC 0029-3207-21 SUP 100s (intended for institutional use only)

37.5-mg blue tablets, engraved with Paxil CR and 37.5

NDC 0029-3208-13 Bottles of 30

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

PAXIL CR is a trademark of GlaxoSmithKline.

GEOMATRIX is a trademark of Jago Pharma, Muttenz, Switzerland.

GlaxoSmithKline
Research Triangle Park, NC 27709

Month 2003 PC:LX

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-936/S-012

MEDICAL REVIEW(S)

CLINICAL REVIEW

NDA 20-936/SE1-012

Sponsor: GlaxoSmithKline

Drug Name: Paroxetine CR (Paxil CR™)

Proposed Indication: Acute treatment of social anxiety disorder

Date Submitted: 12/20/02

User Fee Due Date: 10/20/03

Final Review Completed: 7/30/03

Reviewer: Cara Alfaro, Pharm.D.

Table of Contents

Clinical Review for NDA 20-936

Executive Summary

I. Recommendations

A. Recommendation on Approvability

I recommend that the Division take an approvable action for supplemental NDA 20-936/SE1-012. The Sponsor seeks a claim indicating paroxetine CR for the acute treatment of social anxiety disorder.

If feasible, labeling should be coordinated with the recent approvable action (4/11/03) for the indication premenstrual dysphoric disorder.

In the Precautions section of the currently approved labeling, the section entitled "discontinuation of treatment with Paxil CR" contains the statement "adverse events while discontinuing therapy with Paxil CR were not systematically evaluated in the clinical trials" with the remaining information in this section referring to the immediate release dosage form. Since the pivotal trial for social anxiety disorder does contain some data with regard to the withdrawal syndrome occurring with paroxetine CR, the Sponsor should evaluate all clinical trials with this dosage form and include language in this section of labeling pertinent to the controlled release dosage form.

A number of requests for information were sent to the Sponsor during the review of this application. Some of these requests were pending at the time this review was completed, though this reviewer does not believe that the responses to these requests would likely impact the recommended approvable action. Requests that were pending at the time this review was completed are listed in Section XI (Requests for Information from Sponsor). These requests could be included in the action letter.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The immediate release form of paroxetine hydrochloride is currently approved for the (acute) treatment of social anxiety disorder. Per prior discussion with the Sponsor, the Division stated that one adequate and well-controlled trial could suffice for approval of an indication for a controlled release formulation of a

product that is already approved for that indication in an immediate release dosage form.
The Sponsor submitted one clinical trial (Study 790) to support the efficacy of paroxetine CR in the acute treatment of social anxiety disorder. This pivotal trial was a non-IND trial conducted in 36 centers in Europe and South Africa. No supportive clinical trials were included in this submission.

B. Efficacy

Data from one controlled clinical trial demonstrated the efficacy of paroxetine CR (flexible-dose 12.5 to 37.5 mg/day) in improving the symptoms of social anxiety disorder was submitted. In pivotal trial 790, paroxetine CR was statistically significantly superior to placebo with respect to both co-primary efficacy variables: the Liebowitz Social Anxiety Scale (LSAS) change in score from baseline to week 12 (study endpoint) and the percentage of responders defined by a Clinical Global Impression – Improvement (CGI-I) score of 1 (very much improved) or 2 (much improved) at week 12. A greater decrease in LSAS score at week 12 was demonstrated in the paroxetine CR group (-31) compared to placebo (-17.6) [LOCF analysis, $p < 0.001$]. For the co-primary measure, the CGI-I, a higher proportion of treatment responders was demonstrated in the paroxetine CR group (57%) versus the placebo group (30%) at week 12 [LOCF analysis, $p < 0.001$].

C. Safety

Safety results of one 12-week pivotal clinical trial in social anxiety disorder support the conclusion that paroxetine CR, in doses between 12.5 – 37.5 mg/day, is reasonably safe and well tolerated. No significant medical concerns or adverse events were identified in subjects with social anxiety disorder that had not been identified in safety profiles of paroxetine CR in the treatment of subjects with major depression and panic disorder. The dosing recommendation for paroxetine CR in the treatment of social anxiety disorder, 12.5 to 37.5 mg/day, is similar to the dosing recommendations for other indications though the maximum dose is lower. The recommended dose ranges for major depressive disorder is 25 to 62.5 mg/day and the dose range for panic disorder is 12.5 to 75 mg/day.

The adverse events that occurred in the social anxiety disorder studies had been reported in the current Paxil CR product label. There were no deaths reported in this study and there were no serious adverse events or adverse events associated with study discontinuation which were unexpected or drug-related and unlabeled. It is noteworthy that the current product labeling for the section "discontinuation of treatment with Paxil CR" contains information relevant to the immediate release paroxetine dosage form only. The clinical trial in this submission did include some information on adverse events occurring after paroxetine CR discontinuation as subjects were followed out to 28 days after the end of the

clinical trial. Three of these adverse events were consistent with a withdrawal/discontinuation syndrome and were classified as serious adverse events. The Sponsor should include data relevant to the CR dosage form in this section in labeling.

D. Dosing

Directions for use conveyed in the Sponsor's proposed labeling are as follows: Usual initial dosage: Paxil CR should be administered as a single daily dose, usually in the morning, with or without food. The recommended initial dose is 12.5 mg/day. Patients were dosed in a range of 12.5 mg to 37.5 mg/day in the clinical trial demonstrating the effectiveness of Paxil CR in the treatment of social anxiety disorder. [ ]

[ ]

The clinical trial supports this dosing recommendation.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Paroxetine CR (Paxil CR™) is a selective serotonin reuptake inhibitor first approved on 2/16/99 for the treatment of major depressive disorder. Paroxetine CR is a controlled release dosage formulation for oral administration.
The Sponsor's proposed indication for paroxetine CR for this submission is "for the treatment of social anxiety disorder, also known as social phobia, as defined in DSM-IV (300.23)."

Directions for use conveyed in the Sponsor's proposed labeling are as follows:
Usual initial dosage: Paxil CR should be administered as a single daily dose, usually in the morning, with or without food. The recommended initial dose is 12.5 mg/day. Patients were dosed in a range of 12.5 mg to 37.5 mg/day in the clinical trial demonstrating the effectiveness of Paxil CR in the treatment of social anxiety disorder. [redacted]

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

B. State of Armamentarium for Indication(s)

The immediate release formulation of paroxetine was the first medication approved for the indication social anxiety disorder [social phobia]. Recently two other medications have received approval for social anxiety disorder: sertraline (Zoloft) was approved on 2/7/03 and venlafaxine (Effexor XR) was approved on 2/11/03.

C. Important Milestones in Product Development

Immediate release paroxetine was first approved on 12/29/92 for the treatment of major depressive disorder (NDA 20-031). Additional approved indications for the immediate release formulation include obsessive-compulsive disorder (5/7/96), panic disorder (5/7/96), social anxiety disorder (5/17/99), generalized

anxiety disorder (4/13/01) and posttraumatic stress disorder (12/14/01). The paroxetine oral suspension (NDA 20-710) and capsule (NDA 20-885) dosage forms were approved 6/25/97 and 10/9/98 respectively.

The IND for paroxetine CR was filed with the Division on 7/18/96 (IND #51,171). Paroxetine CR, the controlled release formulation of paroxetine hydrochloride, was first approved on 2/16/99 for the treatment of major depressive disorder. An additional approved indication includes panic disorder (2/12/02). Recently, an approvable action was taken for the indication premenstrual dysphoric disorder (4/11/03).

In a 7/2/02 correspondence, the Sponsor had requested a pre-sNDA teleconference regarding planned supplemental applications for the treatment of generalized anxiety disorder and social anxiety disorder. The request for the teleconference was denied as it was deemed not to be necessary. In lieu of the teleconference, correspondence was sent to the Sponsor (8/29/02) that addressed the questions posed by the Sponsor. One of these questions asked the Division to re-confirm the guidance originally provided in a 8/14/96 letter in which it was recognized that one adequate and well-controlled trial could suffice for approval of a controlled release formulation of an already approved product. The Division responded that one adequate and well-controlled trial could suffice for approval of an indication for a controlled release formulation of a product that is already approved for that indication in an immediate release dosage form.

On 6/10/03, the United Kingdom Department of Health issued a press release stating that paroxetine must not be used to treat children and teenagers under the age of 18 for depressive illness. The UK concluded that there is an increase in the rate of self-harm and potentially suicidal behavior in this age group when paroxetine is used for depressive illness. Canada recently issued a similar statement. The FDA is currently reviewing the clinical trials data on which these statements were based. On 6/19/03, the FDA issued a Talk Paper recommending that paroxetine not be used in children and adolescents for the treatment of major depressive disorder (paroxetine is currently approved for use in adults only). The clinical trial in this application included adult subjects only. However, the results of the safety data analysis in children/adolescents may have implications for the pediatric development plan for paroxetine CR.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

There are no chemistry or animal pharmacology/toxicology issues in this submission.

III. Human Pharmacokinetics and Pharmacodynamics

Reference is made to approved NDA 20-031 for immediate release paroxetine for major depressive disorder and approved NDA 20-936 for paroxetine CR for major depressive disorder.
Bipharmaceutics submitted a brief review for this submission because an over-encapsulated product of the approved tablet was used in pivotal trial 790. The reviewer concluded that the Sponsor had provided adequate dissolution data for the paroxetine CR tablets and the over-encapsulated tablets to show similarity in the dissolution profiles of the two.

IV. Description of Clinical Data and Sources

A. Overall Data

The efficacy and safety of paroxetine CR in social anxiety disorder was evaluated in a single 12- week clinical trial involving 370 subjects (185 paroxetine CR, 184 placebo).

B. Tables Listing the Clinical Trials

The submission included a single non-IND clinical trial, Study 790. No supportive studies were included in the submission.

C. Postmarketing Experience

Paroxetine CR, the controlled release formulation of paroxetine hydrochloride, was first approved on 2/16/99 for the treatment of major depressive disorder. The Sponsor did not include an analysis of their post-marketing safety database in this submission. The Sponsor will be asked to submit this information to the Division.

D. Literature Review

This supplement did not include a literature review for paroxetine CR. The Sponsor has been asked to submit this information to the Division.

E. Foreign Regulatory Review

As of November 1, 2002, marketing authorization applications for paroxetine CR for the treatment of social anxiety disorder have not been submitted to any foreign country. Paroxetine hydrochloride has not been withdrawn from any country for any reason related to safety or effectiveness. The Sponsor did not provide any information stating in which countries paroxetine CR is currently approved and for which indications. The Sponsor has been asked to submit this information to

the Division. See Sections I.C. and IX.C for comments regarding regulatory decisions in the use of paroxetine in children/adolescents in the U.K. and Canada.

V. Clinical Review Methods

A. How the Review was Conducted

This submission contained a single study report for the non-IND pivotal trial, Study 790. Efficacy and safety data from this clinical trial were reviewed. No supportive trials were included in this submission. The immediate release dosage form of paroxetine was approved for social anxiety disorder on 5/17/99. The Division had informed the Sponsor that one adequate and well-controlled trial could suffice for approval of an indication for a controlled release formulation of a product that is already approved for that indication in an immediate release dosage form.
Results of the analyses were compared with those conducted by the Sponsor. This reviewer consulted with reviewers from other disciplines, including Biometrics and the Division of Scientific Investigations.

B. Overview of Materials Consulted in Review

Supplement SE1-012 to NDA 20-936 was an electronic submission. Correspondences filed under IND 51,171 were consulted to review regulatory issues and decisions made with respect to this supplement. Additionally, clinical reviews for the original NDA for paroxetine CR for major depressive disorder and for the immediate release paroxetine dosage form for social anxiety disorder were consulted during the review of this supplement.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

Raw data were submitted to the Division of Biometrics via SAS transport files and analyzed according to the methods described in the Sponsor's protocol. The submission was also examined for internal consistency. DSI was consulted to inspect two foreign sites that recruited subjects for the single pivotal study. This was a non-IND study, no U.S. sites enrolled subjects.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The trial was conducted according to Good Clinical Practice guidelines and in accordance with the declaration of Helsinki and its subsequent revisions.

E. Evaluation of Financial Disclosure

The Sponsor has provided documentation of financial disclosure. There are no discernable indications of conflict of interest that would impact the integrity of the

outcomes of the studies. None of the investigators disclosed a proprietary interest in paroxetine CR or a significant equity in the Sponsor.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Data from one controlled clinical trial demonstrated the efficacy of paroxetine CR (flexible-dose 12.5 to 37.5 mg/day) in improving the symptoms of social anxiety disorder were submitted. In pivotal trial 790, paroxetine CR was statistically significantly superior to placebo with respect to both co-primary efficacy variables: the Liebowitz Social Anxiety Scale (LSAS) change in score from baseline to week 12 (study endpoint) and the percentage of responders defined by a Clinical Global Impression – Improvement (CGI-I) score of 1 (very much improved) or 2 (much improved) at week 12. A greater decrease in LSAS score at week 12 was demonstrated in the paroxetine CR group (-31) compared to placebo (-17.6) [LOCF analysis, $p < 0.001$]. For the co-primary measure, the CGI-I, a higher percentage of treatment responders was demonstrated in the paroxetine CR group (57%) versus the placebo group (30%) at week 12 [LOCF analysis, $p < 0.001$].

B. General Approach to Review of the Efficacy of the Drug

Efficacy data from the single pivotal trial were reviewed in detail. The results obtained by the clinical and biometrics reviewers were compared with the Sponsor's efficacy analyses.

C. Detailed Review of Trials by Indication

The Sponsor submitted one clinical trial to support the indication social anxiety disorder:
Study 790 – "A double-blind, placebo-controlled, flexible-dose study of paroxetine CR in the treatment of patients with social anxiety disorder".
This study was initiated on 10/23/01 and completed on 7/16/02. This pivotal study is a non-IND study.

C-1 Investigators and Sites

A list of investigators and sites may be found in Table C-1-A in the Appendix. A total of 36 centers in Europe and South Africa recruited subjects in this multicenter study. No U.S. sites were used in this study.

C-2 Objectives

To compare the efficacy and safety of paroxetine CR with placebo in the treatment of outpatients with social anxiety disorder.

C-3 Study Population

This study enrolled generally healthy outpatients (≥ 18 years of age) with a DSM-IV primary diagnosis of social anxiety disorder. Subjects were diagnosed using the Mini International Neuropsychiatric Interview (MINI), Clinician Rated version 5.0 according to DSM-IV criteria.

Exclusion criteria are listed in Table C-3-A in the Appendix. Briefly, subjects were excluded if they scored 1 or 2 on the CGI-I at baseline; scored ≥15 on the HAM-D_{17} at baseline; met DSM-IV criteria for dysthymia, simple phobia, major depression, obsessive-compulsive disorder or panic disorder as a primary diagnosis currently or within 6 months prior to screening; taken psychotropic drugs within specified time intervals prior to screening; and were SSRI nonresponders.

C-4 Design

This was a double-blind, placebo-controlled, flexible-dose, multicenter study. A one-week placebo run-in period preceded randomization. Subjects were randomized (1:1) to paroxetine CR or placebo for 12 weeks. Study visits occurred at weeks 1, 2, 3, 4, 6, 8 and 12. The dose range of paroxetine CR was 12.5 to 37.5 mg/day. In the protocol, dosing was referred to as "Dose Levels". Dose Level 1 = paroxetine 12.5 mg or placebo, Dose Level 2 = paroxetine 25 mg or placebo, Dose Level 3 = paroxetine 37.5 mg or placebo. The initial dose of paroxetine CR was 12.5 mg for 2 weeks, thereafter investigators could increase the dose in 12.5 mg increments no more frequently than every 7 days. After week 2, the dose of paroxetine CR could be decreased, based on tolerability issues, by 12.5 mg/day; only one dose reduction was allowed. A one week "down titration" period followed completion of the trial (or premature withdrawal) for subjects receiving study medication at Dose Level 3 (paroxetine 37.5 mg or placebo). These subjects received Dose Level 2 for a one week period as the "down titration". No down titration period occurred for subjects at Dose Levels 1 or 2. After completion of the end of the study/down titration phase, 14-day and 28-day follow-up visits occurred.

C-5 Statistical Analysis Plan

This study had co-primary efficacy variables: change from baseline in the Liebowitz Social Anxiety Scale total score at week 12 and proportion of responders [subjects scoring 1 (very much improved) or 2 (much improved)] on the CGI Global Improvement scale at week 12 evaluating paroxetine CR versus placebo. The planned analysis used the LOCF in the ITT population. Statistical significance at alpha = 0.05 was required for both efficacy variables.

As stated in the statistical analysis plan, the statistical model included terms for center, baseline LSAS total score and treatment group. The analysis plan stated that if the number of patients at one or more centers is small, centers may be grouped.

C-6 Assessments (See Schedule of Assessments, Table C-6-A in the Appendix)

Primary efficacy variables – co-primary variables:

1. Change from baseline in the Liebowitz Social Anxiety Scale (LSAS) at week 12
2. The proportion of responders who scored 1 or 2 (very much improved or much improved) on the CGI-I item at week 12

Secondary efficacy variables: a number of secondary efficacy variables were explored in this study. None of the secondary variables were identified as "key secondary variables" in the protocol. Secondary efficacy variables are listed in Table C-6.1-A in the Appendix.

Safety assessments included medical/psychiatric history, adverse events, concomitant medications, physical examination, vital signs (sitting blood pressure and pulse), ECG, and the following laboratory assessments:

Serum pregnancy test

Hematology: hemoglobin, hematocrit, red blood cells, white blood cells (total and differential), platelets

Clinical chemistry: urea, creatinine, total bilirubin, alkaline phosphatase, ALT, AST, total protein, globulin, albumin

Thyroid function tests: TSH, free thyroxine, free triiodothyronine

C-7 Subject Disposition

A total of 375 subjects were randomized (189 to paroxetine and 186 to placebo). Five randomized subjects withdrew from the study (3-paroxetine, 2-placebo) prior to receiving study medication and were not included in the ITT population. Seventy-eight percent of subjects (293/370) completed the study. Reasons for subject withdrawal from the study were noted in the CRFs: adverse experience, lack of efficacy, protocol deviation (including noncompliance), lost to follow-up and other (with specifier).

Table C-7. Subject Disposition (Sponsor's table)

Table 8 Number (%) of Randomized Subjects Who Completed the Study or were Withdrawn by Reason for Withdrawal (ITT Population)

	Treatment Group			
	Paroxetine CR		Placebo	
Reason for Study Conclusion	N=186		N=184	
Completed Study*	156	(83.9)	137	(74.5)
Total Withdrawn	30	(16.1)	47	(25.5)
AE	5	(2.7)	3	(1.6)
Lack of Efficacy	4	(2.2)	29	(15.8)
Protocol Deviation **	7	(3.8)	7	(3.8)
Lost to follow-up	6	(3.2)	4	(2.2)
Other†	8	(4.3)	4	(2.2)

Data Source: Data Source Table 12.6.

* Subjects were considered to have completed the study if they remained in the study up to and including Week 12 of the double-blind treatment phase.

** Including non-compliance.

† Including unknown and non-study-related personal reasons.

The reasons for subject withdrawal from the clinical trial were fairly similar between the paroxetine CR and the placebo groups with the exception that many more subjects withdrew from the placebo group due to lack of efficacy (15.8% vs. 2.2%). The Sponsor was contacted to provide the reasons for the "other" withdrawals. The predominant specifier was "withdrew consent" (see Table C-7-A in the Appendix). Three of the "other – withdrew consent" withdrawals in the paroxetine CR group could have indicated lack of efficacy since subjects either had adverse events of anxiety and/or received treatment shortly after discontinuing the trial. This would have increased the number of withdrawals due to lack of efficacy to 3.7% in the paroxetine CR group, still considerably fewer than in the placebo group.

C-8 Baseline Demographics/Severity of Illness

Table C-8.1 Patient Demographics at Screening and Randomization (mean ? SD)

	Paroxetine CR (N = 186)	Placebo (N = 184)
Sex		
Female	98 (53%)	87 (47%)
Male	88 (47%)	97 (53%)
Race		
White	174 (93%)	175 (95%)
Black	3 (2%)	3 (2%)
Asian	2 (1%)	0
Other	7 (4%)	6 (3%)
Age (years)	39 ± 11	39 ± 12
Weight (kg)	72 ± 15	74 ± 15
Height (cm)	173 ± 9	174 ± 10

Modified from Sponsor table 11

Table C-8.2 Baseline Severity of Illness

	Paroxetine CR (N = 186)	Placebo (N = 184)
LSAS Total Score		
Mean (SD)	78 (25)	79 (23)
Median	81	82
Range	13 - 136	18 - 136
LSAS Fear/Anxiety Subscale		
Mean (SD)	42 (12)	42 (12)
Median	43	44
Range	9 - 71	12 - 71
LSAS Avoidance Subscale		
Mean (SD)	37 (13)	37 (12)
Median	38	39
Range	4 - 66	6 - 70
CGI-S		
Mean (SD)	4.5 (0.8)	4.5 (0.8)
Median	4	4
Range	3 - 7	3 - 6
SADS* [Mean (SD)]	22 (6)	22 (5)
SDS* [Mean (SD)]		
Work	6 (3)	6 (3)
Social life	7 (2)	7 (2)
Family life	3 (3)	3 (3)
$HAM\text{-}D_{17}$ baseline		
Mean (SD)	4.1 (3.2)	4.4 (3.4)
Median	4	4
Range	0-14	0-14

Modified from Sponsor tables 11, 12, 13.3, 13.10, 13.13, 13.15

*SADS = Social Avoidance and Distress Scale, SDS = Sheehan Disability Scale

Though the protocol inclusion criteria did not specify a severity of illness via LSAS total score (see discussion in Section VI.C-10.2), the mean LSAS total score indicated significant symptoms of social anxiety disorder in both treatment groups. Subjects with significant depressive symptoms ($HAM\text{-}D_{17} \geq 15$) were excluded from the study; the low baseline HAM-D scores reflect this.

C-9 Concomitant Medications

The only concomitant psychotropic medication allowed during the clinical trial was chloral betaine up to 828 mg at bedtime or chloral hydrate up to 1000 mg at bedtime for sleep disturbance. Only one patient in the placebo group used concomitant chloral hydrate/betaine. For those countries in which chloral hydrate/chloral betaine was not available (France, Holland and Sweden), no concomitant psychotropic medications were allowed during the trial. Subjects who had been receiving psychotherapy for 6 months or longer prior to enrollment could be enrolled and continue receiving psychotherapy.

The most common nonpsychotropic concomitant medications were hormonal products or analgesics, use was fairly similar between treatment groups. Very

few subjects received concomitant psychotropic medications during the clinical trial. Three subjects received benzodiazepines (alprazolam, diazepam, chlordiazepoxide) in the paroxetine CR group (see Division's Analysis section of review). The concomitant medication table in the submission (Table 12.21) indicates that one subject in the paroxetine CR group and 2 subjects in the placebo group received paroxetine during the clinical trial. The Sponsor was contacted to clarify the concomitant use of paroxetine in the trial. The Sponsor commented that only two subjects received paroxetine during the trial and in both cases the first dose was taken on the last day of study medication – the third subject was listed in error (error in the recorded start date for paroxetine).

C-10 Efficacy Results
C-10.1 Sponsor's Analysis

The Sponsor's analysis did not include an assessment of paroxetine CR versus placebo at each weekly timepoint to determine when a statistical separation occurred that was maintained until the study endpoint. See Division's analysis for this statistical analysis.

The average paroxetine CR dose at week 12 was 32.3 ± 8.5 mg/day (LOCF) [33.3 ± 7.7 OC]. At week 12 (LOCF) 11% of subjects were receiving 12.5 mg/day, 20% were receiving 25 mg/day and 69% were receiving 37.5 mg/day.

LSAS Total Score Change From Baseline

The changes from baseline in LSAS total score were adjusted by country group and baseline LSAS total score.

Table 10.1.1. LOCF Analysis: LSAS Total Score Change from Baseline

	Paroxetine CR (N = 185)		Placebo (N = 184)		Difference (95% CI)
	LS Mean	SE	LS Mean	SE	
Week 1	-1.1	0.78	-3.5	0.78	
Week 2	-4.9	1.02	-6.2	1.01	
Week 3	-8.9	1.18	-8.8	1.17	
Week 4	-13.5	1.31	-11.1	1.31	
Week 6	-19.7	1.54	-14.5	1.53	
Week 8	-24.5	1.70	-16.8	1.69	
Week 12	-31.0	1.81*	-17.6	1.80*	-13.3 (-18.2, -8.4) $p < 0.001$

From Sponsor tables 13.41
*Standard deviation at week 12 = 24.6 for paroxetine CR and 24.4 for placebo

Table 10.1.2. OC Analysis: LSAS Total Score Change from Baseline

	Paroxetine CR (N = 185)		Placebo (N = 184)		Difference (95% CI)
	LS Mean	SE	LS Mean	SE	
Week 1	-1.1	0.78	-3.5	0.78	
Week 2	-5.1	1.06	-6.2	1.09	
Week 3	-9.0	1.27	-8.7	1.26	
Week 4	-14.1	1.38	-11.0	1.37	
Week 6	-21.2	1.63	-15.0	1.65	
Week 8	-27.1	1.82	-18.8	1.86	
Week 12	-34.1	2.08*	-20.9	2.14*	-13.2 (-19.0, -7.4) p < 0.001

From Sponsor table 16

*Standard deviation at week 12 = 28.3 for paroxetine CR and 29.0 for placebo

Proportion of CGI-I Responders

The proportion of CGI-I responders were adjusted by country group.

Table 10.1.3. LOCF Analysis: CGI-I Responders (Score 1 or 2)

	Paroxetine CR (n = 186)*	Placebo (n = 184)	Odds Ratio (95% CI)
	No. Responders (%)	No. Responders (%)	
Week 1	4 (2%)	7 (4%)	
Week 2	14 (7%)	15 (8%)	
Week 3	24 (13%)	26 (14%)	
Week 4	36 (19%)	38 (21%)	
Week 6	60 (32%)	42 (23%)	
Week 8	82 (44%)	57 (31%)	
Week 12	106 (57%)	56 (30%)	3.1 (2.0, 4.8) p < 0.001

From Sponsor table 13.43

*ITT analysis for CGI has one additional subject in paroxetine CR group compared to LSAS analysis

Table 10.1.4. OC Analysis: CGI-I Responders (Score 1 or 2)

	Paroxetine CR		Placebo		Odds Ratio (95% CI)
	No. Responders (%)	N	No. Responders (%)	N	
Week 1	4 (2%)	184	7 (4%)	181	
Week 2	14 (8%)	179	14 (8%)	169	
Week 3	23 (14%)	168	24 (14%)	167	
Week 4	36 (21%)	173	37 (21%)	175	
Week 6	59 (35%)	169	40 (25%)	162	
Week 8	81 (49%)	164	54 (35%)	153	
Week 12	87 (64%)	136	43 (35%)	124	3.4 (2.01, 5.74) p < 0.001

From Sponsor table 18

Secondary outcome efficacy results are in Table 10.1.5-A in the Appendix. Statistically significant differences favoring paroxetine CR were noted for all secondary efficacy variables, including the LSAS fear/anxiety subscale and the LSAS avoidance subscale scores.

C-10.2 Division's Analysis

Unlike panic disorder, obsessive-compulsive disorder, major depression, dysthymia and simple phobia, generalized anxiety disorder (GAD) as a primary Axis I disorder was not an exclusion criterion. Comorbid GAD has been an exclusion criterion for a number of other NDA submissions for social anxiety disorder. If a significant number of subjects were to have comorbid GAD, it would be difficult to know if the demonstrated efficacy of paroxetine CR was due to a reduction in symptoms of GAD (for which immediate release paroxetine has an approved indication) or symptoms of social anxiety disorder (SAD).

Though the LSAS rating scale includes questions that seem specific to social anxiety disorder (e.g. fear or anxiety when speaking up at a meeting or writing while being observed), no published data are available to evaluate how subjects with other anxiety disorders without SAD score on this instrument (discriminant validity). This reviewer contacted a researcher who has been involved in various psychometric assessments of the LSAS to ascertain whether any data are available regarding LSAS scores in patients with GAD *without* comorbid SAD. This researcher did have some preliminary data which, though based on a limited sample size, suggested that patients with GAD without comorbid SAD have mean scores around 35 compared to patients with GAD and comorbid SAD who have mean scores around 55 (personal communication 4/28/03, [redacted] Ph.D.). Therefore, it would appear that LSAS scores alone would not reliably discriminate between these two populations. It is also possible that a reduction in GAD symptoms alone would decrease LSAS scores.

The Sponsor was contacted and asked to provide the numbers of subjects with comorbid GAD enrolled in the pivotal trial. The Sponsor responded that no subjects enrolled in the study had comorbid GAD. In the submission, the Sponsor had included 10 CRFs and an additional 12 were requested by this reviewer (assessment of subject withdrawals due to "other"). These CRFs were reviewed and it was noted that the psychiatric history page of the CRF did have a checkbox for GAD. The CRFs were reviewed and none of these few subjects had comorbid GAD. The diagnosis of SAD was performed via the Mini International Neuropsychiatric Interview according to DSM-IV criteria and was not determined via LSAS scores. Therefore it is reasonable to conclude that the appropriate subjects were enrolled in this clinical trial and that no subjects had comorbid GAD.

Similarly, it is important to distinguish the effects of paroxetine CR on symptoms of social anxiety disorder from effects on depressive symptoms (major depressive disorder, dysthymia). Subjects with a score on the HAM-$D_{17} \geq 15$ were excluded from the study. The actual HAM-D scores for subjects enrolled in the study were much lower than the exclusion cut-off score. The mean ± SD for the paroxetine

CR group was 4.1 ± 3.2 and for the placebo group 4.4 ± 3.4 (the median for both groups was 4.0, max score for both groups was 14.0). Scores of ~4 on the HAM-D_{17} do not indicate significant symptoms of depression. It is possible that symptoms of depression could have worsened during the trial. The HAM-D was administered at baseline and at the end of the study only. HAM-D_{17} scores at week 12 (LOCF) were similar to baseline, paroxetine CR = 3.3 ± 3.5 (median = 2.0, max = 18), placebo = 4.3 ± 4.2 (median = 3.5, max = 23). The mean HAM-D_{17} scores at week 12 were not significantly different from the scores at baseline, therefore it is unlikely that the improvement in symptoms of social anxiety disorder are due to improvement in symptoms of depression.

Interestingly, while other SAD protocols have included some minimum severity score on the LSAS, this protocol did not. LSAS baseline scores as low as 13 were noted in the data files. Inclusion of low scores could potentially decrease the chance of finding an efficacy signal if the low scores were equally distributed between the paroxetine CR and placebo groups. While no consensus is available regarding the minimum severity score on the LSAS for inclusion in clinical trials, some Sponsors have used a score of ≥ 50. Approximately 11% of subjects in each treatment arm had baseline LSAS scores < 50. A separate analysis was performed including only those subjects with baseline LSAS scores ≥ 50. The results of this analysis were similar to the original results.

One further analysis was performed to exclude the three subjects in the paroxetine CR group who received concomitant benzodiazepines (see Concomitant Medication section of review). The Sponsor was contacted to submit additional information regarding these subjects. An analysis was performed prior to receiving further information from the Sponsor to determine whether excluding these individuals would impact the overall results of the clinical trial. The exclusion of these three subjects did not change the overall results of the clinical trial.

Although this trial was conducted in non U.S. sites, this reviewer feels that the results are generalizeable to the U.S. population. The sNDA for immediate-release paroxetine for social anxiety disorder contained three pivotal trials, two were conducted primarily in the U.S. (Studies 382 and 454). For all three trials, the primary efficacy variables were the same as those in the current pivotal trial for paroxetine CR (Study 790): co-primary endpoints of change in LSAS score and proportion of CGI-I responders at study endpoint (week 12). All three pivotal trials supported the efficacy of paroxetine in the treatment of social anxiety disorder compared to placebo. The mean decrease in the LSAS total score was similar in the paroxetine immediate-release clinical trials (week 12: -24 to –30 LOCF) compared to the paroxetine CR 790 trial (week 12: -31 LOCF). The proportion of subjects defined as responders based on CGI-I criteria were also similar in the paroxetine immediate-release clinical trials (week 12: 45% to 66%

LOCF) compared to the paroxetine CR 790 trial (week 12: 57% LOCF). The results in the placebo groups were also comparable.

The Sponsor did not report a week-by-week analysis of the results for both co-primary variables. The statistician performed this analysis and found that the paroxetine CR group separated from placebo at week 6 and maintained this separation up to study endpoint (week 12).

Table 10.2.1. LOCF Analysis: LSAS Total Score Change from Baseline

	Paroxetine CR (N = 185)		Placebo (N = 184)		Difference (95% CI)
	LS Mean	SE	LS Mean	SE	
Week 1	-1.1	0.78	-3.5	0.78	2.3 (0.21, 4.5) p = 0.03
Week 2	-4.9	1.02	-6.2	1.01	1.3 (-1.5, 4.0) p = 0.36
Week 3	-8.9	1.18	-8.8	1.17	-0.05 (-3.2, 3.1) p = 0.97
Week 4	-13.5	1.31	-11.1	1.31	-2.4 (-6.0, 1.2) p = 0.19
Week 6	-19.7	1.54	-14.5	1.53	-5.2 (-9.3, -1.0) p = 0.01
Week 8	-24.5	1.70	-16.8	1.69	-7.8 (-12.4, -3.1) p = 0.001
Week 12	-31.0	1.81	-17.6	1.80	-13.3 (-18.2, -8.4) p < 0.001

Table 10.2.2. OC Analysis: LSAS Total Score Change from Baseline

	Paroxetine CR (N = 185)		Placebo (N = 184)		Difference (95% CI)
	LS Mean	SE	LS Mean	SE	
Week 1	-1.1	0.78	-3.5	0.78	2.3 (0.21, 4.5) p = 0.03
Week 2	-4.9	1.02	-6.2	1.01	1.1 (-1.8, 4.0) p = 0.47
Week 3	-8.9	1.18	-8.8	1.17	-0.3 (-3.8, 3.1) p = 0.85
Week 4	-13.5	1.31	-11.1	1.31	-3.1 (-6.9, 0.60) p = 0.10
Week 6	-19.7	1.54	-14.5	1.53	-6.2 (-10.7, -1.7) p = 0.007
Week 8	-24.5	1.70	-16.8	1.69	-8.2 (-13.2, -3.2) p = 0.001
Week 12	-31.0	1.81	-17.6	1.80	-13.2 (-19.0, -7.3) p < 0.001

Table 10.2.3. LOCF Analysis: CGI-I Responders (Score 1 or 2)

	Paroxetine CR (n = 186)*	Placebo (n = 184)	Odds Ratio (95% CI)
	No. Responders (%)	No. Responders (%)	
Week 1	4 (2%)	7 (4%)	0.5 (0.1, 1.8) p = 0.30
Week 2	14 (7%)	15 (8%)	0.9 (0.4, 1.9) p = 0.78
Week 3	24 (13%)	26 (14%)	0.9 (0.5, 1.6) p = 0.69
Week 4	36 (19%)	38 (21%)	0.9 (0.6, 1.6) p = 0.78
Week 6	60 (32%)	42 (23%)	1.6 (1.0, 2.6) p = 0.05
Week 8	82 (44%)	57 (31%)	1.8 (1.1, 2.7) p = 0.01
Week 12	106 (57%)	56 (30%)	3.1 (2.0, 4.8) p < 0.001

Table 10.2.4. OC Analysis: CGI-I Responders (Score 1 or 2)

	Paroxetine CR (n = 186)*	Placebo (n = 184)	Odds Ratio (95% CI)
	No. Responders (%)	No. Responders (%)	
Week 1	4 (2%)	7 (4%)	0.5 (0.1, 1.8) p = 0.30
Week 2	14 (7%)	15 (8%)	1.0 (0.4, 2.1) p = 0.91
Week 3	24 (13%)	26 (14%)	0.9 (0.5, 1.7) p = 0.80
Week 4	36 (19%)	38 (21%)	1.0 (0.6, 1.7) p = 1.0
Week 6	60 (32%)	42 (23%)	1.6 (1.0, 2.7) p = 0.04
Week 8	82 (44%)	57 (31%)	1.8 (1.2, 2.9) p = 0.009
Week 12	106 (57%)	56 (30%)	3.4 (2.0, 5.7) p < 0.0001

D. Efficacy Conclusions

Data from one controlled clinical trial demonstrated the efficacy of paroxetine CR (flexible-dose 12.5 to 37.5 mg/day) in improving the symptoms of social anxiety disorder was submitted. In pivotal trial 790, paroxetine CR was statistically significantly superior to placebo with respect to both co-primary efficacy variables: the Liebowitz Social Anxiety Scale (LSAS) change in score from baseline to week 12 (study endpoint) and the percentage of responders defined by a Clinical Global Impression – Improvement (CGI-I) score of 1 (very much improved) or 2 (much improved) at week 12. A greater decrease in LSAS score at week 12 was demonstrated in the paroxetine CR group (-31) compared to placebo (-17.6) [LOCF analysis, $p < 0.001$]. For the co-primary measure, the CGI-I, a higher percentage of treatment responders was demonstrated in the paroxetine CR group (57%) versus the placebo group (30%) at week 12 [LOCF analysis, $p < 0.001$].

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Safety results of one 12-week pivotal clinical trial in social anxiety disorder support the conclusion that paroxetine CR, in doses between 12.5 – 37.5 mg/day, is reasonably safe and well tolerated. No significant medical concerns or adverse events were identified in subjects with social anxiety disorder that had not been identified in safety profiles of paroxetine CR in the treatment of subjects with major depression and panic disorder. The dosing recommendation for paroxetine CR in the treatment of social anxiety disorder, 12.5 to 37.5 mg/day, is similar to the dosing recommendations for other indications though the maximum dose is lower. The recommended dose ranges for major depressive disorder is 25 to 62.5 mg/day and the dose range for panic disorder is 12.5 to 75 mg/day.

The adverse events that occurred in the social anxiety disorder studies had been reported in the current Paxil CR product label. There were no deaths reported in

this study and there were no serious adverse events or adverse events associated with study discontinuation which were unexpected or drug-related and unlabeled. It is noteworthy that the current product labeling for the section "discontinuation of treatment with Paxil CR" contains information relevant to the immediate release paroxetine dosage form only. The clinical trial in this submission did include some information on adverse events occurring after paroxetine CR discontinuation as subjects were followed out to 28 days after the end of the clinical trial. Three of these adverse events were consistent with a withdrawal/discontinuation syndrome and were classified as serious adverse events. The Sponsor should include data relevant to the CR dosage form in this section in labeling.

B. Description of Patient Exposure

This submission included patient exposure data from Study 790, the pivotal trial, only. A total of 375 subjects were randomized to study medication in this 12-week trial; 370 subjects were included in the ITT population. The overall exposure in the paroxetine CR group was 40.4 years. The overall exposure was similar between males and females (19.3 vs. 21.1 years respectively). This study included too few subjects $\geq$ 65 years of age and too few non-Caucasian subjects to make meaningful exposure comparisons. The mean duration of exposure in the paroxetine CR group was 79 $\pm$ 20 days.
Study 790 was a flexible-dose study, subjects received 12.5 – 37.5 mg/day of paroxetine CR. At week 12, 69% of subjects were receiving 37.5 mg, the highest dose of paroxetine CR allowed; 20% received 25 mg/day and 11% received 12.5 mg/day (LOCF). The mean dose of paroxetine CR at week 12 (LOCF) was 32.3 $\pm$ 8.5 mg/day.

C. Methods and Specific Findings of Safety Review

This review focuses on one 12-week efficacy trial. Paroxetine CR has been on the market since 1999. Adverse events were coded using the World Health Organization (WHO) coding system. No significant medical concerns or adverse events were identified in subjects with social anxiety disorder that had not been identified in safety profiles of paroxetine CR in the treatment of subjects with major depression and panic disorder.
This submission did not include a worldwide literature review or safety data from the Sponsor's postmarketing database, therefore this information could not be reviewed. The Sponsor has been asked to provide this information to the Division.

D. Adequacy of Safety Testing

Generally, the methods used to monitor safety were adequate for this outpatient clinical study. The acute trial included a placebo treatment arm so that

comparisons between paroxetine CR and placebo could be made. Safety assessments were performed at baseline and end of study (or early withdrawal). The protocol also included a 14-day and 28-day follow-up phase which provided, among other things, adverse event data for the post study drug discontinuation phase.

E. Summary of Critical Safety Findings and Limitations of Data

E-1 Deaths in Controlled Trials

No deaths occurred during the course of pivotal trial 790. This includes the 30-day period following the last dose of study medication.

E-2 Serious Adverse Events

A total of 7 subjects experienced serious adverse events, these are summarized in Table E-2.

Table E-2. Serious Adverse Events

Treatment	Serious Adverse Event	Onset Days relative to start of study medication	Onset Days relative to stop of study medication	Severity	Hospitalization?
Paroxetine CR	Dizziness	-	4*	Moderate	Yes
	Trauma	21	-	Moderate	Yes
	Withdrawal syndrome	-	4*	Severe	Unknown
	Withdrawal syndrome	-	14*	Severe	Yes
	Accidental overdose**	24	-	Mild	No
Placebo	Depression	45	-	Moderate	No
	Meningitis	70	-	Severe	Yes

Modified from Sponsor table 42.

*Day of onset in table is from narrative summaries, Sponsor table had different day of onset (13, 11, and 21 respectively).

**Subject ingested two capsules of study medication instead of one

Three of the 5 serious adverse events in the paroxetine CR group occurred soon after discontinuation of paroxetine CR and are consistent with a withdrawal syndrome. The subject with dizziness was hospitalized, the adverse event spontaneously resolved 6 days after onset. For the two subjects with "withdrawal syndrome", paroxetine was reinitiated as a clinical intervention with resolution of the symptoms.

No pregnancies occurred during the clinical trial.

E-3 Discontinuations Due to Adverse Events

A total of 5/186 (2.7%) of subjects in the paroxetine CR group and 3/184 (1.6%) of subjects in the placebo group withdrew from the study due to adverse events.

Table E-3. Sponsor's Table. Subject Discontinuations Due to Adverse Events

Table 43 Summary of Treatment-Emergent AEs Reported by Subjects Who Withdrew from the Study Due to an AE. Number (%) of Subjects (ITT Population)

	Treatment Group			
AE Preferred Term	Paroxetine CR N=186		Placebo N=184	
Total subjects with at least 1 AE leading to withdrawal	5	(2.7)	3	(1.6)
Nausea	4	(2.2)	1	(0.5)
Headache	3	(1.6)	1	(0.5)
Diarrhea	2	(1.1)	1	(0.5)
Abnormal Vision	1	(0.5)	0	
Asthenia	1	(0.5)	1	(0.5)
Depression	1	(0.5)	1	(0.5)
Dizziness	1	(0.5)	0	
Hostility	1	(0.5)	0	
Hypertension	1	(0.5)	0	
Insomnia	1	(0.5)	1	(0.5)
Tachycardia	1	(0.5)	0	
Tremor	1	(0.5)	0	
Weight Gain	1	(0.5)	0	
Abdominal Pain	0		1	(0.5)
Meningitis	0		1	(0.5)
Pharyngitis	0		1	(0.5)

Most of the adverse events leading to discontinuation in the paroxetine CR group had an onset of 7 – 16 days after the start of study medication.

E-4 Adverse Events

The following Sponsor's table lists the most common adverse events occurring during the treatment phase of the study (excluding the down titration phase). The Sponsor defines these most frequent adverse events as ≥ 3% in any treatment group in the study report. Current labeling for paroxetine CR contains various tables of treatment-emergent adverse events (by indication) that list adverse events occurring in ≥ 1% or ≥ 5% of subjects in clinical trials. The proposed labeling for the adverse events table for social anxiety disorder list adverse events occurring in ≥ 1% of subjects.

Table E-4.1. Sponsor's Table. Treatment-Emergent Adverse Events

Table 30 Number (%) of Subjects with the Most Frequently Reported Treatment Emergent AEs (≥3% in Any Treatment Group) Occurring During the Treatment Phase (ITT Population)

	Treatment Group			
	Paroxetine CR		Placebo	
AE Preferred Term	N=186		N=184	
Headache	43	(23.1)	31	(16.8)
Nausea	40	(21.5)	11	(6.0)
Asthenia	33	(17.7)	13	(7.1)
Abnormal Ejaculation*	13	(14.8)	1	(1.0)
Sweating	26	(14.0)	5	(2.7)
Impotence*	8	(9.1)	0	
Somnolence	17	(9.1)	7	(3.8)
Diarrhea	16	(8.6)	15	(8.2)
Insomnia	16	(8.6)	8	(4.3)
Libido Decreased	15	(8.1)	2	(1.1)
Dizziness	12	(6.5)	7	(3.8)
Abdominal Pain	10	(5.4)	7	(3.8)
Constipation	9	(4.8)	4	(2.2)
Respiratory Disorder	9	(4.8)	22	(12.0)
Infection	8	(4.3)	16	(8.7)
Tremor	8	(4.3)	3	(1.6)
Back Pain	7	(3.8)	2	(1.1)
Dry Mouth	6	(3.2)	4	(2.2)
Female Genital Disorders**	3	(3.1)	0	
Pharyngitis	4	(2.2)	7	(3.8)

Data Source: Data Source Table 14.2 and Data Source Table 14.3.
Female genital disorders includes delayed orgasm, sexual dysfunction and anorgasmia.
* Percentages based on male subjects only. N=88 for paroxetine CR group and N=97 for placebo group.
** Percentages based on female subjects only. N=98 for paroxetine CR group and N=87 for placebo group.

A review of the data listings for adverse events occurring in < 3% of subjects was conducted. The adverse events listed in Table E-4.2 were noted to occur in twice the number of paroxetine CR subjects compared to placebo.

Table E-4.2. Adverse Events Occurring in < 3% of Paroxetine CR Subjects and Twice the Rate of Placebo-Treated Subjects

	Paroxetine CR (N = 186)	Placebo (N = 184)
Weight gain	5 (2.7%)	2 (1.1%)
Trauma	5 (2.7%)	1 (0.5%)
Hypertension	4 (2.2%)	0
Migraine	4 (2.2%)	0
Tachycardia	4 (2.2%)	2 (1.1%)
Depression	4 (2.2%)	2 (1.1%)
Abnormal vision	4 (2.2%)	0
Dyspepsia	3 (1.6%)	1 (0.5%)
Concentration impaired	3 (1.6%)	0
Yawn	3 (1.6%)	0
Abnormality of accomodation	3 (1.6%)	0
Decreased appetite	2 (1.1%)	1 (0.5%)
Weight loss	2 (1.1%)	0
Eczema	2 (1.1%)	0

Compared to the studies in major depressive disorder in which paroxetine CR was dosed from 25 to 62.5 mg/day, the study in social anxiety disorder was associated with less diarrhea (9 vs. 18%), somnolence (9 vs. 22%), insomnia (9 vs. 17%), dizziness (6 vs. 14%), abnormal ejaculation (15 vs. 26%), female genital disorder (3 vs. 10%) but more frequent sweating (14 vs. 6%) and impotence (9 vs. 5%). However, it is difficult to compare adverse event rates between studies due to different dosing methods employed (maximum doses and titration schedules), potentially different methods in assessing adverse events and different subject populations. Overall, the adverse event profile for paroxetine CR in the treatment of social anxiety disorder is similar to that in current labeling for major depressive disorder and panic disorder.

E-5 Laboratory

The following laboratory assessments were performed at baseline and at end of study:

Hematology: hemoglobin, hematocrit, red blood cells, white blood cells (total and differential), platelets

Clinical chemistry: urea, creatinine, total bilirubin, alkaline phosphatase, ALT, AST, total protein, globulin, albumin

Thyroid function tests: TSH, free thyroxine, free triiodothyronine

Though 156 subjects in the paroxetine CR and 137 subjects in the placebo groups completed the study, it appears that laboratory assessments are available for only 63% (~96/156) and 80% (~109/137) subjects in these groups. The Sponsor has been asked to address this issue.

Lab values of potential clinical concern (per Sponsor a priori definition) are listed in Table E-5. Increases in both eosinophils and AST are listed in currently approved labeling for paroxetine CR. Of note, most of these lab values were outside the normal range at screening.

Table E-5. Lab Values of Potential Clinical Concern

	Screening	Week 12	Comments
Placebo			
Total Bilirubin (0 - 22 µmol/L)	44	51	
	37	50	
Eosinophils (0 – 7%)	11.5	12.9	
	9.3	10.6	
Creatinine (44 – 124 µmol/L)	70	201	WNL at 14 day follow-up
Hematocrit (35 – 46% female)	29.1	31.3	
AST (0 – 42 IU/L)	20	227	WNL at 14 day follow-up
Paroxetine CR			
Eosinophils (0 – 7%)	8.3	10.8	
	9.6	16.9	
	8.6	10.1	
AST (0 – 42 IU/L)	96	196	

E-6 Vital Signs

Table E-6.1. Vital Signs at Baseline and Week 12 - *Placebo*

	Baseline	Mean Change LOCF Analysis (N = 184)	Mean Change OC Analysis	Max Decrease (LOCF)	Max Increase (LOCF)
Systolic BP (mmHg)	128	-1.8	-2.6 (n = 123)	45	41
Diastolic BP (mmHg)	79	-1.2	-1.9 (n = 123)	26	29
Pulse (bpm)	72	-0.6	-1.2 (n = 123)	27	26
Weight (kg)	74	0.2	0.2 (n = 119)	7	12

From Sponsor table 14.30

Table E-6.2. Vital Signs at Baseline and Week 12 – *Paroxetine CR*

	Baseline	Mean Change LOCF Analysis (N = 186)	Mean Change OC Analysis	Max Decrease (LOCF)	Max Increase (LOCF)
Systolic BP (mmHg)	128	-0.4	-1.2 (n = 133)	31	35
Diastolic BP (mmHg)	81	-1.1	-1.8 (n = 133)	30	20
Pulse (bpm)	73	-0.9	-1.6 (n = 133)	34	39
Weight (kg)	72	0.1	0.2 (n = 129)	7	15

From Sponsor table 14.30

One subject in the paroxetine CR group had an increase in systolic blood pressure that met criteria for potential clinical concern (a priori definition by Sponsor – see Table E-6-A in Appendix), systolic blood pressure was 191 mmHg at visit 1 and normalized thereafter. The overall mean changes in vital signs were small and similar between the paroxetine CR and placebo groups.

A standard 12-lead ECG was performed during the screening visit and at the end of Week 12 or during the last visit for subjects who prematurely discontinued treatment. No subjects in the paroxetine CR group had clinically significant ECG abnormalities during the 12-week efficacy trial, down-titration phase, or follow-up phases.

E-7 Special Searches – Discontinuation Effects

Incorporated into the protocol was a one week down-titration phase (dose taper phase) following the 12-week efficacy trial. Only subjects receiving dose level 3 (paroxetine CR 37.5 mg/day or placebo) continued into the down-titration phase that consisted of decreasing the dose to 25 mg/day paroxetine CR/placebo for an additional week. The other subjects receiving dose levels 1 and 2 (paroxetine CR 12.5 mg/placebo or 25 mg/placebo) did not participate in the down-titration phase of the protocol. One clinic visit occurred at the end of the one-week down-titration phase (week 13), adverse events were assessed at this visit. The protocol also included a 14 day follow-up visit and 28 day follow-up visit in which adverse events were assessed.

There were 121 subjects in the paroxetine CR group and 130 subjects in the placebo group who entered the down-titration phase of the protocol. During this phase of the protocol, 18/121 (15%) of subjects in the paroxetine CR group and 9/130 (7%) of subjects in the placebo group reported at least one adverse event.

Table E-7.1. Sponsor's Table. Most Frequent Adverse Events During Down-Titration Phase.

Table 38 Number (%) of Subjects with the Most Frequently Reported (≥1% in Any Treatment Group) AEs Occurring During the Down-Titration Phase (ITT Population)

	Treatment Group			
	Paroxetine CR N=121		Placebo N=130	
AE Preferred Term				
Abnormal Ejaculation*	1	(1.7)	0	
Anxiety	2	(1.7)	0	
Headache	2	(1.7)	0	
Insomnia	2	(1.7)	0	
Dizziness	1	(0.8)	3	(2.3)

Data Source: Data Source Table 14.4 and Data Source Table 14.5.
* Percentages based on male subjects only, N=58 for paroxetine CR group.

A list of all adverse events during the down-titration phase is in Table 7.1-A in the Appendix. The majority of these adverse events were characterized as either mild to moderate. Only two adverse events were characterized as severe: dizziness in the paroxetine CR group (n = 1) and neurosis in the placebo group (N = 1). Of note, a narrative provided by the Sponsor for one serious adverse event, "withdrawal syndrome", had an onset during the down-titration phase of the protocol (see Serious Adverse Event section). However, the Sponsor's table in the study report indicated an onset of 11 days after stopping paroxetine CR. The Sponsor has been contacted to clarify this discrepancy.

The protocol also included a 14-day follow-up phase (occurred 2 weeks after the efficacy trial or 1 week after the end of the down-titration phase) and a 28-day follow-up phase (occurred 4 weeks after the efficacy trial or 3 weeks after the end of the down-titration phase). The Sponsor submitted tables for adverse events occurring during these follow-up phases which are summarized in Table E-7.2.

Table E-7.2. Adverse Events Emerging During the 14-Day and 28-Day Follow-up Visits

	Paroxetine CR (N = 178)	Placebo (N = 174)
Dizziness	25 (14%)	1 (0.6%)
Withdrawal syndrome*	10 (5.6%)	1 (0.6%)
Headache	8 (4.5%)	8 (4.6%)
Nausea	8 (4.5%)	4 (2.3%)
Paresthesia	8 (4.5%)	0
Insomnia	6 (3.4%)	4 (2.3%)
Vertigo	6 (3.4%)	0
Anxiety	4 (2.2%)	3 (1.7%)
Diarrhea	3 (1.7%)	0
Asthenia	3 (1.7%)	3 (1.7%)
Sweating	3 (1.7%)	3 (1.7%)
Vasodilatation	2 (1.1%)	0
Depersonalization	2 (1.1%)	0
Emotional lability	2 (1.1%)	0
Somnolence	2 (1.1%)	0
Abnormal dreams	1 (0.6%)	0
Abnormal vision	1 (0.6%)	1 (0.6%)
Back pain	1 (0.6%)	0
Constipation	1 (0.6%)	1 (0.6%)
Depression	1 (0.6%)	1 (0.6%)
Fever	1 (0.6%)	0
Infection	1 (0.6%)	1 (0.6%)
Hypertension	1 (0.6%)	0
Hypertonia	1 (0.6%)	0
Hypotension	1 (0.6%)	0
Lack of emotion	1 (0.6%)	0
Myalgia	1 (0.6%)	0
Myasthenia	1 (0.6%)	0
Myoclonus	1 (0.6%)	0
Neuralgia	1 (0.6%)	0
Neurosis	1 (0.6%)	0
Respiratory disorder	1 (0.6%)	0
Tinnitus	1 (0.6%)	0
Tooth disorder	1 (0.6%)	0
Tremor	1 (0.6%)	1 (0.6%)
Abnormal ejaculation**	0	2 (2.2%)
Allergic reaction	0	1 (0.6%)
Tachycardia	0	1 (0.6%)
Decreased appetite	0	2 (1.1%)
LFTs abnormal	0	1 (0.6%)
Mydriasis	0	1 (0.6%)
Concentration impaired	0	1 (0.6%)
Cough increased	0	1 (0.6%)
Nervousness	0	1 (0.6%)
Pharyngitis	0	1 (0.6%)
Urinary retention	0	1 (0.6%)
Yawn	0	1 (0.6%)

From Sponsor Table 14.8

*Withdrawal syndrome =

** Percentage based on male subjects (N = 93 in placebo group)

The majority of these adverse events were characterized as mild to moderate – of note the majority of the cases of withdrawal syndrome and paresthesia were of moderate intensity (N = 6 and N = 5 respectively). Adverse events occurring in the paroxetine CR group that were characterized as severe included asthenia (n = 1), vasodilatation (n = 1), diarrhea (n = 1), dizziness (n = 3) and withdrawal syndrome (n = 3). Three of these adverse events were considered serious adverse events: withdrawal syndrome (n = 2, both severe) [see discussion above for one of these cases] and dizziness (n = 1, moderate).

The Sponsor has been asked to provide a separate table summarizing the adverse events occurring in the follow-up phases for subjects who underwent the down-titration phase and for subjects who did not. The Sponsor was further asked to separate the adverse events occurring during the 14-day follow-up phase and those occurring during the 28-day follow-up phase.

Adverse events listed in Table E-7.2 that are consistent with a withdrawal or discontinuation syndrome per current labeling include: dizziness, nausea, paresthesia, anxiety, sweating and abnormal dreams. In the 14 and 28-day follow-up phases, 33% (59/178) in the paroxetine CR group experienced these symptoms (including those with "withdrawal syndrome") compared to 7% (12/174) in the placebo group.

The Sponsor was contacted to provide further information regarding the symptoms that subjects experienced that were termed "withdrawal syndrome". At the time this review was completed, this information was pending. The withdrawal adverse events for two of these subjects were classified as serious adverse events, therefore, narratives were included in the current submission. Both subjects required hospitalization due to the symptoms and symptoms resolved upon clinical treatment with paroxetine. Both of these subjects had been down titrated from 37.5 mg/day. Symptoms in one subject included dizziness, vertigo, anxiety, "strange" feelings in head, sweating and faintness. Symptoms in the other subject included vertigo.

Prior clinical trials with paroxetine CR have included a taper phase:
Three clinical trials for major depressive disorder (NDA 20-936) incorporated a flexible-dose design (up to 62.5 mg/day) for a 12-week duration. At the conclusion of the study, a taper phase followed that included a gradual reduction in dosage over a maximum of 10 days. It is not known whether adverse event data was assessed during this brief 10-day taper phase (this information was not included in the clinical review).
Three clinical trials for panic disorder (NDA 20-982) incorporated a flexible-dose design (up to 75 mg/day) for a 10-week duration. At the termination of the trials, subjects entered a 2-week taper phase "at the investigator's discretion". It is not known whether adverse event data was assessed during this 2-week taper phase.

VIII. Dosing, Regimen, and Administration Issues

Most of the proposed labeling for the social anxiety disorder indication for Paxil CR is consistent with the currently approved labeling for this same indication for Paxil (immediate-release dosage form).

Proposed labeling in the Clinical Trials, Indications and Usage, and Dosage and Administration sections reflect the trial design and results from the single pivotal trial for the acute treatment of social anxiety disorder. Some modifications of labeling in specific sections is suggested in Section X. of this review (Labeling Issues). No data are available regarding the maintenance treatment of social anxiety disorder with paroxetine CR. In proposed labeling, the Sponsor also states that: "...patients should be periodically reassessed to determine the need for continued treatment".

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

In the study report, the Sponsor stated that there were no gender-related differences in the results compared with the total treatment group. However, it is unclear whether the Sponsor compared the two co-primary efficacy variables between males and females. A statistical analysis was not included, only summary tables of the gender results – the Sponsor has been asked to provide further information. Though this information is lacking, the efficacy results between males and females appear to be very similar.

Table IX-A.1. LSAS Change from Baseline - *Females*

	Paroxetine CR			Placebo		
	Mean	SE	N	Mean	SE	N
Week 1 OC	-1	1.1	97	-2	1.1	85
Week 2 OC	-5	1.3	89	-5	1.7	79
Week 3 OC	-8	1.8	90	-8	1.7	80
Week 4 OC	-13	2.0	90	-10	1.9	82
Week 6 OC	-21	2.4	88	-15	2.7	75
Week 8 OC	-27	2.6	87	-20	3.3	71
Week 12 OC	-36	3.1	68	-20	3.5	60
Week 12 LOCF	**-32**	**2.7**	**97**	**-18**	**2.9**	**87**

From Sponsor's table 17

Table IX-A.2. LSAS Change from Baseline - *Males*

	Paroxetine CR			Placebo		
	Mean	SE	N	Mean	SE	N
Week 1 OC	-1	1.0	86	-5	1.1	95
Week 2 OC	-5	1.5	87	-8	1.5	88
Week 3 OC	-10	2.0	78	-10	1.7	88
Week 4 OC	-16	2.2	83	-13	1.7	92
Week 6 OC	-23	2.5	80	-16	2.0	87
Week 8 OC	-29	2.9	76	-18	2.2	82
Week 12 OC	-36	3.4	68	-22	2.6	64
Week 12 LOCF	**-31**	**3.1**	**88**	**-18**	**2.1**	**97**

From Sponsor's table 17

Table IX-A.3. Proportion of Responders (CGI-I = 1 or 2) by Gender - *Females*

	Paroxetine CR No. Responders/N (%)	Placebo No. Responders/N (%)
Week 1 OC	3/98 (3%)	4/86 (5%)
Week 2 OC	9/91 (10%)	6/79 (8%)
Week 3 OC	12/90 (13%)	12/80 (15%)
Week 4 OC	19/90 (21%)	20/83 (24%)
Week 6 OC	30/88 (34%)	21/75 (28%)
Week 8 OC	42/87 (48%)	29/71 (28%)
Week 12 OC	43/68 (63%)	21/60 (35%)
Week 12 LOCF	**57/98 (58%)**	**26/87 (30%)**

From Sponsor table 19

Table IX-A.4. Proportion of Responders (CGI-I = 1 or 2) by Gender - *Males*

	Paroxetine CR No. Responders/N (%)	Placebo No. Responders/N (%)
Week 1 OC	1/86 (1%)	3/95 (3%)
Week 2 OC	5/88 (6%)	8/90 (9%)
Week 3 OC	11/78 (14%)	12/87 (14%)
Week 4 OC	17/83 (20%)	17/92 (18%)
Week 6 OC	29/81 (36%)	19/87 (22%)
Week 8 OC	39/77 (51%)	25/82 (30%)
Week 12 OC	44/68 (65%)	22/64 (34%)
Week 12 LOCF	**49/88 (56%)**	**30/97 (31%)**

From Sponsor table 19

Treatment-emergent adverse events gender analysis.
A lower proportion of male subjects reported > 1 gender non-specific adverse event during the treatment phase for both paroxetine CR and placebo groups [males: paroxetine CR 63/88 (72%), placebo 54/97 (56%); females: paroxetine CR 79/98 (81%), placebo 54/87 (62%)]. A higher proportion of males reported gender specific adverse events in the paroxetine CR group [males: 19/88 (22%), females: 4/98 (4%)].

Table Table IX-A.5. Sponsor's table. Frequent Adverse Events by Gender

Table 32 Number (%) of Subjects with Frequently Occurring AEs Occurring During the Treatment Phase (≥5% in any Treatment Group) by Gender (ITT Population)

	Males		Females	
AE Preferred Term	Parox CR N=88	Placebo N=97	Parox CR N=98	Placebo N=87
Headache	17 (19.3)	16 (16.5)	26 (26.5)	15 (17.2)
Nausea	14 (15.9)	4 (4.1)	26 (26.5)	7 (8.0)
Sweating	14 (15.9)	1 (1.0)	12 (12.2)	4 (4.6)
Abnormal Ejaculation	13 (14.8)	1 (1.0)	0	0
Asthenia	11 (12.5)	8 (8.2)	22 (22.4)	5 (5.7)
Libido Decreased	11 (12.5)	1 (1.0)	4 (4.1)	1 (1.1)
Insomnia	10 (11.4)	5 (5.2)	6 (6.1)	3 (3.4)
Somnolence	9 (10.2)	4 (4.1)	8 (8.2)	3 (3.4)
Impotence	8 (9.1)	0	0	0
Dizziness	7 (8.0)	3 (3.1)	5 (5.1)	4 (4.6)
Back Pain	5 (5.7)	0	2 (2.0)	2 (2.3)
Diarrhea	5 (5.7)	8 (8.2)	11 (11.2)	7 (8.0)
Infection	3 (3.4)	6 (6.2)	5 (5.1)	10 (11.5)
Constipation	2 (2.3)	1 (1.0)	7 (7.1)	3 (3.4)
Pharyngitis	2 (2.3)	1 (1.0)	2 (2.0)	6 (6.9)
Tremor	2 (2.3)	2 (2.1)	6 (6.1)	1 (1.1)
Abdominal Pain	1 (1.1)	2 (2.1)	9 (9.2)	5 (5.7)
Dry Mouth	1 (1.1)	2 (2.1)	5 (5.1)	2 (2.3)
Respiratory Disorder	1 (1.1)	12 (12.4)	8 (8.2)	10 (11.5)

Adverse events which appeared to differ between gender included libido decreased (males > females); diarrhea, nausea, asthenia, constipation, tremor, abdominal pain, dry mouth and respiratory disorder (females > males). The two subjects with the serious adverse event "withdrawal syndrome" were female.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The Sponsor did provide data for subjects < 65 (n = 366) and ≥ 65 years of age (n = 3). No statistical analysis between these two groups was performed due to the small number of subjects ≥ 65 years of age.

Table IX-B.1. LSAS Change from Baseline

	Paroxetine CR			Placebo		
	Mean	SE	N	Mean	SE	N
< 65 Years						
Week 12 OC	-36	2.3	135	-21	2.2	122
Week 12 LOCF	-32	2.0	184	-18	1.8	182
≥ 65 Years						
Week 12 OC	-19	-	1	-16	4.0	2
Week 12 LOCF	-19	-	1	-16	4.0	2

From Sponsor Table 17

Table IX-B.2. Proportion of Responders (CGI-I = 1 or 2) by Age

	Paroxetine CR No. Responders/N (%)	Placebo No. Responders/N (%)
< 65 Years		
Week 12 OC	87/135 (64%)	43/122 (35%)
Week 12 LOCF	106/185 (57%)	56/182 (31%)
≥ 65 Years		
Week 12 OC	0/1	0/2
Week 12 LOCF	0/1	0/2

From Sponsor Table 19

The Sponsor also provided data for Caucasian (n = 349) and Non-Caucasian (n = 21: Black = 6, Asian = 2, "Other" = 13) subjects. No statistical analysis between these two groups was performed due to the small number of Non-Caucasian subjects.

Table IX-B.3. LSAS Change from Baseline

	Paroxetine CR			Placebo		
	Mean	SE	N	Mean	SE	N
Caucasian						
Week 12 OC	-34	2.4	126	-21	2.2	119
Week 12 LOCF	-30	2.1	173	-18	1.8	175
Non-Caucasian						
Week 12 OC	-50	8.3	10	-14	10.8	5
Week 12 LOCF	-47	7.4	12	-15	7.3	9

From Sponsor Table 17

Table IX-B.4. Proportion of Responders (CGI-I = 1 or 2) by Ethnicity

	Paroxetine CR No. Responders/N (%)	Placebo No. Responders/N (%)
Caucasian		
Week 12 OC	80/126 (57%)	41/119 (34%)
Week 12 LOCF	99/174 (57%)	53/175 (30%)
Non-Caucasian		
Week 12 OC	7/10 (70%)	2/5 (40%)
Week 12 LOCF	7/12 (58%)	3/9 (33%)

From Sponsor Table 19

Table IX-B.5. Sponsor's Table. Treatment-Emergent Adverse Events by Ethnicity

Table 33 Number (%) of Subjects with 5 Most Frequently Occurring AEs During the Treatment Phase by Race in Both Paroxetine CR Treatment Groups (ITT Population)

	Caucasian		Non-Caucasian	
AE Preferred Term	Parox CR N=174	Placebo N=175	Parox CR N=12	Placebo N=9
Headache	41 (23.6)	30 (17.1)	2 (16.7)	1 (11.1)
Nausea	37 (21.3)	11 (6.3)	3 (25.0)	0
Asthenia	32 (18.4)	13 (7.4)	1 (8.3)	0
Sweating	22 (12.6)	5 (2.9)	4 (33.3)	0
Abnormal Ejaculation*	9 (11.5)	1 (1.1)	4 (40.0)	0
Somnolence	15 (8.6)	6 (3.4)	2 (16.7)	1 (11.1)
Libido Decreased	12 (6.9)	2 (1.1)	3 (25.0)	0
Dizziness	10 (5.7)	6 (3.4)	2 (16.7)	1 (11.1)
Constipation	7 (4.0)	3 (1.7)	2 (16.7)	1 (11.1)
Decreased Appetite	0	1 (0.6)	2 (16.7)	0

Data Source: DAP Table 14.15.

* Percentages based on male subjects only: Caucasian, N=78 for paroxetine CR group and N=91 for placebo group; Non-Caucasian, N=10 for paroxetine CR group and N=6 for placebo group.

Due to the small number of subjects in the non-Caucasian group, it is difficult to make meaningful comparisons of adverse events between these two groups. Additionally, the non-Caucasian group includes a number of different ethnic/racial groups as noted above.

C. Evaluation of Pediatric Program

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials.

On 6/10/03, the United Kingdom Department of Health issued a press release stating that paroxetine must not be used to treat children and teenagers under the age of 18 for depressive illness. The UK concluded that there is an increase in the rate of self-harm and potentially suicidal behavior in this age group when paroxetine is used for depressive illness. The FDA is currently reviewing the clinical trials data on which this statement was based. On 6/19/03, the FDA issued a Talk Paper recommending that paroxetine not be used in children and adolescents for the treatment of major depressive disorder (paroxetine is currently approved for use in adults only).

The Sponsor has performed one trial in children/adolescents with social anxiety disorder using the immediate release dosage form of paroxetine. The efficacy results from this trial have not yet been submitted to the Division.

The Sponsor requested a waiver of the pediatric study requirement until the review of the adult-use supplemental application had been completed. Since the data regarding the potential increase in suicidal behavior in children/adolescents in major depressive disorder clinical trials is under review, the outcome of this analysis may impact the advice to the Sponsor regarding further studies of paroxetine CR in this population. Additionally, the results from the child/adolescent social anxiety disorder clinical trial with the immediate release dosage form should be reviewed as these results may impact the Division's advice to the Sponsor regarding the need for further studies of paroxetine CR in this population.

X. Labeling Issues

Most of the proposed labeling for the social anxiety disorder indication for Paxil CR is consistent with the currently approved labeling for this same indication for Paxil (immediate-release dosage form). A few modifications are being recommended:

- In the Precautions section of the currently approved labeling, the section entitled "discontinuation of treatment with Paxil CR" contains the statement "adverse events while discontinuing therapy with Paxil CR were not systematically evaluated in the clinical trials" with the remaining information in this section referring to the immediate release dosage form. Since the pivotal trial for social anxiety disorder does contain some data with regard to the withdrawal syndrome occurring with paroxetine CR, the Sponsor should evaluate all clinical trials with this dosage form and include language in this section of labeling pertinent to the controlled release dosage form.

  This section in labeling does include the following information regarding dose reduction: "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". This information also appears in the Dosage and Administration section of labeling.

  Since data do exist with regard to symptoms occurring upon discontinuation of Paxil CR, it is important that this information be reflected in labeling. It is currently not known if the adverse events associated with the discontinuation of Paxil CR is different in frequency, severity, onset or duration compared to Paxil. Many clinicians may believe that these adverse events would be less frequent with the controlled-release dosage form compared to the immediate release dosage form. For this reason, any data relevant for a particular dosage form should be included in the labeling for that dosage form.

- In the Clinical Trials section of the proposed labeling for social anxiety disorder, the data for responders is given for completers only: "For patients who completed the

trial, 64% of patients treated with Paxil CR compared to 34.7% of patients treated with placebo were CGI Improvement responders". Since the Division relies on LOCF data to determine the efficacy of clinical trials, it may be somewhat misleading to include responder data for completing patients only in labeling. The responder rate in the LOCF analysis was 57% for Paxil CR and 30% for placebo. Of note, the current labeling for Paxil also contains data for completing patients only.

- In the Clinical Trials section for social anxiety disorder it is stated "Subgroup analysis did not indicate that there were any differences in treatment outcomes as a function of gender". In the study report it is commented that "overall there were no gender related differences in the results compared with the total treatment group..." however, it is not clear that the Sponsor performed an analysis of the efficacy variables between male and female subjects. The Sponsor has been asked for this information.

XI. Requests for Information from Sponsor

Several requests for information were sent to the Sponsor during the review of this application. At the time the review was completed, several requests were still outstanding. This reviewer does not believe that the responses to these information requests would change the recommended approvable action. These requests for information could be reiterated in an approvable letter.

- Statistical analysis of efficacy data by gender (male versus female).
- Worldwide literature review
- More data with regard to adverse events occurring upon discontinuation of paroxetine CR/placebo:
  - Definition of "withdrawal reaction"
  - Separate adverse events occurring at 14 day follow-up and 28-day follow-up
  - Separate adverse events occurring in subjects who participated in the down titration phase from those did not
- Clarification of adverse events "coma" (n = 1 paroxetine CR) and "trauma" (n = 5 paroxetine CR)
- Update on foreign regulatory action. Specifically whether any applications for Paxil CR for the treatment of social anxiety disorder have been submitted to any foreign country since November 1, 2002 (date indicated in submission). Which countries have approved Paxil CR and for what indications?
- Explanation/rationale for the small number of subjects with complete laboratory assessments in Paxil CR group (~63% of completing subjects in this group)

Additionally, the Sponsor did not include a section on the analysis of their post-marketing safety database, nor did they submit a 120-day safety update with this information. This should be requested.

XII. Conclusions and Recommendations

A. Conclusions

Data from one controlled clinical trial demonstrated the efficacy of paroxetine CR (flexible-dose 12.5 to 37.5 mg/day) in improving the symptoms of social anxiety disorder. In pivotal trial 790, paroxetine CR was statistically significantly superior to placebo with respect to both co-primary efficacy variables: the Liebowitz Social Anxiety Scale (LSAS) change in score from baseline to week 12 (study endpoint) and the percentage of responders defined by a Clinical Global Impression – Improvement (CGI-I) score of 1 (very much improved) or 2 (much improved) at week 12. A greater decrease in LSAS score at week 12 was demonstrated in the paroxetine CR group (-31) compared to placebo (-17.6) [LOCF analysis, $p < 0.001$]. For the co-primary measure, the CGI-I, a higher percentage of treatment responders was demonstrated in the paroxetine CR group (57%) versus the placebo group (30%) at week 12 [LOCF analysis, $p < 0.001$].

Safety results of one 12-week pivotal clinical trial in social anxiety disorder support the conclusion that paroxetine CR, in doses between 12.5 – 37.5 mg/day, is reasonably safe and well tolerated. No significant medical concerns or adverse events were identified in subjects with social anxiety disorder that had not been identified in safety profiles of paroxetine CR in the treatment of subjects with major depression and panic disorder. The dosing recommendation for paroxetine CR in the treatment of social anxiety disorder, 12.5 to 37.5 mg/day, is similar to the dosing recommendations for other indications though the maximum dose is lower. The recommended dose ranges for major depressive disorder is 25 to 62.5 mg/day and the dose range for panic disorder is 12.5 to 75 mg/day.

The adverse events that occurred in the social anxiety disorder studies had been reported in the current Paxil CR product label. There were no deaths reported in this study and there were no serious adverse events or adverse events associated with study discontinuation which were unexpected or drug-related and unlabeled. It is noteworthy that the current product labeling for the section "discontinuation of treatment with Paxil CR" contains information relevant to the immediate release paroxetine dosage form only. The clinical trial in this submission did include some information on adverse events occurring after paroxetine CR discontinuation as subjects were followed out to 28 days after the end of the clinical trial. Three of these adverse events were consistent with a withdrawal/discontinuation syndrome and were classified as serious adverse events. The Sponsor should include data relevant to the CR dosage form in this section in labeling.

B. Recommendations

I recommend that the Division take an approvable action for supplemental NDA 20,936/SE1-012. The Sponsor seeks a claim indicating paroxetine CR for the acute treatment of social anxiety disorder.

If feasible, labeling should be coordinated with the recent approvable action (4/11/03) for the indication premenstrual dysphoric disorder.

In the Precautions section of the currently approved labeling, the section entitled "discontinuation of treatment with Paxil CR" contains the statement "adverse events while discontinuing therapy with Paxil CR were not systematically evaluated in the clinical trials" with the remaining information in this section referring to the immediate release dosage form. Since the pivotal trial for social anxiety disorder does contain some data with regard to the withdrawal syndrome occurring with paroxetine CR, the Sponsor should evaluate all clinical trials with this dosage form and include language in this section of labeling pertinent to the controlled release dosage form.

A number of requests for information were sent to the Sponsor during the review of this application. Some of these requests were pending at the time this review was completed, though this reviewer does not believe that the responses to these requests would likely impact the recommended approvable action. Requests that were pending at the time this review was completed are listed in Section XI (Requests for Information from Sponsor). These requests could be included in the action letter.

Cara Alfaro, Pharm.D.
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FDA CDER ODE1 DNDP HFD-120
July 30, 2003

cc: Laughren/Andreason/Homonnay/Kong

Appendix

Table C-1-A. List of Sites for Study 790

	# Pts Randomized	# Pts Completed
Denmark		
#060 J. Sogaard	17	12
#061 K. Behnke	26	21
#062 B. Bahr	17	14
#063 S. Rasmussen	22	18
Finland		
#010 U. Lepola	25	18
#011 J. Aer	22	13
#012 A. Ahokas	25	23
#013 H. Koponen	10	9
#014 S. Korhonen	9	6
France		
#040 E. Tana	2	1
#041 F. Gheysen	8	5
#042 P. Leclercq	10	10
#043 J. Gailledreau	12	10
#044 M. Faure	9	8
#045 E. Tanneau	4	4
Germany		
#020 H. Wittchen	2	1
#021 S. Kasper	0	0
#022 T. Sobanski	3	3
#023 B. Bandelow	9	8
#024 A. Hause	9	8
#025 E. Schumacher	3	1
#026 B. Bergholdt	23	11

	# Pts Randomized	# Pts Completed
Netherlands		
#031 M. Willems	10	7
South Africa		
#070 C. Hollands	2	2
#071 D. Rossouw	2	0
#072 P. Strong	9	8
#073 K. Vukovic	5	5
#074 I. Westmore	5	5
#075 D. Wilson	10	7
#076 G. Hart	9	8
#077 D. Stein	3	1
Spain		
#050 J. Bobes	2	1
#051 J. De La Torre	6	4
Sweden		
#001 C. Allgulander	18	18
#002 I Sjodin	19	15
#003 A. Lowenstein	8	8

For the statistical analysis, centers were grouped as follows: Denmark, Finland, France & Spain, Germany & Netherlands, South Africa, and Sweden.

Table C-3-A Exclusion Criteria

- Patients who score 1 or 2 on the CGI-I at baseline
- Patients who score 15 or more on the HAM-D_{17} at baseline
- Patients who meet DSM-IV criteria for Axis I disorders such as dysthmia, simple phobia, major depression, obsessive-compulsive disorder or panic disorder as a primary diagnosis currently or within 6 months prior to the screening visit
- Patients with body dysmorphic disorder
- Patients with a history of schizophrenia or bipolar affective disorder
- Patients who meet DSM-IV criteria for substance abuse (alcohol or drugs) currently or within 3 months prior to screening
- Patients who meet DSM-IV criteria for substance dependence currently or within 6 months prior to screening
- Patients who have taken psychotropic drugs or antidepressants (including MAOIs) within the time frames specified below prior to the screening visit:
  Depot neuroleptics: at least 12 weeks
  MAOIs or fluoxetine: at least 4 weeks
  Antidepressants (other than MAOIs or fluoxetine), lithium, oral antipsychotics: at least 14 days
  Hypnotics, benzodiazepines, and all other sedatives (including sedating antihistamines): 5 half-lives or at least 14 days, whichever is longer
  Any CNS-active herbal/natural supplement or preparation known or thought to have any psychoactive effects: at least 14 days
- Patients requiring concomitant therapy with beta-blockers, MAOIs, benzodiazepines or other psychoactive medications other than chloral betaine
- Any previous treatment for social anxiety disorder with SSRIs at a dose and for a duration which would have been adequate to show a response (equivalent to 3 months treatment with Prozac 20 – 40 mg)
- Patients who have used an investigational drug within the past month (or 5 half-lives, whichever is the longest) prior to screening
- Patients who have had electroconvulsive therapy within 3 months of the screening visit
- Patients receiving psychotherapy (except stabilized psychotherapy regimens which have been ongoing for at least 6 months)
- Patients who have been unresponsive to paroxetine
- Patients with a history of seizure disorders (except for febrile seizures in childhood)
- Patients who have exhibited intolerance to paroxetine
- Patients having clinically significant abnormal laboratory, or ECG findings not resolved by the baseline visit
- Patients who, in the investigator's judgement pose a current, serious suicidal or homicidal risk
- Women who have a positive pregnancy test or who are lactating
- Women of child-bearing potential who are not practicing a clinically accepted method of contraception.

C-6-A Study Schedule of Assessments

Visit	Screen Visit 1	Baseline Visit 2	Wk 1 Visit 3	Wk 2 Visit 4	Wk 3 Visit 5	Wk 4 Visit 6	Wk 6 Visit 7	Wk 8 Visit 8	Wk 12 Visit 9	Wk 13 Visit 10	14 Day F/U Visit 11	28 Day F/U Visit 12	EWD
Informed Consent	X												
Demography	X												
Inclusion/Exclusion	X	X											
Vitals	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Weight		X							X				X
BAE's/AE's		X	X	X	X	X	X	X	X	X	X	X	X
Medical Procedures		X	X	X	X	X	X	X	X	X	X	X	X
Prior/Con. Meds	X	X	X	X	X	X	X	X	X	X	X	X	X
Med/Surg. History	X												
Psychiatric History	X												
Physical Examination	X								X				X
Lab. Evaluation	X	X*							X	X*	X*	X*	X
Pregnancy Test	X								X				X
ECG	X	X*							X	X*	X*		X
MINI	X												
HAM-D 17 Item		X							X				X
CGI Global Improvement		X	X	X	X	X	X	X	X				X
CGI Severity of Illness		X	X	X	X	X	X	X	X				X
LSAS		X	X	X	X	X	X	X	X				X
SADS		X	X	X	X	X	X	X	X				X
SDS		X	X	X	X	X	X	X	X				X
Medication Dispensed	X	X	X	X	X	X	X	X					
Medication Record	X	X	X	X	X	X	X	X	X	X			X
DT* Medication Dispensed									X				X
Study Conclusion											X**	X	

X*- perform repeat laboratory evaluation/ECG if abnormal at previous visit; X** - to be completed if patient does not attend 28-Day Follow-Up Visit. DT* – Down Titration medication will be dispensed if patients withdraw prematurely or complete the study on Dose Level 3; BAE's/AE's – baseline adverse experiences/adverse experience

Table C-6.1-A. Secondary Efficacy Variables

- Change from baseline in the CGI-S score at week 12
- Change from baseline on the LSAS Fear subscale score at week 12
- Change from baseline on the LSAS Avoidance subscale score at week 12
- Change from baseline on the SADS total score at week 12
- Change from baseline on the SDS family life item at week 12
- Change from baseline on the SDS work item at week 12
- Change from baseline on the SDS social life item at week 12

Table C-7-A Subject Withdrawals Due to "Other"

Patient Number	Treatment	Reason for Withdrawal*
38695	Paroxetine CR	No contraception
38691	Placebo	Withdrew consent
38768	Paroxetine CR	Misattribution of treatment by pharmacy
38745	Paroxetine CR	Withdrew consent
39091	Paroxetine CR	Lack of patient availability
39182	Paroxetine CR	Withdrew consent
39351	Paroxetine CR	Completed 12 week trial, follow-up visit done early by request of monitor (database)
38968	Placebo	Withdrew consent
38972	Placebo	Trouble with Ramos**
38995	Placebo	Gave patient wrong medication
39177	Paroxetine	Withdrew consent
38892	Paroxetine	Patient took alprazolam privately

*Specified in CRF in line provided by "other" checkbox

**Randomization and Medication Ordering System

C-10.1.5-A Secondary Efficacy Variables – Change from Baseline
Scores adjusted for country and baseline scores

	Paroxetine CR		Placebo		
	Mean (SE)	N	Mean (SE)	N	Difference (95% CI), p-value
CGI-S					
Week 12 OC	-1.5 (0.1)	136	-0.9 (0.1)	124	-0.65 (-0.92, -0.38) p < 0.001
Week 12 LOCF	–1.4 (0.1)	186	–0.7 (0.1)	184	–0.63 (-0.85, -0.40) p < 0.001
LSAS Fear or Anxiety Subscale					
Week 12 OC	-17 (1.1)	136	-11 (1.1)	124	-6.8 (-9.8, -3.8) p < 0.001
Week 12 LOCF	–16 (0.9)	185	–9 (0.9)	184	–6.9 (-9.4, -4.3) p < 0.001
LSAS Avoidance Subscale					
Week 12 OC	-17 (1.1)	136	-10 (1.1)	124	-6.4 (-9.3, -3.4) p < 0.001
Week 12 LOCF	–15 (0.9)	185	-9 (0.9)	184	-6.5 (-9.0, -4.0) p < 0.001
SADS Total Score					
Week 12 OC	-7 (0.6)	135	-5 (0.6)	122	-2.5 (-4.3, -0.7) p = 0.006
Week 12 LOCF	–7 (0.5)	185	–4 (0.5)	180	-2.4 (-3.8, -1.0) p < 0.001
Sheehan Disability Scale Family Life Subscale					
Week 12 OC	-1.5 (0.1)	130	-0.9 (0.1)	119	-0.6 (-1.0, -0.2) p = 0.006
Week 12 LOCF	-1.3 (0.1)	185	-0.7 (0.1)	182	–0.6 (-1.0, -0.3) p < 0.001
Sheehan Disability Scale Work Subscale					
Week 12 OC	-2.3 (0.2)	128	-1.1 (0.2)	117	-1.1 (-1.7, -0.6) p < 0.001
Week 12 LOCF	–2.1 (0.2)	183	–1.0 (0.2)	180	-1.1 (-1.6, -0.6) p < 0.001
Sheehan Disability Scale Social Life Subscale					
Week 12 OC	-3.1 (0.2)	130	-2.0 (0.2)	119	-1.1 (-1.7, -0.5) p < 0.001
Week 12 LOCF	–2.7 (0.2)	185	–1.6 (0.2)	182	-1.1 (-1.6, -0.6) p < 0.001

From Sponsor tables 20, 21, 22, 23

Table E-6-A. Sponsor's Table. Definition of Vital Sign Changes of Potential Clinical Concern

Table 5 Criteria for Assessment of Vital Signs Changes of Potential Clinical Concern

Parameter	Normal Range	Change from Baseline of Potential Clinical Concern	
		Decrease	Increase
Systolic BP (mmHg)	90 - 180	≥ 30	≥ 40
Diastolic BP (mmHg)	50 - 105	≥ 20	≥ 30
Pulse Rate (bpm)	50 - 120	≥ 30	≥ 30
Weight	-	≥ 7%	≥ 7%

Table 7.1-A. All Adverse Events Occurring During the Down-Titration Phase

	Paroxetine CR (N = 121)	Placebo (N = 130)
Anxiety	2 (1.7%)	0
Insomnia	2 (1.7%)	0
Headache	2 (1.7%)	0
Abnormal ejaculation*	1 (1.7%)	0
Asthenia	1 (0.8%)	1 (0.8%)
Dizziness	1 (0.8%)	3 (2.3%)
Constipation	1 (0.8%)	0
Nausea	1 (0.8%)	1 (0.8%)
Pharyngitis	1 (0.8%)	0
Back pain	1 (0.8%)	0
Pain	1 (0.8%)	0
Trauma	1 (0.8%)	0
Vasodilatation	1 (0.8%)	0
Flatulence	1 (0.8%)	1 (0.8%)
AST increased	1 (0.8%)	0
ALT increased	1 (0.8%)	0
Tendinous disorder	1 (0.8%)	0
Respiratory disorder	1 (0.8%)	0
Sweating	1 (0.8%)	0
Abdominal pain	0	1 (0.8%)
Infection	0	1 (0.8%)
Myalgia	0	1 (0.8%)
Sinusitis	0	1 (0.8%)
Neurosis	0	1 (0.8%)

*Percentage based on male subjects only (N = 58 for paroxetine CR group)

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

/s/

Cara Alfaro
7/30/03 08:55:43 AM
PHARMACIST

Thomas Laughren
8/1/03 01:29:12 PM
MEDICAL OFFICER
I agree that this supplement is approvable; see memo to file for more detailed comments.--TPL

Review and Evaluation of Clinical Data

NDA # 20-936 SE1-012

Sponsor: GlaxoSmithKline

Drug: Paroxetine CR (Paxil CR)

Drug category: Antidepressant

Material submitted: Response to Division queries during review of NDA

Indication: Acute Treatment of Social Anxiety Disorder

Correspondence date: 8/11/03, 8/21/03 and 8/25/03

Date Review Completed: 9/2/03

Background

The supplemental NDA for paroxetine CR for the acute treatment of Social Anxiety Disorder was submitted to the Division on 12/20/02. The clinical review of this supplement was completed on 7/30/03 though a number of queries to the Sponsor were still outstanding at that time (not thought to impact the overall recommendation). The recommendation per this reviewer was for an approvable action – this action letter would outline data requests still outstanding. The Sponsor has recently submitted data to the Division addressing some of these queries. The purpose of this review is to evaluate the data submitted by the Sponsor in order to reduce the number of additional requests for information that will be contained in the action letter.

Division Requests for Information and Sponsor Response

1. Provide the statistical analysis by gender for both co-primary endpoints, specifically for week 12 OC and week 12 LOCF timepoints.

   In the 8/11/03 submission, the Sponsor provided this analysis. The efficacy of paroxetine CR compared to placebo was demonstrated for both male and female subjects.

Table 1. LSAS Score Adjusted for Country Group and Baseline LSAS Total Score

	Paroxetine CR			Placebo			Difference (95% CI)
	N	LS Mean	SE	N	LS Mean	SE	
Females							
Week 12 OC	68	-34	2.9	60	-19	3.1	-14 (-23, -6) $p < 0.001$
Week 12 LOCF	97	-32	2.5	87	-18	2.6	-14 (-21, -7) $p < 0.001$
Males							
Week 12 OC	68	-35	3.0	64	-22	3.0	-13 (-22, -5) $p = 0.002$
Week 12 LOCF	88	-31	2.6	97	-18	2.5	-13 (-20, -6) $p < 0.001$

Table 2. Number (%) of Subjects with CGI-I Score of 1 or 2 Adjusted for Country Group

	Paroxetine CR			Placebo			Odds Ratio (95% CI)
	N	n	%	N	n	%	
Females							
Week 12 OC	68	43	63%	60	21	35%	3.8 (1.7, 8.4) $p < 0.001$
Week 12 LOCF	98	57	58%	87	26	30%	3.6 (1.9, 7.0) $p < 0.001$
Males							
Week 12 OC	68	44	65%	64	22	34%	3.3 (1.6, 6.9) $p = 0.001$
Week 12 LOCF	88	49	56%	97	30	31%	2.9 (1.6, 5.3) $p < 0.001$

N = total sample size, n = # with CGI-I of 1 or 2

2. According to the NDA submission, as of November 1, 2002, marketing authorization applications for Paxil CR for the treatment of social anxiety disorder had not been submitted to any foreign country. Is this still correct?

   In the 8/11/03 submission, the Sponsor stated that a marketing application for Paxil CR for the treatment of social anxiety disorder was submitted in Canada on 12/19/02.

   In the 8/25/03 submission, the Sponsor noted the various countries in which Paxil CR was approved or submitted for registration:

Table 3. Countries in which Paroxetine CR is Approved or Registered

Country	Approval or Registration	Date of Approval/Registration	Indication
Argentina	Approval	12/19/02	Depression, Panic Disorder
Australia	Registration	4/29/03	Depression, Panic Disorder
Brazil	Registration	5/30/03	Depression, Panic Disorder
Canada	Registration	7/19/02	Depression, Panic Disorder
Chile	Registration	6/11/03	Depression, Panic Disorder
[redacted]			

3. Please provide narrative summaries for the subjects with "trauma" and "coma" in the paroxetine CR group.

   In the 8/21/03 submission, the Sponsor submitted very brief narratives for these adverse events. Five subjects in the paroxetine CR group had the adverse event "trauma" compared to one in the placebo group. One of the "trauma" adverse events (denoted with an asterisk) was considered a SAE and a narrative had been previously provided in the original submission.

Table 4. Description/Demographics for Paroxetine-Treated Subjects with Trauma and Coma Adverse Events

Subject	Gender/Age	Adverse Event Preferred Term	Adverse Event Verbatim Term	Day of Onset
790.024.38703	Female, 39	Trauma	Whiplash injury	61
790.041.38732	Female, 53	Trauma	Fall in street	41
790.044.38755	Female, 32	Trauma	Broken ribs	91
790.010.39031	Male, 34	Trauma	Eye trauma	85
*790.010.39037	Female, 26	Trauma	Broken leg	21

No data was submitted that further described these adverse events. Other adverse events experienced by the subjects were included. For the trauma, fall in street adverse event, no adverse events such as dizziness were recorded to have occurred around that same time period.

The subject with "coma" was a 37 year old male. The verbatim term was "unconsciousness" that occurred on Day 71. The narrative states that the subject experienced feelings of vertigo and lost consciousness for several minutes. No corrective therapy was given for this event and it resolved on the same day.

4. Please define the constellation of symptoms that comprises the adverse event term "withdrawal syndrome" (noted in Sponsor's Table 14.8, Follow-up Emergent Adverse Events)

   In the 8/21/03 submission, the Sponsor provided the verbatim and actual events experienced for each of these cases.

Table 5. Sponsor's Tables. Symptoms for Subjects with the Adverse Event "Withdrawal Syndrome"

PID	Adverse event (Preferred Term)	Verbatim	Actual Events Experienced
001.38605	Withdrawal Syndrome	Withdrawal Syndrome	Dizziness and Nausea
001.38618	Withdrawal Syndrome	Withdrawal Syndrome	Dizziness and Nausea
041.28729	Withdrawal Syndrome	Withdrawal Syndrome	Dizziness
041.38732	Withdrawal Syndrome	Withdrawal Syndrome	Dizziness, nausea, noises in the ears, headache and irritability
041.38733	Withdrawal Syndrome	Withdrawal Syndrome	dizziness, burning sensation and numbness

PID	Adverse event (Preferred Term)	Verbatim	Actual Events Experienced
073.38872	Withdrawal Syndrome	Detached Feeling/Discontinuation and Dizziness/Discontinuation	Detached Feeling and Dizziness
074.38884	Withdrawal Syndrome	Paroxetine Discontinuation Syndrome	Dizziness, "strange feeling in head", vertigo, faint feelings
074.38888	Withdrawal Syndrome	Mild Discontinuation Symptoms	Vertigo, dizziness
074.38890	Withdrawal Syndrome	Paroxetine Discontinuation Syndrome	Somatic sensation of "brain shifting left and right"

In Table 14.8 of the study report, 10/178 paroxetine CR subjects experienced the adverse event "withdrawal syndrome". The Sponsor provided symptom information for 9 of these subjects.

5. Tables 14.8 and 14.16 (of original submission) list adverse events occurring during the follow-up phases of the study. Please provide the following breakdown for these adverse events:
Please separate the adverse events occurring in the group that underwent the down-titration phase and the adverse events occurring in the group that did not.
Please separate the adverse events as above, but also separate those that occurred during the 14-day follow-up visit and those that occurred during the 28-day follow-up visit.

In the 8/21/03 submission, the Sponsor provided this data as indicated in the request. The primary reason for the request was to evaluate potential differences in adverse events occurring in subjects who participated in the down titration and those who did not – specifically those adverse events related to a withdrawal syndrome. Subjects in the down titration phase received 37.5 mg/day of paroxetine CR and entered a one-week down titration period where they received 25 mg/day and then stopped. Subjects who received 25 mg/day or 12.5 mg/day of paroxetine CR did not enter a down titration period, therapy was stopped at the end of the trial. These groups are similar, however, in that once 25 mg/day was reached therapy was abruptly stopped.
The data was also requested to evaluate potential differences in adverse events occurring at the first follow-up visit (14 days after the trial) and the second follow-up visit (28 days after the trial) [e.g. more acute versus delayed adverse events].

The data is summarized below with emphasis on symptoms likely associated with a withdrawal syndrome (per current labeling). These symptoms include dizziness, nausea, paresthesia, anxiety, sweating and abnormal dreams.

Since data was reported as occurring during the 14- or 28-day follow-up, the exact date of occurrence is not known. For example, for adverse events that occurred during the 28-day follow-up, it is not known whether most of the events occurred at the 15th day (these would not be captured in the 14-day follow-up visit) or towards the end of the follow-up period.

Table 6. Adverse Events Occurring in Subjects Who Entered Down-Titration Phase vs. Subjects Who Did Not

Down-Titration Phase

Adverse Event*	Paroxetine CR (N = 119)	Placebo (N = 124)
Nausea	5 (4.2%) [2-mild, 3-moderate]	1 (0.8%) [1-moderate]
Dizziness	22 (18.5%) [7-mild, 13-moderate, 2-severe]	1 (0.8%) [1-moderate]
Paresthesia	7 (5.9%) [4-mild, 3-moderate]	0
Anxiety	2 (1.7%) [2-mild]	3 (2.4%) [3-moderate]
Sweating	2 (1.7%) [2-mild]	2 (1.6%) [1-mild, 1-moderate]
"Withdrawal syndrome"	9 (7.6%) [2-mild, 4-moderate, 3-severe]	1 (0.8%) [1-mild]

*For the paroxetine CR adverse events dizziness, paresthesia and withdrawal syndrome, the total number of subjects with the adverse event was slightly fewer compared to the tables with severity listed (e.g. n = 20 for dizziness but n = 22 when add from the severity tables). Data in the table reflect the data from the severity tables.

No Down-Titration Phase

Adverse Event	Paroxetine CR (N = 59)	Placebo (n = 50)
Nausea	3 (5.1%) [2-mild, 1-moderate]	3 (6.0%) [2-mild, 1-moderate]
Dizziness	6 (10.2%) [4-mild, 2-moderate]	0
Paresthesia	2 (3.4%) [2-moderate]	0
Anxiety	2 (3.4%) [2-mild]	0
Sweating	1 (1.7%) [1-mild]	1 (2.0%) [1-moderate]
"Withdrawal syndrome"	2 (3.4%) [2-mild]	0

*For the paroxetine CR adverse event dizziness, the total number of subjects with the adverse event was slightly fewer compared to the tables with severity listed. Data in the table reflect the data from the severity tables.

In general, subjects who entered the down-titration phase had more adverse events consistent with a withdrawal syndrome compared to subjects who did not enter the down-titration phase. The adverse events in the subjects in the down-titration phase also were more severe than adverse events in subjects who did not enter the down-titration phase (esp. dizziness, paresthesia and withdrawal syndrome). This may be more reflective of the fact that subjects entering the down-titration phase were receiving a higher dose of paroxetine (37.5 mg/day) compared to the other subjects (12.5 – 25 mg/day).

The Sponsor submitted adverse event data occurring during the first follow-up visit (14-day) and the second follow-up visit (28-day) for subjects who entered the down-titration phase and those who did not. The Sponsor clarified (per email 8/28/03) that these follow-up visits occurred 14 and 28 days after subjects received the last dose of down titration study medication in the down-titration group. For subjects who did not enter the down titration phase, these follow-up visits occurred 14 and 28 days after the last dose of study medication.

Table 7. Adverse Events Occurring in Subjects Who Entered Down-Titration Phase vs. Subjects Who Did Not – 14 Day Follow-up Visit

Down-Titration Phase

Adverse Event	Paroxetine CR (N = 119)	Placebo (N = 124)
Nausea	3 (2.5%) [1- mild, 2-moderate]	0
Dizziness	16 (13.4%) [5-mild, 9-moderate, 2-severe]	0
Paresthesia	4 (3.4%) [2-mild, 2-moderate]	0
Anxiety	1 (0.8%) [1-mild]	1 (0.8%) [1-moderate]
Sweating	1 (0.8%) [1-mild]	1 (0.8%) [1-moderate]
"Withdrawal syndrome"	6 (5.0%) [1-mild, 3-moderate, 2-severe]	0

No Down-Titration Phase

Adverse Event	Paroxetine CR (N = 59)	Placebo (n = 50)
Nausea	3 (5.1%) [2-mild, 1-moderate]	3 (6.0%) [2-mild, 1-moderate]
Dizziness	5 (8.5%) [4-mild, 2-moderate, 1-severe)	0
Paresthesia	2 (3.4%) [2-moderate]	0
Anxiety	2 (3.4%) [2-mild]	0
Sweating	2 (3.4%) [1-mild, 1-moderate]	1 (2.0%) [1-moderate]
"Withdrawal syndrome"	2 (3.4%) [2-moderate]	0

Table 8. Adverse Events Occurring in Subjects Who Entered Down-Titration Phase – 28 Day Follow-up Visit

Down-Titration Phase

Adverse Event	Paroxetine CR (N = 119)	Placebo (N = 124)
Nausea	2 (1.7%) [1-mild, 1-moderate]	1 (0.8%) [1-moderate]
Dizziness	6 (5.0%) [2-mild, 4-moderate]	1 (0.8%) [1-moderate]
Paresthesia	3 (2.5%) [2-mild, 1-moderate]	0
Anxiety	1 (0.8%) [1-mild]	2 (1.6%) [2-moderate]
Sweating	1 (0.8%) [1-mild]	1 (0.8%) [1-mild]
"Withdrawal syndrome"	3 (2.5%) [1-mild, 1-moderate, 1-severe]	1 (0.8%) [1-mild]

For the 28-day follow-up, no subjects in the group who did not participate in the down-titration phase reported adverse events. This may reflect overall underreporting of adverse events rather than the absence of any adverse events.
In comparing the 14-day and 28-day follow-up adverse events in the subjects who did enter the down-titration phase, it is clear that more adverse events emerged early (in the 14-day follow-up) than later (in the 28-day follow-up). However, some adverse events did emerge > 14 days after paroxetine CR was stopped. One-third of the subjects who reported dizziness had the emergence of this adverse event after 14 days. Similarly, 1/3 of subjects reporting withdrawal syndrome had the emergence of this adverse event after 14 days and 40% of subjects reporting paresthesia had the emergence of this adverse event after 14 days. Again, based on these summary data, it is not known when the true onset of these adverse events occurred – whether on day 15 or towards the end of the 28-day follow-up period.

6. In Table 45 of the study report, it is noted that 96 subjects in the Paxil CR group had AST assessments; only 63% of all completers in the Paxil CR group. Please provide an explanation as to why so few subjects completed laboratory assessments in this study.

   In the 8/25/03 submission, the Sponsor provided an explanation for the perceived low rate of subjects with end-of-study laboratory assessments. It appears that the summary data in the study report included only subjects with baseline and end-of-study laboratory assessments where the end-of-study assessment occurred at the 12-week timepoint. Laboratory assessments were assigned as post week 12 if they had occurred on the last day of treatment but were outside the week 12 window (after day 91). If the assessment occurred on or after the first dose of down titration medication and before the last dose of down titration medication, those laboratory assessments were captured in the "down titration phase" and not reflected in the 12-week end-of-study timepoint. Similarly, for end of study laboratory assessments performed during the follow-up phases, those were captured at the follow-up timepoints and were not reflected in the 12-week end-of-study timepoint. The Sponsor commented that 149 subjects in the paroxetine CR group had a post-baseline (during treatment, down titration or follow-up phases) laboratory assessment; this reflects 95% of all completing subjects in the paroxetine CR group.
   The Sponsor should provide a summary of the end-of-study laboratory assessments occurring during the follow-up phases and the down titration phase including summary data for those subjects with potentially clinically significant changes occurring during these various phases.

This reviewer could not find any detailed data other than the laboratory assessments from baseline to week 12.

7. Please provide a summary of the worldwide literature for Paxil CR.
In the 8/25/03 submission, the Sponsor provided this information. The literature search covered the time period up until 8/5/03 and was conducted in Medline, Embase, the Derwent Drug File, SciSearch and Biosis. The Sponsor provided abstracts for the citations identified in the literature search; very few citations were relevant to paroxetine CR (search terms such as sustained release identified articles unrelated to paroxetine CR). This reviewer reviewed these abstracts and did not note any new serious or unexpected safety findings.

Conclusions and Recommendations

The Sponsor has submitted data in response to several queries that arose during review of supplemental NDA 20-936 SE1-012 for paroxetine CR in the acute treatment of social anxiety disorder. Most of the queries have been adequately addressed. The proposed labeling that was submitted with the application contained a section entitled Discontinuation of Treatment with Paxil CR that contained information pertaining to the immediate release dosage form of paroxetine only. This section of labeling was addressed during review of the supplemental NDA 20-936 SE1-011 for paroxetine CR for the treatment of premenstrual dysphoric disorder. The revised labeling, which included information regarding discontinuation symptoms with paroxetine CR, was approved on 8/28/03. However, as approved, this section does not include any information regarding the severity of the discontinuation symptoms – per this supplemental NDA, four subjects had SAEs consistent with discontinuation symptoms. The Sponsor will be asked to modify that section of labeling to include this information.

The laboratory assessment summary tables in the study report include only summaries for subjects with baseline and 12-week end-of-study assessments. No summaries are available for subjects with laboratory assessments during the follow-up phases or down titration phase. The Sponsor should provide a summary for the end-of-study laboratory assessments occurring during the follow-up phases and the down titration phase including summary data for those subjects with potentially clinically significant changes occurring during these various phases.

Cara Alfaro, Pharm.D.
Interdisciplinary Scientist/Pharmacist
Division of Neuropharmacological Drug Products

September 2, 2003

cc: Laughren/Andreason/Homonnay/Alfaro

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/s/

Cara Alfaro
9/2/03 01:17:11 PM
PHARMACIST

Thomas Laughren
9/12/03 10:24:10 AM
MEDICAL OFFICER
I agree that this supplement is approvable; see memo to file for more detailed comments.--TPL

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: October 6 , 2003

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 CR (paroxetine controlled release tablets) for the treatment of social anxiety disorder

TO: File NDA 20-936/S-012
[**Note:** This overview should be filed with the 12-20-02 original submission.]

1.0 BACKGROUND

Paroxetine is a selective serotonin reuptake inhibitor currently approved and marketed for depression in an immediate release formulation, i.e., Paxil (NDA 20-031, approved 12-29-92) and also in the delayed and extended release formulation, i.e., Paxil CR (NDA 20-936, approved 2-16-99). Paxil is also approved for OCD, panic disorder, social anxiety disorder, GAD, and PTSD. Paxil CR is also approved for panic disorder and PMDD. In this supplement, Paxil CR is proposed for the treatment of social anxiety disorder. Paxil CR is recommended for qd dosing, as is the immediate release formulation, Paxil. The recommended initial dose for Paxil CR in social anxiety disorder is 12.5 mg/day, with increases up to a maximum dose of 37.5 mg/day as needed.

At the present time, there are only 3 drugs approved for the treatment of social anxiety disorder in the US, i.e., Paxil (paroxetine immediate release), Zoloft (sertraline), and Effexor XR (sustained release venlafaxine).

The sponsor did request a preNDA meeting for this supplement in 7-2-02 correspondence, however, we denied the meeting and responded instead with an 8-29-02 letter. In that letter, we confirmed that a single adequate and well-controlled trial would suffice to support the social anxiety disorder claim for Paxil CR, given that Paxil is already approved for this indication. Study 790, the single trial supporting this claim was not conducted under the IND for Paxil CR (IND 51,171), but rather, was conducted at nonUS sites.

Since the proposal is to use the currently approved Paxil CR controlled release tablets for this expanded population, there was no need for chemistry, pharmacology, or biopharmaceutics reviews

of this supplement. The focus was on clinical data. The primary review of the efficacy and safety data was done by Cara Alfaro, Ph.D., from the clinical group. Fanhui Kong, Ph.D., from the Division of Biometrics, also reviewed the efficacy data.

The original application for this expanded indication was submitted 12-20-02, and the application was considered adequate for filing on 2-11-03.

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

2.0 CHEMISTRY

As Paxil CR tablets are already approved, there are no CMC issues requiring review for this application.

3.0 PHARMACOLOGY

As Paxil CR tablets are already approved, there are no pharmacology/toxicology issues requiring review for this application.

4.0 BIOPHARMACEUTICS

While Paxil CR tablets are already approved, there was a need for dissolution testing of the over-encapsulated tablets used in study 790 compared to Paxil CR, and OCPB staff concluded that the dissolution profiles for these two products were similar.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Summary of Study 790

This study was the sole focus of our efficacy review. This was a nonUS study, involving 36 sites in Europe and South Africa. It was a double-blind, randomized, 12-week, flexible dose comparison of Paxil CR (in a dose range of 12.5 to 37.5 mg/day, given on a qd basis) with placebo in adult outpatients meeting DSM-IV criteria for social anxiety disorder. All subjects were initiated with 12.5 mg/day for 2 weeks, and they could then be titrated in increments of 12.5 mg/day at intervals of no less than 7 days. There was a taper period of 1 week for patients receiving the 37.5 mg/day dose, i.e., down to 25 mg/day. There were followup visits at 2 and 4 weeks following study termination.

There were co-primary outcomes for this trial: (1) change from baseline in the LSAS, and (2) proportion of "responders," i.e., 1 or 2 on CGI-I. All analyses were conducted on a modified ITT

population, i.e., all patients randomized who received at least one dose of assigned treatment and who had both baseline and at least 1 followup assessment. The analyses models utilized were (1) ANCOVA for the LSAS data, with terms for center, treatment group, and baseline LSAS, and (2) logistic regression for % responder data.

The ITT population was as follows:
-Paxil CR: 186
-Placebo: 184

Patient completion to the 12-week endpoint was as follows:
-Paxil CR: 156/186 (84%)
-Placebo: 137/184 (75%)

The M:F distribution was roughly 50:50; the mean age was approximately 39; and subjects were predominantly white (approximately 94%). The mean dose of Paxil CR for completers at week 12 was 33 mg/day, indicating that most subjects were pushed to the high end of the dose range.

The results of the analyses for the 2 co-primary endpoints were as follows:

Efficacy Results on LSAS for Study 970 (LOCF)

	Mean Baseline LSAS	**Mean Δbaseline LSAS**	**[P-value(vs pbo)]**
Paxil CR	**78**	**-31**	**< 0.001**
Placebo	**79**	**-18**	

Efficacy Results on CGI-I "Responder" Analysis for Study 970 (LOCF)

	Proportion of "Responders"	**[P-value(vs pbo)]**
Paxil CR	**57%**	**< 0.001**
Placebo	**30%**	

Results on the OC analyses were also highly significant, as were analyses on all secondary outcomes.

The drug placebo difference became significant at 6 weeks and remained significant for the remainder of the trial.

In addition, Dr. Alfaro explored several concerns regarding the efficacy data for this study:
-One concern was for the potential to include patients with comorbid GAD, and the possibility that the changes in the LSAS would reflect improvment in GAD symptoms rather than social anxiety disorder sympoms. While this is theoretically possible, as it turned out, there were no patients included with comorbid GAD.
-A related concern was that, even though patients with comorbid MDD were excluded, there was the possibility that the changes in the LSAS would reflect improvment in depressive symptoms rather than social anxiety disorder sympoms. While this is theoretically possible, as it turned out, mean HAMD scores at baseline were very low (around 4).

-While this was an entirely nonUS study, the results were very similar to those for the US Paxil studies in this indication.

Comment: Both Drs. Alfaro and Kong considered this to be a positive study in support of the claim of effectiveness for Paxil CR in social anxiety disorder, and I agree.

5.1.3 Comment on Other Important Clinical Issues Regarding Paxil CR in the Treatment of Panic Disorder

Evidence Bearing on the Question of Dose/Response for Efficacy

There were no data in this development program pertinent to the issue of dose/response for the CR formulation. There were 3 studies supporting the approval of this indication for Paxil, including 1 fixed dose study (20, 40, and 60 mg/day) that showed no advantage for the 2 higher doses over the 20 mg/day dose. Thus, labeling for Paxil recommends 20mg/day, and notes this finding of a lack of advantage for higher doses. Based on study 790 for Paxil CR, one can at most recommend dosing patients in the range utilized and on the incremental schedule utilized in this trial supporting the effectiveness of this new formulation.

Clinical Predictors of Response

While there was a very limited potential for detecting subgroup interactions on the basis of demographics, especially for age and race/ethnicity, there was no pattern of findings suggestive of any such interactions.

Size of Treatment Effect

The effect size observed in this trial was very similar to that seen in the earlier studies supporting this indication for Paxil.

Duration of Treatment

While there were no data in this development pertinent to duration of effect, this is a chronic condition and we will recommend consideration of longer-term treatment here as we have for Paxil.

5.1.3 Conclusions Regarding Efficacy Data

Given the approved status of Paxil for social anxiety disorder, the positive results from study 790 support the claim of effectiveness of Paxil CR for this indication.

5.2 Safety Data

Clinical Data Sources for Safety Review

The safety data for paroxetine CR were reviewed by Dr. Alfaro. Her review was based entirely on safety data derived from study 790, including n=186 patients exposed to Paxil CR.

Adverse Event Profile for Paxil CR

Given our extensive knowledge of the safety profile for immediate release paroxetine, and our recent reviews of paroxetine CR exposures in the other Paxil CR programs in a somewhat higher dose range compared to that proposed for the treatment of social anxiety disorder, the focus in the safety review was on any differences between the recognized safety profile for this drug, both in the immediate and controlled release formulations, in its approved indications from that observed in this program.

Overall, the side effect profile of paroxetine CR in this study was as expected for this SSRI. There were no new, unrecognized serious adverse events that could be considered related to paroxetine CR use or that would impact on the labeling of this product. However, Dr. Alfaro noted that current Paxil CR labeling includes discontinuation data only for Paxil, and none from Paxil CR programs. In fact, of 5 SAEs reported in this program, 3 appeared to represent discontinuation symptoms. Requests for additional data for patients during the downtitration phase were pending at the time of Dr. Alfaro's review was finalized, and the responses will be the subject of a subsequent review. We will ask the sponsor to update labeling regarding such symptoms for the various Paxil CR programs for which they have such data, including this program. Also, this program did not include a literature update or a postmarketing reports update. We will also request these updates in the approvable letter, along with a safety update.

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

A literature review was not included in this supplement. We will ask for a literature update in the approvable letter.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, Paxil CR is not marketed anywhere at this time for social anxiety disorder. We will ask for an update on the regulatory status of Paxil CR for social anxiety disorder in the approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take Paxil CR for social anxiety disorder to the PDAC.

9.0 DSI INSPECTIONS

The single critical study for this application was an international study conducted in the following countries: Denmark; Finland; France; Spain; Germany; Netherlands; South Africa; and Sweden. DSI inspected sites in Finland (Ahokas) and Denmark (Behnke). Data from both sites were judged to be acceptable.

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 modified the sponsor's draft dated 12-20-02.

10.2 Foreign Labeling

Paxil CR is not marketed anywhere at this time for social anxiety disorder.

10.3 Approvable Letter

The approvable letter includes draft labeling and requests for a safety update, a literature update, and a regulatory status update.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that GSK has submitted sufficient data to support the conclusion that Paxil CR is effective and acceptably safe in the treatment of social anxiety disorder. 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 20-982 (Paxil CR/Social Anxiety Disorder)
HFD-120/Div File
HFD-120/TLaughren/RKatz/PAndreason/CAlfaro/AMHomonnay

DOC: MEMPXRSA.AE1

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/s/

Thomas Laughren
10/6/03 01:35:09 PM
MEDICAL OFFICER

DIVISION OF INFORMATION DISCLOSURE POLICY

POLICY NOTE:

Per Review Division, no APPROVABLE LETTER was issued for this supplement.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-936/S-012

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

Medical Division: Neuropharm Drug Products (HFD-120)
Biometrics Division: Division of Biometrics I (HFD-710)

NDA NUMBER:	20-936
DRUG NAME:	Paroxetine CR
INDICATION:	Social Anxiety Disorder
SPONSOR:	SmithKline Beecham
STATISTICAL REVIEWER:	Fanhui Kong, Ph.D. (HFD-710)
DATE OF DOCUMENT:	December 20, 2002

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Statistical Review and Evaluation

1. Executive Summary

This submission of efficacy study consists of one 12-week, Phase III, randomized, double-blind, parallel group multi-center, placebo-controlled, flexible dose study that evaluates the efficacy and safety of paroxetine CR versus placebo in the treatment of patients with Social anxiety disorder. Study 790 was conducted at 36 centers in Europe and South Africa. In this study, a total of 164 patients were randomized and 160 were in the intent-to-treat (ITT) population.

In this submission the primary endpoint was based on the reduction of the LSAS Total Score at Week 12 on therapy evaluation. The study gave a positive result in the reduction of primary endpoint with p-values below 0.001 in ITT-LOCF analysis.

2. Introduction

The current submission of NDA 20-936 for paroxetine CR consists of a phase-III study to compare the efficacy and safety of paroxetine CR with placebo in patients with Social anxiety disorder.

Study 790 is a double-blind, placebo-controlled, flexible-dose study of paroxetine CR in the treatment of patients with social anxiety disorder.

In the LOCF analysis of Study 790, paroxetine CR significantly reduced the LSAS Total score for patients at Week 12 and therefore supports the conclusion that paroxetine CR is more effective than placebo in improving clinical conditions of Social anxiety disorder.

3. Study 790

The first subject entered the study on October 23, 2001, and the last study visit was on July 16, 2002. The original protocol was approved on July 3, 2001. There were 2 amendments to the original protocol on July 30, 2001 and February 1, 2002. No significant statistically related changes were made in these amendments.

3.1 Study Objectives

The primary objective of this study was to compare the efficacy of paroxetine CR with that of placebo in the treatment of social anxiety disorder.

The secondary objective was to compare the safety of paroxetine CR with that of placebo in the treatment of social anxiety disorder.

3.2 Study Design

This was a multicenter, double-blind, randomized, placebo-controlled, two-arm, parallel group study to assess the efficacy and safety of 12 week dosing with 12.5mg to 37.5mg of paroxetine CR versus placebo in subjects with a primary diagnosis of social anxiety disorder. The study was designed to screen 370 subjects so that approximately 296 subjects could be randomized equally among the two treatment groups (148 subjects per group). Following a 1-week placebo run-in period, subjects who met all inclusion/exclusion criteria were randomized in a 1:1 ratio to receive either paroxetine CR or placebo for a 12 week, double-blind treatment period. The dose range of paroxetine CR during the double-blind treatment phase was 12.5 mg to 37.5 mg daily. In order to achieve blinding, doses were referred to as Dose Level 1 through to 3. Subjects remained at Dose Level 1 for 2 weeks after which dose elevation was permitted in 12.5 mg increments no more frequently than every 7 days (determined by the investigator's clinical judgement according to clinical response and tolerability). Dosage reduction to the next lowest level consequent to an AE was permitted after Week 2, provided the subject had been uptitrated to Dose Level 2 or 3. The subject could return to the original dose upon resolution of the AE. Subjects requiring a dosage reduction prior to the Week 2 visit or requiring more than 1 dosage reduction were to be withdrawn from the study. Subjects who either completed the trial or who withdraw prematurely on Dose Level 3 were subjected to a gradual reduction of the study medication dose over a further period of 1-week (down-titration phase). Assessments for safety were carried out at all visits, and assessments for efficacy were carried out at Visits 2 to 9 and the early withdrawal visit, if applicable. Subjects were diagnosed with social anxiety disorder using the Mini International Neuropsychiatric Interview (MINI), Clinician Rated version 5.0 according to DSM-IV criteria (300.23).

There are two amendments to the protocol approved on July 30, 2001 and February 1, 2002. No significant statistically related changes were made in these amendments.

3.3 Efficacy Measures

The primary endpoints are the change from baseline in the LSAS Total score and the proportion of responders who scored 1 or 2 (very much improved or much improved) on the CGI global improvement item at the Week 12.

The secondary efficacy variables are: change from baseline in the CGI severity of illness item score; change from baseline on the LSAS fear or anxiety subscale score; change from baseline on the LSAS avoidance subscale score; change from baseline on the SADS Total score; change from baseline on the SDS Family Life item; change from baseline on the SDS Work item and change from baseline on the SDS Social Life item.

3.4 Statistical Analysis Plan

Two populations were evaluated: ITT and PP. Primary inferences have been based on the ITT population. The ITT population consisted of all randomized subjects who received at least one dose of study medication and had at least one post-baseline assessment (including AEs). The ITT population consisted of a total of 370 subjects. Of these subjects, 186 received paroxetine CR and 184 received placebo.

The primary comparisons of interest were the change from baseline in LSAS Total score at the Week 12 LOCF endpoint for paroxetine CR versus placebo and the proportion of responders who scored 1 or 2 (very much improved or much improved) on the CGI global improvement item at the Week 12 LOCF endpoint, in the ITT population. Statistically significant and clinically relevant differences had to be observed between paroxetine CR and placebo on both primary efficacy variables. Other comparisons of interest included an analysis of the secondary efficacy parameters based on the LOCF dataset at the protocol defined Week 12 endpoint. In addition, the primary efficacy variables and the secondary efficacy variables were analyzed using the observed cases (OC) dataset at the Week 12 endpoint. A PP analysis of the primary endpoint was undertaken for the LOCF, and OC datasets at the Week 12 endpoint. Analyses using the 70% LOCF endpoint (defined as the latest time point where at least 70% of the subjects in each treatment group remained in the study) were to be carried out, but were not required because more than 70% of the subjects were still in the study at Week 12. Statistical tests for efficacy measures were two-sided and performed at the 0.05 level of significance. Tests of interaction were performed at the 0.1 significance level.

Prior to database freeze centers were reviewed to determine their sizes and small centers (with less than 8 subjects to the ITT population) were combined. In addition to the primary model, the following supplementary analyses for the ITT population were performed to assess the robustness of the primary model. Initially, candidate covariates "duration of social anxiety disorder (years)" and "gender (Male, Female)" were entered separately into the primary model. Those covariates that achieved statistical significance at the 5% level were included together in a supplementary model. Since both of the primary comparisons between paroxetine CR versus placebo had to be significant for the study to be considered a success, no multiplicity adjustment were performed.

For each subject, to account for missing data for a rating scale at a particular visit, the LOCF method was used, i.e. the last available on-therapy observation for a subject is carried forward to estimate subsequent missing data points. This method was used to impute data points if a subject withdrew early and was also used to impute data points if a subject missed a single visit within the study. However, for the OC analysis the data point would remain missing. Subjects were omitted from an analysis if they had missing baseline data, or baseline assessments only for the corresponding analysis variables.

The number and percentage of subjects by age group, race and by treatment group were tabulated for the ITT and PP populations. Summary statistics (n, mean, standard deviation, median, minimum and maximum) for age, height, weight, BMI and by treatment group were tabulated for the ITT and PP populations. Baseline characteristics were summarized by treatment group for the ITT population. Summary statistics (n, mean, standard deviation, median, minimum and maximum) for the efficacy rating scales at baseline were presented by treatment group for the ITT population.

Efficacy Analyses

The change from baseline to study endpoint in the LSAS Total score was analyzed using the analysis of covariance model (i.e. a linear model assuming normal errors). The assumptions of normality and homogeneity of variance, underlying the statistical analysis were checked. The statistical model on which the primary inference was based included terms for center, baseline LSAS Total score and treatment group, regardless of their significance. No interaction terms were included in this primary model.

The proportion of responders on the CGI global improvement was analyzed using a logistic regression model, and the residuals were assessed to check the assumptions of the analysis. The statistical model on which the primary inference was based included terms for center and treatment group, regardless of their significance. No interaction terms were included in this primary model. The following supplementary analyses, restricted to the ITT population, and the primary variables using the Week 12 LOCF dataset, were performed to assess the robustness of the primary model. Initially, the following candidate covariates were entered separately into the primary model: duration of social anxiety disorder (years) and gender (Male, Female)

Those covariates that achieved statistical significance at the 5% level were to be included together in a supplementary model. Two additional datasets were analyzed to assess the robustness of the results. These were the LOCF dataset at the latest time point where at least 70% of the subjects remain in each treatment group (70% LOCF) and an OC dataset at the Week 12 endpoint. The principal analysis (i.e. LOCF at Week 12) as well as these two additional approaches (i.e. 70% LOCF and OC), were repeated for the PP population.

Applying the primary model (i.e. treatment, center, and corresponding baseline score), normal, linear models were fitted to each continuous secondary variable. Since the analysis of the CGI severity of Illness score from previous paroxetine clinical trials has shown this measure to be skewed in distribution, Non-Parametric Analysis of Covariance

was also used for the comparison of treatment groups for this response to assess the robustness of the findings of the parametric analysis. All efficacy measures over the course of the study are presented and summarized in graphs and tables. Continuous data are summarized by means, standard deviations, medians, maxima, minima and numbers of subjects, and categorical data are summarized by counts and proportions.

3.5 Study Population

The target population for this study consisted of patients who were at least 18 years of age with primary diagnosis of Social Anxiety Disorder/Social Phobia (DSM-IV, 300.23). Patients were 1-1 randomized to paroxetine CR and placebo.

This study was carried out in 36 centers in Europe and South Africa. One center in Germany did not randomize any subjects, and one center in South Africa did not provide any subjects who were eligible for the ITT population. A total of 426 subjects were screened of whom 375 subjects were randomized to receive double-blind treatment at 35 centers in Europe and South Africa. Of the 375 randomized subjects, 293 (78.1%) completed the study. Five randomized subjects, 3 in the paroxetine CR treatment group, and 2 in the placebo treatment group, withdrew from the study before starting study medication, and were therefore not included in the ITT populations. The reasons for withdrawal were: lost to follow-up (2 paroxetine CR subjects), protocol deviation (1 placebo subject), withdrew consent (1 placebo subject) and AE (1 paroxetine CR subject).

Table 3.5.1 The Number of Subjects by Study Status and Population (All Subjects)

Study Stage	Treatment Groups Paroxetine CR	Placebo	Total
Screened	-	-	426
Screening Only Population	-	-	51
Randomized	189	186	375
Completed*	156	137	293
Early Withdrawal	30	47	77
Randomized Non-ITT Population	3	2	5
ITT Population	186	184	370
PP Population	162	162	324

* Subjects were considered to have completed the study if they remained in the study up to and including Week 12 of the double-blind treatment phase.

The proportion of subjects who withdrew prematurely was lower in the paroxetine CR treatment group, compared with the placebo group: 30/186 (16.1%) subjects in the paroxetine CR treatment group and 47/184 (25.5%) subjects in the placebo group. The primary reason for early withdrawal in the paroxetine CR treatment group was "other" (4.3%), while in the placebo group the primary reason was lack of efficacy (15.8%). Only 2.2% of paroxetine CR-treated subjects withdrew due to lack of efficacy.

Table 3.5.2 Number (%) of Randomized Subjects Who Completed the Study or were Withdrawn by Reason for Withdrawal (ITT Population)

Reason for Study Conclusion	Treatment Group			
	Paroxetine CR N=186		Placebo N=184	
Completed Study*	156	(83.9)	137	(74.5)
Total Withdrawn	30	(16.1)	47	(25.5)
AE	5	(2.7)	3	(1.6)
Lack of Efficacy	4	(2.2)	29	(15.8)
Protocol Deviation **	7	(3.8)	7	(3.8)
Lost to follow-up	6	(3.2)	4	(2.2)
Other†	8	(4.3)	4	(2.2)

* Subjects were considered to have completed the study if they remained in the study up to and including Week 12 of the double-blind treatment phase.

** Including non-compliance.

† Include unknown and non-study-related personal reasons.

Similar proportions of ITT subjects in the two treatment groups violated the protocol sufficiently to be excluded from the PP population, paroxetine CR: 24/186 (12.9%); placebo: 22/184 (12.0%). The most common protocol violation in both treatment groups was "non-compliance". Protocol deviations were considered to have little effect on treatment and did not warrant subject withdrawal from the PP population. Only one subject (placebo treatment group) recorded a protocol deviation, which was "inadequate or non-use of contraception for women of child bearing potential".

Demographic data (date of birth, race, gender), vital signs data (height, blood pressure and heart rate), medical, psychiatric, and surgical history, MINI, physical examination, and psychoactive medication history were collected at the screening visit (Visit 1). In addition a blood sample was taken for hematology and blood chemistry, and a 12-lead ECG was carried out. Baseline characteristics including vital signs (weight, blood pressure and heart rate), recent medical procedures, baseline AEs and baseline assessments for all the efficacy rating scales were assessed at the baseline visit (Visit 2), together with the HAMD. In addition, a 12-lead ECG and/or laboratory assessments were repeated at the baseline visit if any abnormalities had been found during the screening assessments.

Table 3.5.3 summarizes demographic characteristics by treatment group for the ITT population. The demographic characteristics of the two treatment groups were generally similar with respect to gender, race, age, height, weight, BMI and HAMD assessment. The mean age of subjects was 38.7 years in the paroxetine CR treatment group and 39.0 years in the placebo treatment group.

Table 3.5.3 Demographic Characteristics (ITT Population)

	Treatment Groups	
	Paroxetine CR N=186	**Placebo N=184**
Gender: No. (%)		
N=	186	184
Female	98 (52.7)	87 (47.3)
Male	88 (47.3)	97 (52.7)
Race: No. (%)		
N=	186	184
White	174 (93.5)	175 (95.1)
Black	3 (1.6)	3 (1.6)
Oriental	2 (1.1)	0
Other	7 (3.8)	6 (3.3)
Age: Years		
N=	186	184
Mean (s.d.)	38.7 (10.50)	39.0 (11.52)
Median	39.0	40.0
Range	18.0-69.0	18.0-67.0
18 – 24: n (%)	20 (10.8)	24 (13.0)
25 – 34: n (%)	43 (23.1)	43 (23.4)
35 – 44: n (%)	65 (34.9)	53 (28.8)
45 – 54: n (%)	46 (24.7)	49 (26.6)
55 – 64: n (%)	11 (5.9)	13 (7.1)
≥65: n (%)	1 (0.5)	2 (1.1)
Height: cm		
N=	185	184
Mean (s.d.)	172.6 (8.79)	173.6(9.97)
Median	172.0	172.5
Range	145.0-195.0	150.0-198.0
Weight: kg		
N=	182	183
Mean (s.d.)	71.6 (14.93)	74.2 (14.55)
Median	69.7	71.0
Range	44.0-114.8	48.0-132.5
BMI: kg/m^2		
N=	181	183
Mean (s.d.)	23.8 (3.87)	24.6 (4.27)
Median	23.4	24.0
Range	16.2-39.2	16.6-41.4
HAMD Total Score		
N=	186	183
Mean (s.d.)	4.1 (3.17)	4.4(3.39)
Median	4	4
Range	0-14	0-14

Table 3.5.4 summarizes the mean baseline score by treatment group in the following efficacy variables: LSAS Total score, fear or anxiety subscale and avoidance subscale; CGI severity of illness; SADS Total score; and SDS Work, Social Life and Family Life scores. The treatment groups were similar with respect to their baseline scores for all the efficacy rating scales investigated.

Table 3.5.4 Baseline Scores in Efficacy Rating Scales by Treatment Group (ITT Population)

	Treatment Groups					
	Paroxetine CR			Placebo		
Instrument	**n**	**Mean**	**s.d.**	**n**	**Mean**	**s.d.**
LSAS						
Total Score	185	78.3	24.72	184	78.6	23.44
Fear or Anxiety Subscale	185	41.5	12.45	184	41.7	11.84
Avoidance Subscale	185	36.8	12.94	184	36.9	12.35
CGI						
Severity of Illness	186	4.5	0.84	184	4.5	0.80
SADS						
Total Score	186	21.6	5.68	180	21.8	5.31
SDS						
Work	184	5.6	2.77	180	5.7	2.71
Social Life	186	6.6	2.12	182	6.6	2.19
Family Life	186	3.4	2.79	182	3.4	2.73

3.6 Sponsor's Efficacy Results

3.6.1 Primary Efficacy Results

The analyses of the efficacy data were conducted using the ITT population for both primary and all secondary efficacy variables. The analyses of efficacy data were also conducted for the PP population for the primary variables only. In addition to the results of LOCF dataset at Week 12, the OC results are presented as supportive evidence for the Week 12 LOCF results.

Primary inferences were based on the ITT population LOCF dataset at Week 12. The LOCF dataset contained all data for the Week 12 visit, plus the last on-treatment assessment for subjects who withdrew before the Week 12 visit. Negative changes from baseline such as for LSAS Total score, CGI severity of illness, LSAS fear or anxiety, and avoidance subscales, SADS Total score and SDS item scores indicate an improvement for that parameter.

The changes from baseline in LSAS Total score adjusted for country group and baseline LSAS Total score together with differences in least square means, 95% CIs and p-values are shown in Table 3.6.1. A statistically significant and clinically relevant difference was demonstrated in favor of paroxetine CR versus placebo for the Week 12 LOCF endpoint [adjusted mean difference = -13.33, 95% CI (-18.25, -8.41), $p<0.001$]. The results of the Week 12 OC endpoint analysis were similar to the results of the Week 12 LOCF endpoint analysis with a statistically significant difference in favor of paroxetine CR.

Table 3.6.1 Efficacy for Change from Baseline in LSAS Total Score and CGI Improvement (ITT Population)

Primary Efficacy Parameters	Placebo	Paroxetine CR	P-value[a]
LSAS Total Score: Change from Baseline			
Week 12 OC	124	136	
Mean (SE)	-20.9 (2.14)	-34.1 (2.08)	<0.001
95% Confidence Interval[b]		-13.16 (-18.97, -7.36)	
Week 12 LOCF	184	185	
Mean (SE)	-17.6 (1.80)	-31.0 (1.81)	<0.001
95% Confidence Interval[b]		-13.33 (-18.25, -8.41)	
CGI Global Improvement Score of 1 or 2			
Week 12 OC			
Percentage	43/124 (34.7)	87/136 (64.0)	<0.001
Odds Ratio 95% CI		3.40 (2.01, 5.74)	
Week 12 LOCF			
Percentage	56/184 (30.4)	106/186 (57.0)	<0.001
Odds Ratio 95% CI		3.12 (2.01, 4.83)	

[a] Comparison of treatment groups using ANCOVA with linear model for change of LSAS Total score (with treatment, baseline and center group) and logistic model for CGI improvement (with treatment and center group). [b] Computed for least squared difference between changes of primary endpoint in paroxetine CR and placebo.

Changes of LSAS total score for the Week 12 OC and Week 12 LOCF endpoints show the advantage of the paroxetine CR treatment compared to placebo. Covariates duration of social anxiety disorder and gender are not statistically significant at the 5% level so they are not included in the primary analysis. The interaction of treatment with each of the other main effects was also assessed for the ITT population at the Week 12 LOCF endpoint but none is statistically significant at the 10% level (i.e. $p<0.1$).

The proportions of subjects who responded on the CGI global improvement adjusted for country group together with odds ratios, 95% CIs and p-values are shown in Table 3.6.1. The odds of being a responder on paroxetine CR relative to the odds of being a responder on placebo at the Week 12 LOCF endpoint was 3.12 (95% CI [2.01, 4.83], $p<0.001$). This was also the case for the Week 12 OC endpoint. Covariates duration of social anxiety disorder and gender are not statistically significant at the 5% level so they are included in the primary analysis. The interaction of treatment with center group was also assessed for the ITT population at the Week 12 LOCF endpoint and they are statistically significant at the 10% level (i.e. $p<0.1$).

3.6.2 Secondary Efficacy Results

Changes from baseline at Week 12 for the secondary efficacy endpoints: CGI Severity of Illness Score, LSAS Fear or Anxiety Subscale, LSAS Avoidance Subscale, SADS Total score, Sheehan Disability Subscales (SDS Family Life Subscale, SDS Work Subscale and

SDS Social Subscale) were displayed separately in Tables 3.6.2, together with their differences in least square means, 95% CIs and p-values. Treatment effect was assessed using analysis of covariance (ANCOVA) adjusted with country group and their respective baseline score as the covariate.

Statistically significant differences were demonstrated in favor of paroxetine CR versus placebo for the Week 12 LOCF endpoints: CGI Severity of Illness Score [paroxetine CR: adjusted mean difference = -0.63, 95% CI (-0.85, -0.40), $p<0.001$], both the fear or anxiety, and avoidance subscales [fear or anxiety subscale, paroxetine CR: adjusted mean difference = -6.86, 95% CI (-9.42, -4.30), $p<0.001$; avoidance subscale, paroxetine CR: adjusted mean difference = -6.47, 95% CI (-8.98, -3.96), $p<0.001$], SADS Total score [paroxetine CR: adjusted mean difference = -2.43, 95% CI (-3.84, -1.01), $p<0.001$], and all 3 SDS items [Family Life, paroxetine CR: adjusted mean difference = -0.64, 95% CI (-0.99, -0.29), $p<0.001$; Work, paroxetine CR: adjusted mean difference = -1.10, 95% CI (-1.56, -0.65), $p<0.001$; Social Life, paroxetine CR: adjusted mean difference = -1.10, 95% CI (-1.57, -0.63), $p<0.001$].

The results of the Week 12 OC endpoint analysis were similar to the results of the Week 12 LOCF endpoint analysis with a statistically significant difference in favor of paroxetine CR. As planned, a non-parametric analysis was performed for this endpoint, based on evidence from previous studies. The non-parametric analysis yielded similar results to the parametric analysis.

Table 3.6.2 Secondary Efficacy Measure at Endpoint for ITT Population—LOCF Analysis

Secondary Efficacy Parameters At Endpoint	Placebo N = 184	Paroxetine CR N = 186	P-value [b]
CGI Severity of Illness Score			
Mean change from baseline (SE)[a]	-0.7 (0.08)	-1.4 (0.08)	<0.001
95% CI of difference		-0.63 (-0.85, -0.4)	
N	184	186	
LSAS Fear or Anxiety Subscale			
Mean change at baseline (SE)[a]	-8.9 (0.94)	-15.7 (0.94)	<0.001
95% CI of difference		-6.86 (-9.42,-4.30)	
N	184	185	
LSAS Avoidance Subscale			
Mean change at Week 8 (SE)[a]	-8.7 (0.92)	-15.2 (0.92)	<0.001
95% CI of difference		-6.47 (-8.98,-3.96)	
N	184	185	
SADS Total Score			
Mean change at baseline (SE)[a]	-4.1 (0.52)	-6.6 (0.52)	<0.001
95% CI of difference		-2.43 (-3.84,-1.01)	
N	180	185	
Sheehan Disability Scale			
SDS Family Life Subscale			
Mean change at baseline (SE)[a]	-0.7 (0.13)	-1.3 (0.13)	<0.001
95% CI of difference		-0.64 (-0.99,-0.29)	
N	182	185	
SDS Work Subscale			
Mean change at Week 8 (SE)[a]	-1.0 (0.17)	-2.1 (0.17)	<0.001
95% CI of difference		-1.10 (-1.56,-0.65)	
N	180	183	
SDS Social Life Subscale			
Mean change at Week 8 (SE)[a]	-1.6 (0.17)	-2.7 (0.17)	<0.001
95% CI of difference		-1.10 (-1.57,-0.63)	
N	182	185	

(a) These are the least square adjusted means and standard errors. (b) The p-values are derived based on the least square adjusted means and standard errors.

3.7 Reviewer's Analysis

Using the ITT-LOCF data set provided by the sponsor, the reviewer duplicated the sponsor's analysis according to the protocol and obtained the same results for both OC and LOCF analyses. Only the LOCF results are depicted in Table 3.7.1. Similar significant levels are obtained without adjusting for center groups.

Table 3.7.1 Efficacy for the Reduction of LSAS Total Score and CGI Improvement at Week 12 --- LOCF Analysis (ITT Population)

Primary Efficacy Parameters	Placebo	Paroxetine CR	P-value[a]
LSAS Total Score: Change from Baseline			
	184	185	
Week 12 LOCF			
Mean (SE)	-17.6 (1.80)	-31.0 (1.81)	<0.001
95% Confidence Interval[b]		-13.33 (-18.25, -8.41)	
CGI Global Improvement Score of 1 or 2			
Week 12 LOCF			
Percentage	56/184 (30.4)	106/186 (57.0)	<0.001
Odds Ratio 95% CI		3.12 (2.01, 4.83)	

[a] Comparison of treatment groups using ANCOVA (with treatment, center group and baseline) for reduction of LSAS total score and logistic regression for CGI Improvement.
[b] Computed for difference between changes of primary endpoint in paroxetine CR and placebo.

3.7.1 Results on LSAS Total Score

Normality assumption is tested for the reduction of LSAS Total score from baseline to Week 12. Both the Kolmogorov-Smirnov D test and the Shapiro-Wilks test give p-values below 0.05 for treatment and placebo groups. This indicates that the normality assumption of the primary endpoint is problematic. On the other hand, the skewness of the distributions is low and the histograms show bell shapes for the reduction from baseline for LSAS total score. The reviewer performed nonparametric tests. Both the Wilcoxon and Kruskal-Wilks tests give p-values around 0.0001. These tests confirm the testing results in Table 3.7.1. Parallelism of the regression lines for the placebo and paroxetine CR treatment groups were tested by testing the interaction between the baseline LASA Total score and the treatment indicator. This test yields a nonsignificant result with a p-value of 0.29, indicating an acceptable assumption of parallelism between the regression lines of two treatment groups.

There are 36 investigators in total therefore it is hard to do a subgroup analysis for each site. The effect of sex on the primary outcome is evaluated by testing the significance of sex as a covariate in the model. The p-value of the test is 0.80 so sex does not make a significant difference on the reduction of LSAS Total score at Week 12. The following table gives t-test results for the treatment differences by sex. Diff is the mean change from baseline to Week 12 on the Total score of LSAS. Parodiff is the difference between DIFF of paroxetine CR and Placebo.

Table 3.7.2 Treatment Effect by Sex on the Reduction of Total LSAS Score

Sex	Therapy	Patient	Diff	Parodiff	t-Value
Male	Paroxetine CR	88	-30.76	-12.44	-3.32
	Placebo	97	-18.32		(p=0.001)
Female	Paroxetine CR	97	-32.25	-14.55	-3.66
	Placebo	87	-17.7		(p=0.0003)

The above table shows that paroxetine CR has statistically significant effect on LSAS Total score in both sex groups. However, without the adjustment of other covariates, the nominal p-value should be interpreted with care.

The following table gives t-test results for the treatment differences by age groups. The population is separated into three age groups: patients from 18 to 34 years of age, patients from 35 to 44 years of age and patients from 45 years of age. DIFF is the mean change from baseline to Week 12 on the Total score of LSAS. Parodiff is the difference between DIFF of paroxetine CR and placebo.

Table 3.7.3 Treatment Effect by Age Group on the Reduction of LSAS Total Score at Week 12

Age	Therapy	Patient	DIFF	Parodiff	t-Value
18-34 years	Paroxetine CR	63	-30.27	-12.81	-2.85
	Placebo	67	-17.46		(p=0.005)
35-44 years	Paroxetine CR	65	-34.31	-14.35	-2.90
	Placebo	53	-19.96		(p=0.004)
Above 44 years	Paroxetine CR	57	-29.79	-12.77	-2.73
	Placebo	64	-17.02		(p=0.007)

So the treatment effects of paroxetine CR on LSAS Total score in all the age groups are statistically significant. Again, the nominal p-value should be interpreted with care.

3.7.2 Subgroup Results on CGI Improvement

The effect of sex on the primary outcome of CGI improvement is evaluated by testing the significance of sex as a covariate in the logistic regression model. The p-value of the test is 0.62 so sex does not have a significant effect on the CGI improvement at Week 12. The following table gives Chi-test results for the treatment differences on CGI improvement by sex. Odds Ratio and p-value of Chi-test are given for testing the significance of paroxetine CR with respect to Placebo.

Table 3.7.4 Treatment Effect by Sex on CGI Improvement

Sex	Therapy	Patient	CGI Iprovement	Odds Ratio	p-Value (Chi-square)
Male	Paroxetine CR	88	49	2.81	0.0007
	Placebo	97	30		
Female	Paroxetine CR	98	57	3.26	0.0001
	Placebo	87	26		

The above table shows that paroxetine CR has statistically significant effect on CGI Improvement in both sex groups. Without the adjustment of other covariates, the nominal p-value should be interpreted with care.

The following table gives Chi-test results for the treatment differences on CGI Improvement by age groups. The population is separated into three age groups: patients from 18 to 34 years of age, patients from 35 to 44 years of age and patients from 45 years of age. Odds Ratio and p-value of Chi-test are given for testing the significance of paroxetine CR with respect to Placebo.

Table 3.7.5 Treatment Effect by Age Group on CGI Improvement at Week 12

Age	Therapy	Patient	CGI Improvement	Odds Ratio	p-Value
18-34 years	Paroxetine CR	63	38	3.33	0.0009
	Placebo	67	21		
35-44 years	Paroxetine CR	65	35	2.27	0.031
	Placebo	53	18		
Above 44 years	Paroxetine CR	58	33	3.65	0.0007
	Placebo	64	17		

So the treatment effects of paroxetine CR on CGI improvement in all the age groups are statistically significant. Again, the nominal p-value should be interpreted with care.

There are 94% White and 6% nonwhite patients in the sample. Given the low percentage of nonwhite patients, we did not perform group analysis for White and nonwhite groups.

4. Conclusion

In this submission, the sponsor conducted one Phase III, placebo controlled clinical trial study that evaluated the efficacy and safety of paroxetine CR versus placebo in the treatment of patients with Social anxiety disorder.

In the LOCF analysis of Study 790, treatment significantly reduced the LSAS Total score at Week 12 and increased the rate of CGI improvement (for CGI score reduced to 1 or 2) therefore supported the conclusion that paroxetine CR is more effective than placebo in improving clinical conditions of the patients with Social anxiety disorder. The model assumptions made by the sponsor on the primary endpoints were checked by the reviewer and were found to be acceptable. In addition to the adjustment of covariates in the models presented, the significance of other covariates such as sex and age group was tested and was not found to be significant in the model. The normality assumption was found to be problematic in the test of treatment effect on LSAS Total score so the Wilcoxon nonparametric test was used to test the significance of the treatment effect. The results supported the sponsor's conclusions.

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/s/

Fanhui Kong
8/21/03 05:02:57 PM
BIOMETRICS

Kun Jin
8/25/03 12:01:48 PM
BIOMETRICS

George Chi
8/25/03 12:56:28 PM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-936/S-012

CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Paroxetine HCl
PRODUCT (Brand Name):	PAXIL® CR
DOSAGE FORM:	Controlled Release Tablets
DOSAGE STRENGTHS:	12.5, 25 and 37.5 mg
NDA:	20-936 (SE1-012)
NDA TYPE:	Efficacy Supplement
SUBMISSION DATE:	12/20/02
SPONSOR:	Glaxo SmithKline
REVIEWER:	Veneeta Tandon, Ph.D.
TEAM LEADER:	Ramana Uppoor, Ph.D.
OCPB DIVISION:	DPE I, HFD 860
OND DIVISION:	HFD 120

TABLE OF CONTENTS

RECOMMENDATION

The sponsor has provided adequate dissolution data for the Paxil CR tablets and over encapsulated tablets to show similarity in the dissolution profiles of the two. Therefore it is acceptable to use the over encapsulated paroxetine CR tablets in the clinical Study 790 instead of the paroxetine CR tablets without compromising the study results obtained.

Veneeta Tandon 4/14/03

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation I

Team Leader: Ramana Uppoor, Ph.D. 04/14/03

BACKGROUND

N20-936 (012) is an efficacy supplement for the treatment of social anxiety disorder. The application consists of a single, randomized, double-blind, placebo-controlled, 12-week flexible dose (12.5 to 37.5 mg/day) trial.

The sponsor used over-encapsulated tablets in this trial for the sake of blinding the trial. The marketed strengths of Paxil CR, 12.5, 25 and 37.5 mg are yellow, pink and blue in color, respectively and have the strength and tradename engraved on them. The sponsor has used [redacted] for the capsules.
The unit formulation for the tablets and overencapsulated tablets is attached in the Appendix Table 1. The sponsor has conducted dissolution with the paroxetine CR tablets and the overencapsulated paroxetine CR tablets.

DISSOLUTION

The sponsor has used the approved dissolution method for evaluating the dissolution profile of the 12.5, 25 and 37.5 mg tablets and the over encapsulated tablets.

The method is as follows:

Apparatus: USP II (paddle) at 150 rpm (as per approval letter dated 8/17/00 for N 20-936/S002)

Dissolution Media: Step 1: 0.1 N HCl (750 mL) for 2 hours
Step 2: pH 7.5 Tris Buffer (1000 mL) containing 50 mmol Tris

Specifications: Step 1 (In 0.1 N HCl): 2 Hours -NMT [redacted]% dissolved
Step 2 (In 0.05 M Tris Buffer at pH 7.5):
1 hour -NMT [redacted]% dissolved
2 hours -between [redacted]% dissolved
4 hours -between [redacted]% dissolved
6 hours -NL T[redacted]% dissolved

The sponsor did not conduct a F2 comparison to show similarity in the dissolution data of the paroxetine CR tablets and over encapsulated paroxetine CR tablets, though the dissolution data was provided. The reviewer performed the calculations. The mean dissolution data for the tablets and over encapsulated tablets is attached in the Appendix on pages 5-6. The F2 values for the various strengths is given in the following Table:

Tablet Strength	F2
12.5 mg	54.87
25 mg	81.49
37.5 mg	95.59

Conclusions:

The F2 values for all the strengths used in the clinical trial were within 50-100 and therefore the dissolution profiles for the paroxetine CR tablets and over encapsulated paroxetine CR tablets are similar. Therefore the overencapsulated tablets used in the Clinical Study 790 would be representative of the paroxetine CR tablets.

APPENDIX

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

Clinical Pharmacology/Biopharmaceutics

1 Paroxetine CR (Controlled Release) Tablets

Initial analyses used for release of the clinical batch were performed in accordance with the current R&D specifications. Details of the clinical batches and batch analyses details are presented in tables 1 and 2.

Table 1: Paroxetine CR 12.5, 25 and 37.5 mg Tablets, Clinical Batches, Formula Codes GG, GH and ED, Respectively

Strength (mg)	Batch Number	Drug Substance Lot No.	Site of Manufacture	Manufacture Date	Batch Size	Package Type
12.5	N00332	00P70134	GSK Cidra	27-Sep-2000	[redacted]	Bulk
25	N00338	00P7-004	GSK Cidra	28-Sep-2000		Bulk
37.5	N00345	00P70331	GSK Cidra	29-Sep-2000		Bulk

Table 2: Batch Analysis for Paroxetine CR 12.5 mg, 25 mg and 37.5 mg Tablets, Clinical Batches, Formula Codes GG, GH and ED, Respectively

Batch No.	N00332	N00338	N00345
Formula	GG	GH	ED
Strength	12.5 mg	25 mg	37.5 mg
Appearance	A round normal biconvex pale yellow coloured film coated tablet.	A round normal biconvex dark salmon coloured film coated tablet.	A round normal, biconvex, bilayer enteric coated tablet with bevelled edges. One layer is white to off white and the other is pale yellow.
Dimensions	7.26 x 4.94 mm	7.25 x 5.18 mm	8.23 x 4.29 mm
Identification	Confirmed	Confirmed	Confirmed
% Dissolution[1]			
2 hours 0.1M HCl	0	0	0
1 hour pH 7.5 buffer	6	6	4
2 hours pH 7.5 buffer	27	26	26
3 hours pH 7.5 buffer	53	52	53
4 hours pH 7.5 buffer	73	74	75
5 hours pH 7.5 buffer	89	92	92
6 hours pH 7.5 buffer	99	98	99
Paroxetine Base Content (mg/tablet)	[redacted]		
Uniformity of Content	Complies with USP	Complies with USP	Complies with USP
Uniformity of Weight	Complies with USP	Complies with USP	Complies with USP
Moisture Content (% w/w)	[redacted]		

[1] USP Stage 2 Dissolution Testing

2 Overencapsulated Paroxetine CR Tablets

Paroxetine 12.5 mg and 25 mg CR tablets were overencapsulated in [ ] [ ] and the 37.5mg CR tablets were overencapsulated in [ ] The overencapsulated tablet batches were tested in accordance with the current R&D specifications. Details of the clinical batches and batch analyses are presented in tables 3 and 4.

Table 3: Paroxetine CR 12.5, 25 and 37.5 mg Overencapsulated Tablets, Clinical Batches, Formula Codes GL, GM and GK, Respectively

Strength (mg)	Batch Number	Tablet batch	Site of Manufacture	Batch Size	Package Type
12.5	U00150	N00332	GSK Upper Providence	[ ]	Bulk
25	U00151	N00338	GSK Upper Providence		Bulk
37.5	N00352	N00345	GSK Harlow		Bulk

Table 4: Batch Analysis for Overencapsulated Paroxetine CR 12.5, 25 and 37.5 mg Tablets, Clinical Batches, Formula Codes GL, GM and GK, Respectively

Batch No.	U00150	U00151	N00352
Formula	GL	GM	GK
Batch No. of tablets	N00332	N00338	N00345
Strength	12.5 mg	25 mg	37.5 mg
Appearance	An off white powder and a round normal biconvex pale yellow coloured film coated tablet, contained in a [ ] [ ]	An off white powder and a round normal biconvex dark salmon coloured film coated tablet, contained in a [ ] [ ]	An off white powder and a round normal biconvex bilayer enteric coated tablet with bevelled edges. Contained in a [ ] [ ] One of the tablets layers is white and the other is pale yellow.
Identification	Confirmed	Confirmed	Confirmed
% Dissolution[1]			
2 hours 0.1M HCl	1	0	0
1 hour pH 7.5 buffer	12	5	5
2 hours pH 7.5 buffer	35	22	26
3 hours pH 7.5 buffer	61	50	53
4 hours pH 7.5 buffer	82	75	74
5 hours pH 7.5 buffer	99	91	92
6 hours pH 7.5 buffer	106	100	100

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-936/S-012

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-936\S-012

SmithKline Beecham Pharmco Puerto Rico, Inc. d/b/a
GlaxoSmithKline
Attention: P. Kaia Agarwal
Senior Director, U.S. Regulatory Affairs
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101

Dear Ms. Agarwal:

We acknowledge receipt of your November 17, 2003 submission containing final printed labeling in response to our October 16, 2003 letter approving your supplemental new drug application for Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets.

We have reviewed the labeling that you submitted in accordance with our October 16, 2003 letter and we find it acceptable.

If you have any questions, call Richardae C. Taylor, Pharm.D., Regulatory Health Project Manger, at (301) 594-5793.

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

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/s/

Russell Katz
1/21/04 08:24:57 AM

REGULATORY PROJECT MANAGER
LABELING REVIEW

Date: January 14, 2004
Application Number: NDA 20-936/S-012
Name of Drug: Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets
Sponsor: GlaxoSmithKline
Indication: Social Anxiety Disorder (SAD)

Material Reviewed:
Submission Date(s): November 17, 2003
Receipt Date(s): November 18, 2003

Background and Summary
The approval letter, dated October 16, 2003, for Paxil CR for the indication of SAD contained the agreed upon labeling text.

The final printed labeling (FPL) was submitted on November 17, 2003. A side-by-side labeling comparison of the November 17, 2003 FPL to the Division's October 16, 2003 AP labeling was performed.

Review
NDA 20-936/S-012
Date: January 17, 2004
CBE: No; FPL Post AP
Label Code No: PC:L7
Reviewed by Medical Officer: N/A

The FPL, submitted on November 17, 2003, contains only minor editorial and grammatical changes, in addition to the agreed upon labeling text, which are acceptable.

Conclusions
1. The FPL, submitted on November 17, 2003, contains only minor editorial and grammatical changes and is otherwise consistent with approved labeling contained within the October 16, 2003 approval letter.
2. An acknowledge and retain letter can issue for this submission.

Richardae Taylor, Pharm.D.
Regulatory Project Manager

Robbin Nighswander, R.Ph., M.S.
Chief, Project Management Staff

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/s/

Richardae Taylor
1/15/04 11:11:00 AM
CSO

Robbin Nighswander
1/15/04 05:43:23 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

CLINICAL INSPECTION SUMMARY

DATE: October 2, 2003

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

THROUGH: Khin Maung U, M.D., Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

FROM: Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspection

NDA: NDA 20-936/SE1-012

APPLICANT: GlaxoSmith Kline

DRUG: Paxil CR (paroxetine hydrochloride controlled release) Tablets

THERAPEUTIC CLASSIFICATION: Type S, Standard Review

INDICATION: Social Anxiety Disorder

CONSULTATION REQUEST DATE: March 6, 2003

ACTION GOAL DATE: October 20, 2003

I. BACKGROUND:

Paroxetine hydrochloride is a selective serotonin reuptake inhibitor, which is currently marketed under the brand name of Paxil®. Paxil® is approved in the U.S. for use in the treatment of major depressive disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder and generalized anxiety disorder. In this supplemental NDA, the sponsor has requested the use of Paxil CR (paroxetine controlled release) in the Treatment of Social Anxiety Disorder (also known as social phobia).

The NDA submission included the results from protocol #29060/790 entitled "A double-blind,

placebo-controlled, flexible dose study of paroxetine CR in the treatment of patients with social anxiety disorder." The study was conducted in all non-U.S. sites.

The study was a multicenter, randomized, double-blind, placebo-controlled, two-arm, flexible dose, parallel group study to assess the efficacy and safety of paroxetine CR versus placebo in subjects with a diagnosis of Social Anxiety Disorder. Subjects were age at least 18 years, outpatients with a diagnosis of Social Anxiety Disorder/Social Phobia according to the DSM-IV (300.23). Subjects who were eligible at the screening visit received placebo for a 1-week run-in period. Subjects who met all inclusion/exclusion criteria were randomized to either paroxetine CR (dose range 12.5 mg to 37.5 mg daily) or placebo for a 12-week, double-blind treatment period. The primary efficacy end points were:

1) change from baseline in Liebowitz Social Anxiety Scale (LSAS) total score at week 12;
2) the proportion of responders who scored 1 or 2 (very much improved or much improved) on the CGI Global Improvement item at week 12.

An inspection assignment was requested to the Division of International Operations in April 2003 for two non-US sites: Drs. Ahokas (site 012) and Behnke (site061) to review their conduct in protocol 790. These two investigators enrolled a large number of study subjects.

II. RESULTS (by site):

NAME	CITY	Country	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
Dr. Ahokas	Helsinki	Finland	04-16-2003	Pending*	Pending*
Dr. Behnke	Copenhagen	Denmark	04-16-2003	Pending*	Pending*

* findings based on communication with the FDA field investigators; EIR still pending

Dr. Ahokas

At this clinical site, 27 subjects were screened; 26 subjects were randomized and 24 subjects completed the study. Two subjects (790.012.38830 and 39042) from placebo group discontinued from the study due to lack of efficacy.

No Form FDA-483 was issued. Inspection revealed no discrepancies between source documents, CRFs and data listing provided in the NDA submission. All subjects who participated in the study signed the consent form. Overall, data appear acceptable.

Dr. Behnke

At this clinical site, 27 subjects were screened; 26 subjects were randomized to receive either Paxil CR or Placebo; 21 subjects completed the study. Five subjects discontinued from the study. Discontinuation reasons included adverse event (790.061.38971), non-compliance (38966), or other reasons (withdrew consent, gave wrong medication at visit 6).

An audit of records conducted revealed no major objectionable conditions or any data

discrepancies. All subjects signed the informed consent. Data appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As stated above, there was no major objectionable conditions noted at both sites. Overall, the data from these two sites appear acceptable for use in support of this NDA supplement.

Note: Should the EIR and exhibits from the audit of Drs. Ahokas and Behnke, when received, contain additional information that would significantly affect the classification or have an impact on the acceptability of the data, the review division will be informed accordingly.

Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

Khin Maung U, M.D, Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAIr= Deviation(s) form regulations, response requested. Data acceptable
OAI = Significant deviations for regulations. Data unreliable
Pending = Inspection completed but EIR still pending

cc:
NDA 20-936/SE1-012
HFD-45/Program Management Staff (electronic copy)
HFD-45/ Division File/Reading File
HFD-46/Khin
HFD-46/George GCPB1 Files

rd: NK: 10/2/03
O:\NK\CIS\NDA20936SE1012 PaxilCR SAD CIS.DOC

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/s/

Ni Aye Khin
10/2/03 01:46:41 PM
MEDICAL OFFICER

Khin U
10/2/03 03:32:08 PM
MEDICAL OFFICER

DSI CONSULT: Request for Clinical Inspections

Date: February 12, 2003

To: Ni Khin, M.D., GCPB Reviewer/HFD-46

Through: Martin H. Cohen, M.D., Acting Director, DSI, HFD-45
Russell Katz, M.D., Director, HFD-120

From: Anna Marie H. Weikel, Regulatory Project Manager, HFD-120

Subject: **Request for Clinical Inspections**
NDA 20-936/S-012
GlaxoSmithKline
Paxil CR (paroxetine hydrochloride) Controlled-release Tablets

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

This Supplement provides for the following new indication: the treatment of social anxiety disorder

Indication	Protocol #	Site (Name and Address)	Number of Subjects
Social anxiety disorder	12	Laakarikeskus Mehilainen Runeberginkatu 47 III krs 00260 Helsinki Finland	25
"	61	Falkoner Ale 112, 200 Fredieriksberg C Denmark	26
"	63	Slotsgade 65 C, 3400 Hillerod Denmark	22

Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.

International Inspections:

We have requested inspections because (please check appropriate statements):

____ There are insufficient domestic data

__X__ Only foreign data are submitted to support an application

____ Domestic and foreign data show conflicting results pertinent to decision-making

____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.

____ Other: SPECIFY

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **9/20/03**. We intend to issue an action letter on this application by (action goal date) **10/20/03**.

Should you require any additional information, please contact Anna Marie H. Weikel (301) 594-5535.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NOV 18 2003

Antti Ahokas, M.D.
Mehilainen Clinic
Runeberginkatu 47 A
Fin-00260
Helsinki, Finland

Dear Dr. Ahokas:

Between September 15 and 18, 2003, Ms. Iris C. MacInnes, representing the United States Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol #29060/790 entitled "A double-blind, placebo-controlled, flexible dose study of paroxetine CR in the treatment of patients with social anxiety disorder") of the investigational drug paroxetine controlled release (Paxil CR), performed for GlaxoSmithKline. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator MacInnes during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3003996216
Field Classification: NAI
Headquarters Classification:
__X _1)NAI
__ __2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

cc:
HFA-224
HFD-120 Doc.Rm. NDA 20-936/SE1-012
HFD-120 Review Div.Dir. Katz
HFD-120 Reviewer Alfaro
HFD-120 PM Homonnay-Weikel
HFD-46 c/r/s GCP File #11016
HFD-46 MO Khin
HFD-46 CSO Friend
HFR-SW150 DIB Thornburg
HFR-SW1540 BIMO Martinez
HFR-SW1575 Field Investigator MacInnes
HFC-134 Kadar
GCF-1 Seth Ray

r/d:NK(10/28/03)
reviewed:KMU(11/03)
f/t:sg(11/13/03)
O:\NK_Letters\Ahokas.nai.doc

Reviewer Note to Rev. Div. M.O.

- At this clinical site, 27 subjects were screened; 2 subjects were screen failures and 23 subjects completed the study. Two subjects (790.012.38830 and 39042) from placebo group discontinued from the study due to lack of efficacy.
- An audit of all subjects' records was conducted.
- Inspection revealed no discrepancies between source documents, CRFs and primary efficacy and adverse events data listing provided in the NDA submission. No serious adverse events were noted at the site.
- All subjects signed the informed consent.
- No Form FDA-483 was issued.
- Based on the information provided in the EIR, no major objectionable conditions noted.
- Overall, data appear acceptable.

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/s/

Joseph Salewski
11/24/03 10:02:44 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Kirsten Behnke, M.D.
Falkoneralle 112
2000 Frederiksberg C Denmark

NOV 18 2003

Dear Dr. Behnke:

Between September 22 and 25, 2003, Ms. Iris C. MacInnes, representing the United States Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol #29060/790 entitled "A double-blind, placebo-controlled, flexible dose study of paroxetine CR in the treatment of patients with social anxiety disorder") of the investigational drug paroxetine controlled release (Paxil CR), performed for GlaxoSmithKline. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator MacInnes during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3003996213
Field Classification: NAI
Headquarters Classification:
__X _1)NAI
__ __2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

cc:
HFA-224
HFD-120 Doc.Rm. NDA 20-936/SE1-012
HFD-120 Review Div.Dir. Katz
HFD-120 Reviewer Alfaro
HFD-120 PM Homonnay-Weikel
HFD-46 c/r/s GCP File #11015
HFD-46 MO Khin
HFD-46 CSO Friend
HFR-SW150 DIB Thornburg
HFR-SW1540 BIMO Martinez
HFR-SW1575 Field Investigator MacInnes
HFC-134 Kadar
GCF-1 Seth Ray

r/d:NK(10/28/03)
reviewed:KMU(11/11/03)
f/t:sg(11/13/03)
O:\NK_Letters\Behnke.nai.doc

Reviewer Note to Rev. Div. M.O.

- At this clinical site, 26 subjects were enrolled and 21 subjects completed the study. Five subjects discontinued from the study. Reason for discontinuation included adverse event, withdrawal of consent, non-compliance, randomization system (RAMOS) problem and dispense of wrong medication for one subject.
- An audit of all subjects' records was conducted.
- Inspection revealed no discrepancies between source documents, CRFs and primary efficacy and adverse events data listing provided in the NDA submission. No serious adverse events were noted. No underreporting of adverse events at the site.
- All subjects signed the informed consent.
- No Form FDA-483 was issued.
- Based on the information provided in the EIR, no major objectionable conditions noted.
- Overall, data appear acceptable.

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/s/

Joseph Salewski
11/24/03 11:21:22 AM

Homonnay Weikel, Anna M

From: Homonnay Weikel, Anna M
Sent: Wednesday, July 23, 2003 9:14 AM
To: 'Matt.Whitman-1@gsk.com'
Cc: Homonnay Weikel, Anna M
Subject: RE: FDA Information Request

Hi Matt,
Thanks alot; we needed those ASAP!

It turns out that we have some additional questions listed below:

1)In Table 45 of the study report, it is noted that 96 subjects in the Paxil CR group had AST assessments; only 63% of all completers in the Paxil CR group. Please provide an explanation as to why so few subjects completed laboratory assessments in this study (similar percentages were noted for most laboratory assessments).

2)Please provide a summary of the worldwide literature for Paxil CR or state where this information can be found in the submission.

3)In which countries has Paxil CR been approved or an application for approval pending? For each country, please state for which indication Paxil CR has been approved (or approval pending).

4)Table 12.21 lists concomitant medications taken during the study. Three subjects in the Paxil CR group received concomitant benzodiazepines (alprazolam, chlordiazepoxide, diazepam). Please provide details regarding the concomitant use of benzodiazepines for these subjects and provide study numbers for these subjects.

Regards,

Anna Marie

Anna Marie H. Weikel, R.Ph.
Divison of Neuropharmacological Drug Products
Office of Drug Evaluation I
FDA Center for Drug Evaluation and Research
Senior Regulatory Project Manager
(301) 594-5535

-----Original Message-----
From: Matt.Whitman-1@gsk.com [mailto:Matt.Whitman-1@gsk.com]
Sent: Wednesday, July 23, 2003 8:59 AM
To: HOMONNAYA@cder.fda.gov
Subject: RE: FDA Information Request

Homonnay Weikel, Anna M

From:	Homonnay Weikel, Anna M
Sent:	Thursday, July 17, 2003 11:06 AM
To:	'Matt.Whitman-1@gsk.com'
Cc:	Homonnay Weikel, Anna M
Subject:	re: FDA Information Request

Matt,
Some additional clarifications for NDA 20-936/S-012 attached are sought. Please provide a desk copy with your response.

Also, the response to the previous question from July 7th, restated below, is needed as soon as possible.

"Please provide the CRFs for the 12 subjects who discontinued the study due to "other" (Table 8 in the study report)."

I would appreciate it if you could acknowledge receipt of this E-mail and provide an estimated time for your response.

Thank You,

Anna Marie

Anna Marie H. Weikel, R.Ph.
Divison of Neuropharmacological Drug Products
Office of Drug Evaluation I
FDA Center for Drug Evaluation and Research
Senior Regulatory Project Manager
(301) 594-5535

FDA
ation Request 1

Homonnay Weikel, Anna M

From: Homonnay Weikel, Anna M
Sent: Monday, July 07, 2003 2:49 PM
To: 'Matt.Whitman-1@gsk.com'
Cc: Homonnay Weikel, Anna M
Subject: re: FDA Info Request for NDA 20-936/S-012 for Paxil CR

Matt:
The following information is requested:

Please provide the statistical analysis by gender (female vs. male) for both co-primary endpoints, specifically for week 12 OC and week 12 LOCF timepoints.

Table 12.21 lists concomitant medications taken during the study. This table lists 1 subject in the Paxil CR group who received concomitant paroxetine and 2 subjects in the placebo group who received concomitant paroxetine. Please provide details regarding the concomitant use of paroxetine for these 3 subjects (e.g. dose of paroxetine, number of days of concomitant use, etc.). Please provide the study numbers for these three subjects.

According to the NDA submission, as of November 1, 2002, marketing authorization applications for Paxil CR for the treatment of social anxiety disorder had not been submitted o any foreign country. Is this still correct as of July 2003?

Please provide the CRFs for the 12 subjects who discontinued the study due to "other" (Table 8 in the study report).

Table 13 in the study report lists the number of subjects with a psychiatric history other than social anxiety disorder. It is assumed that this table includes subjects with a current and past history of other Axis I disorders. Since the protocol allowed for enrollment of subjects with another Axis I disorder as long as it was not a primary diagnosis, please provide the numbers of subjects who had a current comorbid diagnosis other than social anxiety disorder.

Thanks Alot,
Anna Marie

Anna Marie H. Weikel, R.Ph.
Divison of Neuropharmacological Drug Products
Office of Drug Evaluation I
FDA Center for Drug Evaluation and Research
Senior Regulatory Project Manager
(301) 594-5535

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-936/S-012

FILING ISSUES IDENTIFIED

GlaxoSmithKline
U.S. Regulatory Affairs
Attention: Matthew Whitman
Associate Director, Regulatory Affairs
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101

Dear Mr. Whitman:

Please refer to your December 20, 2002, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Paxil CR (paroxetine hydrochloride) Controlled-release Tablets

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 20, 2003, in accordance with 21 CFR 314.101(a).

We also request that you submit the following information:

1. The efficacy tables (13.1, 13.5 and others) include OC data for weeks 1 through 12 and LOCF data for week 12 only. Please provide the LOCF analysis for weeks 1 through 12 for all of the primary and secondary efficacy endpoints.

If you should have any questions, please call Ms. Anna Marie H. Weikel, R.Ph., Senior Regulatory Affairs 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

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/s/

Russell Katz
3/13/03 10:11:47 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-936/S-012

GlaxoSmithKline
U.S. Regulatory Affairs
Attention: Matthew Whitman
Associate Director, Regulatory Affairs
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101

Dear Mr. Whitman:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Paxil CR Controlled-release Tablets

NDA Number: 20-936

Supplement number: S-012

Date of supplement: December 20, 2002

Date of receipt: December 20, 2002

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 20, 2003, in accordance with 21 CFR 314.101(a).

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

Sincerely,

{See appended electronic signature page}

Robbin Nighswander, R.Ph.
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Anna-Marie Homonnay
1/14/03 02:02:04 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 51,171

GlaxoSmithKline
Attention: Matthew Whitman
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-0989

Dear Mr. Whitman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Paxil CR™ (paroxetine hydrochloride) Controlled-release Tablets .

We also refer to your correspondence dated July 2, 2002, (serial # 0111), regarding a request for a pre-sNDA teleconference regarding your planned supplemental applications for the treatment of [ ] social anxiety disorder. The purpose of this letter is to provide responses to your list of specific questions that were provided in Attachment 1. Our responses are provided below.

1. *The [ ] SAD sNDAs will each be supported by a single clinical study report. In lieu of providing full Integrated Summaries of Efficacy and Safety, we propose to include supplementary sections/tables normally placed in an Integrated Summary of Safety or Efficacy (i.e., drug-drug interactions, subgroup analyses) in the clinical study report for each of these indications.*

   Comparisons of adverse events across approved indications (depression. panic disorder) for the controlled release formulation will be described in the Item 3 clinical summary section. Comparisons to the immediate release formulation safety profile for [ ] SAD will also be provided in the Item 3 clinical summary section of each supplement.

   Information from published literature and post-marketing spontaneous adverse event reporting will also be provided in the Item 3 clinical summary section of these supplements.

   Under these conditions, does the overall content of the applications fulfill FDA's expectations with regard to fileability of an application? Specifically, are these applications fileable and adequate without an Integrated Summary of Efficacy or Safety as long as those elements are included elsewhere within the applications?

FDA Response: We agree that there is no need for separate Integrated Summaries of Efficacy and Safety as long as those elements are included elsewhere within the applications. In the outlines provided, you appear to have addressed what is needed for filing, but the decision will be made based on what you actually submit.

Can the Agency also re-confirm the guidance provided in an August 14, 1996, letter to IND 23,280 (provided here in Attachment 2) in which it was recognized that one adequate and well-controlled trial could suffice for approval of a controlled release formulation of an already approved product?

Response: We agree that one adequate and well-controlled trial could suffice for approval of an indication for a controlled release formulation of a product that is already approved for that indication in an immediate release form.

2. *Although not presented here in detail, the organizational content for the Social Anxiety Disorder supplemental application will be identical in format and structure to that of the [ ] sNDA. Can the Division also confirm the acceptability of this structure and format for the Social Anxiety Disorder supplement?*

Response: The proposed structure and format for these supplements is acceptable.

3. *GSK plans to submit the archival copy of these applications in accordance with the Agency's Electronic Guidance? Are there any specific Division requirements in this regard, particularly with regards to the need for hardcopy printouts of any sections?*

Response: The Agency's electronic guidances, available on the CDER website, should be followed. Paper copies should also be provided of the clinical study reports.

Does the Division have any specific organizational requests in this regard?

Response: As stated above, the electronic guidances should be followed.

If you should have any questions, please call Ms. Anna Marie H. Weikel, R.Ph., Regulatory Affairs 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

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/s/

Russell Katz
8/29/02 09:45:47 AM