CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-936/S-011

Name:	Paxil CR Controlled-Release Tablets
Generic:	paroxetine hydrochloride
Sponsor:	GlaxoSmithKline
Approval Date:	October 28, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-936/S-011

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-936/S-011

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-936/S-011

GlaxoSmithKline
Attention: Matthew Whitman
Associate Director, Regulatory Affairs
2301 Renaissance Blvd.
Bldg. 510 (RN0210)
P.O. Box 61540
King of Prussia, PA 19406-2772

Dear Mr. Whitman:

Please refer to your supplemental new drug application dated June 26, 2003, received June 26, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets.

We acknowledge receipt of your submission dated July 8, 2003 and August 15, 2003. The July 8, 2003 submission constituted a complete response to our April 11, 2003 action letter.

This supplemental new drug application provides for the use of Paxil CR in the treatment of premenstrual dysphoric disorder (PMDD).

We have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 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-011." Approval of this submission by FDA is not required before the labeling is used.

Request for Promotional Materials: In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of Neuropharmacological Drug Products 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, MD 20857

and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Richardae Taylor, Pharm.D., Regulatory Project Manager, 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

Enclosure
- Package Insert

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
8/28/03 04:30:18 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-936/S-011

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-639/S-011

GlaxoSmithKline
Attention: Matthew Whitman
One Franklin Place
PO Box 7929
Philadelphia, PA 19101-7929

Dear Mr. Whitman:

Please refer to your supplemental new drug application dated June 26, 2002, received June 26, 2002, which was submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets.

We also acknowledge receipt of your submissions dated August 6, 2002, November 6, 2002, December 13, 2002, and February 12, 2003.

This supplemental new drug application provides for the use of Paxil CR in the treatment of premenstrual dysphoric disorder (PMDD), using a continuous (once daily) dosing regimen.

Supplement Approvable: Request for Revised Labeling (Draft Format). We have completed our review of this application as amended, and it is approvable. Before the application may be approved, however, you must submit draft labeling revised as indicated in the attached marked-up labeling. We have included bracketed comments in the text, which explain our changes to the clinical and pre-clinical sections of labeling.

Our most substantive change in your draft labeling relates to the choice of primary efficacy variable. We have based our assessment of the approvability of Paxil-CR® on the VAS-total score, which we believe is a more appropriate outcome measure to support a PMDD claim than the VAS-MOOD score.

We realize that you may have questions about our draft changes and points that you may wish to clarify and we are willing to meet with you via teleconference if you wish.

In addition to the changes we have indicated in the attached labeling, all other previous revisions to labeling, as reflected in the most recently approved package insert, must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that clearly shows all changes.

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

Chemistry, Manufacturing, and Controls (CMC): Request for Categorical Exclusion. We note your request for categorical exclusion from the environmental assessment requirements, as per 21 CFR 25.31(b). We have reviewed this request, and it has been found acceptable. A categorical exclusion will be approved at the time of approval of the supplemental NDA.

Request for Safety Update. When you respond to this letter, please include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, please incorporate new safety data as follows:
   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Please present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Pediatric Studies: Applicant's Request for Deferral; Status of Pediatric Rule. Your December 13, 2002 amendment to this supplemental application included a request for deferral of pediatric studies pending approval of Paxil CR for use in adult PMDD.

As you are aware, FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] has been challenged in court. On October 17, 2002, the court ruled that FDA did not have authority to issue the Pediatric Rule and has barred FDA from enforcing it.

The Department of Health and Human Services (DHHS) has decided not to pursue an appeal in the courts. However, DHHS intends to work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule.

In the meantime, it is important for you to know that although the Pediatric Rule as originally promulgated is no longer in force, we consider your request for a deferral to be reasonable, and we would therefore grant such a deferral at this time if the Rule remained in effect. We will revisit this issue at the time of our next action on this supplemental application.

It is also important for you to note that the pediatric exclusivity provisions of FDAMA, as reauthorized by the Best Pharmaceuticals for Children Act, are distinct from the Pediatric Rule, and thus are not affected by the court ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the

Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details.

Request for Promotional Materials (Draft Format). In addition, please submit three copies of the introductory promotional materials that you propose to use for this product in this indication. Submit all proposed materials in draft or mock-up form, not final print. Send 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, MD 20857

Request for Notification of Intent to Amend Application. Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Opportunity for Informal Meeting or Teleconference. Under 21 CFR 314.102(d), you may request an informal meeting or teleconference with this Division, to discuss what steps need to be taken before the application may be approved.

Potential for Misbranding. This product may be considered misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed for the proposed new indication before approval of this supplemental application.

If you have any questions, please call Doris J. Bates, Ph.D., Regulatory Project Manager, at (301) 594-2850.

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

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

Approvable Letter

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
4/11/03 02:40:16 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-936/S-011

LABELING

PRESCRIBING INFORMATION

PAXIL CR™

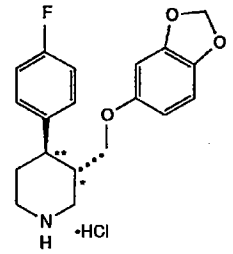
brand of

(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 is:



paroxetine hydrochloride

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

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 hydroxypropyl methylcellulose, polyvinylpyrrolidone, lactose monohydrate, magnesium stearate, colloidal silicon dioxide, glyceryl behenate, methacrylic acid copolymer type C, sodium lauryl sulfate, polysorbate 80, talc, triethyl citrate, and one 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 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 (paroxetine hydrochloride) tablets contain a degradable polymeric matrix (Geomatrix™, a trademark of Jago Pharma, Muttenz, Switzerland) 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 *Paxil CR* tablets 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 four 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 *Paxil CR* doses. 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 two 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 one 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 to 40 mg daily for the elderly and 20 to 50 mg daily for the nonelderly, some nonlinearity was observed in both populations, again reflecting a saturable metabolic pathway. In comparison to C_{min} values after 20 mg daily, values after 40 mg daily were only about 2 to 3 times greater than doubled.

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 two-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 18-65 years, and a second study included elderly patients, ranging in age from 60-88. 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 three 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 two of these three variables. Study 3 failed to consistently demonstrate a significant difference between *Paxil CR* and placebo on any of these variables.

For all three studies, the mean *Paxil CR* dose 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.

Premenstrual Dysphoric Disorder

The effectiveness of *Paxil CR* for the treatment of Premenstrual Dysphoric Disorder has been established in 2 placebo-controlled trials. Patients in these trials met DSM-IV criteria for Premenstrual Dysphoric Disorder (PMDD). 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 (paroxetine hydrochloride) 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).

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 five of the following nine symptoms during the same two 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). 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 (paroxetine hydrochloride) 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 four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

Long-term maintenance of efficacy 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). 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.

Premenstrual Dysphoric Disorder

Paxil CR (paroxetine hydrochloride) 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 (paroxetine hydrochloride) 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 1441 patients with major depressive disorder, panic 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 1441 patients who received *Paxil CR* in controlled clinical trials in major depressive disorder, panic disorder or PMDD, one 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 (paroxetine hydrochloride) 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 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 their daily dose by 12.5 mg/day to a dose of 25 mg/day for one 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% vs 1.3%), nausea (5.4% vs 2.7%), nervousness (2.4% vs 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% vs 0.3%).

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 than 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.

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

Use in Patients with Concomitant Illness: Clinical experience with 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 (paroxetine hydrochloride) tablets should not be chewed or crushed, and should be swallowed whole.

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 *Paxil CR* therapy does not affect their ability to engage in such activities.

Completing Course of Therapy: While patients may notice improvement with *Paxil CR* therapy 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 co-administered. 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.

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 q.d.) was dosed orally for 4 weeks, steady-state plasma concentrations of paroxetine were increased by approximately 50% during co-administration with oral cimetidine (300 mg t.i.d.) for the final week. Therefore, when these drugs are administered concurrently, dosage adjustment of *Paxil 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 q.d. for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 25% and 38%, respectively) compared to paroxetine administered alone. The effect of paroxetine on phenobarbital pharmacokinetics was not studied. Since paroxetine exhibits nonlinear pharmacokinetics, the results of this study may not address the case where the two drugs are both being chronically dosed. No initial *Paxil CR* dosage adjustment is considered necessary when co-administered with phenobarbital; any subsequent adjustment should be guided by clinical effect.

Phenytoin—When a single oral 30 mg dose of immediate-release paroxetine was administered at phenytoin steady state (300 mg q.d. for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 50% and 35%, respectively) compared to 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 q.d. for 14 days), phenytoin AUC was slightly reduced (12% on average) compared to phenytoin administered alone. Since both drugs exhibit nonlinear pharmacokinetics, the above studies may not address the case where the two drugs are both being chronically dosed. No initial dosage adjustments are considered necessary when *Paxil CR* is co-administered 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 one study, daily dosing of immediate-release paroxetine (20 mg q.d.) under steady-state conditions increased single-dose desipramine (100 mg) C_{max}, AUC, and $T_{½}$ by an average of approximately two-, five-, and three-fold, respectively. Concomitant use of *Paxil 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 (paroxetine hydrochloride) or the other drug.

Therefore, co-administration 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 co-administered (see CONTRAINDICATIONS and WARNINGS).

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

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

Tricyclic Antidepressants (TCAs): Caution is indicated in the co-administration 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 co-administered 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.

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

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

Theophylline: Reports of elevated theophylline levels associated with 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 a mg/m^2 basis. These studies have

revealed no evidence of teratogenic effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg/day or approximately one-sixth of the MRHD on a 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 (paroxetine hydrochloride) is administered to a nursing woman.

Pediatric Use

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

Geriatric Use

In worldwide premarketing 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 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 9 placebo-controlled clinical trials. Three of these studies were conducted in patients with major depressive disorder, three studies were done in patients with panic disorder, and three 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 (ages 60 to 88), 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 *Paxil CR* patients discontinued treatment due to an adverse event in a pool of two 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 *Paxil CR* patients 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 *Paxil CR* patients 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%

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 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)

Commonly Observed Adverse Events

Major Depressive Disorder

The most commonly observed adverse events associated with the use of *Paxil CR* in a pool of two trials (incidence of 5.0% or greater and incidence for *Paxil CR* at least twice that for placebo, derived from Table 1 below) 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).

Premenstrual Dysphoric Disorder

The most commonly observed adverse events associated with the use of *Paxil CR* (incidence of 5.0% or greater and incidence for *Paxil CR* at least twice that for placebo, derived from Table 4 below) 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 *Paxil CR*-treated patients, aged 18-65, who participated in two short-term (12-week) placebo-controlled trials in major depressive disorder in which patients were dosed in a range of 25 to 62.5 mg/day. Table 2 enumerates adverse events reported at an incidence of 5% or greater

among elderly *Paxil CR*-treated patients (ages 60-88) 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 to 50 mg/day. Table 3 enumerates adverse events reported at an incidence of 1% or greater among *Paxil CR*-treated patients (ages 19-72) who participated in short-term (10-week) placebo-controlled trials in panic disorder in which patients were dosed in a range of 12.5 to 75 mg/day. Table 4 enumerates adverse events that occurred at an incidence of 1% or more among *Paxil CR*-treated patients 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 which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Table 1. Treatment-Emergent Adverse Events Occurring In ≥1% of *Paxil CR* Patients 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 (paroxetine hydrochloride) 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 *Paxil CR* Patients 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 (paroxetine hydrochloride) 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 *Paxil CR* Patients in a Pool of Three 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		

Body System/Adverse Event	% Reporting Event	
	Paxil CR (n=444)	Placebo (n=445)
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		
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 *Paxil CR* reporting rate 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 Events Occurring in ≥1% of *Paxil CR* Patients in a Pool of Three 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%
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%

Body System/Adverse Event	% Reporting Event *Paxil CR* (n=681)	Placebo (n=349)
Cough Increased	1%	<1%
Skin and Appendages		
Sweating	7%	<1%
Urogenital System		
Female Genital Disorders[3]	8%	1%
Menorrhagia	1%	<1%
Vaginal Monoliasis	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, pruritis, 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 Three 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 two placebo-controlled trials in non-elderly patients with major depressive disorder, in the pool of three placebo-controlled trials in patients with panic disorder and in the pool of three placebo-controlled trials in female patients with PMDD are as follows:

	Major Depressive Disorder		**Panic Disorder**		**PMDD**	
	Paxil CR	**Placebo**	***Paxil CR***	**Placebo**	***Paxil CR***	**Placebo**
n (males)	**78**	**78**	**162**	**194**	**n/a**	**n/a**
Decreased libido	10%	5%	9%	6%	n/a	n/a
Ejaculatory disturbance	26%	1%	27%	3%	n/a	n/a
Impotence	5%	3%	10%	1%	n/a	n/a
n (females)	**134**	**133**	**282**	**251**	**681**	**349**
Decreased libido	4%	2%	8%	2%	12%	5%
Orgasmic disturbance	10%	<1%	7%	1%	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 (paroxetine hydrochloride), 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 two 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-vs.-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, three of 104 *Paxil CR* patients and none of 109 placebo patients experienced liver transaminase elevations of potential clinical concern.

Two of the *Paxil CR* patients 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 three studies of patients with panic disorder, four of 444 *Paxil CR* patients and none of 445 placebo patients experienced liver transaminase elevations of potential clinical concern. Elevations in all four 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* tablets 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 and PMDD, multiple doses of *Paxil CR* were administered to 1441 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 1441 patients exposed to Paxil CR (paroxetine hydrochloride) controlled-release who experienced an event of the type cited on at least one occasion while receiving *Paxil CR*. All reported events are included except those already listed in Tables 1, 2, 3, or 4 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 one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

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 chest pain, chills, face edema, fever, flu syndrome, malaise; rare were abscess, anaphylactoid reaction, 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 tests abnormal, melena, pancreatitis, rectal hemorrhage, toothache, ulcerative stomatitis; rare were glossitis, gum hyperplasia, hepatosplenomegaly, increased salivation, intestinal obstruction, peptic ulcer, stomach ulcer, throat tightness; also observed were aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, cholelithiasis, colitis, 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, hypochromic anemia, leukocytosis, leukopenia, lymphadenopathy, purpura; rare were eosinophilia, thrombocytopenia; also observed were anisocytosis, basophilia, bleeding time increased, lymphedema, lymphocytosis, lymphopenia, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia.

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

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

Nervous System: Frequent were depression; infrequent were amnesia, convulsion, depersonalization, dystonia, emotional lability, hallucinations, hyperkinesia, hypesthesia, hypokinesia, incoordination, libido increased, neuralgia, neuropathy, nystagmus, paralysis, vertigo; rare were ataxia, diplopia, paranoid reaction, torticollis, withdrawal syndrome; also observed were abnormal gait, akathisis, akinesia, aphasia, choreoathetosis, circumoral paresthesia, delirium, delusions, dysarthria, dyskinesia, euphoria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hostility, 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 abnormality of accommodation, 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 enlargement*, breast pain*, breast neoplasm*, cystitis, dysuria, prostatitis*, pregnancy and puerperal disorders*, urinary retention, uterine fibroids enlarged*; rare were female lactation, hematuria, kidney calculus, nephritis, nocturia, salpingitis, urinary incontinence; 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-Schőnlein purpura). There has been a case report of an elevated phenytoin level after 4 weeks of immediate-release paroxetine and phenytoin co-administration. 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 (paroxetine hydrochloride) 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 *Paxil CR* misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE

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

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

Overdosage Management: Treatment should consist of those general measures employed in the management of overdosage with any 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 Drugs Metabolized by Cytochrome $P_{450}IID_6$ under PRECAUTIONS).

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

DOSAGE AND ADMINISTRATION

Major Depressive Disorder

Usual Initial Dosage: Paxil CR (paroxetine hydrochloride) 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 the *Paxil CR* tablet 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 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 the *Paxil CR* tablet 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.

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 the *Paxil CR* tablet 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, 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 *Paxil CR* therapy. 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 100's (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].

DATE OF ISSUANCE: MONTH, YEAR

GlaxoSmithKline
Research Triangle Park, NC 27709

PC:LX

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-936/S-011

MEDICAL REVIEW(S)

REVIEW AND EVALUATION OF CLINICAL DATA

NDA:	20-936 SE1-011
Sponsor:	GlaxoSmithKline
Drug	
Established Name:	Paxil CR™
Chemical Name:	Paroxetine hydrochloride, Controlled Release Tablets
Code Name:	No code name provided on Form FDA 356h
Formulation:	12.5 mg and 25 mg Paroxetine CR tablets (within a [ ] capsule) and placebo [ ] capsules.
Indication:	Premenstrual Dysphoric Disorder
Dates of Submission:	June 26, 2002
Materials Reviewed:	Supplemental NDA (refer to Section V.A. for details)
Clinical Reviewer:	Karen L. Brugge, M.D.
Review Completion Date:	12/13/02

EXECUTIVE SUMMARY

Purpose of this review: This review and summary are to assist the Team Leader and Director of the Division of Neuropharmacological Drug Products in the regulatory processing of the supplemental NDA 20-936 SE1-011. The summary provides a brief overview of this Clinical review.

Background and Overview of Clinical Studies. Paxil CR™ (PaxCR) is a controlled release table formulation of paroxetine hydrochloride and is a selective serotonin reuptake inhibitor (SSRI). This drug is approved for Major Depressive disorder and Panic Disorder. The sponsor is now seeking approval for a new indication of Premenstrual Dysphoric Disorder (PMDD). The submission describes three Phase III trials conducted on patients with PMDD (Studies 677, 688 and 689). These trials were virtually identical in study design. Each study is a multicenter, placebo controlled, double-blind trial that employs a fixed-dose parallel group design. Subjects (Ss) were screened over at least 2 consecutive menstrual (Reference) cycles and received single-blind placebo over the last Reference cycle. Eligible subjects (Ss) were randomized (1:1:1) to placebo, 12.5 mg or 25 mg of PaxCR groups. Double-blind treatment was administered daily (orally) over a period of 3 menstrual cycles. Efficacy assessments included a daily self-rating using a 100 mm visual analogue scale (VAS) to rate the severity of each of 11 symptoms (Ss kept daily diaries with 11 VAS scales for each day). A number of secondary efficacy assessments were conducted at study visits scheduled after the end of each menstrual cycle in the study.

Study Populations. Approximately 100 to 120 Ss of the Intent-to-Treat (ITT) population were in each treatment group of each study (N=1030 of the ITT population). The ITT population was defined as randomized Ss who had at least one dose of double-blind treatment and at least one post-baseline assessment. To be eligible for randomization, Ss had to meet DSM-IV criteria for PMDD, had to be regularly menstruating and had to be between 18 to 45 or 46 years old. Ss also had to meet specified cut-off criteria on rating scores assessing the severity of PMDD symptoms during the luteal phase (LP) and the follicular (FP) phase of two consecutive menstrual cycles (Reference Cycles). Other eligibility criteria were employed. Treatment groups were generally similar on various demographic features and 65 to 79% of Ss in each group completed the study. The mean exposure of Ss to their assigned study drug in each treatment group of the studies, combined, was approximately 66 patient-years. The majority of Ss had at least 61 days of treatment (74% to 84%/group in the studies combined).

Primary Efficacy and Safety Results. The primary efficacy variable was the mean change from baseline to treatment endpoint (treatment cycle 3) on the mean LP VAS Mood score. The mean LP VAS Mood score was calculated by using daily VAS scores over the last 5 days of the LP for each of the following symptoms: irritability, tension, depression and mood swings. Studies 677 and 689 revealed highly significant ($p<0.01$ to 0.001) treatment group effects on the mean change of the VAS Mood score. Greater improvement was observed in each PaxCR group (high and low dose groups) compared to placebo. Less significant treatment group effects ($p<0.02$) were revealed in trial 688, but only for the high dose group of PaxCR. The low dose group in Study 688 only showed a numerical trend in favor of PaxCR over placebo. Secondary variables generally revealed similar results.

The VAS Mood score only rates a subset of PMDD symptoms, whereas the VAS total score is the total score of VAS ratings for each of all 11 symptoms that are similar to the 11 symptoms listed in the DSM-IV. Therefore, the VAS-total more accurately reflects the full symptom profile and criteria required for a DSM-IV diagnosis of PMDD. Drugs previously

approved for the PMDD indication were based on results of trials using either the VAS-total score or a comparable rating scale that rates the 11 symptoms, similar to those listed in the DSM-IV. Hence, the sponsor, upon request reanalyzed results on the LP VAS-total score. This reanalysis showed numerical differences between the PaxCR and placebo treatment groups in each study, similar to results on the LP VAS Mood score. Currently, the sponsor is determining if a significant group effect can be revealed in favor of PaxCR over placebo using statistical methods similar to those employed for the VAS Mood score (raw datasets on VAS total scores were also requested).

The safety profile of PaxCR, as revealed by the integrated safety results of the three PMDD trials, combined, is generally similar to that observed in other patient populations, as described in current labeling. A few exceptions are described in Section VII of the review. One exception is regarding results on follow-up (post-treatment) phase adverse events (AEs). Current PaxCR labeling does not described AEs observed after treatment cessation in clinical trials of other patient populations (these trials employed a flexible dose design). However AEs reported during the taper phase in trials using the immediate release formulation are described. In the present submission follow-up phase AEs were reported within at least 14 days after abrupt cessation of treatment in the PMDD trials (fixed dose design). The most commonly reported follow-up phase AEs were as follows (incidence rates in the high-dose PaxCR group, the low-dose PaxCR group and the placebo group are provided, respectively): dizziness (9%, 7% and 0%, respectively), nausea (3%, 1% and 1%), and nervousness (2%, 3%, and 0%).

Overall Conclusion. From a Clinical perspective, the LP VAS-Mood Score is not an adequate primary efficacy variable for studies used to support an efficacy claim. However, the LP VAS-total score is considered to be an acceptable primary efficacy variable, as previously described. Consequently, from a Clinical perspective, it is not recommended that this supplemental NDA be given an approvable status on the basis of results on the LP VAS-Mood score. However, from a Clinical perspective, an approvable status is recommended, if the following criteria are met:

- The sponsor reveals significantly greater improvement on the LP VAS total score (from baseline to Treatment Cycle 3 endpoint) in at least the high dose PaxCR group compared to placebo in at least two trials of the three trials
- If the sponsor reveals positive results, as above, then it is recommended that these results be confirmed by the Biometric consultant.
- The consultative review from the Division of Scientific Investigation (which is pending at this time) should also reveal no remarkable findings that would impact on the interpretation of the sponsor's results.

Based on the safety results in the submission, together with previous experience in other patient populations, PaxCR is adequately safe for use in PMDD patients as proposed by the sponsor. Additional conclusions and recommendations are provided in the review.

I. Introduction and Background.

This review is to assist the Team Leader and Director of the Division of Neuropharmacological Drug Products in the regulatory processing of NDA 21-323.

A. Indication and Proposed Direction of Use

Paxil CR™ (PaxCR) is a controlled release tablet formulation of paroxetine hydrochloride and is a selective serotonin reuptake inhibitor (SSRI).

The proposed indication of PaxCR is for the treatment of Premenstrual Dysphoric disorder (PMDD). The proposed direction of use for this indication is a recommended starting dose of 12.5 mg a day of PaxCR administered orally. Some patients who do not respond to this starting dose "may benefit" from an increase in the daily dose to 25 mg, as proposed. At least a one-week interval should occur before increasing the dose. Other sections of approved labeling indicate no food effect with PaxCR.

The following summarizes recommended treatment regimens for approved indications that are described in currently approved labeling for PaxCR:

- Major Depressive disorder (MDD): a daily dose of 25 mg but nonresponders may benefit from an increase in the dose. Daily dose increments of 12.5 mg at intervals of at least one week is recommended with the maximum daily dose not to exceed 62.5 mg.
- Panic Disorder: a starting daily dose of 12.5 mg is recommended with incremental dose increases similar to those for MDD, up to maximum dose of 75 mg/day.

B. State of Armamentarium for Indication

Classes of pharmacological drug products or specific drug products (generic names) currently approved for treatment of PMDD include the following:

- Other SSRIs. Fluoxetine (Sarafem®) and sertraline hydrochloride (Zoloft®) for continuous (daily dosing) and luteal phase (daily dosing during the luteal phase, as specified) treatment regimens.

C. Administrative History

NDA 20,936 was approved for the treatment of Major Depressive disorder (the current DMS-IV diagnosis) with PaxCR on February 16, 1999. Studies were conducted under IND 51,171. NDA 20-982 was then approved for Panic disorder on February 12, 2002. This NDA was administratively incorporated into NDA 20-936 as a supplement to the NDA (supplement no. 008 on January 25, 2002). This section does not describe or address administrative matters pertinent to the class of SSRIs.

D. Related Reviews

Supplemental NDA 18-936 (S067) and 19-839 (S039) are related NDAs for the PMDD indication. NDA 18-936 was approved for Sarafem™ (fluoxetine) given as a continuous dosing regimen for the PMDD indication. The supplemental application (S067) was for a luteal phase dosing regimen and was approved on June 12, 2002. sNDA 19-839 S039 was approved on 5/16/02 for both intermittent and continuous dosing regimens of Zoloft™ (sertraline) for the PMDD indication.

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

This sNDA does not contain any new preclinical, chemistry or biopharmaceutical data.

III. Human Pharmacokinetics and Pharmacodynamics

This submission does not contain new pharmacokinetic or pharmacodynamic information. For the purposes of this review the following outlines pharmacokinetic properties, as described in currently approved labeling for PaxCR:

- Tmax = 6-10 hours
- T ½ = 15-20 hours
- Steady state is achieved by two weeks with a daily dose of 25 mg
- Accumulation occurs with multiple dosing and enzymes are highly saturable
- Metabolism is primarily oxidation, conjugation and methylation showing no more than 1/50th SSRI activity compared to the parent compound.
- Metabolism is primarily via CYP2D6

IV. Description of Clinical Data and Sources

A. Overall Data: Materials from NDA/IND

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

Documents Utilized in Clinical Review

DATE	DESCRIPTION
March 23, 2001	• sNDA 20-936 SE1-01, electronic submission: Cover letter, FDA Form 356h, Items 2, 3, 4, 8, 11, 12, 13, 14, 16, 18, 19, Case Report Forms (Files for each Study, 677, 689, 699, and ongoing studies 711 and 717). Case Report Tabulations were provided as SAS Transport files. • BM submissions: dated 8/6/02 (response to questions emailed to the sponsor dated 7/15/02), an 11/6/02 submission in response to questions e-mailed on 9/30/02

B. Tables Listing the Clinical Trials

All three studies in this sNDA are identically designed as multi-centered, randomized, double-blind, placebo-controlled, fixed-dose parallel group trials.

Table IV.B.1. Clinical Studies Reviewed from this Submission

Protocol No	Study Design	Treatment Groups	N (Completers) per Treatment group (% of ITT Efficacy Pop.*)	N (ITT Pop.) * per Treatment group
Study 688 Fixed Dose 3 Treatment Cycle Trial	Multicenter, Double blind, Randomized, Fixed dose, Parallel group 46 sites (in Germany, Netherlands, Sweden, Ireland, Norway, Finland, U.K and South African)**	12.5 mg/day PaxCR group 25 mg/day oral PaxCR group Placebo group	97 (79%) 87 (74%) 90 (76%) **Total: 274**	123 117 118 **Total: 358**
Study 677 Fixed Dose 3 Treatment Cycle Trial	Multicenter, Double blind, Randomized, Fixed dose, Parallel group 43*** US sites	12.5 mg/day PaxCR group 25 mg/day oral PaxCR group Placebo group	70 (74%) 72 (65%) 79 (74%) **Total: 221**	95 111 107 **Total: 313**
Study 689 Fixed Dose 3 Treatment Cycle Trial	Multicenter, Double blind, Randomized, Fixed dose, Parallel group 47 sites US and Canada	12.5 mg/day PaxCR group 25 mg/day oral PaxCR group Placebo group	89 (77%) 82 (68%) 96 (77%) **Total: 267**	115 120 124 **Total: 359**

*ITT population: randomized subjects having at least one dose of double blind study drug and at least one post-baseline assessment.
**Refer to Section V.D. (Evaluation of Financial Disclosure) regarding a change in investigators at sites 063, 064 and 065 (as described in a 8/6/02 response submission to inquiries about investigator listings and financial disclosure information and listings).
***3 additional sites recruited, but did not randomize Ss.

C. Post-Marketing Experience
To date (5/3/02) the sponsor has not submitted any marketing authorization applications for Paxil CR™ for the PMDD indication in any foreign country. Paroxetine hydrochloride has not been withdrawn from the market in any country for safety or efficacy related reasons. The sponsor provides information on post-marketing experience of spontaneous reports for paroxetine for the PMDD indication or for PMDD as a concomitant disorder. These reports are described under a safety section of this review (Section VII. M).

D. Literature Review
The sponsor provided search methods for conducting a literature review in a 8/6/02 response submission. The sponsor conducted the literature search on April 8, 2002 using the terms and databases itemized below.
Databases:
- Embase (1974- present)
- Biosis (1934- present)
- SciSearch (1966- present)
- Medline (1966- present)

Terms:
- Paroxetine
- Paxil
- Premenstrual
- Premenstrual disorder
- PMDD
- Late Luteal Phase Dysphoric disorder

The results of this search are described in a later section of this review (see Section VII).

V. Clinical Review Methods
A. Materials Reviewed.
Refer to Section IV, above, regarding materials utilized for this review and for a summary of the clinical trials described in the submission.

B. Adequacy of Clinical Experience.
The sponsor provides data from three Phase III trials (Studies 677, 688 and 689) involving 1030 subjects (Ss) in the Intent-to-Treat (ITT) population (those who received at least one dose of double-blinded study drug and at least one post-baseline assessment). A total of 681 of the 1030 ITT Ss received at least one daily dose of either 12.5 mg or 25 mg of PaxCR. Refer to a summary table of these trials and the samples sizes of various study populations in the previous section (Section IV.B.). Additional Ss were included in 2 ongoing trials (Trials 711 and 717). Finally, PaxCR is currently on the market for treatment of Major Depressive disorder and Panic disorder (also refer to Section IVC for other post-marketing experience). Given this experience with PaxCR together with that of three Phase III trials (Studies 677, 688 and 689), the data described in the submission are adequate to review.

C. Data Quality and Completeness

This section describes various comparisons made between listings, tables, Case Report Forms (CRFs), and/or narratives. The results of these comparisons are described in more detail below, but generally appear to show adequate accuracy, consistency and content of information. On the basis of these observations, the quality and completeness of the data described in the submission appears to be adequate.

Each item below describes various comparisons made of listings, CRFs and narratives in the submission.

- Tables 18 and 19 on pages 73 and 74 of the Integrated Summary of Safety (ISS) section (listings of serious adverse events in completed trials) were compared to the narratives on the following items (age, "relative to onset," preferred term and S numbers). Only minor discrepancies were found for only a few Ss on age (i.e. narrative and Tables differed by one year) or on days "relative to onset" (differed by approximately one day). These differences may simply reflect slight differences in methods for determining these values and are not considered of a magnitude to be clinically significant or relevant. The sponsor also noted some minor discrepancies, as well (refer to footnotes of the tables) that were adequately described.
- Compared the "Index of Patient CRFs..." (in the CRF folder) to each of the following tables (tables and CRF Index were found to be consistent):
  - Listing of Ss with Serious Adverse Events (SAEs) in Tables 18 and 19 in the ISS
  - Listing of Ss who were adverse dropouts in Table 53 of the Study Report for Study 677 (page 167).
- Compared CRFs[1] to narratives on the following arbitrarily selected Ss (it is noted that actual values of laboratory and other safety parameters could not be found in the electronic CRFs of the below Ss, but the submission included dataset folders for safety parameters as SAS transport files):
  - 677.016.13183
  - 677.013.12946
  - 689.120.16705

  It is noted that the information compared between the CRFs and narratives of the above Ss were generally consistent with a few exceptions (such as regarding concurrent medications, in which the narrative did not mention multivitamins or an allergy medication for a given S).

D. Evaluation of Financial Disclosure

Several investigators are listed as being no longer with the company (or with the site) or as being unable to contact. However, the majority were contacted and had no disclosable financial arrangements. The following paragraphs describe investigators with financial arrangements/interests or provide clarification and additional information requested from the sponsor. This information does not appear to impact on the final interpretation of study results and recommendations made in this review regarding proposed labeling. This conclusion is based in part, on the following reasons (either or a combination of these reasons apply to a given study site/investigator). One reason was that several sites only involved a few subjects.

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[1] Comparisons between these arbitrarily selected CRFs and narratives were on the following somewhat arbitrarily selected items: age, gender, ethnicity, concurrent medications, the listing and time-course (stop and start dates) of adverse events resulting in the action of "Drug Stopped," start and stop date of study drug treatment.

Problems existed at some study sites in which the chance of having a failed rather than a positive study would appear to be more likely (Sites 63, 64, 65 in Study 688 had changed hands involving multiple investigators at different phases). The studies were designed to minimize potential bias (e.g. double-blind, randomized, and others).

Two investigators had financial arrangements or interests. Dr. [ ] received funds of up to $31,504 ([ ]) and Dr. [ ] spouse is employed by the sponsor. Both investigators were involved with Study [ ], while the former investigator was also involved in two ongoing trials ([ ] and [ ]). Dr. [ ] had ✓% (✓ Ss) of randomized Ss in each treatment group of the ITT population for Study [ ] (study site [ ]). The sponsor later clarified that Dr. [ ] was a sub-investigator rather than a principal investigator at site [ ](as provided upon request in a 11/6/02 response submission). Only [ ] randomized Ss ([ ]% of the ITT population) were at site [ ] (as shown in Table 12.10 in the Study [ ] Report section of the SE1-011 submission). All ✓ of these randomized Ss completed the trial.

The sponsor submitted a response submission dated 8/6/02 to inquiries pertaining to financial information. Clarification was requested regarding differences between investigator listings in the Financial Information and listings in other sections (Section 8.A.1 and Study Reports, Section 8.D.2). Three study sites for Study 688 had changed hands either due to economical reasons, bankruptcy or were taken over by another company. These changes resulted in the involvement of multiple investigators during different phases of the study. Financial information from some of the investigators at these sites were not provided in the original submission, but one investigator was successfully contacted upon request for the information and signed the Form 3455 (as provided in the 8/6/02 response submission). Financial information from others involved with the three sites (63, 64 and 65) was also requested and provided in a 11/6/02 response submission (the sponsor was unable to contact 2 out of 13 investigators and the remaining 11 investigators were listed as having no disclosable information). The total number of Ss at for the 3 sites, combined, consisted of 4 to 5% of ITT Ss in any given treatment group in Study 688.

VI. Integrated Review of Efficacy

A. Review of Studies for Which Efficacy Claims Are Made

The sponsor proposes that PaxCR is indicated for PMDD based on results of three pivotal Phase III trials, Studies 677, 688 and 689 in 18 to 46 year old outpatients with PMDD. One study (Study 677) was conducted in the US. The other studies were conducted in North America (including the US) or in primarily European countries. These three trials are identical in study design employing a multi-center, double-blind, randomized placebo controlled, fixed dose parallel group design. Double-blind treatment involved continuous daily oral doses of placebo, 12.5 mg PaxCR or 25 mg PaxCR. The treatment period was over three consecutive menstrual cycles referred to as Treatment Cycles. Each treatment group in each study had approximately 100 to 120 Ss in the ITT population.

Efficacy assessments included a daily self-rating 100 mm visual analogue scale (VAS) employed for each of 11 symptoms (Ss kept daily diaries). These 11 symptoms are similar to the 11 PMDD symptoms specified in the DSM-IV (listed under Criterion A for PMDD). Other efficacy measures were conducted at study visits scheduled after the end of each menstrual cycle in the study. These additional assessments included the Premenstrual Tension Scale Observer Rated (PMTS-O), as well as other clinician/observer rating scales intended for detecting changes

in global functional of clinical status. Several patient self-rating scales were also completed at the study visits.

The primary efficacy variable was the mean change from baseline to treatment endpoint (treatment cycle 3) on the mean luteal phase (LP) VAS Mood score. The mean LP VAS Mood score was calculated by using daily VAS scores over the last 5 days of the LP for each of the following symptoms: irritability, tension, depression and mood swings. Efficacy results are described in more detail below. In summary the sponsor's results revealed highly significant ($p<0.01$ to 0.001) treatment group effects in each PaxCR group (high and low dose groups) compared to placebo in two of the trials (677 and 689) on the VAS Mood score. Less significant treatment group effects ($p<0.02$) were revealed in trial 688, but only for the high dose group of PaxCR. The low dose group in Study 688 only showed a numerical trend in favor of PaxCR over placebo. Generally similar results were revealed on secondary variables.

The VAS Mood score only rates a subset of PMDD symptoms, whereas the VAS total score involves rating 11 symptoms corresponding to the 11 symptoms listed in the DSM-IV. Therefore, an analysis of the mean change from baseline to treatment endpoint on the VAS total score was conducted by the sponsor that appears to show numerical treatment group differences similar to those observed with the VAS Mood score for each study. Statistical analysis of results on the VAS total score is underway at the time of this writing, with confirmation by Biometrics still pending (the sponsor will be providing raw datasets). Section VII of this review describes the integrated safety results of these studies, as well as some safety observations in ongoing trials (Studies 711 and 717).

B. Studies 677, 688 and 689, each entitled "A Double-blind, Placebo-Controlled, 3-Arm Fixed Dose Study of Paroxetine CR Continuous Treatment (12.5 mg and 25 mg/day) for Premenstrual Dysphoric Disorder

1. Investigators and Sites

See Tables VI.B.1-3 in the appendix for a listing of investigative centers for the three PMMD trials, Studies 677, 688 and 689, respectively.

2. Objectives

The primary objective of each study was to compare the efficacy of continuous daily doses of placebo treatment to that of PaxCR (12.5 mg/day or 25 mg/day) in patients with PMDD. The secondary objective was to assess the safety of PaxCR treatment in this patient population.

3. Study Population

Ss were 18-45 year old (except that Study 688 included 46 year old patients) generally healthy outpatients with PMDD (DSM-IV). Ss were required to have regular menstrual cycles (a 22-35 day cycle) and to meet the following key eligibility criteria (a selected listing):

- A Montgomery Asberg Depression Rating Scale (MADRS) score of ≤ 10 in the follicular phase (FP) of the menstrual cycle at the initial screening visit (Visit 1)
- Meet DSM-IV Criteria A-C at screening and Criterion D (confirmation of meeting Criteria A-C) over two consecutive menstrual cycles (on Visits 2-3).
- Have PMDD for at least 9 out of 12 menstrual cycles in the past year
- A Clinical Global Impression (CGI)-Severity of Illness score of ≥ 3 at the baseline visit that preceded the double-blind treatment phase of the trial (Visit 3)
- During each of two consecutive menstrual cycles (referred to as Reference Cycles) Ss were also required to meet specified criteria (at Visits 2-3). These criteria were based on LP and

FP VAS self-ratings on each of 4 "core symptoms" (irritability, depressed mood, tension or affective lability). These "core symptoms" are similar to the first 4 symptoms of the 11 total symptoms listed under Criterion A for PMDD in the DSM-IV. One of the DSM-IV criteria for the diagnosis of PMDD is that patients must have at least one of these 4 symptoms as part of their symptom profile. The VAS rating score criteria employed during each of the two Reference Cycles (at Visits 2-3) were as follows:

- A mean LP VAS score of at least a 200% higher (worse) on one of the four "core symptoms" or at least 100% higher on two or more "core symptoms" than the mean FP VAS score:

  % worsening = 100 x (mean LP score- mean FP score)/ mean FP score

  The "core symptoms" that met this criterion for first Reference Cycle did not have to be the same "core symptoms" that qualified for the second Reference Cycle.
- For each of the above qualifying VAS "core symptom" item, Ss were required to have the following cut-off scores:
  - A mean VAS FP score $\leq$ 20 mm
  - A mean VAS LP score$\geq$ 40 mm
- Ss could not have any other Axis I disorder (except for specific phobias) over the 6 months prior to study entry.
- The use of any oral or systemic hormonal method of contraception was prohibited. The submission describes other prohibited medications (prescription, over-the-counter) and supplements.

Definitions for LP and FP are provided in the next subsection. This subsection also indicates which LP and FP days were used for calculating LP and FP VAS scores for determining eligibility and efficacy. A complete listing of eligibility criteria was provided in the submission.

Table IV.B.1 (in section IV B above) shows the samples sizes of study populations. Subsection 7 (below) provides a further breakdown and disposition of Ss, as well as a description of the demographic features of the study populations.

4. Study Design

Each study employed a randomized, double blind, placebo controlled, multi-center, 2-arm, fixed dose, parallel group design. Ss underwent a prescreening (advertising) contact by telephone, which was followed by a screening visit at the study site (Visit 1). Ss who met initial eligibility criteria at this initial visit underwent screening over at least 2 consecutive menstrual cycles referred to as Reference Cycles 1 and 2 (Visits 2-3). Ss meeting eligibility criteria for each of two consecutive menstrual cycles (as previously specified) entered the double-blind treatment phase of the study. If a S failed to meet eligibility criteria upon completion of their first Reference Cycle, then the investigator had the option of having the S undergo an additional Reference Cycle (Reference Cycle 1a). If the S met eligibility criteria upon completion of Reference Cycle 1 a (Visit 2a), then they could proceed to Reference Cycle 2.

A single-blind treatment phase was also employed in each study. This lead-in phase occurred during the second or last reference cycle (Reference Cycle 2) during which Ss received a daily oral dose of single-blind placebo (one capsule daily). The lead-in phase was followed by randomization of eligible Ss to one of the 3 double-blind treatment groups (1:1:1):

- 12.5 mg/day PaxCR (Supro B capsule formulation)
- 50 mg/day Pax CR
- Placebo.

Double-blind treatment was administered over 3 menstrual cycles referred to as Treatment Cycles. Ss received one capsule of assigned study drug to be taken orally each morning during each treatment phase of the study (the single-blind placebo and double-blind treatment phases).

After completing the double-blind treatment phase, Ss had the option to enter an extension study (Study 711, which is ongoing). Ss who did not participate in Study 711 underwent a follow-up visit (14 days after the double-blind treatment phase). A second follow-up visit (at 28 days post-double-blind treatment) was employed for Ss with adverse events or unresolved laboratory values.

See Table VI.B.4 in the appendix for the study schedule of visits and assessments. Ss were instructed to complete daily VAS ratings (for 11 symptom items) before bedtime starting on the "first day of continuous menses/bleeding (not spotting)" beginning on Day 1 of Reference Cycle 1.

Operationally Defined Terms. The following summarizes operationally defined terms employed in each study:

- **Day 1 of a Menstrual Cycle:** the onset of continuous menses (not spotting).
- **Luteal Phase (LP):** the last 14 days of a menstrual cycle prior to the onset of menses (Day 1) of the next cycle. Calculations for eligibility and for efficacy were based on a mean LP VAS symptom score using the daily scores from the last 5 days of the LP (refer to subsection 6 below for details on statistical methods).
- **Follicular Phase (FP):** the period between Day 1 and the onset of the LP of the cycle. Calculations for eligibility and for efficacy were based on a mean FP VAS symptom score using daily scores from Days 6-10 of the cycle, as described elsewhere.

5. Assessments Employed

Refer to Table VI.B.4 in the appendix for the study flow chart regarding efficacy, safety and screening assessments (as provided by the sponsor).

Efficacy Assessments

The MADRS was only conducted at screening. Primary and secondary efficacy measures are listed below (refer to Table VI.B.4 for the assessment schedule) followed by a brief discussion:

- **Primary Efficacy Assessments:**
  - VAS-Mood score. This score is the mean of the VAS scores for each of the four "core symptoms" (depressed mood, tension, affective lability and irritability).
- **Secondary Efficacy Assessments:**
  - Individual VAS assessments for each of the 11 symptoms, as described below.
  - Premenstrual Tension Scale Observer Rated (PMTS-O)
  - Clinical Global Impressions Scale for Improvement (CGI-I) and for Severity (CGI-S)
  - Patient Global Evaluation (PGE)
  - Sheehan Disability Scale (SDS)
  - Patient Evaluation of Study Medication (PESM)
  - Other assessments, as described in the submission.

VAS rating scales. Ss conducted daily self-ratings using 100 mm VAS scales provided (in diaries) to each S at each study visit. A total of 11 VAS scales were completed daily in which Ss rated 11 symptoms on the basis of severity (ranging from "not at all" to "extreme symptoms").

These symptoms are the following, and are similar to those listed under Criterion A of the DSM-IV for PMDD:

- Four "core" symptoms (depressed mood, tension, affective lability, and irritability). The mean VAS rating for these four "core" symptoms score was the primary efficacy variable, referred to as the VAS-Mood score.
- "Physical symptoms (breast tenderness/swelling, headaches, sensations of 'bloating')."
- 6 additional symptoms: decreased interest, difficulty concentrating, lack of energy, change in appetite, change in sleep pattern, and feeling out of control.

Non-VAS efficacy variables. These efficacy measures were obtained at the study visits (as shown in Table VI.B.4 in the appendix) and consisted of S rating scales (e.g. SDS, PGE) as well as observer rating scales (e.g. PMTS-O, CGI, PESM). The PMTS-O is described in the following.

Premenstrual Tension Scale Observer Rated (PMTS-O). Investigators were instructed to rate Ss on the PMTS-O in reference to the most recent LP of a given S (i.e. the LP of the cycle that had just ended at a given study visit). This scale involves rating ten symptoms: irritability and hostility, tension, efficiency, dysphoria, motor coordination, mental-cognitive functioning, eating habits, sexual drive and activity, physical symptoms and social impairment. Each item is rated by degree of severity on a scale ranging from 0 (no symptoms) to 4 (severe symptoms), except for items 7 (eating habits) and 8 (sexual drive) which are rated on a scale from 0 to 2. The maximum possible total score on this scale is 36.

Safety Assessments:

- Recording of adverse events
- Vital signs (sitting blood pressure and pulse rate, as well as body weight)
- Physical examination
- Laboratory parameters:
  - Hematology, blood chemistry screen (includes measures of renal function, liver function tests, among others)
  - Serum beta-HCG in women of childbearing potential at screening only
  - Thyroid Function Tests

A Mini International Neuropsychiatric Interview (MINI), obstetrics/gynecological and other information were obtained at the End of Reference Cycle 2 a (between Days 1-3 of the FP of Reference Cycle 2).

6. Statistical Analysis Plan

Dataset Analyzed. The primary analysis was conducted on the ITT efficacy, last observation carried forward (LOCF) dataset at the LP Treatment Cycle 3 Endpoint. The ITT dataset is data obtained from randomized Ss who had at least one dose of double blind study drug and at least one post-baseline assessment. Secondary analyses were conducted on other datasets as described in the submission. One of the datasets analyzed was the Per Protocol (PP) dataset (Ss violating protocol "to the extent that would impact on efficacy" and Ss who did receive double-blind treatment for at least one menstrual cycle). Additional datasets used for secondary analyses

included the observed cases (OC) dataset and the 70% LOCF dataset (a subset of the LOCF dataset in which at least 70% of Ss remained in each treatment group).

Primary efficacy variable:
The mean change from baseline to treatment endpoint on the VAS Mood score (mean score of the VAS ratings for the four "core" symptoms: irritability, depressed mood, tension or affective lability). The mean baseline and treatment endpoint VAS Mood scores were calculated using data from the last 5 days of a given cycle (mean LP scores). Mean LP scores were calculated for Reference Cycle 2 (Baseline) and for Treatment Cycle 3 (Treatment Endpoint). Methods for analyzing data with missing values are also described in the submission.[2]

The secondary efficacy variables are listed below.
Non-VAS measures were conducted at study visits. Therefore, baseline for the analysis of data from these measures was defined as Visit 3 (the Baseline Visit). Methods for analyzing data with missing data are described by the sponsor.[3] The following summarizes secondary efficacy variables analyzed by the sponsor:

- **VAS Physical:** the mean change from baseline to treatment endpoint on the LP (last 5 days of the cycle) VAS physical item score.
- **VAS-Mood Area Under the Curve (AUC):** the AUC for each Treatment Cycle was determined for each S using scores from the last 5 days of the LP of each cycle. Then the sum of the AUCs of the 3 Treatment Cycles was calculated and divided by the number of LP days (the days from which Treatment Cycle AUCs were calculated). This calculation provided the mean VAS-Mood AUC for the treatment phase of the study. Using similar methods a mean baseline AUC was calculated using data from the last 5 days of the LP of the Baseline cycle (Reference Cycle 2). Subsequently the change from baseline to the mean Treatment Phase AUC was then determined.
- **Mean change from baseline to treatment endpoint on other secondary measures.**
- **Responder analyses** were conducted. The percentage of responders in each treatment group was determined for each of the three different methods for defining a responder, as in the following. A responder was defined by each of the following ways:

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[2] **A Summary of Methods for Missing Data on the Primary Efficacy Variable.**
Screening Cycle VAS Mood Data. If no more than one day out of the last 5 LP days and no more than one day were missing on Days 6-10 of the FP, then the mean LP and mean FP scores were determined (mean = sum of non-missing scores/number of non-missing data).
Menstrual Cycle VAS Mood Data. If no more than 1 day out of the 5 last days of the menstrual cycle (representing the LP) was missing then the mean VAS score for a given "core" symptom was determined (mean = sum of non-missing scores/number of non-missing data). If more than one day of data was missing on a given "core" symptom VAS rating, then the data for that S for that particular time-point was excluded from the analysis. See Table VI.B.5 in the appendix for the algorithm for calculating the VAS Mood score in the presence or absence of missing data (as provided by the sponsor).

[3] **Missing data on the VAS Physical Symptoms Data and Other Secondary Variables.** To be included in the analysis for determining the mean VAS physical symptoms item score, no more than one day of the five designated days could be missing. Methods for calculating missing data on other secondary variables are also described in the submission.

- A mean LP VAS-Mood score at Treatment Endpoint ≤ Baseline mean FP VAS-Mood score
- A 50% reduction in the mean VAS Mood score from baseline to treatment endpoint.
- A CGI-I score of 1 (very much improved) or 2 (much improved) a treatment endpoint.

Additional secondary variables and analyses are described in the submission.

Statistical Tests Employed. Treatment and center main effects and interaction effects analysis of covariance (ANCOVA) model was employed on the primary variable, as well as on secondary variables unless otherwise specified (in Section 9 below). The final model also included terms for baseline score and age (in years at study entry). Small study sites were combined according to methods in the sponsor's "Reporting and Analysis Plan."

7. Patient Disposition

A total of 1059 Ss were randomized to double-blind treatment of which only 29 Ss were not included in the ITT population. Six of the 29 Ss did not receive study drug and the remainder (23 Ss) did not have a post-baseline assessment. Table VI.B.6 summarizes the disposition of randomized Ss in each study (as provided by the sponsor). The number of Ss remaining in the study at each visit (the baseline visit and Treatment cycle visits 1-3) is shown in Table VI.B.7 in the appendix (as provided by the sponsor).

The following are observations on the distribution of Ss that withdrew from the study due to lack of efficacy or due to an adverse event (AE) and are based on examination of results shown in Table VI.B.6. The high dose PaxCR group (25 mg) showed greater numerical incidence rates of withdrawals due to an AE than the incidence rates in the 12.5 mg PaxCR and placebo groups (groups were not compared statistically). The 12.5 mg PaxCR group had incidence rates that were numerically intermediate among the three groups. The reverse numerical pattern was observed for the incidence of dropouts due to lack of efficacy when comparing the 25 mg PaxCR group to the placebo group, while the 12.5 mg PaxCR group and placebo groups were numerically similar.

Table VI.B.7 in the appendix enumerates Ss in each treatment group of the ITT population remaining in each study at each study visit.

8. Baseline Demographics, Medical and Psychiatric Comorbidity, and Baseline Efficacy Scores

Baseline Demographics. Treatment groups (ITT Population) were similar on various demographic parameters (mean age, weight, BMI and the proportion of Caucasian versus non-Caucasian Ss). The mean age and mean weight of the Ss was approximately 36±5 years and 72±17 kg, respectively with approximately 95% of Ss being Caucasian. The majority of Ss were over 36 years of age (approximately 60%). Refer to Section VII B for a summary table (Table VII.B.1) of these results for the three trials, combined (Studies 677, 688 and 689).

Table VI.B.8 in the appendix (as provided by the sponsor) shows results of demographic features of each treatment group for each individual study. Treatment groups were numerically similar on most features across studies except for the following observations. The mean weight of each treatment group in Study 688 was numerically less than that of treatment groups of the other two studies (a mean of approximately 2 to 9 kg less in each group of Study 688 compared

to groups in either Study 689 or 677). Study 688 had only 2 non-Caucasian Ss out of the 357 total ITT Ss, compared to 3 to 13% non-Caucasian Ss in treatment groups in the other two studies. No statistical comparisons were conducted. Other differences between the studies include the geographic location of where the trials were conducted, as previously shown in a summary table (Table IV. B. 1 in section IV.B.1).

Medical and Psychiatric Comorbidity. Treatment groups (ITT population) in each study and across studies were generally similar in each of the following: past/current psychiatric, past/current medical conditions, mean baseline efficacy scores and on demographic features regarding their PMDD diagnosis. The following paragraphs provide a summary of these results.

The majority of Ss had previous and current medical conditions (approximately 86% of Ss in each group in the 3 trials, combined). The following were the most common current conditions: headache, female genital disorders (e.g. premenstrual syndrome, menstrual cramps, dysmenorrhea, ovarian cyst, endometriosis and others) and nose/mouth operations. Some studies had additional conditions identified as being common current conditions such as allergies, pregnancy complications and others.

The incidence of prior or concomitant psychiatric illness was generally 10% or less in each treatment group of each study. An exception to this observation was in Study 688, which showed incidence rates of 14% and 11% in placebo and 25 mg PaxCR groups, respectively (9% in the 12.5 mg PaxCR group). The most common psychiatric comorbidity was Major Depressive disorder or Panic disorder. Only 4 to 7 Ss out of all Ss in the ITT population had ongoing concomitant psychiatric illness during the treatment phase of the study.

Treatment groups (Safety Population) were generally similar on various demographic features regarding their PMDD, such as the age of onset of PMDD (approximately 25±8 years), duration of the disorder if it persisted (approximately 11±7 years) and in other features. The onset of PMDD coincided with childbirth or menarche in approximately 32% or 13% of Ss, respectively.

The table VI.B.9 in the appendix shows the mean baseline scores for the primary efficacy measure (the VAS-Mood Score) and on several secondary variables by treatment group of the ITT Population of each study. Treatment groups within each study and between studies were generally similar on each measure given the large standard deviations. As noted by the sponsor, the 25 mg PaxCR group in Study 688 had the lowest numerical values on the mean VAS-Mood score (48 points) compared to the other treatment groups of this study (55 or 58 points) and compared to treatment groups in other studies (51 to 60 points). However, these differences did not appear to be significant and the statistical analysis of data on the primary efficacy variable included a statistical adjustment for variance on baseline scores (refer to statistical section VI.B.6).

Concomitant Medications. Treatment groups were similar in the percentage of subjects taking concomitant medications during the double-blind treatment phase of the study (approximately 66 to 85% in a given group of a given study). The most common (≥10%) concomitant medications in each of the three studies were the following: analgesics, non-steroidal anti-inflammatory agents, and vitamins. Pseudophedrine was an additional commonly used medication in studies 677 and 689.

9. Efficacy Results

Results of a Primary Analysis and Secondary Analyses on the Primary Efficacy Variable (the mean change from baseline to Treatment Cycle 3 on the LP VAS Mood Score)

The table below summarizes results on the primary efficacy variable for each of the three studies and the studies combined (similar to that provided by the sponsor). Table VI.B.10. (Panels A-C) and Figure VI.B.11 (Panels A-C) in the appendix (as provided by the sponsor) show results of secondary analyses (mean LP VAS mood scores by Treatment Cycle or adjusted mean change from baseline to each Treatment Cycle for each of the three trials). Note in Table VI.B.10. that treatment groups showed numerical differences of up to approximately 10 points at baseline, on the raw mean LP VAS-Mood score. These numerical differences did not appear to be statistically significant, as the standard deviations were approximately 20 points. The baseline score was one of the covariates in the ANCOVA analysis (the primary analyses conducted by the sponsor). The table below shows treatment group differences on the least square mean values adjusted for baseline scores (age and treatment sites were additional coviariates in the analyses). No interaction effects were observed between treatment group and each covariate in each study.

Summary of Analysis of Change from Baseline in Adjusted Mean Luteal Phase VAS-Mood score. Studies 677, 689 and 688 and Pooled Analysis. Treatment Cycle 3 LOCF endpoint – ITT Population

	Paroxetine CR 25 mg – Placebo			Paroxetine CR 12.5 mg - Placebo		
Study	Treatment Difference (mm)*	95% CI	p- value	Treatment Difference (mm)*	95% CI	p- value
677	-12.10	[- 18.91, -5. 29]	<0.001	-8. 72	[- 15.72, -1. 71]	0.015
689	-12.58	[- 18.40, -6. 76]	<0.001	-7. 51	[- 13.40, -1. 62]	0.013
688	-7. 53	[- 14.71, -0. 35]	0.019	-4. 63	[- 10.52, 1.26]	0. 123
Pooled Analysis	-11.03	[- 14.60, -7. 47]	<0.001	-7. 44	[- 10.98, -3. 90]	<0.001

Data Source: ISE Table 1.1.2; Study 677, Table 13. 3; Study 689, Table 13. 3; Study 688, Table 13. 3
*Difference in adjusted least square means are shown

Approximately 5% to 7% of Ss in Studies 677 and 688 had missing LP VAS Mood scores at Treatment Cycle 3 (up to 8.9% had missing values in the 12.5 mg PaxCR group in Study 677). Approximately 1 to 2% of Ss in each study had missing scores at Baseline.

Secondary dataset analyses on the primary efficacy variable in each study showed at least trends for a treatment group effect for the OC and 70% LOCF datasets. This observation is based on a comparison of the 25 mg PaxCR group to placebo on the change from baseline on the adjusted mean LP VAS-Mood score (p values, without correcting for multiple comparisons, ranged from 0.02 to 0.001 and treatment group differences in adjusted least square means ranged from –7 to –17 units). Similar comparisons between the 12.5 mg Pax CR group and placebo groups of each study on the OC and 70% LOCF datasets showed trends for group differences as well. But group differences and p values were generally smaller (based on numerical comparisons) than those observed with numerical comparisons between the high dose PaxCR and placebo groups

(the range of group differences between 12.5 mg PaxCR and placebo groups was –5 to –11 units, and the range in p values without correcting for multiple comparisons, was 0.08 to 0.001). The PP dataset analyses on the primary efficacy variable is reported as revealing significant treatment group effects for each PaxCR group compared to placebo in Studies 689 and 677 (except for the 70% LOCF population) but not in Study 688.

Normal probability plots and residual plots of the data were examined for assumptions on normality and homogeneity and appeared to show that data from each study was not normally distributed. Nonparametric analyses on the primary efficacy variable was conducted to support the primary results (results using parametric tests). The Wilcoxon Rank Sum Test and a non-parameteric ANCOVA (SAS system) developed by Zinc and Koch to allow for adjusting for covariates (age, center and baseline score) generally revealed results similar to that observed with parametric testing. Comparisons between the high dose group 25 mg PaxCR and placebo groups in Studies 677 and 689 (using the LOCF, OC and 70% LOCF datasets) showed group median differences of –12 to -16 ($p < 0.01$ without correcting for multiple comparisons). Results of Study 688 showed numerical trends for treatment group median differences of only –3 to –5 points between the 25 mg Pax CR and placebo groups (p values were 0.2-0.4) using nonparametric tests on various datasets. Comparisons between the lower dose group (12.5 mg PaxCR) and the placebo group of each of the studies, 677 and 689 generally showed trends for treatment group effects that were numerically smaller than that observed for the high dose group in these studies. Study 688 failed to show a significant treatment group effect between the 12.5 mg PaxCR and placebo groups (median difference of –1 to –3 and p values of 0.4-0.8).

Results on the VAS Total Score. Because the VAS Mood score only encompasses a subset of the PMDD symptoms, the sponsor was asked to provide statistical results on the more comprehensive measure, the VAS Total Score which includes a rating of 11 symptoms of PMDD, comparable to all 11 symptoms of PMDD listed in the DSM-IV (refer to Attachment 2 of this review of a 10/28/02 Telefax with Biometric comments/requests). The VAS-total was a scale previously used to support labeling for fluoxetine (Sarafem™). Another scale (the Daily Record of Severity of Symptoms scale) was used to support labeling for Zoloft™ for the PMDD indication that also encompasses 11 symptoms similar to those listed in the DSM-IV.

The following tables (provided upon request by the sponsor in an 11/6/02 submission) show results on the raw mean change in LP VAS total scores from baseline to treatment endpoint (Treatment Cycle 3) of the LOCF dataset. PaxCR treatment groups generally showed a greater numerical decrease in the raw mean LP VAS total score than the placebo group in each study. The sponsor is currently conducting a statistical analysis of these results (using an ANCOVA model, similar to that employed for the VAS Mood score, that includes the following terms: treatment group, age, baseline scores and study sites). These results and the receipt of the data sets are still pending (the Biometric consultant plans to analyze the data, as described in Attachment 2).

Summary Statistics for Baseline and Change from Baseline on VAS Total Score for Study 677*

	Paroxetine CR 25 mg Group N=111		Paroxetine CR 12.5 mg Group N=65		Placebo Group N=107	
	FP	LP	FP	LP	FP	LP
Baseline Cycle						
N	110	110	94	93	107	105
MEAN	69.9	566.0	66.3	622.2	60.2	567.9
STD	79.62	226.71	59.69	240.19	65.25	250.89
MEDIAN	41.2	577.5	41.6	623.8	40.3	583.0
MIN	0.0	121.2	0.0	183.6	0.8	43.2
MAX	539.2	1049.2	222.4	1036.2	437.8	1055.4
Treatment Cycle 3 LOCF Endpoint						
N	101	97	90	89	103	99
MEAN	15.5	-320.4	6.3	-331.4	9.7	-222.9
STD	89.89	293.56	68.44	303.77	87.49	290.53
MEDIAN	-1.0	-313.2	-2.5	-286.5	0.8	-200.0
MIN	-168.6	-990.8	-181.8	-1000.0	-415.0	-1000.5
MAX	362.6	370.0	299.0	277.0	448.0	404.8

*Data source: Table 38 in the 11/6/02 submission
Abbreviations FP=follicular phase, LP=luteal phase, LOCF=last observed carried forward data, STD=standard deviation, MIN=minimum, MAX=maximum

Summary Statistics for Baseline and Change from Baseline on VAS Total Score for Study 688*

	PaxCR 25 mg Group N=117		PaxCR 12.5 mg Group N=123		Placebo Group N=118	
	FP	LP	FP	LP	FP	LP
Baseline Cycle						
MEAN	72.6	506.7	61.7	564.7	68.2	585.1
STD	111.00	242.09	104.48	262.64	76.03	261.18
MEDIAN	45.1	468.0	38.4	530.5	41.5	563.8
MIN	0.4	97.1	0.2	88.0	0.6	85.0
MAX	1061.2	1090.4	1037.8	1100.0	409.0	1100.0
Treatment Cycle 3 LOCF Endpoint						
N	105	96	120	114	112	112
MEAN	8.9	-272.8	6.0	-302.9	-13.2	-262.6
STD	153.17	260.38	134.63	262.57	81.20	284.86
MEDIAN	-0.2	-263.8	-1.8	-272.9	-0.2	-250.0
MIN	-1036.2	-1059.0	-961.6	-1030.0	-337.2	-1008.9
MAX	691.4	501.6	723.2	189.5	232.4	427.2

*Data Source: Table 40 in the 11/6/02 submission
Abbreviations FP=follicular phase, LP=luteal phase, LOCF=last observed carried forward data, STD=standard deviation, MIN=minimum, MAX=maximum

Summary Statistics for Baseline and Change from Baseline on VAS Total Score for Study 689*

	PaxCR 25 mg Group N=120		PaxCR 12.5 mg Group N=115		Placebo Group N=124	
	FP	LP	FP	LP	FP	LP
Baseline						
N	120	120	114	114	124	124
MEAN	70.4	527.6	69.8	585.1	71.2	559.5
STD	80.62	243.00	75.36	250.14	77.01	248.35
MEDIAN	36.8	461.5	41.7	564.4	44.4	518.3
MIN	0.0	167.8	0.0	85.2	3.4	112.8
MAX	449.8	1087.0	341.8	1026.4	356.3	1100.0
Treatment Cycle 3 LOCF Endpoint						
N	114	105	103	103	117	118
MEAN	-0.7	-324.1	-5.7	-317.4	9.1	-223.7
STD	102.19	244.45	70.19	313.58	90.72	284.98
MEDIAN	-3.2	-310.4	-2.3	-298.9	1.2	-189.3
MIN	-299.8	-993.2	-224.3	-1013.8	-269.2	-1076.2
MAX	581.0	236.2	232.6	672.6	421.6	456.4

*Data Source: Table 42 in the 11/6/02 submission
Abbreviations FP=follicular phase, LP=luteal phase, LOCF=last observed carried forward data, STD=standard deviation, MIN=minimum, MAX=maximum

The previous tables also show descriptive statistical results on the FP VAS total scores. Upon examination of this table and a numerical comparison between FP and LP scores, the results appear to be consistent with eligibility criteria employed in the trials and with a PMDD diagnosis in the study population. Observations based on results of the tables that support this conclusion are described in the following. The mean FP VAS total scores are generally about 10 to 14% of the mean LP scores in each treatment group. The mean change from baseline to treatment endpoint in mean FP scores was also markedly smaller than the mean change in LP scores in each treatment group (based on visual examination of the above tables). Furthermore, the observed change in mean FP scores was either in the positive or negative direction, while the mean change in LP scores was consistently in the negative direction (these observations are based on a numerical, non-statistical examination of results in the above tables).

Secondary Efficacy Variables.

The table below summarizes results of secondary variables when comparing the high dose PaxCR group to the placebo group in each study.

Summary of Secondary Efficacy Results of Each Study for the 25 mg PaxCR group (ITT population)

	Study 677			Study 689			Study 688		
Efficacy Variable	**Treatment Difference***	**95% CI**	**p- value**	**Treatment Difference***	**95% CI**	**p- value**	**Treatment Difference***	**95% CI**	**p- value**
VAS Physical	-9. 87mm	-17.07, -2. 66	0. 007	-7. 21mm	-14.48, 0. 05	0.052	-6. 13mm	-13.63, 1. 37	0.109
VAS- Mood AUC	-11.36mm	-16.71, -6. 02	<0.001	-11.35mm	-15.64, -7. 07	<0.001	-8. 93mm	-13.19, -4. 66	<0.001
SDS Total $	-3.40	-5. 60, -1. 20	0. 003	-2. 45	-4.35, -0. 55	0. 012	-4. 39	-6.72, -2. 06	<0.001
SDS Social	-1. 51	-2.28, -0. 74	<0.001	-0. 78	-1.42, -0. 14	0. 017	-1. 71	-2.49, -0. 93	<0.001
SDS Work	-0. 82	-1.54, -0. 10	0. 026	-0. 68	-1.34, -0. 03	0. 042	-1. 09	-1.84, -0. 33	0. 005
SDS Family	-1. 42	-2.22, -0. 61	<0.001	-0. 94	-1.66, -0. 22	0. 010	-1. 73	-2.56, -0. 89	<0.001
PMTS- O	-3. 54	-5.70, -1. 39	0. 001	-3. 37	-5.29, -1. 45	<0.001	-4. 49	-6.62, -2. 37	<0.001
CGI Severity	-1**	-	<0.001	-1**	-	<0.001	-1**	-	0. 008

Results are for the TC3 LOCF analysis, except for AUC in VAS- Mood which was calculated for the treatment phase as a whole.
Adjusted for centre group, baseline score and age.
* Difference in adjusted least square means are shown; treatment differences are calculated as paroxetine CR (25 mg group) minus placebo. Negative values indicate improvement.
** Difference in medians are shown; treatment differences are calculated as paroxetine CR (25 mg group) minus placebo.
$ SDS total score was not one of the original secondary outcome measures but was analysed in the DAP

Efficacy Variable	**Odds Ratio#**	**95% CI**	**p- value**	**Odds Ratio#**	**95% CI**	**p- value**	**Odds Ratio#**	**95% CI**	**p- value**
VAS- Mood 50% reduction##	2.80	1.52, 5.18	<0.001	3.37	1.86, 6.13	<0.001	2.04	1.10, 3.78	0.023
VAS- Mood Luteal< Foll+	2.93	1.30, 6.64	0.010	5.41	2.46, 11.87	<0.001	2.09	0.95, 4.60	0.065
CGI (GI)++	2.88	1.55, 5.38	<0.001	3.87	2.13, 7.05	<0.001	3.94	2.13, 7.29	<0.001
PGE	3. 23	1. 72, 6.08	<0.001	3.16	1.73, 5.77	<0.001	3.38	1.84, 6.20	<0.001

Results are for the TC3 LOCF analysis.
The odds ratio represents the odds of improving with paroxetine CR (25 mg group) relative to placebo.
Responders were defined by a 50% reduction in VAS- Mood scores. Adjusted for centre group, baseline score and age.
+ Responders were defined by a return to baseline mean follicular phase VAS- Mood score. Adjusted for centre group, baseline score and age.
++ CGI Global Improvement: A responder was defined as having a score of 1 (very much improved) or 2 (much improved) at endpoint. Adjusted for centre group and age

Data Source: This table is almost identical to the summary table on page 000030 of the ISE in the submission.

Dose Dependent Efficacy Analysis

A description of results of statistical comparisons between the high and low dose PaxCR groups on efficacy variables could not be found in the submission. Results on the primary

variable the groups generally showed a pattern for a numerically greater mean change in the high dose group compared to the low dose group.

Subgroup Analysis

Age and race were included as covariates in the efficacy analysis, as indicated by the sponsor on page 000172 of the Integrated Summary of Efficacy section of the submission. The majority of Ss were Caucasian with few in other ethnic categories such that subgroup analysis on the basis of race is not considered interpretable (due to insufficient sample size). Age group analysis is also not considered meaningful, given the narrow age-range of Ss. Regarding gender subgroup analysis, all Ss were female.

10. Conclusions

Two of the three trials show highly significant ($p<0.01$ to 0.001) treatment group effects on the LP VASMood score (change from baseline to treatment cycle 3 endpoint) in favor of PaxCR over placebo treatment. The third trial (688) only showed a significant effect ($p<0.02$) when comparing the high dose PaxCR group to placebo. The lower PaxCR group in Study 688 showed trends for a greater improvement on the LP VASMood score. Overall the results show that both dose levels of PaxCR showed greater improvement on the LP VASMood score compared to placebo. Because the VASMood score does not encompass all 11 symptoms of PMDD, but rather only rates 4 symptoms, the sponsor is currently conducting an analysis on the LP VAS total score (refer to the previous subsection, 9 and to Attachment 2 of this review of a 10/28/02 Telefax to the sponsor). The Biometric consultant will also analyze the sponsor's data on the LP VAStotal score upon receipt of the datasets as requested on 10/28/02. If at least two of the three trials show significant treatment group effects for at least the high dose PaxCR group compared to placebo, then these results would support the sponsor's claim for a PMDD indication for PaxCR.

A statistical analysis to determine whether or not the low and high PaxCR treatment groups were significantly different on efficacy could not be found in the submission. The lower dose appears to be better tolerated based on the safety analysis, as described in a later section of this review (refer to section VII H). The sponsor recommends a starting daily dose of 12.5 mg PaxCR that may be increased after a minimum period of one week to the daily dose of 25 mg in nonresponders. This recommendation appears to be reasonable, as long as similar results are revealed with the LP VAStotal score used as the primary efficacy variable.

Some potential caveats that generally apply to the interpretation of results of trials supporting a PMDD claim are discussed below. However, these caveats are not substantial or of great enough concern to refute the overall conclusion regarding the sponsor's trials, for reasons as described below (given that at least two of the three trials are positive on LP VAS-total score, as above).

Some Potential Caveats to Consider

The population examined in the sponsor's trials appeared to be an enriched population in that cut-off criteria were employed to potentially ensure minimal symptoms during the FP and greater symptomatology during the LP. Women using oral contraceptive (OC) agents were excluded from the study, yet a significant proportion of PMDD patients are likely to be using OC agents, given that they have childbearing potential. Other investigators in the field hypothesize a

potentially therapeutic effect of OC agents on PMDD symptoms. However, there are no OC agents approved for the indication of PMDD. Therefore, labeling should reflect that women using OC agents were excluded from the PMDD trials (given that this sNDA is granted an approvable status).

Another consideration regarding any PMDD drug trial is the issue of diagnostic specificity, particularly in differentiating a mood disorder (i.e. Major depressive disorder, dysthymia, etc) from PMDD. By definition in the DSM-IV symptoms are in remission, at least during the first week of the FP and the sponsor used eligibility criteria using cut-off scores such that subjects would have minimal to no symptoms during the FP relative to the LP. Based on results on LP and FP efficacy scores provided by the sponsor upon request (in a 11/6/02 submission), the study population of each trial, appeared to show markedly higher VAS-Mood and VAS-total scores during the LP compared to the FP. Furthermore, FP scores were numerically low. Consistent with other eligibility criteria employed in the trials, few subjects had concomitant, current psychiatric Axis I disorders in addition to their PMDD.

The potential for pseudospecific treatment effects of PaxCR in the PMDD trials, such as a possible therapeutic effect on an underlying or co-existing anxiety or major depressive disorder, is another possible caveat regarding the interpretation of study results. Given the low incidence of psychiatric comorbidity in the study population examined and that subjects were screened cyclical variation of symptomatology (LP relative to the FP of the menstrual cycle), potential pseudospecific effect of PaxCR is considered to be unlikely.

Little is known about women with hysterectomies, but have intact ovaries, regarding the prevalence of PMDD and about other possible populations that may benefit from treatment for PMDD. Finally, little is understood about the underlying mechanisms of PMDD and chronobiological factors regarding PMDD, given the periodicity of the menstrual cycle and of the pulsatile release of various reproductive hormones. Consequently, these are some of the areas of the field that remain for further exploration.

VII. Integrated Safety Information

A. Background Information

Safety results were of the ITT population in the 3 PMDD trials (at least one dose of study drug and at least one post-baseline assessment). Only serious adverse events (SAEs) were provided for the ongoing trials 711 and 717. Study 711 is a double blind fixed dose parallel group extension study (12.5 mg and 25 mg PaxCR groups and placebo). Study 717 is an intermittent dose double blind fixed dose, parallel group study (12.5 mg and 25 mg PaxCR groups and placebo). See the summary table of trials (Table IV.B.1) in a previous Section IV.B.

B. Demographic Characteristics

Demographic features in the three PMDD trials combined (Studies 677, 688 and 689). The following table summarizes the demographic features for the ITT population (Ss who received at least one dose of study medication and had at least one post baseline assessment). Treatment groups were generally similar on each demographic feature, as shown in the table, below.

Table VII.B.1. Summary of Demographic Features for Treatment Groups in Studies 677, 688 and 689, Combined*				
	Placebo N=349	Paroxetine CR 25 mg N=348	Paroxetine CR 12.5 mg N=333	Total N=1030
Mean±SD Age (years)	36±6	36±5	36±5	36±5
Age range (years)	19-46	19-45	18-46	18-46
% Caucasian	94	95	95	95
% Non-Caucasian	6	5	5	5
Mean±SD Weight (kgs)	72±17	73±18	70±16	72±17
Mean ±SD BMI (kg/m^2)	26.3±5.96	26.8±6.26	25.5±5.54	-
BMI range (kg/m^2)	18-50	17-55	17-60	17-60
*ITT Population, Data source: Table 3 on page 42 of the ISS of the submission and Table 9, page 76 of the ISE				

Refer to a previous section (Section VI. 8) for more detailed demographic information on the study population.

C. Extent of Exposure

Exposure in Completed PMDD Trials (Studies 677, 688 and 689). A total of 1030 Ss had at least one dose of study drug and at least one post-baseline assessment (ITT population). An additional 29 Ss were randomized to double-blind treatment of which 23 received at least one dose of PaxCR. A total of 781 out of the 1030 Ss in the ITT population were assigned to PaxCR and received at least one dose. Tables VI.B.6-7 in the appendix shows the number of completers in each treatment group of each study (of the ITT population). Table VII.C.1 in the appendix provides a breakdown of the duration of treatment by treatment days, as well as descriptive statistical results on duration of exposure for each treatment group (as provided in an 11/6/02 submission, as requested). The following outlines the mean duration of exposure (in days) and the cumulative exposure (in subject years) of each treatment group in the three PMDD trials combined:

- PaxCR 25 mg group: 67±28 days, 64 subject-years
- PaxCR 12.5 mg group: 73±23 days, 66 subject-years
- Placebo group: 72±22 days, 69 subject-years

Approximately 65% to 77% of Ss among treatment groups were completers (Ss recorded as attending all visits up to the End-of-Treatment Cycle 3 visit). The cumulative exposure in PaxCR groups corresponds to approximately 70 days of treatment in each S. The following shows the percentage of Ss who received at least 61 days of treatment:

- PaxCR 25 mg group: 74%
- PaxCR 12.5 mg group: 84%
- Placebo group: 82%

Exposure in Ongoing Studies.

Study 717 is an ongoing placebo-controlled, fixed dose, parallel group, intermittent treatment PMDD trial. A total of 297 Ss received double-blind treatment of PaxCR (25 mg/day or 12.5 mg/day or placebo in this study (treatment is intermittent over 3 cycles).

Study 711 is an ongoing double-blind, placebo-controlled, fixed dose, parallel group, extension study to Studies 677, 688 and 689. A total of 485 Ss who completed one of these three

completed trials are randomized to double-blind treatment of PaxCR (12.5 mg or 25 mg, daily) or placebo (the treatment phase is continuous over 3 cycles).

D. Deaths

No deaths were reported in the three completed (Studies 677, 688 and 689) and the two ongoing (Studies 711 and 717) PMDD trials.

E. Serious Adverse Events

SAEs in 3 Completed PMDD Studies (Studies 677, 688 and 689). Serious adverse events (SAEs) during the Treatment and Follow-up phase are listed in Tables VII.E.1 and VII.E.2, respectively, in the appendix (as provided by the sponsor). A total of 13 Treatment and Follow-up Phase SAEs were reported in 12 Ss out of 1030 Ss in the ITT population. Most SAEs did not appear to be related to the study drug.

SAEs in which a potential direct or indirect role of study drug may be more likely was a stillbirth (S689.117.16473) and supraventicular tachycardia (S677.029.22211). Paxil and PaxCR are Pregancy Category C drugs. The SAE of supraventicular tachycardia (also accompanied with chest pain) appeared to be due to distress upon awakening during a bad dream (S677.029.22211) based on that described in the narrative. These two Ss are described in more detail in Attachment 1 in the appendix.

The following enumerates Ss with SAEs by treatment groups (includes SAEs during either the Treatment Phase or the Follow-up Phase):

- **25 mg PaxCR group:** 5 Ss
- **12.5 mg PaxCR group:** 4 Ss
- **Placebo group:** 3 Ss

The most common SAE was unintended pregnancy, which occurred in 1 Placebo S and in 6 PaxCR Ss (the SAE of one of these Ss was identified as abortion, which was elective). Most of the pregnancies were reported during the follow-up phase (the subgroup of Ss not entering in an extension study, Study 711, underwent a 14-Day follow-up visit and for Ss with ongoing events, an additional 28-Day follow-up visit). To be eligible for study entry, Ss were required to use a non-hormonal method of contraception (a double barrier method of was used in at least 6 out of 7 Ss), have regular menses were young adult women. Consequently, these unintended pregnancies are not unexpected for the study population and do not appear to be drug-related.

The following outlines pregnancy outcomes in PaxCR Ss.

- Outcome unknown (refused follow-up) in 1 PaxCR S (S677.012.12868)
- Delivery of a healthy baby in 2 PaxCR Ss (677.035.22658, 689.115.16294). One delivery was by Ceasarian section at 38 weeks. The neonate had jaundice. The other delivery was at full-term.
- Abortions in 3 Ss of which 1 S had a stillbirth:
  - The abortion in S689.120.16705 was elective.
  - The narrative of on S677.023.21765 indicates that dilation and curettage was performed at 6 weeks.
  - The third abortion involved a stillbirth which may be drug-related (S689.117.16473 described in Attachment 1 in the appendix).

SAEs in Ongoing Studies 711 and 717 as of 2/28/02 Cut-off Date

Eleven Ss out of a total of 297 Ss who received double-blinded study medication had SAEs in Study 711. Two Ss out of a total of 485 Ss who received double-blinded study medication had SAEs in Study 711. Table VII.E.3 in the appendix lists the SAEs in these two studies (as provided by the sponsor). The potential relationship between most SAEs and study drug appeared to be unlikely, while others did not appeared to be unexpected or appeared to be associated with underlying conditions (or not atypical events in the study population) or were events already described in labeling. The study drug assignment also remains blinded in many of these Ss. Some of these SAEs are listed below and are described in Attachment 1 in the appendix (unless otherwise specified below):

- **S717.701.32111: Hypersensitivity** involving **laryngeal angioedema with dyspnea.**
- **S711.024.21827: Bronchitis NOS** (not described in the appendix), asthmatic bronchitis after 5 days of treatment of blinded study drug.
- **S717.069.15006: Spontaneous abortion.**
- **S711.144.18557: Pregnancy NOS** (not described in the appendix). This S had a therapeutic **abortion due to death of the fetus from intra-uterine asphyxia.** Given that the S has a history of 5 miscarriages it is unlikely that the outcome of her pregnancy was drug-related.
- **S717.701.32125: Abortion NOS.** The S underwent therapeutic abortion within approximately 4 weeks after the reported date of conception. The reason for the abortion was not specified other than as a "therapeutic abortion".
- **S711.084.20209: Calculus Renal, Abdominal Pain** (not described in the appendix): study drug remains blinded.
- **711.092.21115: Myocardial Infarction.** This S had pre-existing medical conditions likely to have resulted in this SAE.

F. Dropouts due to Adverse Events

Adverse Dropouts in Completed PMDD Studies 677, 688, and 689

The incidence of adverse dropouts (ADOs) in the 3 completed PMDD trials were as follows (based on results shown in Table 7.6.1.1 on page 307 of the ISS):

- **25 mg PaxCR group:** 51 out of 348 Ss (14.7%)
- **12.5 mg PaxCR group:** 32 out of 333 Ss (9.6%)
- **Placebo group:** 22 out of 345 Ss (6.3%)

The following table enumerates ADOs with an incidence rate of 1% or greater in PaxCR groups (combined) that was also twice that of placebo. As shown in the table the observed ADOs were generally similar to that observed in other patient populations (refer to current PaxCR labeling) with one possible exception. The possible exception is "Concentration Impaired" which did not meet the ≥1% and twice placebo criteria for various approved indications but did meet these criteria in the PMDD study population.

Incidence Rates (%) of Adverse Dropouts (≥1% in PaxCR groups, combined, and Twice Placebo) by Preferred Term in Each Treatment Group*		
	PaxCR groups (combined) N=681	Placebo N=349
Preferred Term:		
Nausea	23 (3.4%)	3 (0.9%)
Asthenia	24 (3.5%)	4 (1.1%)
Somnolence	19 (2.8%)	1 (0.3%)
Concentration Impaired	9 (1.3%)	1 (0.3%)
Dry Mouth	8 (1.2%)	1 (0.3%)
Insomnia	11 (1.6%)	0 (0%)
Datasource: Table 7.6.1.1		

Section VII.I.2 on Ss that dropped out due to meeting outlier criteria on laboratory parameters describes one PaxCR S (S689.117.16470) who had increase liver transaminase levels during treatment (refer to Section VII.I.2 for details). No other outliers on clinical assessments (on laboratory parameters or on vital sign parameters) were described as requiring cessation of treatment due to meeting outlier criteria.

Dose-Dependent ADOs in Completed PMDD Studies 677, 688 and 689. The following table shows the incidence rates of the most common ADOs by selected AE (Preferred Term) categories for each treatment group of the 3 PMDD trials, combined (using Table 7.6.1.X as the Data source). Common events are defined as ADOs with an incidence of at least 1% associated in either Paxil CR group. The table includes ADOs that were dose dependent (indicated with an asterisk), as defined as events having an incidence rate in the high dose Paxil CR group that was at least twice that of the low dose Paxil CR group and placebo.

	25 mg Paxil CR N=348	12.5 ~~25~~ mg Paxil CR N=333	Placebo N=349
TOTAL	53 (15%)	33 (9.9%)	22 (6.3%)
Preferred Term:			
Nausea*	21 (6.0%)	8 (2.4%)	3 (0.9%)
Asthenia	17 (4.9%)	10 (3.0%)	5 (1.4%)
Somnolence*	15 (4.3%)	6 (1.8%)	1 (0.3%)
Insomnia*	8 (2.3%)	5 (1.5%)	0 (0.0%)
Concentration Impaired*	7 (2.0%)	2 (0.6%)	1 (0.3%)
Dry Mouth*	7 (2.0%)	2 (0.6%)	1 (0.3%)
Dizziness*	6 (1.7%)	2 (0.6%)	2 (0.6%)
Decreased Appetite*	5 (1.4%)	2 (0.6%)	0 (0.0%)
Sweating*	5 (1.4%)	0 (0.0%)	1 (0.3%)
Tremor*	5 (1.4%)	1 (0.3%)	0 (0.0%)
Yawn*	4 (1.1%)	0 (0.0%)	(0.0%)
Diarrhea	3 (0.9%)	4 (1.2%)	0 (0.0%)

*Events considered to be dose dependent as defined as events having an incidence rate in the high dose Paxil CR group that was at least twice that of the low dose Paxil CR group (as well as the placebo group)

G. Specific Search Strategies

Follow-up Phase AEs in Completed PMDD Trials (677, 688 and 689). The sponsor provided the incidence rates of AEs occurring within 14 days of discontinuing the study drug. Only Ss that did no enter into the extension Study 711 were captured in this data analysis (Ss were either ineligible or declined consent to participate). The total number of Ss who underwent follow-up assessments were 457 out of the 1030 Ss of the ITT population (of which 138 to 168 Ss were in a given treatment group). A 28-day follow-up visit occurred for unresolved AEs or laboratory values observed on the Day 14 follow-up assessment. Dizziness was the only common follow-up AE that occurred with an incidence rate in either PaxCR group that was twice that of placebo Ss. A more detailed discussion of follow-up AEs are described below.

Dizziness, the only common Preferred Term AE (defined as an AE occurring in at least 5% of Ss in a PaxCR group) was reported in 9%, 7% and 0% of high dose PaxCR Ss, low dose Pax CR Ss and placebo Ss, respectively. Other AEs showed a dose-related trend on incidence rates but only occurred in 1 to no more than 3% of Ss within either PaxCR groups. These AEs were the following: nausea (3% in the high dose group compared to 1% in the low dose and placebo groups, respectively), nervousness (2%, 3%, and 0%), anxiety, menstrual disorder and infection (each reported in 2% in the high dose group compared to 1% and 0% in low dose and placebo groups, respectively) and vertigo (in 1% of high and low dose PaxCR groups and 0% in placebo Ss). These incidence rates are taken from Table 23 in the ISS of the submission (rounding off the percentages according to general standard procedures).

Most SAEs in the follow-up phase of the study and as listed in Table VII.E.2. in the appendix were unintended pregnancies and none of the SAEs (refer to the previous Section D above on SAEs).

Special Populations. The submission did not include any trials on special populations.

H. Adverse Events in the Completed PMDD Studies 677, 688 and 689.

An incidence of 79.9% (278/348) of 25 mg PaxCR Ss, 72.1% (240/333) of 12.5 mg PaxCR Ss and 61.6% (215/349) placebo Ss had at least one treatment emergent adverse event (AE). Tables VII.H.1 and VII.H.2, in the appendix, show the incidence rates of AE's in the placebo group and in the PaxCR groups combined (Table VII.H.1) and for each high dose and low dose PaxCR group (Table VII.H.2.), as provided by the sponsor. Table VII.H.1 shows AEs with an incidence rate of at least 1% in the PaxCR groups combined, while Table VII.H.2 shows AEs with an incidence rate of at least 2% of either PaxCR group. AE's with an incidence of at least 5% in PaxCR Ss (combined) that was also at least twice that of placebo Ss were the following:

Asthenia	Female genitial disorders
Libido decreased	Sweating
Somnolence	Dizziness
Insomnia	Diarrhea
Constipation	Nausea

Dose-Related AEs in PMDD Studies 677, 688 and 689, combined. The following table shows common AEs defined as ≥ 1% in the high dose PaxCR group that was also at least twice that of the low dose PaxCR group, as well as that of the placebo group.

Incidence of Common Adverse Events* in Placebo, Low and High Dose PaxCR Treated Subjects in Fixed-Dose PMDD Trials, Combined (Studies 677, 688, 689)			
	25 mg PaxCR Group (N=348)	12.5 mg PaxCR Group N=333	Placebo Group N=349
	n (%)	n (%)	n (%)
Common Adverse Event:*			
Sweating	31 (8.9)	14 (4.2)	3 (0.9)
Tremor	21 (6.0)	5 (1.5)	1 (0.3)
Concentration Impaired	15 (4.3)	5 (1.5)	2 (0.6)
Yawn	11 (3.2)	3 (0.9)	1 (0.3)
Hyperkinesia	4 (1.1)	1 (0.3)	0 (0.0)
Paresthesia	5 (1.4%)	1 (0.3)	1 (0.3)
Vaginitis	4 (1.1%)	1 (0.3)	1 (0.3)
*Adverse events with an incidence rate of at least 1% in either of the PaxCR groups that also showed an incidence in the 25 mg PaxCR group of at least twice that of the 12.5 mg PaxCR group and the placebo group. Datasource: Table 7.3.1X of the ISS			

Other common AEs showed numerical trends for a dose-related effects but did not meet the criteria to be included in the above table as follows (incidence rates for the high dose PaxCR group, the low dose PaxCR group and placebo group, respectively are provided): nausea (22%, 12%, 7%), insomnia (10%, 6%, 2%), dry mouth (5%, 3%, 2%), increased appetite (3.2%, 1.8%, 0.9%), and anxiety (2.3%, 1.2%, 1.1%).

Subgroup Analyses of AEs on the Basis of Age-group or Race. Since Ss were within an age-range of 19-46 years old, a subgroup analysis of AEs on the basis of age was not conducted. The number of non-Caucasian Ss (5%) was insufficient for a subgroup analyses on the basis of race.

I. Laboratory Findings

In summary safety results on laboratory parameters did not reveal any new or unexpected events that are not currently described in labeling.

Hematology, clinical chemistry and thyroid function tests were conducted at baseline, treatment endpoint (the end of Treatment Cycle 3) or upon early withdrawal. Baseline for laboratory parameters was at the end of Reference Cycle 1 or 1a (Visit 2 or 2a) or the last assessment conducted prior to initiating double-blind treatment (in the case of a repeat testing during Reference Cycle 2). Follow-up assessments were conducted 14 days after the treatment phase for Ss with unresolved laboratory abnormalities.

Less than 30% of the ITT population had available results from "On-Treatment" laboratory assessments. An On-Treatment assessment is defined as an assessment that was conducted during the double-blind treatment phase (the date of the assessment coincided within the time-period from the onset of treatment to the last day of treatment during the double-blind treatment phase).

1. Analysis of Central Tendency in Completed PMDD Trials (677, 688 and 689).
Hematology and Chemistry. As shown in Tables VII.I.1 and VII.I.2 in the appendix treatment groups were generally similar on mean baseline and mean change from baseline to treatment endpoint on each parameter.

2. Analysis of Outliers in Completed PMDD Trials (677, 688 and 689).

Hematology and Chemistry. Table VII.I.3 in the appendix provides the criteria employed for classifying Ss as meeting potentially clinically significant (PCS) levels on a given laboratory parameter. Treatment groups generally demonstrated similar incidence rates of Ss meeting criteria for being PCS on each parameter (0% on most parameters, with 1 to 2 outliers on a few parameters).

An examination of the narratives of outliers revealed that only one PaxCR subject discontinued treatment due to abnormal laboratory values. This S (S689.117.16470) had elevated liver transaminase levels (5-12 fold increase from baseline) during treatment but also had slight neutropenia at baseline. While a potential role of study drug cannot be ruled out in this S, the baseline neutropenia suggests a pre-existing condition. [4] Another S (S689.115.16294) was listed as an SAE of diabetes mellitus and unintended pregnancy (previously described in the section of SAEs). One ADO (S689.138.18118) who withdrew due to exacerbation of acne and was also listed as meeting PCS criteria for a laboratory parameter. The abnormal parameters in these two Ss (S689.115.16294, S689.138.18118) did not appear to be drug-related.[5]

An examination of the narratives of outliers also revealed several Ss that did not have on-treatment assessments but had assessments within a few days of treatment cessation. Four Ss had eosiniphilia (S677.009.12677, 688.055.13915, 688.063.14548, 688.079.19814) involving approximately a 2 to 8 fold increase in eiosinophil count from baseline to Treatment Cycle 3. Eosinophilia in some of these Ss was probably not due to the study drug, as two Ss had pre-existing allergies and a third S showed a time-course of eosinophilia that was not consistent with a treatment related event. Eosinophilia is currently listed in current labeling in the "Other Events Observed During the Clinical Development of Paroxetine" section.

S688.051.13603 showed baseline to End of Treatment Cycle 3 changes in thyroid function tests that included a marked increase in TSH levels (from 7.1 to 112.6 mU/l, 0.4-5.5 normal range), a decrease in Free T3 (from 3.1 to <2.3 pmole/l, normal range: 3.5-6.5 and a decrease in total free Thyroxine (from 13.4 to 5.4 pmole/l, normal range: 10.3-23.2). However, the TSH was slightly above normal at baseline, suggestive of a pre-existing condition. The narrative of this S indicates that this S had not reported any thyroid function related AEs. Current labeling includes hyperthyroidism and hypothyroidism in the list of "Other Events Observed During..."

J. Vital Signs

In summary results of vital sign parameters did not appear to reveal in remarkable, new or unexpected safety findings that are not already described in current PaxCR labeling. Vital signs (pulse rate, systolic and diastolic blood pressure) were obtained at each study visit (at Screening, the end of each reference cycle and treatment cycle and on follow-up visits) as shown in Table

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[4] S689.117.16470 had an increase in ALT (SGPT) and AST (SGOT) levels (approximately 5 and 12 fold increases, respectively) from baseline to the End of Treatment Cycle 1. Treatment was terminated and levels normalized on follow-up. A possible role of study drug must be considered in this S. The S also had a slight neutropenia on visits on each of 2 Reference Cycles, suggestive of a pre-existing condition.

[5] The S (S689.115.16294) with an SAE involving hyperglycemia and the diagnosis of diabetes mellitus who was later found to be pregnant , as previously described (Section VII.E above). Her pregnancy is likely to be related to the new onset of hyperglycemia. Only one ADO is listed as an outlier (S689.138.18118) but the S discontinued the study drug because of acne. This S had abnormal hematology parameters consistent with anemia at baseline, as well as on Day 3 of treatment.

VI.B.4 in the appendix. While weight was also obtained at baseline and at the end of treatment cycle 3, data on weight or use of outlier criteria for flagging outliers on weight or weight change were not conducted. Instead, the investigator recorded weight gain or loss as an AE.

J.1 Analysis of Central Tendency in Completed PMDD Trials (677, 688 and 689).
Table VII.J.1, in the appendix and shows the mean change from baseline to treatment endpoint of each vital sign parameter for each treatment group for the three PMDD trials, combined. Treatment groups were generally similar on mean baseline and mean change from baseline on each parameter.

J.2 Analysis of Outliers in Completed PMDD Trials (677, 688 and 689).
Table VII.J.2. in the appendix provides the outlier criteria for vital sign parameters. Out of 887 Ss from which a baseline and post-baseline assessment was obtained, only one S met outlier criteria. This S (S677.029.22187) had low systolic blood pressure that appeared to be pre-existing is not described as being associated with AEs (also it did not result in treatment cessation).[6] One S (S677.029.22211) had an SAE of supraventricular tachycardia, as previously described under Section VII.E on SAEs. None of the ADOs were described as being due to meeting outlier criteria on vital sign parameters or for abnormal values on these parameters.

The table below shows the incidence rates of vital sign related AEs in which vital sign values did not meet PCS (also referred to as outlier) criteria. Four Ss in each PaxCR group (a total of 8 PaxCR Ss) had AEs of tachycardia or supraventricular tachycardia in contrast to no placebo Ss having these AEs. The investigators considered these events to be possibly drug related in 3 out of 4 Ss in each PaxCR group (a total of 6 PaxCR Ss). No other information was provided, on these 3 Ss. The sponsor includes supraventricular tachycardia in the "Other Events Observed During the Clinical Development of Paroxetine" subsection of the "Adverse Reactions" section of proposed labeling.

Treatment Phase Emergent Adverse Events Pertaining to Vital Signs that Did Not Meet Outlier Criteria - Studies 677, 688 and 689 Combined (ITT Population)*

	Treatment Group					
	Paroxetine CR 25mg N = 348		Paroxetine CR 12.5mg N = 333		Placebo N = 349	
Preferred Term	**n**	**%**	**n**	**%**	**n**	**%**
Total subjects with at least one vital sign AE	6	1.7	5	1.5	4	1.1
Hypertension	2	0.6	1	0.3	2	0.6
Hypotension	1	0.3	0	-	2	0.6
Supraventricular Tachycardia	2	0.6	0	-	0	-
Tachycardia	2	0.6	4	1.2	0	-

*This is Table 30 in the ISS (Data Source: ISS Table 7. 2. 1)

[6] Low blood pressure values occurred at several study visits in S S677.029.22187 including the end of Reference Cycle 1 (80 mmHg), with the same reading at the end of Treatment Cycle 2. Her blood pressure fluctuated over time, with a reading of 120 mmHg at end of Reference Cycle 2.

L. Overdose Experience

The sponsor described two postmarketing SAEs of overdose (A0269210A and B0207337A) that did not reveal any new information not already described in the Overdosage section of current, approved labeling. No overdoses were reported during the PMDD trials described in the submission.

M. Safety Results from Other Sources

Literature. Only 3 articles were revealed from the literature search conducted by the sponsor (refer to IV.D. for search methods employed). These articles did not report any new or unexpected findings.

Post Marketing Reports. The postmarketing history of PaxCR was previously provided under Sections I and IV.C of this review. A search of the sponsor's postmarketing database revealed 18 reports that meet ICH guidelines for an SAE classification. These SAEs did not reveal any new or unexpected findings or appeared to be events related to other factors.

N. Conclusions on Safety Results.

Overall safety results appear to show that PaxCR is adequately safe for treatment of patients with PMDD as proposed. The safety profile of PaxCR in PMDD patients is generally similar to that observed in other patient populations, as described in current labeling with a few exceptions summarized below. Recommendations for labeling based on these safety results are provided in Section X B, "Conclusions and Recommendations."

ADOs (≥1% incidence rate in PaxCR groups, combined, and twice that of placebo) listed in the summary table in Section VII.F were generally similar to those observed in other patient populations (refer to current PaxCR labeling) with a possible exception of "Concentration Impaired." This event did not meet the incidence rate criteria of ≥1% and twice placebo in clinical trials of other patient populations described in current labeling. Perhaps this observation is confounded by the presence of the PMDD symptom of "difficulty in concentration," which is listed as one of the symptoms of PMDD in the DSM-IV. Furthermore, the incidence rate of PaxCR ADOs due to "Impaired Concentration" (only 1.3%) just makes the cut-off criteria (1% or greater) to be included in the summary table in Section VII.F and is therefore only considered a minor exception to that observed in other patient populations.

Common AEs (≥5% incidence rate) that showed an incidence rate in the PaxCR groups, combined, that was at least twice that of placebo were generally similar to that observed in other patient populations described in current labeling.

Several ADOs and AEs were also found to be dose-dependent (refer to summary tables in Sections VII F and H). Currently labeling notes dose-dependent AEs observed in fixed dose trials of the immediate release formulation (the actual AEs are not listed). Dose dependent ADOs or AEs in PaxCR trials are not described in current labeling (previous clinical trials in other patient populations employed a flexible dose design).

Ss were examined for AEs after cessation of double-blind treatment in the PMDD trials (Ss returned for a follow-up visit, 14 days post-treatment cessation). Several AEs occurred in at least 2% of the 25 mg PaxCR group with an incidence of at least twice that of the 12.5 mg PaxCR group, as well as placebo. These AEs included dizziness, nausea and nervousness among a few others. Current labeling only describes results of AEs reported in clinical trials associated

with cessation of the immediate release formulation in trials using a taper phase regimen, but not with cessation of PaxCR treatment in clinical trials. It is difficult to interpret these follow-up phase results. However, one consideration is that they may be reflecting potential withdrawal effects, as described in a Clinical review of the supplemental NDA for Paxil™ (the immediate release formulation) for the Post Traumatic Stress disorder (PTSD) indication (refer to the review of the original 7/21/00 NDA 20-031 SE1-029 submission). Attachment 3 has selected sections from this earlier Clinical review, provided for the convenience of the reader.

Clinical safety parameters (laboratory and vital sign parameters) failed to reveal any new or unexpected safety results. However, only approximately one third of ITT Ss had an "on-treatment" assessment conducted. According to the protocol safety assessments were conducted on only one time-point during the double-blind treatment phase (at the end of treatment cycle 3). Only one ADO was associated with abnormal laboratory values and one SAE was associated with hyperglycemia, which was likely to be related to pregnancy.

VIII. Dosing, Regimen and Administration Issues

A. Initial Treatment. The sponsor recommends a starting daily dose of 12.5 mg PaxCR that may be increased after a minimum period of one week to the daily dose of 25 mg in nonresponders. For reasons already discussed in section VI.B.10 of this review, the sponsor's treatment recommendation appears to be reasonable, as long as results similar to those on VAS Mood are revealed with the VAS total score used as the primary efficacy variable.

IX. Use in Special Populations

This supplemental NDA did not include special population studies. Refer to current, approved PaxCR labeling for observations and recommendations pertinent to the elderly population, patients with impaired renal or hepatic function.

X. Conclusions and Recommendations

A. Overall Conclusions and Recommendations

Studies 677, 688 and 689 provide evidence for greater improvement on the LP VAS Mood score in PMDD patients administered 12.5 mg or 25 mg of daily PaxCR compared to placebo over 3 treatment cycles. However, the VAS Mood score only assesses a subset of PMDD symptoms. Therefore, this efficacy measure is not adequately comprehensive in assessing all 11 symptoms of PMDD (as listed in the DSM-IV) to support a PMDD claim. The LP VAS-total scale or a comparable rating scale (encompassing all 11 symptoms) was the primary efficacy assessment used in trials to support PMDD claims for drugs, previously approved for this indication. The sponsor is currently conducting an analysis of their data using the LP VAS total score (as described in Attachment 2 of this review). From a Clinical perspective, it is recommended that this sNDA be given an approvable status, if the following criteria are met:

- The sponsor reveals significantly greater improvement on the LP VAS total score (from baseline to Treatment Cycle 3 endpoint) in at least the high dose PaxCR group compared to placebo in at least two trials of the three trials
- If the sponsor reveals positive results, as above, then it is recommended that these results be confirmed by the Biometric consultant.
- The consultative review from the Division of Scientific Investigation (which is pending at this time) should also reveal no remarkable findings that would impact on the interpretation of the sponsor's results.

If the above criteria are not met, then it is recommended from a Clinical perspective, that an approvable status not be granted for this supplemental NDA.

PaxCR treatment in PMDD patients as proposed appears to be adequately safe for the PMDD population. This conclusion is based on results of the sponsor's three trials (677, 688 and 689), coupled with that known regarding other SSRIs (including Sarafem™ and Zoloft™ for the PMDD population) and SSRIs approved for other patient populations, as described in current labeling for these drugs. Refer to Section VII.N for more details on the safety profile of PaxCR in PMDD patients and potential dose-related effects on the incidence rates of AEs and ADOs.

Several safety related concerns pertinent to the class of SSRIs are currently being examined by the Division's Safety Group and the Agency's Office of Drug Safety. The sponsor's PMDD trials fail to reveal any new or remarkable observations relevant to these concerns.

B Key Labeling Recommendations

This subsection provides some key labeling recommendations in the case that this supplemental NDA is given approvable status.

Efficacy claims. The following addresses some key concerns regarding proposed efficacy claims in the case that positive results are revealed with the VAS-total score as the primary variable (as above).

1. It is recommended that statements claiming efficacy on the "VAS Mood" score and "on physical symptoms" are deleted (refer to page 000006 in proposed labeling) for reasons previously given in a Clinical reviews on new protocol or protocol amendment submissions under the sponsor's PaxCR PMDD IND 51,171 N081(in a 6/21/02) submission and N118 (a 9/24/02 submission). Some of the reasons are summarized in the following:

- Regarding the use of the VAS Mood score as a primary variable, this measure does not encompass or reflect symptomatology as required by DSMIV criteria for the PMDD diagnosis, As with previously approved drugs, primary efficacy measures that rate all 11 symptoms corresponding to those listed in the DSM-IV (i.e. VAS total, DRSP) are considered by the Division as acceptable primary efficacy measures
- The trials (677, 688 and 689) do not have any key secondary variables (declared a priori, that must be reproducible in at least one additional trial, with the level of significance adjusted for multiple comparisons). Therefore, results of only the primary efficacy variable may be included, according the general policy of the Division. In this case, the VAS total is considered the primary efficacy variable, as previously discussed. It is also noted that a key secondary variable (such as the VAS-Mood or VAS-physical score) that is redundant to or overlaps with the primary variable is not considered an acceptable key secondary variable.
- The sub-categorization or clustering of PMDD symptoms into "physical" versus "mood" and the use of such nomenclature, present a number of potentially misleading interpretations and/or implications (as described in the Clinical review of the N118 IND 51,171 submission). Furthermore, an established scientific and clinical basis for the proposed subclustering and nomenclature of PMDD symptoms is needed.
- Regarding a justification for using the VAS Mood and VAS physical scores in trials to support claims for efficacy on physical and/or mood symptoms of PMDD, the sponsors cites the following. A publication by Steiner et al., 1999 and data from a recently completed study (refer to page 000044 of the Study report of 689 of the submission). For some of the

following reasons, the scientific and clinical basis for a sub-categorization and nomenclature of physical versus mood items remains unclear and inadequate to this reviewer. The sponsor provided no actual data (other than results in the publications). It is not clear if the two studies cited by the sponsor involved different subjects and if subjects were different from subjects in their pivotal trials. It is not clear if the two studies were conducted independently (and were conducted independently from Studies 677, 688 and 689). Furthermore, it is not clear of subjects were exclusively those meeting DMSIV criteria for PMDD. The study by Steiner and colleagues (1999) is a *post hoc* analysis of data taken from an earlier study (Steiner et al, 1995) and only examines VAS mood items. These are only some of the issues that are not addressed by the sponsor, in addition to concerns already discussed.

2. It is recommended that the following be inserted in the labeling section on PMDD under "Clinical Trials:"

Patients on [ ] were excluded from these trials; therefore, the efficacy of [ ] in combination with [ ] for the treatment of PMDD is unknown.

The above statement is standard language generally used in labeling for PMDD when describing PMDD trials that excluded women using oral contraceptive agents. Since women using any form of systemic hormonal method of contraception were excluded (as in the eligibility criteria), consideration should be given to modifying the above statement to the following (modified language is underlined):

Patients on <u>systemic hormonal</u> contraceptives were excluded...

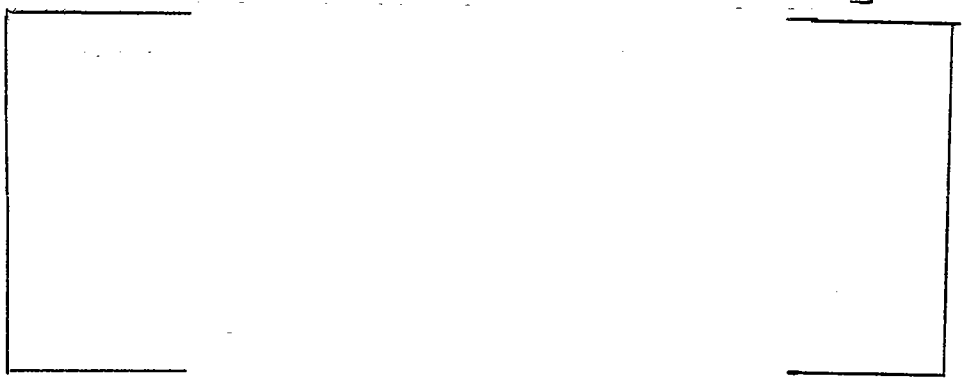
Adverse Reactions Section of Proposed Labeling.

1. It is recommended that ADOs by dose level are shown in labeling rather than collapsing the two groups since fixed doses were employed (clinical trials for current, approved indications employed flexible doses). See the following proposed labeling and a recommended version thereafter.

Proposed:

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 [ ]



Recommended Version: The following (italicized) is the recommended revised version to show events that were not only common (≥1%) but were dose dependent as defined below. The

sponsor uses Table 7.6.1.1 as their datasource for the above table (the table is indicated as showing only AEs resulting in cessation of double-blind treatment). However, Table 7.6.1X shows all AEs resulting in withdrawal during the treatment phase and shows more AEs that meet the twice that greater than placebo criteria than those shown in Table 7.6.1.1. Table 7.6.1X also shows several AEs with higher incidence rates compared to those listed in Table 7.6.1.1. It is general standard practice to include in labeling common adverse dropouts during the treatment phase of the study of the ITT safety population (Ss with at least one dose of study drug and one post-randomized safety assessment). Therefore, Table 7.6.1X was used as the data source for the recommended table below. Perhaps, further clarification is needed as to why the sponsor did not use Table 7.6.1X. Other inconsistencies appear to exist as described in the next item below (item 2). It is not clear why this discrepancy exists. These discrepancies of incidence rates for each category of AE of each PaxCR group. Therefore, the actual numbers need to be verified by the sponsor and corrected accordingly.

The most common events (≥1%) associated with discontinuation in either Paxil CR group [redacted] This table also shows those events that were dose dependent (indicated with an asterisk) as defined as events having an incidence rate [redacted] Paxil CR [redacted] that was at least twice that [redacted] Paxil CR [redacted]

	[redacted] Paxil CR N=348	[redacted] Paxil CR N=333	Placebo N=349
TOTAL	(15%)	(9.9%)	(6.3%)
Preferred Term:			
Nausea*	(6.0%)	(2.4%)	(0.9%)
Asthenia	(4.9%)	(3.0%)	(1.4%)
Somnolence*	(4.3%)	(1.8%)	(0.3%)
Insomnia[redacted]	(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 as defined as events having an incidence rate [redacted] Paxil CR [redacted] that was at least twice that [redacted] Paxil CR [redacted]*

2. Proposed labeling indicates the following:

   Thirteen percent (88/681) of patients treated with Paxil CR in PMDD studies discontinued treatment due to an adverse event.

The annotated version cites Table 7.6.1.1 and Table 21 in the Integrated Summary of Safety (ISS) as the data source (datasouce of Table 21 is Table 7.6.1.1). The above text indicates 88

ADOs among PaxCR Ss, while Table 7.6.1.1 shows a total of 83 PaxCR Ss as ADOs. Table 7.6.1X shows a total of 86 PaxCR ADOs. These differences will need clarification from the sponsor.

3. Proposed labeling does not describe AEs that showed a dose-dependent pattern in incidence. Consideration may be given to including results shown in the summary table in Section VII H of this review, as below.

[redacted]

Incidence of Common Adverse Events in Placebo, Low and High Dose PaxCR Treated Subjects in [redacted]					
	[redacted] *PaxCR* [redacted] *(N=348)*		[redacted] *PaxCR* [redacted] *(N=333)*		*Placebo* [redacted] *(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)*
[redacted]		[redacted]		[redacted]	[redacted]
Vaginitis		*(1.1%)*		*(0.3)*	*(0.3)*

4. Current approved labeling describes taper phase AEs observed with the immediate release formulation and discusses the concern of potential withdrawal effects, under the Precautions section. It is recommended that the following be considered for inclusion in labeling under the subsection of "Discontinuation of Treatment with Paxil CR" under the "Precautions" section (consistent with current labeling on this topic the criterion of an incidence of least 2% used for the immediate release treated subjects was used for the high dose Paxil CR group of the PMDD trials, as below):

[redacted]

Also consider the following. The longer half life of PaxCR in which potential withdrawal effects may be less likely than that which may occur with the immediate release formulation. The PMDD trials were not designed to examine potential withdrawal effects. Some of the follow-up

phase events, such as nervousness, anxiety, and perhaps menstrual disorder may be reflecting a relapse of PMDD symptoms upon cessation of treatment. [ ]

[ ] Also refer to Attachment 3 (for a discussion on the interpretation of results of taper phase AEs with the immediate release formulation).

5. One ADO had 5 to 12 fold increase in liver transaminase levels which can be included in the section of current labeling of adverse dropouts due to abnormal liver function tests in the "Liver Function Tests" subsection in the "Adverse Reactions" section of labeling.

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

cc: HFD 120/ K Brugge, D Bates, T Laughren, O Siddiqui, N Khin

APPENDIX

Appears This Way
On Original

Table VI.B.1 Investigator Information: Study 677

Name	Protocol/ Center	Country
Adson, David E., M.D. University of Minnesota Medical School Minneapolis, MN	677/001	US
Beyerlein, Richard A., M.D. Oregon Center for Clinical Investigations, Inc. Eugene, OR	677/002	US
Grimm, James T., M.D. Oregon Center for Clinical Investigations, Inc. Eugene, OR	677/002	US
Bielski, Robert J., M.D. Institute for Health Studies Okemos, MI	677/003	US
Bowman, Geoffrey K., M.D. Carolina Specialty Care Statesville, NC	677/005	US
Browne, Hillary L., M.D. Alpine Clinical Research Center Boulder, CO	677/006	US
Johnson, Lisa A., M.D. Providence St. Peter Family Practice Olympia, WA	677/007	US
Chiambretti, Thomas J., D.O. Group North of Lansing % Delta Medical Center Dewitt, MI	677/008	US
Cohen, Lee S., M.D. Massachusetts General Hospital Boston, MA	677/009	US

Table VI.B.1 Investigator Information: Study 677

Name Center	Protocol/	Country	Type*
Corder, Clinton N., Ph.D., COR Clinical Research L.L.C. Oklahoma City, OK	677/010	US	C, R, CPC DB, E/S
Corn, Lydia G., M.D. -Clinical Studies Sarasota, FL	677/011	US	C, R, CPC DB, E/S
David, Joseph J., M.D. Charlottesville Medical Research Charlottesville, VA	677/012	US	C, R, CPC DB, E/S
Debus, John R., M.D. Institute of Dallas Dallas, TX	677/013	US	C, R, CPC DB, E/S
Dozer, David W., M.D. Discovery Research International, LLC Greenfield, WI	677/014	US	C, R, CPC DB, E/S
Gordon, Stephen F., M.D. - Clinical Studies Atlanta, GA	677/015	US	C, R, CPC DB, E/S
England, Stephen G., M.D. Paragon Road Centerville, OH	677/016	US	C, R, CPC DB, E/S
Feldman, Robert A., M.D. Research Associates, Inc. Miami, FL	677/017	US	C, R, CPC DB, E/S
Cook, James R., M.D. (formerly Forred) Wenatchee Valley Clinic Wenatchee, WA	677/018 DB, E/S	US	C, R, CPC
Frederiksen, Marilynn C., Northwestern Medical Faculty Foundation Chicago, Il	677/019	US	C, R, CPC DB, E/S
Freeman, Ellen W., Ph.D. University of Pennsylvania Medical Center Philadelphia, PA	677/020	US	C, R, CPC DB, E/S
Steven Sondheimer J., M.D. University of Pennsylvania Medical Center Philadelphia, PA	677/020	US	C, R, CPC DB, E/S

* Report Type: C = Completed Study, O = Ongoing, CPC = Concurrent Placebo Control, DB = Double Blind, E/S = Efficacy/Safety, PK = Pharmacokinetic, R = Random

Table VI.B.1 Investigator Information: Study 677

Name Center	Protocol/	Country	Type*
Grant, Kenneth E., M.D. Merccy Health Research Chesterfield, MO	677/021	US	C, R, CPC DB, E/S
Harari, David, M.D. of San Diego San Diego, CA	677/022	US	C, R, CPC, 677 DB, E/S
Lazar, Burton W., M.D. The Portland Clinic, LLP Portland, OR	677/023	US	C, R, CPC, 677 DB, E/S
Lewis, Frederick T., D.O. S.W. 148 Avenue Suite 127 Sunrise, FL	677/024	US	C, R, CPC, 677 DB, E/S
Brown, Candace S., Pharm.D. University of Tennessee, Memphis Memphis, TN	677/025	US	C, R, CPC DB, E/S
Ling, Frank W., M.D. Jefferson, E-102 Memphis, TN	677/025	US	C, R, CPC DB, E/S
Lipetz, Robert S., D.O. Encompass Clinical Research Spring Valley, CA	677/026	US	C, R, CPC DB, E/S
Londborg, Peter D., M.D. Summit Research Network (Seattle) LLC Seattle, WA	677/027	US	C, R, CPC DB, E/S
Merod, Marjorie E.R., M.D. Wake Research Associates, LLC Raleigh, NC	677/028	US	C, R, CPC DB, E/S
Solloway, Michael L., M.D. (formerly Myers) Jacksonville Center for Clinical Research Jacksonville, FL	677/029	US	C, R, CPC DB, E/S
Palmer, Kenneth E., M.D. TQM Research, Inc. Cincinnati, OH	677/030	US	C, R, CPC DB, E/S

* Report Type: C = Completed Study, O = Ongoing, CPC = Concurrent Placebo Control, DB = Double Blind, E/S = Efficacy/Safety, PK = Pharmacokinetic, R = Random

Table VI.B.1 Investigator Information

Name Center	Protocol/	Country	Type*	Report**
Pearlstein, Teri B., M.D. Women and Infants Hospital Providence, RI	677/031	US	C, R, CPC DB, E/S	
Polan, Mary L., M.D., Ph.D. Stanford University School of Medicine Stanford, CA	677/032	US	C, R, CPC DB, E/S	
Rapkin, Andrea J., M.D. UCLA School of Medicine Los Angeles, CA	677/033	US	C, R, CPC DB, E/S	
Shockey, Gerald R., M.D. Clinic of Physicians and Surgeons, Ltd. Mesa, AZ	677/035	US	C, R, CPC DB, E/S	
Sokolski, Kenneth N., M.D. Advanced Behavioral Research Institute Anaheim, CA	677/036	US	C, R, CPC DB, E/S	
Spinelli, Margaret G., M.D. Columbia Presbyterian Medical Center New York, NY	677/037	US	C, R, CPC DB, E/S	
Tachibana, Ronald A., M.D. 3160 Folsom Boulevard Sacramento, CA	677/038	US	C, R, CPC DB, E/S	
Thoming, Christopher S., M.D. (formerly Tran) Westover Heights Clinic Portland, OR	677/039	US	C, R, CPC DB, E/S	
Warren, L. Ricks, Ph.D. Westover Heights Clinic Portland, OR	677/039	US	C, R, CPC DB, E/S	
Yonkers, Kimberly A., M.D. Yale University School of Medicine New Haven, CT	677/040	US	C, R, CPC DB, E/S	
Adan, Francoise, M.D. Health Research Associates, LLC Cleveland, OH	677/041	US	C, R, CPC DB, E/S	
Macek, Anne L., M.D. The Institute for Advanced Clinical Research Elkins Park, PA	677/042	US	C, R, CPC DB, E/S	

* Report Type: C = Completed Study, O = Ongoing, CPC = Concurrent Placebo Control, DB = Double Blind, E/S = Efficacy/Safety, PK = Pharmacokinetic, R = Random

Table VI.B.2 Investigator Information: Study 677

Name Center	Protocol/	Country	Type*
Rosenthal, Murray H., D.O. Behavioral and Medical Research, LLC San Diego, CA	677/043	US	C, R, CPC DB, E/S
Fabre, Louis F., M.D., Ph.D. Research Clinics, Inc. Houston, TX	677/044	US	C, R, CPC DB, E/S
Taylor, Leslie vH., M.D. Foundation for Health, Research and Education Middleton, WI	677/045	US	C, R, CPC DB, E/S

* Report Type: C = Completed Study, O = Ongoing, CPC = Concurrent Placebo Control, DB = Double Blind, E/S = Efficacy/Safety, PK = Pharmacokinetic, R = Random

Table VI.B.2 Investigator Information: Study 688

Name Center	Protocol/	Country	Type*
Smithers, Andrew J. The Surgery Keresley End Coventry	688/051	UK	C, R, CPC DB, E/S
O'Brien, P.M. Shaunghn North Staffordshire Maternity Hospital City General Hospital Stoke on Trent	688/052	UK	C, R, CPC DB, E/S
Al-Azzawi, Farook Leicester Royal Infirmary Leicester	688/053	UK	C, R, CPC DB, E/S
Wordsworth, Jennifer M. Community Health Sheffield Sheffield	688/054	UK	C, R, CPC DB, E/S
Belton, Mary Town Hall Clinic Bray	688/055	IR	C, R, CPC DB, E/S
Byrne, Alan M. Scholarstown Family Practice Dublin	688/056	IR	C, R, CPC DB, E/S
O'Leary, Bernadette Rossadrehid Glen of Aherlow	688/058	IR	C, R, CPC DB, E/S
Rohde, Anke Gynaekologische Psychosomatik Universitaeklinikum Bonn Bonn	688/059 DB, E/S	GE	C, R, CPC
Lanczik, Mario H. Psychiatrische Klinik der Universitaet Erlangen Erlangen	688/060	GE	C, R, CP DB, E/S
Orengo, Pilar, M.D. GmbH Bereich Medizin München	688/061	GE	C, R, CPC DB, E/S
Schumacher, Elmar C. Private Practice Wilhemstr. 8 Düren	688/062	GE	C, R, CPC, DB, E/S
van Rossum, Tékla G.J. Trial Management Orginisation Good Clinical Practice Rotterdam- Walenburgerweg	688/063	NE	C, R, CPC, DB, E/S

* Report Type: C = Completed Study, O = Ongoing, CPC = Concurrent Placebo Control, DB = Double Blind, E/S = Efficacy/Safety, PK = Pharmacokinetic, R = Random

Table VI.B.2 Investigator Information: Study 688

Name Center	Protocol/	Country	Type*
Hoge-van Veldhuizen, G.K.M. Good Clinical Practice De Bilt	688/064	NE	C, R, CPC, DB, E/S
van Rossum, Tékla G.J. Trial Management Organisation Good Clinical Practice Rotterdam-Walenburgerweg	688/065	NE	C, R, CPC, DB, E/S
Bardelmeijer, Elisabeth A.M., M.D. Trial Management Organisation Good Clinical Practice Heerlen	688/066	NE	C, R, CPC, DB, E/S
Van Erp, Elisabeth J.M., M.D. Ziekenhuis Leyenburg Den Haag	688/067	NE	C, R, CPC, DB, E/S
Kölling, Pieternel, M.D. Medisch Spectrum Twente Enschede	688/068	NE	C, R, CPC, DB, E/S
Dermout, Sylvia M., M.D. Ziekenhuis De Heel Zaandam	688/069	NE	C, R, CPC, DB, E/S
Bremer, G.L., M.D. Justus Medische Expertises Eindhoven	688/070	NE	C, R, CPC, DB, E/S
Weyers, Christina F. Bloem Care Clinic Bloemfontein	688/071	SA	C, R, CPC, DB, E/S
Hollands, Clare E. Kenridge Hospital Parktown Johannesburg 2193	688/072	SA	C, R, CPC, DB, E/S
Magnus, Chané Northcliff Medical Center, Annexe 2 Blackheath Johannesburg	688/073	SA	C, R, CPC, DB, E/S
Ehrenborg, Agneta Specialistläkama Kungsbacka	688/074	Sweden	C, R, CPC, DB, E/S
Hammarström, Margareta, M.D. Oktaviakliniken Stockholm	688/075	Sweden	C, R, CPC, DB, E/S

* Report Type: C = Completed Study, O = Ongoing, CPC = Concurrent Placebo Control, DB = Double Blind, E/S = Efficacy/Safety, PK = Pharmacokinetic, R = Random

Table VI.B.2 Investigator Information: Study 688

Name Center	Protocol/	Country	Type*
Sellgren, Ulla Avenykliniken Göteborg	688/076	Sweden	C, R, CPC, DB, E/S
Kvint, Sonja Kvinnokliniken Skövde	688/077	Sweden	C, R, CPC, DB, E/S
Samsioe, Göran, M.D., Kvinnokliniken Universitetssjukhuset Lund	688/078	Sweden	C, R, CPC, DB, E/S
Bäckström, Torbjörn C., M.D., Ph.D. Umeå University Inst Obstetrics and Gynaecology Umeå	688/079	Sweden	C, R, CPC, DB, E/S
Apter, Dan L., M.D., Ph.D. The Family Federation of Finland The Sexual Health Clinic Helsinki	688/080	Finland	C, R, CPC, DB, E/S
Penttilä, Tuula-Anneli, M.D., Ph.D. The Family Federation of Finland Turku Clinic Turku	688/081	Finland	C, R, CPC, DB, E/S
Tuomivaara, Leena M., M.D., Ph.D. Family Federation of Finland Oulu Clinic Oulu	688/082	Finland	C, R, CPC, DB, E/S
Moen, Mette, M.D., Ph.D. Kvinneklinikken Trondheim	688/083	Norway	C, R, CPC, DB, E/S
Lunde, Tore, M.D. Kongegate 23 Larvik	688/084	Norway	C, R, CPC, DB, E/S
Jerve, Fridtjof, M.D. Ullevål Hospital Oslo	688/085	Norway	C, R, CPC, DB, E/S
Øverlie, Inger Bogstadveien Spesialistklinikk Oslo	688/086	Norway	C, R, CPC, DB, E/S
Huseby, Aage Oslo Gynekologiske Klinikk Olso	688/087	Norway	C, R, CPC, DB, E/S

* Report Type: C = Completed Study, O = Ongoing, CPC = Concurrent Placebo Control, DB = Double Blind, E/S = Efficacy/Safety, PK = Pharmacokinetic, R = Random

Table VI.B.2 Investigator Information: Study 688

Name Center	Protocol/	Country	Type*
Vukovic, Karen M.A. P.O. Box 2288 Houghton Johannesburg	688/089	SA	C, R, CPC, DB, E/S
Linde, Marianne Kvinnoläkarna AB Västerås	688/090	Sweden	C, R, CPC, DB, E/S
Eriksen, Bjarne Chr., M.D., Ph.D.,Haugesund Gyn. Klinikk AS Haugesund	688/091	Norway	C, R, CPC, DB, E/S
Hopwood, Bryan Burngreave Surgery Sheffield	688/092	UK	C, R, CPC, DB, E/S
Fryklund, Torbjörn, M.D. Läkarpraktiken Härnösand	688/093	Sweden	C, R, CPC, DB, E/S
Kelly, Kevin Emmet House Medical Centre Clonmel	688/094	IR	C, R, CPC, DB, E/S
Wade, Alan CPS Ltd. Clinical Research Center Clydebank	688/095	UK	C, R, CPC, DB, E/S
Grimshaw, Bronwyn Synexus Ltd. Reading Clinical Research Centre Reading	688/096	UK	C, R, CPC, DB, E/S
Taylor, Susan D. Synexus Ltd. Chorley Clinical Research Centre Chorley	688/097	UK	C, R, CPC, DB, E/S
Dev, Devapriya Synexus Ltd. Manchester Clinical Research Centre Manchester	688/099	UK	C, R, CPC, DB, E/S

* Report Type: C = Completed Study, O = Ongoing, CPC = Concurrent Placebo Control, DB = Double Blind, E/S = Efficacy/Safety, PK = Pharmacokinetic, R = Random

Table VI.B.3 Investigator Information: Study 689

Name Center	Protocol/	Country	Type*
Marx, Phyllis D., M.D. Chicago Center for Clinical Research Chicago, IL	689/101	US	C, R, CPC, DB, E/S
Cooper, Jay M., M.D. Women's Health Research Phoenix, AZ	689/102	US	C, R, CPC, DB, E/S
England, Donald L., M.D. Radiant Research - Eugene Eugene, OR	689/103	US	C, R, CPC, DB, E/S
Frison, Linda, M.D. PeaceHealth Medical Group Eugene, OR	689/103	US	C, R, CPC, DB, E/S
Hood, E. Walter, M.D. ICSL - Clinical Studies Atlanta, GA	689/104	US	C, R, CPC, DB, E/S
Menza, Matthew, M.D. UMDNJ - Robert Wood Johnson Medical School Piscataway, NJ	689/105	US	C, R, CPC, DB, E/S
Holland, Peter J., M.D. Boca Raton Medical Research, Inc. Boca Raton, FL	689/106	US	C, R, CPC, DB, E/S
Horowitz, Gary M., M.D. University of Missouri-Columbia Columbia, MO	689/107	US	C, R, CPC, DB, E/S
Jain, Rakesh, M.D. R/D Clinical Research, Inc. Lake Jackson, TX	689/108	US	C, R, CPC, DB, E/S
Kyser, James G., M.D. Clinical Research Associates, Inc. Nashville, TN	689/110	US	C, R, CPC, DB, E/S
Nordland, Robert A., M.D. Western OB/GYN Ridgeview Research Chaska, MN	689/111	US	C, R, CPC, DB, E/S

* Report Type: C = Completed Study, O = Ongoing, CPC = Concurrent Placebo Control, DB = Double Blind, E/S = Efficacy/Safety, PK = Pharmacokinetic, R = Random

Table VI.B.3 Investigator Information: Study 689

Name Center	Protocol/	Country	Type*
Seremetis, Stephanie V., M.D. Mount Sinai Medical Center New York, NY	689/113	US	C, R, CPC, DB, E/S
Franck, David B., M.D. Pacific Northwest Clinical Research Center Portland, OR	689/114	US	C, R, CPC, DB, E/S
Smith, Ward T., M.D. Pacific Northwest Clinical Research Center Portland, OR	689/114	US	C, R, CPC, DB, E/S
Dell, Diana L., M.D. Duke University Medical Center Durham, NC	689/115	US	C, R, CPC, DB, E/S
Stout, Anna L., Ph.D. Duke University Medical Center Durham, NC	689/115	US	C, R, CPC, DB, E/S
Adler, Lawrence W., M.D. Clinical Insights Glen Burnie, MD	689/116	US	C, R, CPC, DB, E/S
Jimenez, Raul, M.D. Medical Center Clinic, PA Pensacola, FL	689/117	US	C, R, CPC, DB, E/S
Levy, Barbara S., M.D. Women's Health Center St. Francis Pavilion Federal Way, WA	689/118	US	C, R, CPC, DB, E/S
Harashawat, Paras, M.D. 4733 S. 7th Street Terre Haute, IN	689/119	US	C, R, CPC, DB, E/S
Strauss, Abbey, M.D. ICSL - Clinical Studies Boynton Beach, FL	689/120	US	C, R, CPC, DB, E/S
Patel, Anil S., M.D. Psychiatric Centers at San Diego Vista, CA	689/121	US	C, R, CPC, DB, E/S
Targum, Steven, M.D. ICSL - Clinical Studies Philadelphia, PA	689/122	US	C, R, CPC, DB, E/S
Maizels, Max S., M.D. MedSource, Inc. Richmond, VA	689/123	US	C, R, CPC DB, E/S

* Report Type: C = Completed Study, O = Ongoing, CPC = Concurrent Placebo Control, DB = Double Blind, E/S = Efficacy/Safety, PK = Pharmacokinetic, R = Random

Table VI.B.3 Investigator Information: Study 689

Name Center	Protocol/	Country	Type*
Kerber, Irwin J., M.D. Alpha-Omega Clinical Research, Inc. Dallas, TX	689/124	US	C, R, CPC, DB, E/S
Hertzman, Marc, M.D. 11404 Old Georgetown Road, Suite 203 Rockville, MD	689/125	US	C, R, CPC, DB, E/S
Holemon, M. Lance, M.D. PsyPharma Clinical Research Phoenix, AZ	689/126	US	C, R, CPC, DB, E/S
Albala, A. Ari, M.D. Psychiatric Centers at San Diego Chula Vista, CA	689/127	US	C, R, CPC, DB, E/S
Fuller, William C., M.D. Health Science Center Sioux Falls, SD	689/128	US	C, R, CPC, DB, E/S
Kaye, Neil S., M.D. 5301 Limestone Road Suite 103 Wilmington, DE	689/129	US	C, R, CPC, DB, E/S
Goldman, Clifford D., M.D. ClinSearch, Inc. Kenilworth, NJ	689/132	US	C, R, CPC, DB, E/S
Kapila, Sneh, M.D. Clinical Neuroscience Solutions, Inc. West Palm Beach, FL	689/133	US	C, R, CPC, DB, E/S
Miller, Janice L., M.D. Clinical Neuroscience Solutions, Inc. West Palm Beach, FL	689/133	US	C, R, CPC, DB, E/S
Bergeron, Richard, M.D., Ph.D. Pierre-Janet Hospital Hull, Québec	689/136	CA	C, R, CPC, DB, E/S
Laberge, Louise, M.D. Pierre-Janet Hospital Hull, Québec	689/136	CA	C, R, CPC, DB, E/S
Chokka, Pratap R., M.D. Grey Nuns Hospital Edmonton, Alberta	689/137	CA	C, R, CPC, DB, E/S

Report Type: C = Completed Study, O = Ongoing, CPC = Concurrent Placebo Control, DB = Double Blind, E/S = Efficacy/Safety, PK = Pharmacokinetic, R = Random

Table VI.B.3 Investigator Information: Study 689

Name Center	Protocol/	Country	Type*
Costigan, Norman P., M.D. Red Deer Regional Hospital Centre Red Deer, Alberta	689/138	CA	C, R, CPC, DB, E/S
Dattani, I. Dan Acadia Medical Centre Saskatoon, Saskatchewan	689/139	CA	C, R, CPC, DB, E/S
Filteau, Marie-Josée Polyclinique Saint-Laurent Québec, Québec	689/140	CA	C, R, CPC, DB, E/S
Kjernisted, Kevin, M.D. f St. Boniface Hospital Winnipeg, Manitoba	689/141	CA	C, R, CPC, DB, E/S
Lespérance, Paul, M.D. Hospital Notre-Dame, CHUM Montreal, Québec	689/142	CA	C, R, CPC, DB, E/S
Munshi, Autar K., M.D. f 207 Alexandra Street Sydney, Nova Scotia	689/143	CA	C, R, CPC, DB, E/S
Oakander, Margaret A., M.D. Psychiatric Outpatient Services Peter Lougheed Centre Calgary, Alberta	689/144	CA	C, R, CPC, DB, E/S
Janzen, Jeannette L., M.D. Kells Medical Research Group, Inc. Pointe Claire, Québec	689/145	CA	C, R, CPC, DB, E/S
Whitsitt, Paul F., M.D. Oshawa, Ontario van Zyl, Louis T. Queen's University at Kingston General Hospital Kingston, Ontario	689/146	CA CA	C, R, CPC, C, R, CPC, DB, E/S
Lasko, Benjamin H., M.D. 2930 Islington Avenue Unit 3A Weston, Ontario	689/148	CA	C, R, CPC, DB, E/S
MacDonald, Joanne, M.D. IWK-Grace Health Centre Halifax, Nova Scotia	689/149	CA	C, R, CPC, DB, E/S

*Report Type: C = Completed Study, O = Ongoing, CPC = Concurrent Placebo Control, DB = Double Blind, E/S = Efficacy/Safety, PK = Pharmacokinetic, R = Random

Table VI.B.3 Investigator Information: Study 689

Name Center	Protocol/	Country	Type*
Levitt, Anthony J., M.D. Sunnybrook Health Sciences Centre Toronto, Ontario	689/150	CA	C, R, CPC, DB, E/S
Achyuthan, Geeta, M.D. Regina Medical Centre-203 Regina, Saskatchewan	689/151	CA	C, R, CPC, DB, E/S
Bouchard, Céline, M.D. Clinique R.S.F. Inc. Québec, Québec	689/152	CA	C, R, CPC, DB, E/S
Thérien, Manon, M.D. Clinique Woodward Sherbrooke, Québec	689/153	CA	C, R, CPC, DB, E/S

*Report Type: C = Completed Study, O = Ongoing, CPC = Concurrent Placebo Control, DB = Double Blind, E/S = Efficacy/Safety, PK = Pharmacokinetic, R = Random

Table VI.B.4 Schedule of Assessments for PMDD Trials (677, 688, 689)

	Screening Visit 1	End of Reference Cycle 1 Visit 2	End of Reference Cycle 1(a)* Visit 2 (a)	End of Reference Cycle 2 / Baseline Visit 3	End of Treatment Cycle 1 Visit 4	End of Treatment Cycle 2 Visit 5	End of Treatment Cycle 3 Visit 6	14 Day Follow-up Visit 7	28 Day Follow-up Visit 8	Early Withdrawal Visit
Informed Consent	x									
Demographic Data	x									
Vital Signs	x	x	x	x	x	x	x	x	x	x
Body Weight	x			x			x			x
Prior and Concomitant Medications	x	x	x							
Medical and Surgical History	x									
Physical Examination	x						x			x
DSM-IV Criteria	x**	x**	x**	x**						
MADRS	x									
Inclusion / Exclusion Criteria	x			x						

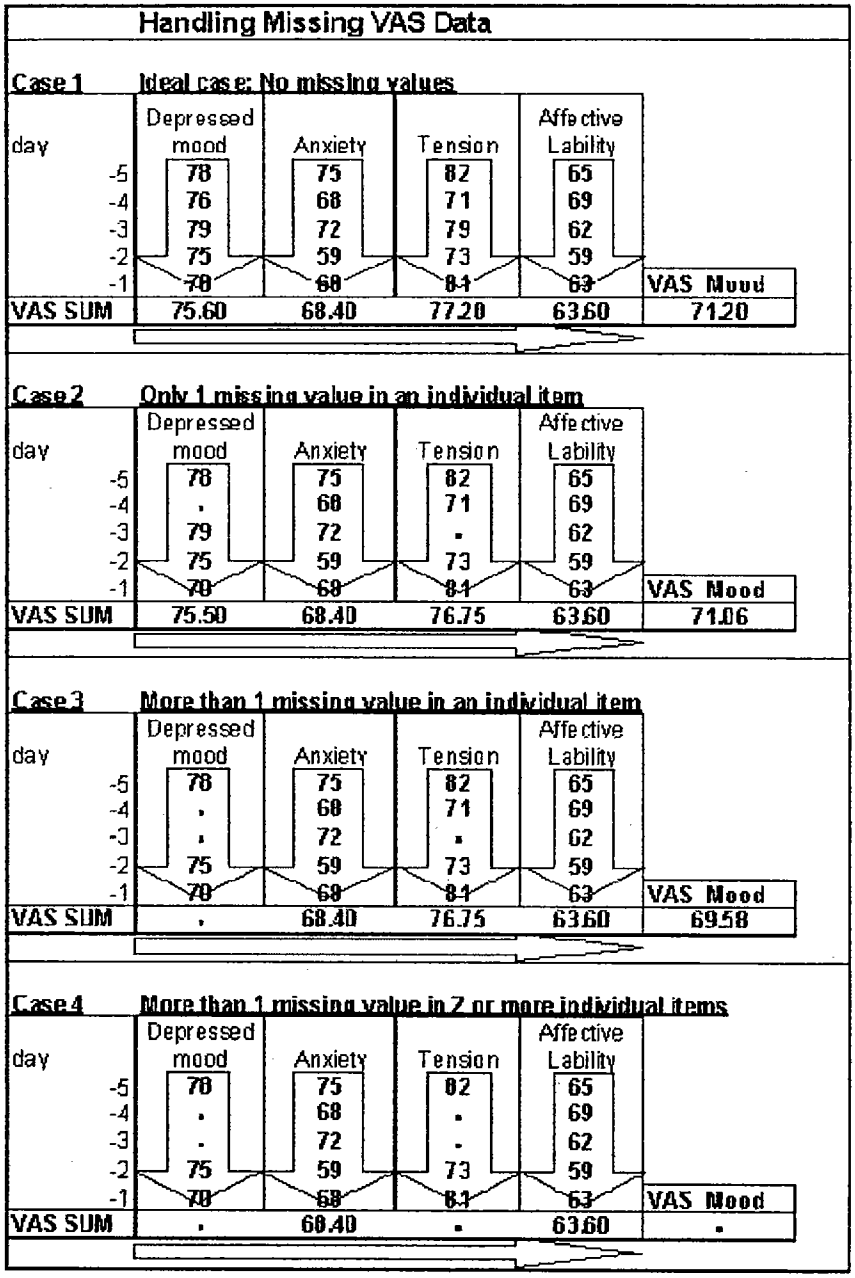
Screening was carried out in the follicular phase prior to reference cycle 1. It was scheduled to take place at least 7 days after premenstrual symptoms from the previous cycle had ended. The Montgomery Asberg Depression Rating Scale (MADRS) was completed at screening to assess depressive symptoms and the timing of this visit meant that it would be unaffected by underlying PMDD symptomatology.
Reference and treatment cycle visits took place in the follicular phase (between days 1 to 3) of the next reference or treatment cycle.
* Reference cycle 1a was only carried out if an additional reference cycle was required to confirm the diagnosis of PMDD (i.e., reference cycle 1 did not meet criteria for difference between luteal and follicular phase). End of reference cycle 1 procedures were only for those subjects who were not eligible for inclusion into the study based on their end of reference cycle 1 VAS scores. Subjects who were eligible for inclusion in the study at the end of reference cycle 1 followed the procedures under visit 2(a).
** Provisional diagnosis of PMDD (on criteria A-C) was checked at screening (visit 1). Confirmation of "on-offness" according to VAS scores was checked during the reference cycles and confirmation of the diagnosis was made at baseline.

Schedule of Assessments, continued.

	Screening Visit 1	End of Reference Cycle 1 Visit 2	End of Reference Cycle 1(a)* Visit 2 (a)	End of Reference Cycle 2 / Baseline Visit 3	End of Treatment Cycle 1 Visit 4	End of Treatment Cycle 2 Visit 5	End of Treatment Cycle 3 Visit 6	14 Day Follow-up Visit 7	28 Day Follow-up Visit 8	Early Withdrawal Visit
Dispense Diaries	x	x	x	x	x	x***	x***			
Collect Diaries		x	x	x	x	x	x			x
Concomitant Medications				x	x	x	x	x	x	x
Adverse Events		x	x	x	x	x	x	x	x	x
Obstetrics / Gynecological History			x							
PMDD History			x							
PMDD Treatment History			x							
Psychiatric History			x							
Pregnancy Test			x				x			x
Lab Evaluations			x				x	x#		x
Medication Dispensed			x	x		x***				
Medication Collected				x	x	x	x			x
CGI				x	x	x	x			x
PGE (Prompt)				x	x	x	x			x
SDS (Prompt)				x	x	x	x			
PMTS-O				x	x	x	x			
Enter Extension Study ?						x				

* Reference cycle 1a was only carried out if an additional reference cycle was required to confirm the diagnosis of PMDD (i.e., reference cycle 1 did not meet criteria for difference between luteal and follicular phase). End of reference cycle 1 procedures were only for those subjects who were not eligible for inclusion into the study based on their end of reference cycle 1 VAS scores. Subjects who were eligible for inclusion in the study at the end of reference cycle 1 followed the procedures under visit 2(a).
*** Only subjects who entered the extension study.
# Only where repeat labs were required.

Table VI.B.5. Handling of Missing Data When Calculating the VAS-Mood Score.



Handling Missing VAS Data

Case 1 Ideal case: No missing values

day	Depressed mood	Anxiety	Tension	Affective Lability	
-5	78	75	82	65	
-4	76	68	71	69	
-3	79	72	79	62	
-2	75	59	73	59	
-1	78	68	81	63	VAS Mood
VAS SUM	75.60	68.40	77.20	63.60	71.20

Case 2 Only 1 missing value in an individual item

day	Depressed mood	Anxiety	Tension	Affective Lability	
-5	78	75	82	65	
-4	.	68	71	69	
-3	79	72	.	62	
-2	75	59	73	59	
-1	78	68	81	63	VAS Mood
VAS SUM	75.50	68.40	76.75	63.60	71.06

Case 3 More than 1 missing value in an individual item

day	Depressed mood	Anxiety	Tension	Affective Lability	
-5	78	75	82	65	
-4	.	68	71	69	
-3	.	72	.	62	
-2	75	59	73	59	
-1	78	68	81	63	VAS Mood
VAS SUM	.	68.40	76.75	63.60	69.58

Case 4 More than 1 missing value in 2 or more individual items

day	Depressed mood	Anxiety	Tension	Affective Lability	
-5	78	75	82	65	
-4	.	68	.	69	
-3	.	72	.	62	
-2	75	59	73	59	
-1	78	68	81	63	VAS Mood
VAS SUM	.	68.40	.	63.60	.

Table VI.B.6. Study Disposition: Studies 677, 689 and 688 (ITT Population)

	Treatment Groups							
	Paroxetine CR 25 mg		Paroxetine CR 12.5 mg		Placebo		Total	
	N=348		N=333		N=349		N=1030	
Study 677	N=111		N=95		N=107		N=313	
	n	%	n	%	n	%	n	%
Completed study*	72	64.9	70	73.7	79	73.8	221	70.6
Total Withdrawn++	39	35.1	25	26.3	28	26.2	92	29.4
Adverse Event **	15	13.5	9	9.5	7	6.5	31	9.9
Lack of Efficacy	1	0.9	4	4.2	5	4.7	10	3.2
Protocol Deviation +	10	9.0	3	3.2	7	6.5	20	6.4
Lost to Follow-up	7	6.3	3	3.2	5	4.7	15	4.8
Other Reason	6	5.4	6	6.3	4	3.7	16	5.1
Study 689	N=120		N=115		N=124		N=359	
	n	%	n	%	n	%	n	%
Completed study*	82	68.3	89	77.4	96	77.4	267	74.4
Total Withdrawn++	38	31.7	26	22.6	28	22.6	92	25.6
Adverse Event **	20	16.7	12	10.4	9	7.3	41	11.4
Lack of Efficacy	0	0.0	3	2.6	3	2.4	6	1.7
Protocol Deviation +	5	4.2	2	1.7	5	4.0	12	3.3
Lost to Follow-up	10	8.3	4	3.5	3	2.4	17	4.7
Other Reason	3	2.5	5	4.3	8	6.5	16	4.5
Study 688	N=117		N=123		N=118		N=358	
	n	%	n	%	n	%	n	%
Completed study*	87	74.4	97	78.9	90	76.3	274	76.5
Total Withdrawn++	30	25.6	26	21.1	28	23.7	84	23.5
Adverse Event **	19	16.2	13	10.6	7	5.9	39	10.9
Lack of Efficacy	2	1.7	5	4.1	6	5.1	13	3.6
Protocol Deviation +	4	3.4	6	4.9	6	5.1	16	4.5
Lost to Follow-up	2	1.7	1	0.8	4	3.4	7	2.0
Other Reason	3	2.6	1	0.8	5	4.2	9	2.5

Data Source: Study 677, Table 12.6; Study 689, Table 12.6; Study 688, Table 12.6.

* In the opinion of the investigator, the subject completed all visits up to and including the end of Treatment Cycle 3.

** Including death as an outcome

+ Including non-compliance

+ + Total Withdrawn in this table does not include the 29 subjects in the non-ITT population who did not receive study medication or have a post baseline assessment.

Table VI.B7. Summary of Subjects Remaining in the Study at Each Visit by Study (ITT Population)

	Treatment Group					
	Paroxetine CR				Placebo	
	25 mg		12.5 mg			
	n	%	n	%	n	%
Study 677						
	N=111		**N=95**		**N=107**	
Baseline	111	100	95	100	107	100
End of TC1	95	85.6	89	93.7	98	91.6
End of TC2	81	73.0	80	84.2	89	83.2
End of TC3	67	60.4	66	69.5	78	72.9
Study 689						
N=120			**N=115**		**N=124**	
Baseline	120	100	115	100	124	100
End of TC1	106	88.3	103	89.6	118	95.2
End of TC2	94	78.3	96	83.5	108	87.1
End of TC3	78	65.0	89	77.4	93	75.0
Study 688						
N=117			**N=123**		**N=118**	
Baseline	117	100	123	100	118	100
End of TC1	96	82.1	115	93.5	113	95.8
End of TC2	90	76.9	108	87.8	102	86.4
End of TC3	86	73.5	93	75.6	82	69.5

Data Source: Study 677, Table 12.8; Study 689, Table 12.8; Study 688, Table 12.8. TC=Treatment Cycle Withdrawals are based on the last known menstrual cycle for which the subject was dosed. Subjects who did not complete dosing to the end of treatment cycle 3 were deemed early withdrawals

Table VI.B.8. Demographic Characteristics by Study - (ITT Population)

			Treatment Group		
			Paroxetine CR 25 mg	Paroxetine CR 12. 5 mg	Placebo
Study 677					
Age (years)	All	N	111	95	107
		Mean (s. d.)	35. 9 (5. 37)	35. 2 (6. 25)	34. 9 (6. 15)
		Median	37. 0	36. 0	36. 0
		Range	19. 0 to 45. 0	18. 0 to 44. 0	20. 0 to 45. 0
	18- 25	n (%)	4 (3. 6)	8 (8. 4)	12 (11.2)
	26- 35	n (%)	46 (41.4)	35 (36.8)	38 (35.5)
	≥ 36	n (%)	61 (55.0)	52 (54.7)	57 (53.3)
Race		N	111	95	107
	Caucasian	n (%)	98 (88.3)	87 (91.6)	93 (86.9)
	Non- Caucasian	n (%)	13 (11.7)	8 (8. 4)	14 (13.1)
Weight (kg)		N	111	94	107
		Mean (s. d.)	77. 6 (20.85)	70. 1 (17.23)	73. 5 (19.60)
		Median	74. 4	63. 5	68. 0
		Range	46. 7 to 158.8	41. 7 to 119.3	45. 4 to 158.8
Study 689					
Age (years)	All	N	120	115	124
		Mean (s. d.)	36. 5 (4. 87)	36. 4 (5. 82)	35. 8 (5. 79)
		Median	37. 0	37. 0	36. 0
		Range	20 to 45	20 to 45	19 to 45
	18- 25	n (%)	2 (1. 7)	7 (6. 1)	7 (5. 6)
	26- 35	n (%)	42 (35.0)	38 (33.0)	49 (39.5)
	≥ 36	n (%)	76 (63.3)	70 (60.9)	68 (54.8)
Race		N	120	115	124
	Caucasian	n (%)	116 (96. 7)	108 (93. 9)	116 (93. 5)
	Non- Caucasian	n (%)	4 (3. 4)	7 (6. 1)	8 (6. 4)
Weight (kg)		N	120	115	124
		Mean (s. d.)	74. 9 (18.19)	70. 4 (15.98)	71. 0 (16.56)
		Median	73. 0	68. 0	66. 7
		Range	45. 8 to 145.2	40. 8 to 129.0	44. 2 to 121.5

Continued on the next page.

Table VI.B.8. Demographic Characteristics by Study - (ITT Population), continued.

Study 688			Treatment Group		
			Paroxetine CR 25 mg	Paroxetine CR 12. 5 mg	Placebo
Age (years)	All	N	117	123	118
		Mean (s. d.)	36. 7 (4. 73)	37. 1 (4. 80)	36. 5 (5. 29)
		Median	37. 0	38. 0	37. 0
		Range	24. 0 to 45. 0	20. 0 to 46. 0	24. 0 to 46. 0
	18- 25	n (%)	2 (1. 7)	2 (1. 6)	3 (2. 5)
	26- 35	n (%)	39 (33.3)	38 (30.9)	48 (40.7)
	≥ 36	n (%)	76 (65.0)	83 (67.5)	67 (56.8)
Race		N	117	123	118
	Caucasian	n (%)	117 (100. 0)	121 (98.4)	118 (100. 0)
	Non- Caucasian	n (%)	-	2 (1. 6)	-
Weight (kg)		N	117	123	117
		Mean (s. d.)	68. 0 (11.91)	68. 5 (13.93)	71. 0 (15.79)
		Median	65. 0	65. 0	66. 0
		Range	50. 0 to 110.0	50. 0 to 162.0	46. 0 to 135.0

Data Source: Study 677, Table 12. 12; Study 677, Table 12. 16; Study 689, Table 12. 12; Study 689, Table 12. 16; Study 688, Table 12.12; Study 688, Table 12. 16

Table VI.B.9. Mean Baseline Efficacy Scores by Study - Studies 677, 689 and 688 (ITT Population)

	Treatment Groups								
	Parox CR 25 mg			**Parox CR 12.5 mg**			**Placebo**		
Rating Scale	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**
Study 677									
N	**111**			**95**			**107**		
VAS-Mood Score	110	*54.5*	20.45	93	*60.3*	21.79	105	*53.9*	22.58
SDS									
Work Item	100	*5.3*	2.52	87	*5.3*	2.58	98	*5.1*	2.62
Social Life Item	103	*5.8*	2.59	90	*6.1*	2.58	99	*5.8*	2.75
Family Life Item	103	*6.6*	2.41	90	*6.6*	2.36	99	*6.6*	2.39
CGI-Severity of Illness	110	*4.3*	0.77	95	*4.2*	0.82	105	*4.3*	0.66
PMTS-O Total Score	109	*22.8*	4.97	95	*22.8*	5.32	105	*23.0*	6.09
Study 689									
N	**120**			**115**			**124**		
VAS-Mood Score	120	*51.5*	22.16	144	*55.1*	21.17	124	*52.6*	21.79
SDS									
Work Item	114	*4.9*	2.36	108	*5.4*	2.49	113	*5.0*	2.53
Social Life Item	115	*5.7*	2.20	110	*6.0*	2.51	117	*5.7*	2.48
Family Life Item	115	*6.5*	2.24	110	*6.9*	2.20	116	*6.8*	2.27
CGI-Severity of Illness	120	*4.4*	0.75	114	*4.5*	0.72	121	*4.5*	0.84
PMTS-O Total Score	120	*21.8*	4.91	114	*22.0*	4.71	121	*22.9*	4.30
Study 688									
N	**117**			**123**			**118**		
VAS-Mood Score	116	*48.0*	22.06	122	*55.1*	24.72	116	*57.9*	23.54
SDS									
Work Item	105	*5.4*	2.72	112	*5.3*	2.51	108	*5.5*	2.75
Social Life Item	113	*6.2*	2.60	114	*5.8*	2.56	110	*6.5*	2.38
Family Life Item	113	*7.0*	2.34	114	*6.7*	2.37	110	*7.1*	2.33
CGI-Severity of Illness	116	*4.7*	0.94	122	*4.8*	1.04	117	*4.7*	1.19
PMTS-O Total Score	117	*22.4*	5.68	122	*22.3*	5.97	117	*22.6*	5.47

Table 18 in the ISE (Data Source: Study 677, Table 13.5; Study 677, Table 13.29; Study 677, Table 13.32; Study 677, Table 13.33; Study 689, Table 13.5; Study 689, Table 13.29; Study 689 Table 13.32; Study 689, Table 13.33; Study 688, Table 13.5; Study 688, Table 13.29; Study 688, Table 13.32; Study 688, Table 13.33)

Table VI.B.10. Summary of Efficacy Results by Treatment Cycle on the Primary Efficacy Variable for Studies 677 (Panel A), 688 (Panel B) and 689 (Panel C).

Panel A. Study 677. Summary Statistics for Mean Luteal Phase VAS-Mood Scores (ITT Population)				
		Treatment Group		
Treatment Cycle	**Statistics**	**Parox CR 25 mg N= 111**	**Parox CR 12.5 mg N= 95**	**Placebo N= 107**
Baseline	N	110	93	105
	Mean (s. d.)	54.5 (20.45)	60.3 (21.79)	53.9 (22.58)
	Median	53.7	60.4	53.0
	Range	5.1 to 99.7	15.0 to 99.5	2.0 to 98.4
Treatment Cycle 1	N	98	89	98
	Mean (s. d.)	20.7 (23.00)	27.4 (24.15)	37.3 (26.97)
	Median	9.4	19.3	30.3
	Range	0.2 to 90.6	0.05 to 91.8	0.6 to 97.8
Treatment Cycle 2	N	80	78	88
	Mean (s. d.)	21.1 (24.79)	27.4 (25.09)	33.6 (28.04)
	Median	10.2	20.2	24.2
	Range	0.45 to 94.7	0.2 to 98.7	0.4 to 96.9
Treatment Cycle 3	N	70	67	79
	Mean (s. d.)	18.2 (21.39)	22.0 (21.89)	30.5 (26.33)
	Median	10.4	16.7	21.7
	Range	0.4 to 96.4	0.5 to 90.4	0.65 to 97.2
Data Source: Table 13. 5 N is the number of subjects with an assessment.				

Panel B. Study 688. Summary Statistics for Mean Luteal Phase VAS-Mood Scores (ITT Population)				
		Treatment Group		
Treatment Cycle	**Statistics**	**Parox CR 25 mg N= 117**	**Parox CR 12.5 mg N= 123**	**Placebo N= 118**
Baseline	N	116	122	116
	Mean (s. d.)	48.0 (22.06)	55.1 (24.72)	57.9 (23.54)
	Median	44.3	51.8	54.4
	Range	6.0 to 99.7	9.1 to 100.0	5.7 to 100.0
Treatment Cycle 1	N	95	114	110
	Mean (s. d.)	18.2 (22.40)	27.7 (27.91)	37.4 (26.26)
	Median	7.9	15.9	32.7
	Range	0.0 to 98.1	0.0 to 99.9	1.2 to 96.2
Treatment Cycle 2	N	89	107	101
	Mean (s. d.)	16.6 (18.48)	22.6 (21.69)	32.2 (28.15)
	Median	11.1	16.1	25.0
	Range	0.6 to 85.7	0.0 to 99.5	0.0 to 100.0
Treatment Cycle 3	N	85	94	86
	Mean (s. d.)	17.2 (20.80)	19.3 (19.20)	24.3 (20.90)
	Median	9.4	15.0	19.6
	Range	0.4 to 99.6	0.0 to 89.1	0.6 to 83.0
Data Source: Table 13. 5 N is the number of subjects with an assessment.				

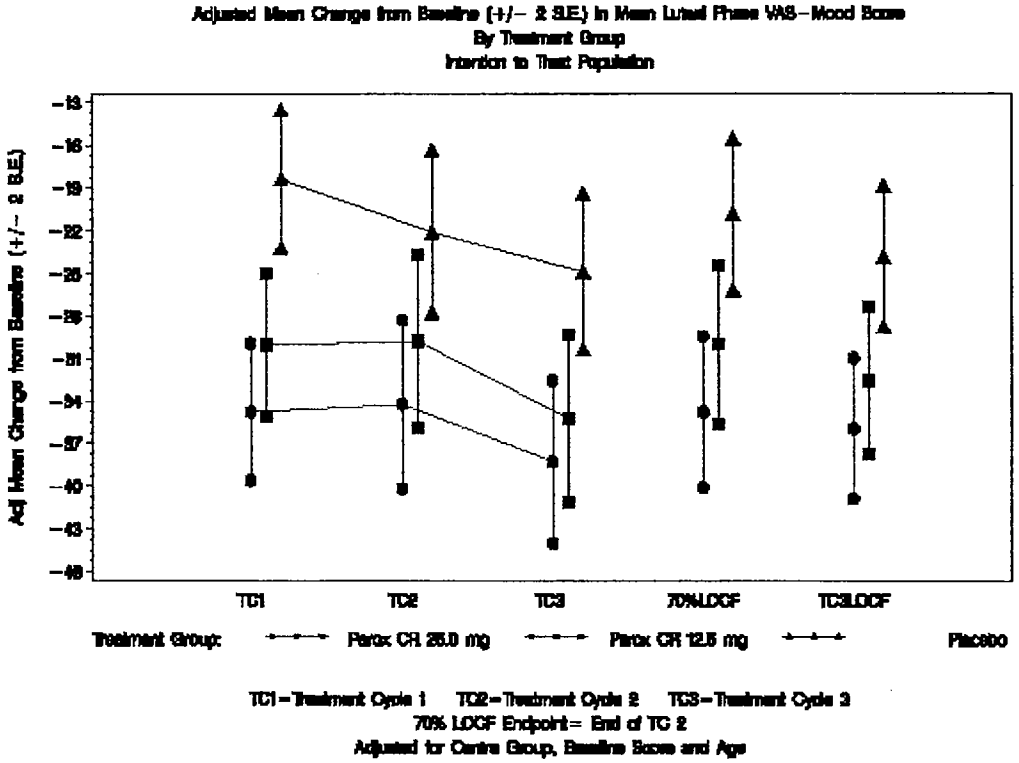
Continued on the next page.

Table VI.B.10. Summary of Efficacy Results by Treatment Cycle on the Primary Efficacy Variable for Studies 677 (Panel A), 688 (Panel B) and 689 (Panel C), Continued.

Panel B. Study 689. Summary Statistics for Mean Luteal Phase VAS-Mood Scores (ITT Population)				
		Treatment Group		
Treatment Cycle	**Statistics**	**Parox CR 25 mg N= 120**	**Parox CR 12.5 mg N= 115**	**Placebo N= 124**
Baseline	N	120	114	124
	Mean (s. d.)	51.5 (22.16)	55.1 (21.17)	52.6 (21.79)
	Median	46.9	52.3	48.9
	Range	12.1 to 99.8	10.5 to 100.0	12.5 to 100.0
Treatment Cycle 1	N	103	103	118
	Mean (s. d.)	20.9 (22.16)	26.9 (26.55)	36.2 (25.47)
	Median	12.1	17.2	33.1
	Range	0 to 98.7	0.1 to 100.0	0 to 96.1
Treatment Cycle 2	N	93	95	107
	Mean (s. d.)	15.5 (20.80)	20.6 (21.46)	32.2 (24.05)
	Median	7.5	12.0	27.0
	Range	0 to 98.3	0.2 to 86.7	0.4 to 97.1
Treatment Cycle 3	N	78	92	95
	Mean (s. d.)	16.9 (19.36)	20.1 (23.09)	27.8 (23.12)
	Median	9.4	9.9	23.3
	Range	0.4 to 97.3	0 to 92.3	0.3 to 95.5
Data Source: Table 13.5				

Figure VI.B.11. Adjusted Mean Change on the LP VAS Mood Score by Treatment Cycle for Studies 677, 688 and 689 (Panels A, B, C, respectively), continued on next page

Panel A. Study 677



Data Source: Figure 13.1

Panel B. Study 688

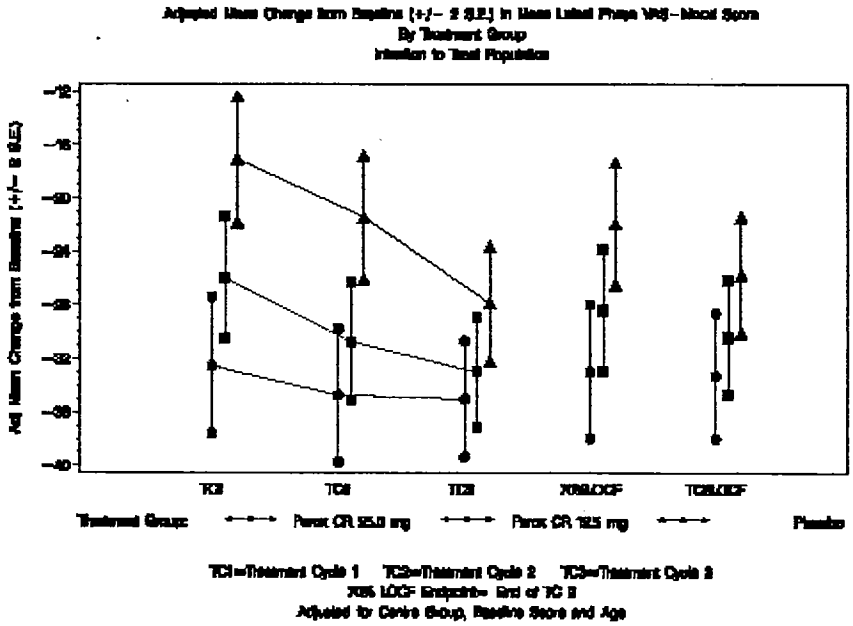


Figure VI.B.11. Adjusted Mean Change on the LP VAS Mood Score by Treatment Cycle for Studies 677, 688 and 689 (Panels A, B, C, respectively), continued

Panel A. Study 689

Adjusted Mean Change from Baseline (± 2 s.e.) in Mean Luteal Phase VAS-Mood Scores by Treatment Group (ITT Population)

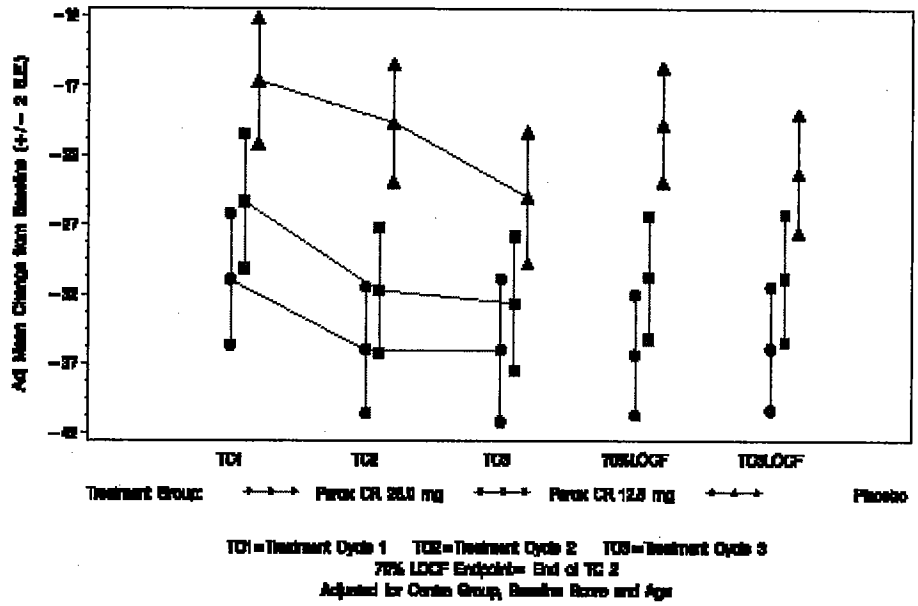


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Table VII.C.1

Overall Duration of Exposure to Study Medication
Studies 677, 688 and 689 Combined
Intention to Treat Population

Patient Exposure (Days)	Parox CR 25.0 mg N	%	Parox CR 12.5 mg N	%	Placebo N	%	Total N	%
1-7 Days	18	5.2%)	11	(3.3%)	7	(2.0%)	36	(3.5%)
8-14 Days	16	4.6%)	6	(1.8%)	4	(1.1%)	26	(2.5%)
15-21 Days	9	2.6%)	2	(0.6%)	6	(1.7%)	17	(1.7%)
22-28 Days	18	5.2%)	12	(3.6%)	7	(2.0%)	37	(3.6%)
29-60 Days	29	8.3%)	23	(6.9%)	38	(10.9%)	90	(8.7%)
>=61 Days	258	(74.1%)	279	(83.8%)	287	(82.2%)	824	(80.0%)
Total	348	(100.0%)	333	(100.0%)	349	(100.0%)	1030	(100.0%)
Overall Mean	66.6		72.5		72.3		70.4	
Std Dev	27.62		22.91		21.54		24.31	
Median	77.5		79.0		78.0		78.0	
Min	1		1		1		1	
Max	107		120		115		120	

Table VII.E.1. Treatment Phase Serious Adverse Events in Studies 677, 688 and 689, combined

Subject Number	Age (years)	Serious AE (preferred term)	Relative Onset Day*	Duration (Days)	Intensity	Relationship	Action on Study Medication
		Treatment Phase Emergent Serious AEs					
Paroxetine CR 25 mg							
677.010.12736	34	Trauma	34 (0)	1	Severe	Unrelated	None
677.029.22211	40	Supraventricular tachycardia	3 (- 88)	1	Severe	Probably Unrelated	None
Paroxetine CR 12.5 mg							
689.115.16294	35	Diabetes mellitus	22 (- 1)	Continuing	Moderate	Unrelated	Drug Stopped
		Unintended pregnancy	5 (- 18)	Continuing	Not Specified	Unrelated	Drug Stopped
Placebo							
688.067.14865	44	Myalgia	27 (- 54)	3	Severe	Unrelated	None
689.123.16916	21	Abortion	13 (- 20)	43	Severe	Unrelated	Drug Stopped

Data Source: Study 677 SAS Datasets, Study 688 SAS Datasets and Study 689 SAS Datasets
*Days relative to start of study medications (days relative to stop of study medication)

Table VII.E.2. Follow-up Phase Serious Adverse Events in Studies 677, 688 and 689, combined

Subject Number	Age (years)	Serious AE (preferred term)	Relative Onset Day*	Duration (Days)	Intensity	Relationship	Action on Study Medication
		Follow- up Phase Emergent Serious AEs					
Paroxetine CR 25 mg							
677.035.22658	37	Unintended pregnancy	29 (2)	Continuing	Severe	Unrelated	Drug Stopped
688.055.13929	39	Infection	99 (4)	65	Severe	Unrelated	None
		Vertigo	99 (4)	65	Severe	Unrelated	None
689.120.16705	39	Abortion**	57 (1)	4	Severe	Unrelated	Drug Stopped
Paroxetine CR 12.5 mg							
677.012.12868	29	Unintended pregnancy	6 (5)	Continuing	Severe	Unrelated	Drug Stopped
677.023.21765	22	Unintended pregnancy†	64 (1)	15	Severe	Unrelated	None
689.115.16294	35	Hyperglycemia	45 (22)	4	Moderate	Unrelated	Not Applicable
689.117.16473	37	Stillbirth	85 (1)	38	Severe	Unrelated	Drug Stopped
Placebo							
677.039.22966	23	Unintended pregnancy	43 (1)	12	Severe	Unrelated	Drug Stopped
		Abortion	54 (12)	1	Severe	Unrelated	None

Data Source: Study 677 SAS Datasets, Study 688 SAS Datasets and Study 689 SAS Datasets
*Days relative to start of study medication (days relative to stop of study medication)
** This event was incorrectly not flagged as a serious AE in the clinical database, but was reported from the OCEANS database for serious AEs.

Table VII.E.3. Serious Adverse Events in Ongoing Studies 711 and 717.

Subject Number	Age (years)	Serious AE (preferred term)	Relationship	Outcome
Study 711				
711.021.13561	41	Hypersensitivity NOS	Unrelated	Resolved
711.024.21827	44	Bronchitis NOS	Unrelated	Resolved
711.052.13701	25	Ovarian cyst	Unrelated	Resolved
711.064.14634	36	Unintended pregnancy	Unrelated	Resolved
711.067.14897	38	Injury NOS	Unrelated	Resolved
711.069.15006	32	Abortion NOS	Unrelated	Resolved
711.084.20209	41	Calculus renal NOS	Unrelated	Resolved
711.092.21115	36	Myocardial infarction	Unrelated	Unknown
711.111.15996	45	Diverticulitis NOS	Unrelated	Resolved
711.139.18182	33	Gastroenteritis	Unrelated	Resolved
711.144.18557*	30	Stillbirth	Unrelated	Resolved
Study 717				
717.701.32111	33	Hypersensitivity NOS	Related	Resolved
717.701.32125	32	Abortion NOS	Unrelated	Resolved

Data Source: OCEANS database, data available upon request.

*The serious AE of stillbirth was reported to GSK as occurring in the follow-up phase of Study 689. However, on review of start dates of study medication for Study 711, this subject was classified as continuing into Study 711. Therefore, this follow-up event is being reported as part of Study 711.

Table VII.H.1. Treatment Emergent Adverse Events that Occurred in at Least 1% of Paroxetine CR Subjects in Studies 677, 688, and 689, Combined (ITT Population)

	Paroxetine CR* (N = 681)	Placebo (N = 349)
Body System/Preferred Term	**n (%)**	**n (%)**
At least one AE	518 (76.1)	215 (61.6)
Body as a Whole		
Asthenia	118 (17.3)	20 (5.7)
Headache	103 (15.1)	42 (12.0)
Infection	42 (6.2)	15 (4.3)
Cardiovascular System		
Migraine	9 (1.3)	3 (0.9)
Digestive System		
Nausea	118 (17.3)	23 (6.6)
Diarrhea	38 (5.6)	7 (2.0)
Constipation	32 (4.7)	4 (1.1)
Dry Mouth	27 (4.0)	7 (2.0)
Increased Appetite	17 (2.5)	3 (0.9)
Decreased Appetite	15 (2.2)	2 (0.6)
Dyspepsia	15 (2.2)	5 (1.4)
Musculoskeletal System		
Myalgia	15 (2.2)	7 (2.0)
Arthralgia	11 (1.6)	5 (1.4)
Nervous System		
Libido Decreased	78 (11.5)	17 (4.9)
Somnolence	62 (9.1)	6 (1.7)
Insomnia	54 (7.9)	7 (2.0)
Dizziness	46 (6.8)	12 (3.4)
Tremor	26 (3.8)	1 (0.3)
Concentration Impaired	20 (2.9)	2 (0.6)
Nervousness	12 (1.8)	2 (0.6)
Anxiety	12 (1.8)	4 (1.1)
Lack of Emotion	10 (1.5)	3 (0.9)
Abnormal Dreams	9 (1.3)	1 (0.3)
Respiratory System		
Yawn	14 (2.1)	1 (0.3)
Pharyngitis	13 (1.9)	6 (1.7)
Cough Increased	7 (1.0)	2 (0.6)
Skin and Appendages		
Sweating	45 (6.6)	3 (0.9)
Pruritis	8 (1.2)	4 (1.1)
Urogenital		
Female Genital Disorders	53 (7.8)	4 (1.1)
Menorrhagia	7 (1.0)	3 (0.9)
Vaginal Moniliasis	7 (1.0)	2 (0.6)

This table is ISS Table 45 (Data Source: ISS Table 15.1.1)

*Adverse events for which paroxetine CR reporting incidence was less than or equal to placebo are not included. These events are: abdominal pain, back pain, pain, trauma, vomiting, weight gain, respiratory disorder, rhinitis, sinusitis, dysmenorrhea, menstrual disorder, urinary tract infection.

Table VII.H.2. Treatment Phase Emergent Adverse Events Occurring in 2% or More of Paroxetine CR Recipients By Body System and Preferred Term -Studies 677, 688 and 689 Combined (ITT Population)

	Treatment Group					
	Paroxetine CR 25mg		Paroxetine CR 12.5mg		Placebo	
Body System	N = 348		N = 333		N = 349	
Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Body as a whole						
Abdominal Pain	5	1.4	7	2. 17		2. 0
Asthenia	64	18.4	54	16.2	20	5. 7
Back Pain	8	2.3	7	2.1	11	3. 2
Headache	57	16.4	46	13.8	42	12.0
Infection	22	6. 3	20	6.0	15	4. 3
Trauma	12	3.4	10	3. 0	11	3.2
Digestive System						
Constipation	18	5. 2	14	4. 2	4	1. 1
Decreased Appetite	8	2. 3	7	2. 1	2	0. 6
Diarrhea	19	5.5	19	5. 7	7	2. 0
Dry Mouth	17	4. 9	10	3.0	7	2.0
Dyspepsia	9	2.6	6	1. 8	5	1. 4
Increased Appetite	11	3. 2	6	1. 8	3	0. 9
Nausea	78	22.4	40	12.0	23	6. 6
Vomiting	7	2.0	3	0. 9	8	2. 3
Metabolic and Nutritional Disorders						
Weight Gain	10	2.9	6	1. 8	8	2. 3
Musculoskeletal System						
Myalgia	6	1.7	9	2. 7	7	2. 0
Nervous System						
Anxiety	8	2.3	4	1. 2	7	1. 1
Concentration Impaired	15	4. 3	5	1. 5	2	0. 6
Dizziness	26	7.5	20	6. 0	12	3.4
Insomnia	35	10.1	19	5. 7	7	2. 0
Libido Decreased	43	12.4	35	10.5	17	4. 9
Nervousness		72.0	5	1. 52		0. 6
Somnolence	36	10.3	26	7. 8	6	1. 7
Tremor	21	6.0	5	1. 5	1	0. 3
Respiratory System						
Pharyngitis	9	2.6	4	1. 2	6	1. 7
Respiratory Disorder	14	4.0	24	7. 2	28	8.0
Sinusitis	9	2. 6	10	3.0	18	5. 2
Yawn	11	3.2	3	0. 9	1	0. 3
Skin and Appendages						
Sweating	31	8. 9	14	4.2	3	0.9
Urogenital System						
Dysmenorrhea	6	1. 7	16	4.8	22	6. 3
Female Genital Disorders	33	9.5	20	6. 0	4	1. 1

This is Table 11 page 000057 of the ISS (Datasource: ISS Table 7. 2. 1)

Table VII.I.1. Mean Baseline Values and Change from Baseline at Endpoint in Hematology Parameters - Studies 677, 688 and 689 Combined (ITT Population)*

Laboratory Parameter	Treatment Group: Paroxetine CR 25mg N = 348			Paroxetine CR 12.5mg N = 333			Placebo N = 349		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
Hemoglobin (G/ L)									
Baseline	345	130.4	9.91	332	130.9	9.61	346	129.8	9.45
Δ at Endpoint	80	-1.5	6.32	90	-0.4	6.78	99	-1.5	5.71
Hematocrit (%)									
Baseline	345	39.0	2.73	332	39.1	2.88	346	38.9	2.72
Δ at Endpoint	80	-0.5	1.92	90	0.1	2.13	99	-0.3	1.76
RBC Count ($x10^{12}$ L)									
Baseline	345	4.3	0.28	332	4.3	0.31	346	4.3	0.33
Δ at Endpoint	80	0.0	0.21	90	0.0	0.21	99	0.0	0.19
WBC Count ($x10^{9}$ L)									
Baseline	345	6.6	1.72	332	6.4	1.95	346	6.6	1.90
Δ at Endpoint	80	0.1	1.46	90	0.3	1.67	99	0.1	1.54
Neutrophils (%)									
Baseline	346	61.1	8.36	332	60.0	8.45	346	61.2	7.73
Δ at Endpoint	83	-0.8	7.57	91	0.9	9.37	100	-0.1	6.65
Lymphocytes (%)									
Baseline	346	30.5	7.32	332	31.4	7.44	346	30.4	6.81
Δ at Endpoint	83	1.0	6.23	91	-0.1	7.94	100	0.4	5.90
Monocytes (%)									
Baseline	346	5.2	2.02	332	5.5	2.20	346	5.4	1.91
Δ at Endpoint	83	0.0	2.35	91	-0.6	2.03	100	-0.3	1.80
Eosinophils (%)									
Baseline	346	2.8	2.01	332	2.8	1.94	346	2.7	1.79
Δ At Endpoint	83	-0.2	1.65	91	-0.3	2.23	100	0.0	1.70
Basophils (%)									
Baseline	346	0.3	0.22	332	0.3	0.21	346	0.3	0.19
Δ At Endpoint	83	0.0	0.22	91	0.0	0.28	100	0.0	0.24
Platelets (x10 L) 9									
Baseline	345	273.2	54.40	332	263.4	55.97	346	270.6	54.25
Δ at Endpoint	80	2.0	28.61	90	9.5	42.86	99	3.9	30.08

*Table 27 in the ISS (Data Source: ISS Table 10. 2. 1)
Δ= change.

Table VII.I.2. Mean Baseline Values and Change from Baseline at Endpoint in Chemistry Laboratory Parameters - Studies 677, 688 and 689 Combined (ITT Population)*

Laboratory Test Groupings	Treatment Group Paroxetine CR 25mg N = 348			Paroxetine CR 12.5mg N = 333			Placebo N = 349		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
Liver Function									
AST (IU/ L)									
Baseline	348	17.9	5.99	332	17.4	4.65	349	17.4	7.63
Δ at Endpoint	82	0.2	6.37	91	3.5	18.90	99	0.4	4.77
ALT (IU/ L)									
Baseline	348	14.7	8.23	332	14.1	6.82	349	14.5	8.18
Δ at Endpoint	82	0.2	7.92	91	1.8	8.46	99	0.5	5.27
Alk Phos (IU/ L)									
Baseline	348	61.2	17.38	332	59.8	17.21	349	60.6	16.54
Δ at Endpoint	82	2.3	8.05	91	2.7	7.54	99	-0.6	7.92
Total Bilirubin (umol/ L)									
Baseline	348	8.7	3.88	332	8.8	4.04	349	8.5	4.22
Δ at Endpoint	82	-0.3	3.31	91	-0.5	3.25	99	0.2	3.48
Renal Function									
Creatinine (umol/L)									
Baseline	348	64.0	10.70	332	62.8	11.00	349	62.2	10.42
Δ at Endpoint	82	-0.9	9.55	91	-0.1	9.60	99	-0.6	11.90
BUN (mmol/ L)									
Baseline	348	4.5	1.13	332	4.5	1.12	349	4.4	1.09
Δ at Endpoint	82	0.0	1.06	91	0.1	0.92	99	0.0	1.06
Thyroid Hormones									
TSH (MU/ L)									
Baseline	344	1.9	1.36	326	1.8	1.60	349	1.7	0.95
Δ At Endpoint	80	-0.1	1.25	89	0.2	2.15	96	-0.1	0.68
FT3 (pmol/ L)									
Baseline	344	4.4	0.55	331	4.4	0.63	348	4.4	0.49
Δ at Endpoint	81	-0.2	0.54	89	-0.1	0.58	96	0.1	0.51
FT4 (pmol/ L)									
Baseline	346	14.3	2.33	331	14.3	2.39	349	14.0	1.83
Δ At Endpoint	81	-0.8	1.91	89	-0.6	2.23	96	0.1	1.87

Data Source: ISS Table 10. 2. 1
Δ = change

Table VII.I 3. Laboratory Criteria of Potential Clinical Concern*

Laboratory Tests Groupings	Age (Years)	Normal Range	Units	Values of Potential Clinical Concern
Hematology				
Hemoglobin	18-46	120.04 - 156.30	g/L	≤95
Hematocrit	18-46	35 – 46	%	≤32
females RBC	18-46	3.9 – 5.2	$x10^{12}$/L	≥10
females WBC	18-46	3.8 – 10.8	$x10^{9}$/L	≤2.8 or ≥16
Lymphocytes	18-46	16 – 46	%	≥75
Monocytes	18-46	0 – 12	%	≥15
Basophils	18-46	0 – 2	%	≥10
Eosinophils	18-46	0 – 7	%	≥10
Neutrophil Bands	18-46	-	%	≥10
Neutrophils Segmented	18-46	40 – 75	%	≤15
Platelet Count	18-46	130 – 400	$x10^{9}$/L	≤75 or ≥700
Liver Function				
AST	18-46	0 – 42	IU/L	≥150
ALT	18-46	0 – 48	IU/L	≥165
Alk Phos	18-19 20 – 125	30 – 165	IU/L	≥390 20-46
Total Bilirubin	18-46	0 – 22	umol/L	≥34.2
Renal Function				
Creatinine	18-46	44 – 124	umol/L	≥176.8
BUN	18-46	2.5 – 9	mmol/L	≥10.71
Thyroid Hormones				
TSH	18-46	0.4 5.5–	MU/L	≥10
FT3	18-46	3.5 – 6.5	pmol/L	≤126 or ≥156 FT4
	18-46	10.3 – 23.2	pmol/L	≤5.15 or ≥46.4

*Table 24 in the ISS (Data Source: Study 677, Section 5.8.6.4; Study 688, Section 5.8.6.4; Study 689, Section 5.8.6.4)

Table VII.J.1. Summary of Treatment Phase Mean Values for Vital Signs at Baseline and Mean Change from Baseline - Studies 677, 688 and 689, Combined (ITT Population)*

Vital Sign Parameter	Treatment Group								
	Paroxetine CR 25mg N = 348			Paroxetine CR 12.5mg N = 333			Placebo N = 349		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
BP Diastolic (mm Hg)									
Baseline	346	74.1	9.31	327	73.5	8.67	339	74.4	9.68
Δ at Endpoint	280	0.2	8.63	292	0.2	8.39	313	-0.2	8.60
BP Systolic (mm Hg)									
Baseline	346	114.7	12.72	327	114.2	11.68	339	115.3	13.25
Δ at Endpoint	280	-0.3	10.32	292	0.2	11.17	313	-0.7	10.96
Pulse Rate (bpm)									
Baseline	347	72.0	9.06	326	71.2	8.17	340	72.4	9.25
Δ at Endpoint	280	0.6	10.15	291	-0.9	8.74	314	0.6	9.72

*This is Table 31 in the ISS (Data Source: ISS Table 9. 2)
Endpoint is the last reading during the randomized medication phase.
Δ = change
Note: Values for N in paroxetine CR 12.5 mg and placebo groups in ISS Table 9. 2 are 332 and 348, respectively, because two subjects who did not have adequate data for calculation of changes from baseline in vital signs were erroneously omitted from the group totals.

Table VII.J.2. Criteria for Assessment of Vital Sign Changes of Potential Clinical Concern

Parameter	Normal Range	Pre- determined change from baseline	
		Decrease	Increase
Systolic BP (mmHg)	90 – 180	>30	>40
Diastolic BP (mmHg)	50 – 105	>20	>30
Pulse Rate (bpm)	50 – 120	>30	>30

This is Table 29 in the ISS (Data Source: Study 677, Section 5.8.6.4; Study 688, Section 5.8.6.4; Study 689, Section 5.8.6.4)

Attachment 1. Description of Selected SAEs (refer to Section VII.D).

S689.117.16473. One SAE of **stillbirth** occurred in a S who was found to be 5 weeks pregnant (positive urine pregnancy test) 85 days after starting 12.5 mg/day of PaxCR. Treatment was discontinued. A fetal heart tone was nondetectable at 9 weeks of pregnancy. The S had no symptoms of miscarriage. Dilation and curettage was subsequently performed. Given this history a potential role of the study drug in this SAE of stillbirth must be considered. However, the narrative also listed a number of concomitant medications (Actifed, Comtrex, Septra and Sudafed and Clarithromycin) although these drugs appeared to be used as needed for upper respiratory symptoms. The S's age of 37 years old may also be another risk factor. The S also had a history of the human papilloma virus, anorexia nervosa and "laporatomy uterine suspension."

S677.029.22211. This 40 year old S had **supraventricular tachycardia** two days after starting daily 25 mg PaxCR. The S woke up from a bad dream with her "heart racing and chest pressure." The chest pain radiated under her left breast but not to her neck or arms. A diagnostic cardiac work-up was negative (chest x-ray, ECG). She was treated with alprazolam and Ecotrin. Her symptoms resolved. PaxCR treatment was continued without any subsequent SAEs reported. This S had a history of the following conditions: insomnia, mitral valve prolapse and was being treated for hypertension. Given these conditions it appears that this S had several risk factors for this SAE. The SAE appeared to be secondary to anxiety due to a bad dream that may or may not be drug-related.

S717.701.32111 had the SAE of **hypersensitivity** that involved **laryngeal angioedema with dyspnea** that appeared to be drug-related (study drug was unblinded and found to be PaxCR, the history of this S is also consistent with this conclusion).

S717.069.15006. This S had a spontaneous **abortion**. The S started treatment on [ ] and stopped treatment on [ ] due to having unprotected sex for 1-2 days before. Twenty three days later the urine pregnancy test was positive. She experience some loss of blood and fetal heart action was detected on ultrasound (US). On the next day she had more blood loss and a nondetectable heart rate on US. She was diagnosed with spontaneous abortion confirmed by US. This event may be drug-related (yet the study drug is blinded). This 32 year old has a history of hypertension and "non-serious small lacunar cerebrovascular infarction" in the previous year, such that she may be at risk of complications with pregnancy. However, she had a previous pregnancy and a healthy child.

S711.092.21115. This 36 year old S had the SAE of **myocardial infarction.** Based on the following reasons it appears that this event was due to an underlying condition. This S had several risk factors (history of ischemic heart disease, obese, taking orlistat) and the event occurred 8 days after her last dose of study drug (blinded) in which she completed the study per protocol.

S717.701.32125: Abortion NOS. The S underwent therapeutic abortion within approximately 2 weeks after having a positive pregnancy test and approximately 4 weeks after the reported date of conception. The reason for the abortion was not specified other than being indicated as a "therapeutic abortion." However, no complications regarding the fetus and the pregnancy before the abortion are described in the narrative (study drug remains blinded).

Attachment 2. Biometric Questions and Comments Sent to the Sponsor Regarding Data Analysis on VAS total score as a Dependent Variable (refer to Section VI.B.9 of the review)

TELEFAX / CYBER MEMO

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

DATE: October 28, 2002 **TO:**
Matthew Whitman **FROM:**
Doris J. Bates, Ph.D.

SUBJECT: **Statistical Questions and Comments / Request for Additional Data**
NDA 20-936/S-011, Paxil CR (paroxetine hydrochloride) Controlled Release Tablets

Please refer to the above cited supplemental NDA. As noted in the e-mail accompanying this transmission, our statistical review team has the following comments and requests for additional data at this time: Please note that these comments refer to the three studies numbered 677, 688, and 689; responses, including additional data, should be provided respective to each of these studies.

1. Statistical inferences concerning our review of the efficacy of PAXIL CR will be drawn from the ITT population, at the protocol defined treatment cycle 3 endpoint, using the LOCF dataset.

2. We will be analysing, as primary variable, change from baseline in the mean luteal phase VAS-total score (that is, the sum of all 11 symptoms rated via Visual Analogue Scale), at treatment cycle 3. We will use the LOCF dataset and analyse this variable as a dependent measure, using parametric analysis of covariance. The ANCOVA model will include terms for treatment group, center group, baseline score (VAS-total) and age.

3. Please provide Observed Case Analysis datasets for all three referenced studies, at Treatment Cycles 2, and 3.

4. Please assess, for all three referenced studies, the interaction of treatment with each of the other main effects included in the model from your principal analysis.

5. Please provide the following additional information for each referenced study: a. A SAS exportable dataset including PID, CENTER GROUP, VISIT, VAS-TOTAL SCORE, AGE, and TRX_0. b. A statement of your approach to the handling of missing items from the 11-item VAS total scores.

If you have any questions, please feel free to contact me directly at 301-594-2850 or via e-mail at batesd@cder.fda.gov,

Attachment 3. Select Sections from the Clinical Review of the 7/21/00 NDA 20-031 SE1-029 submission, Regarding Potential Withdrawal Effects of the Immediate Release Formulation, Paxil™

Regarding the overall safety of paroxetine treatment in PTSD patients, paroxetine treatment appears to be adequately safe in this population. The safety profile as described in the submission is similar to that observed in other patient populations and that described in the labeling for Paxil®. However, consideration may be given to potential withdrawal effects of paroxetine and other selective serotonin reuptake inhibitors, as suggested by spontaneous reports that discontinuation, particularly upon abrupt cessation, may lead to various adverse events as described in the current labeling for Paxil®. These adverse events described in the "Postmarketing Reports" section of the current labeling for Paxil® include the following: dizziness, sensory disturbances, agitation, anxiety, nausea and/or sweating which are "generally self-limiting." [redacted]

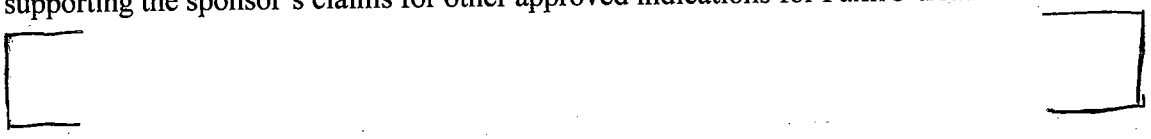
Most clinical trials of paroxetine hydrochloride conducted for approved indications, including trials described in this review, employed a taper phase such that Ss were gradually tapered off of paroxetine treatment. The typical taper phase regimen was a weekly incremental decrease in the daily dose by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

It is difficult to interpret safety results from the Taper Phase and 14-Day post taper phase follow-up visits regarding the potential for withdrawal effects of paroxetine. The trials described in this review and in the submission were not designed to examine or address this issue.

[redacted]. Some studies described in the literature provide evidence suggesting that withdrawal AE's may occur with abrupt cessation of selective serotonin reuptake inhibitors. [redacted]

[redacted] It is recommended that consideration be given to providing advice in the "Dosage and Administration" section of

labeling, that when terminating treatment, the dose should be gradually reduced rather than terminated abruptly. A taper phase regimen to be considered might be similar to that employed in the clinical trials described in the current submission, as well as that employed in previous trials supporting the sponsor's claims for other approved indications for Paxil® treatment.



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/s/

Karen Brugge
1/17/03 02:06:23 PM
MEDICAL OFFICER

Paul Andreason
3/20/03 04:03:01 PM
MEDICAL OFFICER

REVIEW AND EVALUATION OF CLINICAL DATA

NDA:	20-936 SE1-011 AZ: Response to Approvable Letter
Sponsor:	GlaxoSmithKline
Drug	
Established Name:	Paxil CR™
Chemical Name:	Paroxetine hydrochloride, Controlled Release Tablets
Code Name:	No code name provided on Form FDA 356h
Formulation:	12.5 mg, 25 mg, 37.5 mg Paroxetine CR tablets
Indication:	Premenstrual Dysphoric Disorder
Dates of Submission:	Correspondence Date: July 8, 2003 Date Received by HFD120: 7/11/03
Materials Reviewed:	Supplemental NDA Response to AE Letter
Clinical Reviewer:	Karen L. Brugge, M.D.
Review Completion Date:	7/31/03

I. Background.

This is a response submission to an Approvable Letter dated April 11, 2003 for supplemental NDA 20-936/S-011 (sNDA). This sNDA is for a new indication of PaxilCR, for the treatment of Premenstrual Dysphoric Disorder (PMDD). The purpose of this review is to assist the Team Leader and Director of the Division of Neuropharmacological Drug Products in the regulatory processing of this sNDA.

II. A Description of the Contents of This Response Submission.

Safety Update Information. Safety update information (information on serious adverse events and adverse dropouts) was provided from two completed PMDD trials, Study 711 and Study 717 (the trials were completed since the time of the cut-off date of the original sNDA). Post marketing information and results from an updated search of the literature are also included in the submission.

Study 711 was a 3-month, double-blind, placebo controlled, fixed-dose, parallel group, extension trial on PMDD patients who completed Studies 677, 688, and 689 (these are the three trials that were used to support a PMDD indication in the original sNDA). A total of 1030 subjects were randomized to double-blind treatment in this extension trial as follows (doses were given daily): n = 348 in the 25 mg PaxCR group, n = 333 in the 12.5 mg PaxCR group, and n = 349 in the placebo group.

Study 717 was a 3-month, double-blind, placebo-controlled, fixed dose, parallel group, PMDD trial on the efficacy of intermittent dosing in a total of 366 subjects who were in the ITT population, as follows (daily doses were given during the luteal phase): n = 116 in the 25 mg PaxCR group, n = 130 in the PaxCR group, n = 120 in the placebo group).

A listing of serious adverse events (SAEs) and adverse dropouts (ADO's) is provided in Tables 1-4 in the appendix (as provided by the sponsor). The sponsor also provided narratives. In summary, there were no new safety findings (i.e. that are either unexpected or are not likely to be drug-related), except for some possible dose-related events that are not considered by this reviewer to be events that should impact on labeling, at this time. These possible exceptions are described in more detail in Attachment 1 of this review for future reference. Although one possible, yet minor recommendation regarding labeling relevant to safety is described in the Conclusion and Recommendation Section of this Review.

The following provides some comments about the events in Attachment 1 and discusses reasons why, they are not considered as observations that should impact on labeling at this time.

First, it is important to note that information in the narratives for some of the events (myocardial infarction, pulmonary embolus, and convulsion) was very sparse. In the absence of information, the possibility of these events being drug-related must be considered. Still births and unintended pregnancies were also reported, some of which may be drug-related or study-related (i.e. the method of contraception, such as double-barrier method, that was sometimes required of subjects and the potential for non-compliance). Other events are likely to be reflecting the study population (women of childbearing potential) or a pre-existing condition (e.g., history of miscarriages in a subject with a spontaneous abortion or still birth). Nevertheless, PaxCR is a Category C drug.

One subject is described in Attachment 1 who had suicidality, believed by the investigator to be, potentially related to the intermittent treatment regimen in Study 717 (luteal phase dosing). Luteal phase dosing is currently being proposed by the sponsor as a new treatment regimen for PMDD in a sNDA currently under review (S-013). Therefore, this subject with suicidality will be taken under consideration as part of the review of S-013, together with information submitted in this more recent sNDA

[redacted]

In addition to above events, 3 ADOs were due to vertigo and are being noted for future reference and recommendations relevant to these events are included in the Conclusion section later in this review. Three PaxCR subjects (subject 689.147.18800 in Study 711 and subjects 717.403.31507 and 717.403.31528 in Study 717) and no placebo subjects of Studies 711 and 717 had vertigo along with other AEs resulting in treatment cessation (headache in 1 subject, nausea and abnormal thinking in another subject, and mydriasis in the third subject). Vertigo occurred on Day 2 or 3 of treatment in 2 subjects and on Day 84 of treatment in the third subject. Vertigo resolved within 2 days after treatment cessation in the former 2 subjects and after 18 days after treatment cessation in the latter subject. While these events could be drug-related they occurred in less than 1% of the Ss in a given treatment group. Furthermore, vertigo is not listed in the Adverse Reaction section of labeling for clinical trials of other study populations. Yet, dizziness which could be undiagnosed vertigo in some subjects is listed in labeling. Although, vertigo in these 3 ADOs may also be misdiagnosed, as the narratives on these subjects were sparse (e.g. not description of signs and symptoms, of any diagnostic test results or other information that may have led to the diagnosis). Therefore, vertigo is being described in this review for future reference with some recommendations provided in the conclusion/recommendation section, below.

Post marketing Safety Information. The sponsor searched their GSK Clinical Safety data based for Post marketing reports of adverse events between February 28, 2002 and January 1, 2003 in which the following conditions were listed as an indication or a concurrent clinical condition: premenstrual syndrome, premenstrual tension, premenstrual tension syndrome, premenstrual dysphoric disorder, or premenstrual symptoms (the previous search was conducted prior to February 28, 2002 in the original sNDA submission). A total of 22 reports were revealed in which two were listed as SAE's:

- Death NOS (this report is described as being "poorly documented" in which it is not certain whether or not the subject was actually taking paroxetine)
- Hypomania (a literature report: the event occurred after 80 days of paroxetine treatment in a patient being treated for PMDD and may be reflecting an undiagnosed bipolar disorder).

One reported event worth noting, but was not listed as an SAE is cataracts (de novo) in a 38-year-old with premenstrual tension and was also receiving norethisterone acetate/estradiol. The etiology of this event is unclear. However, paroxetine is not known to be associated with cataracts.

Literature Searched Results. The sponsor searched the published literature for new safety information on paroxetine in PMDD patients for the period between April 9, 2002 and January 15, 2003 (the original supplemental NDA provides search results before, April 9, 2002). Only one additional pertinent report is identified by the sponsor, which was also the post marketing report of hypomania described above.

Proposed Labeling.

The sponsor accepts most changes specified in the Approvable Letter. Therefore, the following only focuses on proposed changes in the labeling\proposed.pdf file of the submission (denoted by strikethrough for deletions and underlined text for additions in the pdf file). Most of these changes were only editorial in nature (in summary tables on page 16-17 and page 23 in the labeling\proposed.pdf file under the Adverse Reactions section), along with some clarification (on the number of adverse dropouts which was clarified as being 88 total subjects on page 16). These changes are also shown in Attachment 2 of this review, for the convenience of the reader (sections are copied from the labeling\proposed.pdf file). Another minor editorial change (not shown in Attachment 2) is the deletion of a duplicated term on page 26 ("throat tightness" was deleted in the "Other Events Observed during the Clinical Development of Paroxetine" section). These editorial changes are considered acceptable.

Major changes are proposed in the subsection of "Discontinuation of Treatment with Paxil CR" under the "Precautions" section of labeling (starting on page 7 of the labeling\proposed.pdf file in the submission, and also shown in Attachment 2 of this review). The sponsor proposes to replace the description of the incidence of AE's reported after treatment cessation in the 3 PMDD trials, with similar results obtained from an analysis of taper phase or follow-up phase AE data from seven clinical trials,

combined (Studies 677, 688, 689, 711, 810, 790, and 791). The sponsor's proposed changes generally appear to be reasonable, although comment and recommendations regarding these changes are provided later in the Conclusion and Recommendation section, below. The following paragraphs describe the proposed changes and the sponsor's rationale for these modifications.

The sponsor selected 7 trials for their data analysis because these trials either had a mandatory taper phase or a mandatory follow-up phase. Most of the trials used fixed-dose regimens with dose levels of 12.5 mg and 25 mg of Pax CR daily, although a few used doses up to 37.5 mg using a flexible-dose design. These trials are described in the following:

- **Trials 677, 688, and 689:** the trials that supported the sponsor's new proposed PMDD indication, employing a placebo control, parallel group, fixed-dose design with two dose levels of 12.5 and 25 mg Pax CR.
- **Trial 711** is the continuous dosing PMDD extension trial (the 3 above, PMDD trials were the lead-in studies). This extension trial involved 3 months of double-blind treatment with daily placebo, 12.5 mg or 25 mg Pax CR.
- **Study 810** was also a placebo controlled, fixed-dose trial that had two Pax CR groups at daily doses of 12.5 mg and 25 mg. This trial was conducted on patients with Major Depressive Disorder (MDD).
- **Study 790** was a trial on Social Anxiety Disorder (SAD) using a flexible dose design (12.5-37.5 mg/day of Pax CR).
- **Study 791** was a placebo controlled trial on Generalized Anxiety Disorder (GAD) using a flexible dose design (12.5-30 7.5 mg/day of Pax CR compared to placebo).

The sponsor determined the incidence of AE's during the taper or follow-up phase of these trials (combined). The results are shown in Table 3 in the response submission (N =1081, N=708, for PaxCR and placebo subjects, respectively). AE's were reported in 39% of paroxetine subjects and 23% of placebo subjects. The sponsor did not include data from Trial 717 and from the MDD Study 785 in their analyses. Study 717 used the luteal phase dosing regimen for PMDD, which is a treatment regimen that is currently under review (under S-013). Study 785 did not have a mandatory follow-up phase.

Attachment 2 of this review shows the sponsor's proposed changes based on the results of their results summarized in Table 3 of the submission. These results as described in the sponsor version of proposed labeling are similar to results from the 3 PMDD trials that were described in the version of labeling in the Approvable Letter. The AEs described in both versions of labeling were selected using the criteria that a given AE had to be reported in at least 2% of Pax CR subjects and had an incidence of at least twice that reported in placebo subjects.

Additional AEs, not included in the sponsor's proposed labeling, are noted in this review based on results in Table 3. These additional AE's did not quite make the above criteria. However, these AEs are noted in this review, as they show at least trends for both a dose-related effect (the high-dose PaxCR group had an incidence that was at least twice that of placebo) and a dose-dependent effect (trends for increasing incidence with greater dose-levels). The additional AEs are listed below (with the incidence in placebo, 12.5 mg, 25 mg, and 37.5 mg Pax CR groups also provided):

- Back pain (0.6%, 0%, 0.6%, and 1.3%, respectively).

- Insomnia (1.6%, 1.8%, 3.7%, 4.4%): The incidence of insomnia in all Pax CR subjects, combined (N = 1081), was 3.1% compared to 1.6% in the placebo group. Therefore, this AE did not meet the criterion of showing an incidence in PaxCR subjects of at least twice that of placebo.
- Paresthesia (0%, 1.3%, 1.5%, 3.6%): This AE was also not in proposed labeling, since the incidence in all Pax CR subjects (combined) was only 1.9%.

The incidence of withdrawal syndrome also met the criteria to be included in labeling, but was not referred to as a withdrawal syndrome in the sponsor's proposed version. The incidence of withdrawal syndrome (as a preferred term) was 0.3%, 1.5%, 2.6%, and 3.6%, in the placebo, 12.5 mg, 25 mg, and 37.5 mg Pax CR groups, respectively (an incidence of 2.4% in all Pax CR subjects, combined). The sponsor prefers to list the verbatim terms that occurred in at least 3 subjects (among the subjects reported as having withdrawal syndrome). The sponsor considers the Preferred Term or verbatim term of "withdrawal syndrome" (the term used by the investigators) as uninformative and potentially misleading. Instead the sponsor believes it is more accurate to list the actual type of events (i.e. specific AE's) and described these events as occurring in the taper phase or upon treatment cessation, as follows (see the end of line 291 through line 294 of proposed labeling, also shown in Attachment 2):

> *...additional symptoms described by the investigator as associated with tapering or discontinuing Paxil CR (e.g,. emotional liability headache, agitation, electric shock sensations, fatigue, sleep disturbances) (2.4% vs 0.3%).*

The above incidence rates are the incidence of subjects with "withdrawal syndrome" in all PaxCR treated subjects (rather than for each PaxCR group) and placebo subjects, respectively (based on results in Table 3).

Finally, the sponsor condensed the last part of this section on taper-phase/treatment-cessation AEs reported with the immediate release formulation of Paxil.

Conclusion and Recommendations.

The updated safety information in the response submission, generally failed to reveal any new safety findings. However, several AEs were noted in this review, primarily for future reference (described in greater detail in Attachment 1). Some recommendations are also provided at the end of this section regarding some of the events.

The following conclusions and recommendations focus on the sponsor's proposed labeling. The sponsor has accepted almost all of the labeling changes in the Approvable Letter, but proposes some editorial changes that are reasonable. However, one major change is in the subsection on "Discontinuation of Treatment with Pax CR" under the "Precautions" section of labeling. Most of the changes in this section are reasonable. Although, consideration should be given to describing additional AE's that showed trends for both a dose-related and dose-dependent effect (back pain, insomnia, paresthesia), as described in this review (in which labeling would reflect the incidence for each Pax CR group, instead of combining the Pax CR groups). Furthermore, "withdrawal syndrome" is among AE's that appeared to show both a dose-related and dose-dependent effect. Therefore, it is recommended that the incidence of this event be described for each

treatment group, rather than only showing the incidence for all PaxCR subjects combined (refer to line 294 of proposed labeling. also shown in Attachment 2 of this review).

The sponsor's rationale for not preferring the term "withdrawal syndrome" is acceptable to this reviewer for reasons described later, in the next paragraph. However, as previously recommended, the incidence of these subjects in each treatment group should be shown, rather than showing the incidence in treatment groups, combined. A listing of specific AEs, as proposed by the sponsor is also reasonable. However, consideration should be given to describing these subjects as [ ]

[ ]

That is, if these subjects had a cluster of symptoms, then the term syndrome may be more appropriate, and actual AEs that appeared in clusters should be described. Although, the issue of a cluster of symptoms occurring upon treatment cessation has not be adequately examined and should be considered as an area to examine using their existing data (i.e. AE data from their 7 trials). [ ]

[ ]

One major reason that withdrawal syndrome is not considered an accurate term by this reviewer is that the sponsor's trials were not specifically designed to examine a potential withdrawal syndrome (e.g. trials were not placebo controlled during taper phases, different patient populations were combined rather than considered separately in the sponsor data analyses, among other potential confounding variables that were not controlled for in the data analyses or in the design of the studies). The term withdrawal syndrome implies a drug dependency (psychological and/or physiological). Yet, drug seeking behaviors and behaviors of abuse are not reported or known to exist with PaxCR or with the drug class. Furthermore, "withdrawal syndrome" is a rather nonspecific term, unless it is operationally defined. Finally, the trials do not differentiate symptoms from an actual withdrawal effect from symptoms of the underlying psychiatric disorder that can emerge upon treatment cessation either due to lack of efficacy or spontaneously. For example, nervousness, dizziness, paraesthesia and other symptoms can occur in patients with anxiety disorders and in MDD patients, particularly those with anxiety symptoms (which are common in MDD patients). Finally, consideration should also be given to PK properties of PaxCR and the temporal relationship with treatment cessation and AEs. In conclusion, the trials were not adequately designed to address these issues. [ ]

[ ]

Despite the limitations of the sponsor trials and the problems with interpreting results of the data analyses, labeling includes sections on the issue of discontinuation of treatment and recommendations regarding a gradual reduction in the dose rather than abrupt cessation in patients exhibiting symptoms during discontinuation of treatment. However, because the trials were not designed for examining withdrawal effects of PaxCR, it is recommended that the following statement remain in labeling, [ ]

[ ]

Adverse events while discontinuing therapy with Paxil CR were not systematically evaluated in the clinical trials.

The above should appear as the first sentence of this subsection of labeling as in the version in the Approvable Letter. The next sentence should read as follows (similar to that in the Approvable Letter version):

[redacted]

Therefore, the above two italicized sentences should replace the first sentence of this section of the sponsor's version of labeling.

Finally, the condensed version of the last paragraph of this section is acceptable (this paragraph described treatment cessation AEs with the immediate release Paxil formulation, see lines 350-352 in proposed labeling, also shown in Attachment 2).

The following are additional recommendations to consider, based on safety findings in the current submission and is described in this review:

- It is recommended that the sponsor be advised to assess patients in future trials with dizziness and vertigo in an attempt to ascertain a more accurate diagnosis and etiology.
- Subject 677.042.23200 is reported to have had convulsions in Trial 711 (refer to Attachment 1 of this review. The diagnosis and etiology of this event is unclear. Therefore, in the absence of more information the possibility that the event is drug-related must be considered. Nevertheless, current labeling has a section on seizures under the Precautions Section in which the incidence of seizures in clinical trials is only 0.1%. Consideration should be given to updating this section of labeling to include Subject 677.042.23200 in the incidence of seizures reported in clinical trials (although a single subject may not change the overall incidence).

The following observations are also noted:

- If he is not clear why subject 717.404.31580, who was listed as a withdrawal due to myocardial infarction (and other adverse events) was not considered a serious adverse event, since myocardial infarction is a life-threatening condition that requires emergency medical treatment.

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

cc: HFD 120/ K Brugge, D Bates, T Laughren, O Siddiqui, N Khin

APPENDIX

Appears This Way
On Original

Table 1 Listing of Serious Adverse Experiences in Study 711

Subject ID	AE Preferred Term	Onset[1]	Intensity	Relationship
Parox CR 25mg Group				
677.010.12736[3]	Trauma	34 (0)	Severe	UNR
677.021.13561[3]	Allergic Reaction	158 (-4)	Severe	UNR
677.024.21827[3]	Bronchitis	102 (1)	Severe	UNR
677.029.22211[3]	Supraventricular Tachycardia	3 (-88)	Severe	PBU
677.035.22658[3]	Unintended pregnancy	29 (2)	Severe	UNR
688.055.13929[3]	Infection	99 (4)	Severe	UNR
	Vertigo	99 (4)	Severe	UNR
688.069.15006[3]	Abortion	102 (23)	Severe	UNR
689.120.16705[3]	Abortion	57 (1)	Severe	UNR
689.139.18182[3]	Gastroenteritis	157 (-3)	Severe	UNR
Parox CR 12.5mg Group				
677.012.12868[3]	Unintended pregnancy	6 (5)	Severe	UNR
677.023.21765[2,3]	Unintended pregnancy	64 (1)	Severe	UNR
688.064.14634[3]	Unintended Pregnancy	153 (-22)	Severe	UNR
688.084.20209[3]	Kidney calculus	206 (19)	Severe	UNR
688.092.21115[3]	Myocardial infarction	196 (8)	Severe	UNR
689.111.15996[3]	Colitis	156 (9)	Moderate	UNR
689.115.16294[4]	Unintended Pregnancy	5 (-18)	Unknown	UNR
	Diabetes Mellitus	22 (-1)	Moderate	UNR
	Hyperglycemia	45 (22)	Moderate	UNR
689.117.16473[3]	Stillbirth	85 (1)	Severe	UNR
Placebo Group				
677.039.22966[3]	Unintended pregnancy	43 (1)	Severe	UNR
	Abortion	54 (12)	Severe	UNR
688.067.14865	Myalgia	27 (-126)	Severe	UNR
688.067.14897[3]	Trauma	150 (-18)	Severe	UNR
689.123.16916[3]	Abortion	13 (-20)	Severe	UNR
689.144.18557[3]	Stillbirth	105 (16)	Severe	UNR

1. Days relative to start of study medication (days relative to stop of study medication).
2. This subject's data was incorrectly coded only as unintended pregnancy. Review of information from another source (data on file at GSK) notes that this subject subsequently had an abortion.
3. Previously reported in sNDA 20-936 SE1-011 Paxil CR for PMDD submission

UNR = unrelated, PBU = probably unrelated

Table 2 Listing of Withdrawals due to Adverse Experience in Study 711 for Subjects not Previously Reported as Having Withdrawn During Feeder Studies

Subject ID	AE Preferred Term	Onset[1]	Duration (days)	Intensity	Relationship
Parox CR 25mg Group					
688.061.14428	Hypotension	130 (-7)	16	Moderate	PSR
688.074.19422	Nausea	76 (0)	1	Moderate	PSR
689.129.23830	Decreased Libido	93 (-45)	Con	Severe	REL
	Weight Gain	93 (-45)	Con	Moderate	REL
689.139.18182[2]	Gastroenteritis	157 (-3)	3	Severe	UNR
689.140.18243	Decreased Libido	163 (0)	12	Mild	REL
689.147.18800	Headache	84 (-4)	5	Moderate	REL
	Vertigo	84 (-4)	18	Moderate	REL
689.147.18804	Anxiety	152 (0)	8	Mild	REL
689.147.18810	Headache	94 (-8)	14	Mild	REL
	Somnolence	94 (-8)	14	Severe	REL
	Sweating	94 (-8)	14	Mild	REL
Parox CR 12.5mg Group					
677.042.23200	Convulsion	112 (-20)	Con	Moderate	PSR
688.064.14634[2]	Nausea	161 (-14)	Con	Moderate	UNR
688.075.19482	Weight Gain	15 (-82)	97	Mild	PSR
689.122.16837	Diarrhea	112 (0)	1	Moderate	PSR
689.151.19121	Paresthesia	90 (-12)	24	Mild	PSR
	Purpura	78 (-24)	Con	Severe	PSR
	Urticaria	78 (-24)	Con	Severe	PSR
Placebo					
677.002.12104	Somnolence	106 (-22)	24	Moderate	REL
677.023.21730	Libido Decreased	88 (-20)	29	Moderate	REL
677.041.23155	Amenorrhea	142 (-4)	Con	Moderate	PBU
677.043.23280	Somnolence	123 (-31)	35	Moderate	PSR
688.052.13701[3]	Menorrhagia	149 (54)	1	Severe	UNR
	Ovary Disorder	149 (54)	1	Severe	UNR
	Uterus Disorders	149 (54)	1	Severe	UNR
688.063.14546	Weight Gain	83 (0)	1	Moderate	REL
688.073.19354	Diarrhea	29 (-39)	43	Mild	REL
688.077.19658	Migraine	86 (-6)	12	Moderate	UNR
689.117.16478	Manic Reaction	93 (-3)	5	Moderate	PSR

1. Days relative to start of randomized study medication (days relative to stop of randomized study medication)

Table 3 Listing of Serious Adverse Experiences in Study 717

Subject ID	AE Preferred Term	Onset[1]	Intensity	Relationship
Parox CR 25mg Group				
717.701.32111	Anaphalactoid Reaction	5(0)	Severe	REL
717.701.32152	Abortion	71(5)	Severe	UNR
Parox CR 12.5mg Group				
717.010.30311	Depression	74(3)	Severe	PBU
	Emotional Lability	74(3)	Severe	PBU
717.301.31080	Pulmonary Embolus	33(0)	Moderate	PBU
717.701.32125	Unintended Pregnancy	-5(-22)	Severe	UNR
717.710.32203	Emotional Lability	49(9)	Severe	PBU
Placebo Group				
717.202.30916	Trauma	46(-21)	Severe	UNR
717.404.31592	Trauma	51(-5)	Severe	UNR
No Therapy Dispensed (placebo Run-in)				
717.404.31598	Pneumonia	NA	Severe	NA

NA = Not applicable; subject never received randomized study medication.

1. Days relative to start of randomized study medication (days relative to stop of randomized study medication)

UNR = unrelated, PBU = probably unrelated, PSR = possibly related, REL = related

Table 4 Listing of Withdrawals Due to an Adverse Experience in Study 71

Subject ID	AE Preferred Term[1]	Onset[2]	Duration (days)	Intensity	Relationsl
Parox CR 25mg Group					
717.003.29764	Nausea	29 (-5)	6	Severe	PSR
	Dizziness	29 (-5)	6	Severe	PSR
	Sweating	29 (-5)	6	Severe	PSR
717.005.29908	Diarrhea	2 (-3)	2	Moderate	REL
	Dizziness	2 (-3)	5	Moderate	REL
	Insomnia	2 (-3)	5	Moderate	REL
	Tremor	2 (-3)	5	Moderate	REL
717.008.30154	Lack of Emotion	2 (-12)	13	Mild	PSR
	Libido Decreased	2 (-12)	13	Moderate	PSR
717.101.30438	Asthenia	2 (-5)	6	Severe	PSR
	Depression	2 (-5)	6	Severe	PSR
717.103.30611	Anxiety	2 (-4)	7	Moderate	REL
717.201.30820	Nausea	28 (-1)	3	Moderate	REL
717.201.30834	Vomiting	1 (-9)	8	Severe	REL
717.300.30988	Decreased Appetite	3 (-2)	6	Mild	PSR
	Nausea	3 (-2)	6	Mild	PSR
	Dizziness	3 (-2)	6	Mild	PSR
	Insomnia	3 (-2)	10	Mild	PSR
	Tremor	3 (-2)	6	Mild	PSR
	Abnormal Vision	3 (-2)	2	Moderate	PSR
717.302.31175	Menstrual Disorder	6 (-13)	Con	Mild	PSR
717.305.33958	Menorrhagia	17 (-39)	59	Moderate	PSR
717.306.34014	Headache	49 (-12)	30	Mild	PSR
717.403.31507	Vertigo	2 (-8)	11	Moderate	PSR
	Abnormality of Accommodation	2 (-8)	11	Severe	PSR
	Mydriasis	2 (-8)	11	Moderate	PSR
717.701.32111	Anaphalactoid Reaction	5 (0)	6	Severe	REL
717.704.32356	Nausea	1 (-4)	7	Severe	REL
717.706.32491	Somnolence	5 (-7)	Con	Severe	Rel
717.908.33406	Rash	9 (0)	1	Severe	REL
Parox CR 12.5mg Group					
717.007.30061	Asthenia	27 (-6)	8	Moderate	PSR
	Dry Mouth	27 (-6)	8	Moderate	PSR

Continued on next page.

	Tooth Disorder	13 (-20)	6	Moderate	UNR
717.010.30318	Nervousness	5 (-4)	12	Moderate	REL
717.200.30745	Hypertension	57 (13)	Con	Severe	PSR

1. This table includes only those subjects who had an adverse event during the treatment cycles that led to stopping drug that was not previously reported as an AE leading to withdrawal in studies 677, 688, 689.
2. Days relative to start of randomized study medication (days relative to stop of randomized study medication)

(Continues)

(Continues)

Table 4 Listing of Withdrawals Due to an Adverse Experience in Study 717 (Continued)

Subject ID	AE Preferred Term[1]	Onset[2]	Duration (days)	Intensity	Relationship
Parox CR 12.5mg Group (cont'd)					
717.204.33713	Nausea	1 (-5)	9	Moderate	PSR
	Insomnia	1 (-5)	9	Moderate	PSR
717.301.31080	Pulmonary Embolus	33 (0)	8	Moderate	PBU
717.305.33965	Asthenia	1 (0)	3	Severe	REL
	Nausea	1 (0)	2	Severe	REL
	Dizziness	1 (0)	3	Moderate	REL
717.403.31528	Nausea	3 (0)	2	Severe	PSR
	Thinking Abnormal	3 (0)	2	Severe	PSR
	Vertigo	3 (0)	2	Severe	PSR
717.404.31580	Myocardial Infarct	35 (-2)	3	Moderate	PSR
	Decreased Appetite	35 (-2)	3	Moderate	PSR
	Insomnia	36 (-1)	2	Moderate	PSR
	Tremor	37 (0)	1	Moderate	PSR
717.709.32723	Insomnia	9 (-6)	24	Moderate	PSR
	Female Genital Disorders	7 (-8)	18	Moderate	PSR
717.710.32203	Emotional Lability	49 (0)	2	Severe	PBU
	Insomnia	47 (-2)	32	Moderate	PBU
717.710.32212	Headache	1 (-2)	3	Mild	STP
	Somnolence	1 (-2)	3	Moderate	STP
719.910.33560	Maculopapular	13 (-1)	4	Moderate	PSR
Placebo					
717.003.29784	Gastritis	1 (-6)	7	Moderate	PBU
717.103.30597	Headache	47 (-3)	6	Severe	PSR
717.300.30972	Somnolence	3 (-12)	14	Moderate	REL
717.301.31058	Amenorrhea	8 (-42)	53	Mild	UNR
717.404.31592	Trauma	51 (-5)	Con	Severe	UNR

1. This table includes only those subjects who had an adverse event during the treatment cycles that led to stopping drug that was not previously reported as an AE leading to withdrawal in studies 677, 688, 689.
2. Days relative to start of randomized study medication (days relative to stop of randomized study medication)

UNR = unrelated, PBU = probably unrelated, PSR = possibly related, REL = related

Attachment 1. Descriptions of Selected SAEs and ADOs.

An ADO of Myocardial Infarction (verbatim term: heart attack) on Day 35 of intermittent luteal phase dosing of 12.5 mg PaxCR/day in Subject 717.404.31580. Other AE's reported as events leading to study withdrawal were: loss of appetite, sleep disturbance, and tremor. This ADO is being described for two reasons. Firstly, this event occurred in 42-year-old white female who had no history of medical conditions, risk factors or concurrent medications described in the narrative. Given the lack of information in the narrative, as well as lack of information regarding diagnostic tests and the results on this subject, is difficult to determine whether or not this event was drug-related. However, the narrative indicates that "no corrective therapies were given for these adverse events" and that the "myocardial infarction" resolved within three days. Based on this description, the absence of diagnostic test results to confirm the diagnosis, the lack of treatment followed by a spontaneous resolution, it is not clear if this subject actually had a myocardial infarction. Another reason that this ADO is being described is because it is unclear why this event was not listed as a SAE, if indeed this event was identified as a myocardial infarction as listed. Finally, in the absence of more information, this event must be considered as possibly drug-related. PaxCR is not known to be associated with cardiovascular effects (as described in current labeling) and is not known to be associated with this type of event.

An SAE of Pulmonary Embolus in the 2nd Treatment Cycle of daily luteal phase treatment with 12.5 mg PaxCR in Subject 717.301.31080. This subject was a 39-year-old female who smoked 20 cigarettes a day, but otherwise, the narrative does not describe any current medical conditions or concomitant medications in this subject. This subject was hospitalized and treated with heparin and other medications. An ultrasound was conducted and found to be negative (no specific information was provided). The narrative does not mention use of oral contraceptive agents, which is a known risk factor for this type of event in this population. PaxCR is not known to be associated with coagulopathy or other conditions that could result in this event. The event is most likely associated with this subject's smoking history and possibly other unknown factors not described in the narrative.

Convulsion (Verbatim Term: Possible Seizure Disorder) on Day 112 of daily 12.5 mg PaxCR in Subject 677.042.23200 in Trial 711. This 34-year-old subject has no history of seizure disorder and the narrative does not describe any risk factors, as well as any concomitant medications. The narrative only describes the event as a " moderate convulsion" and that the patient was treated with lamotrigine. Diagnostic tests or any further description of the event are not provided in the narrative (e.g. signs, symptoms and diagnostic tests/results leading to the diagnosis). Therefore, the diagnosis and etiology of this event is unclear and without further information, the possibility that the event is drug-related must be considered. Nevertheless, current labeling has a section on seizures under the Precautions Section in which the incidence of seizures in clinical trials is only 0.1%. This section should be updated to include this S in the incidence of seizures in clinical trials.

An ADO of Purpura, Urticaria on Day 78 and Paresthesia on Day 90 of daily 12.5 mg PaxCR in Subject 689.151.19121 in Study 711. This 31-year-old female has a history of allergic rhinitis and other unrelated medical conditions. The narrative does not describe any concomitant medications in this subject. Purpura was described as continuing at completion of the study. The narrative does not describe any diagnostic tests that were conducted. Therefore, without further information on this subject one cannot rule out that this was drug-related. The event of urticaria is suggestive of a drug-related event and is not unexpected. Purpura is listed in the Post marketing Section of current labeling as a frequent event. As described in the review of the original supplemental NDA for the PMDD indication, the event of purpura was not listed as

an SAE and is not an event associated with ADOs that occur in at least 1% of PaxCR treated subjects with an incidence at least twice that of placebo. This is likely idiosyncratic or possibly due to unknown factors, not described in the narrative.

Unintended Pregnancy and Abortions/Stillbirths. The review of the original submission described these types of SAE's that occurred in several subjects in the three PMDD trials (688, 689 and 677). The current response submission also lists these subjects (as shown in summary Tables xx-xx, in the appendix), as well as additional subjects with these types of events in Studies 711 and 717. The following paragraphs only describe new events or information that was not previously described in the review of the original sNDA. In summary, unintended pregnancy and pregnancies with complications (spontaneous abortions, stillbirths) were observed as shown in the summary tables in the appendix. Some of these events may be drug-related while others appeared to be due to other factors (i.e. a history of miscarriage, the study population or others, as described in the review of the original sNDA). PaxCR is a Category C drug. Furthermore, the study population consisted of primarily young women, in which subjects were required to be regularly menstruating (therefore had childbearing potential). Finally, most of these women were using a double barrier method of contraception. This type of method was required in at least some of the sponsor's trials and is likely to e associated with a greater rate of noncompliance, in contrast to other types of contraceptive methods that are more commonly used in the general population of women with childbearing potential (i.e. oral contraceptive agents and others).

An SAE of Stillbirth in Subject 689.117.16473 that is listed in the current response submission was also described in the review of the original NDA. However, the study drug is now unblinded and reported to be PaxCR 12.5 mg. This subject is using a double barrier method of contraception during the study and began treatment in the study on [ ] She was found to be five weeks pregnant approximately 84 days later. Study medication was discontinued and at nine weeks a fetal heart time was not heard by ultrasound. This subject had no symptoms of miscarriage, but underwent dilation and curettage on [ ]

An SAE of unintended pregnancy and therapeutic abortion was reported in Subject 717.701.32125. This patient was not aware of being pregnant until after study drug was started. She started receiving 12.5 mg PaxCR daily luteal phase dosing on [ ] and had a positive pregnancy test result on [ ] Study drug was stopped on [ ] and the subject underwent therapeutic abortion on [ ] It is not clear why the abortion was referred to as therapeutic (it is not clear from the information in the narrative if this was elective abortion or if there were complications).

Subject 717.701.32152 listed as having the SAE of Abortion under the 25 mg PaxCR group in Table 3. The subject had a positive pregnancy test five days after the last dose of study medication. The pregnancy test was repeated seven days later and became negative. This negative result was confirmed by a repeat test five days later, and the final diagnosis of this SAE was spontaneous abortion.

Suicidality during Intermittent Treatment. In addition to the above events, it should be mentioned that one subject had an SAE of suicidal ideation (Subject 717.710.32203) that was noted to be possibly related to the intermittent treatment regimen being employed. While, this subject is suffering from a mood disorder, which was likely to underlying etiology of this event, it was noted that this event could have been associated with "follicular phase seven cessation of study drug." This event occurred on the day of the first dose of the third treatment cycle of luteal phase daily treatment with 12.5 mg PaxCR. Luteal phase treatment for PMDD is currently under review and a separate supplemental NDA submission for PaxCR (S-013). Therefore, this event is pertinent to supplemental NDA S-013 and will be considered together in the review of this newer sNDA, together with other information submitted under the S-013 submission.

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On Original

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Medical Review (8/19/03)

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/s/

Karen Brugge
7/31/03 06:01:07 PM
MEDICAL OFFICER

Paul Andreason
8/19/03 09:36:05 AM
MEDICAL OFFICER
The sponsor provided a complete response to the Divisions AE letter. See my memo to the file.

M E M O R A N D U M

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

DATE: March 20, 2003

FROM: Paul J. Andreason, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for Supplement for Paxil CR® for PMDD; re-analysis of studies using VAS-total yielded 2 of 3 studies as supportive

TO: File, NDA 20-936 SE1-011
[Note: This memo should be filed with the June 26, 2002 original submission of this NDA.]

1.0 BACKGROUND

Paxil CR® is approved for the treatment of Major Depressive Disorder (25-62.5-mg/day) and Panic Disorder (12.5-75-mg/day). The sponsor seeks approval for the added indication of the treatment of Premenstrual Dysphoric Disorder (PMDD) on the basis of three 12-week, double-blind, placebo controlled, parallel group, multi-center studies. Two other drugs in the SSRI class (fluoxetine and sertraline) are approved for the treatment of PMDD.

The basis for approval of the currently marketed SSRIs was the significant improvement in the baseline to endpoint VAS-total score. The sponsor argued that all three studies were positive based on the VAS-MOOD score; however, the Division has deemed this an inappropriate subset of symptoms of a disorder that has both mood and physical symptoms. Since Paxil CR® was not expected to cause improvement in physical symptoms at the exclusion of mood symptoms as a diuretic or hormonal replacement therapy might, it is not reasonable to examine the VAS-MOOD scale exclusively. The VAS-total therefore is the scale on which approval of the Paxil CR® should be based.

2.0 CHEMISTRY

As Paxil CR® is a marketed product, there were no chemistry issues requiring review for this supplement.

3.0 PHARMACOLOGY

4.0 BIOPHARMACEUTICS

As Paxil CR® is a marketed product, there were no human biopharmaceutical issues requiring review for this supplement.

5.0 CLINICAL DATA

5.1 Efficacy Data

Karen Brugge performed the primary clinical review of efficacy and safety. At the time of her review the sponsor had not submitted the requested analysis of the VAS-total. Her review reflects results and recommendations based on VAS-MOOD data. VAS-total scores were submitted and reviewed by the Division of Biometrics. The primary Statistical Reviewer was Ohidul Siddiqui.

The sponsor bases their claim that Paxil CR® 12.5-25-mg/day is effective in the treatment of PMDD on the results of three, controlled clinical trials-studies 688, 677, and 689. All of these studies were multi-center, double blind, randomized, placebo controlled, fixed dose (12.5 and 25-mg) studies of women with PMDD that lasted over three menstrual cycles (12-weeks).

The ITT population of these studies was approximately 310-350 patients per study divided equally among three treatment groups: placebo, Paxil CR 12.5-mg, and Paxil CR 25-mg. Completion rates were in the range of 65-79% with the highest dropout rate in the Paxil CR25-mg group.

Study 688 was a non-US study with centers in Europe and South Africa. Study 677 had centers in the US and study 689 had centers in the US and Canada.

The sponsor's chosen primary efficacy variable was the VAS-MOOD scale. Though it is not clear when the Division informed the sponsor about our preferred use of the VAS total scale on this particular protocol, the Division has made the policy clear on subsequent protocols that the VAS total score or other scale that examined all the symptoms of the disorder was more appropriate. Labeling for SSRIs currently approved for the treatment of PMDD use the VAS total score for the evaluation of both physical and mood symptoms associated with PMDD. The sponsor claims efficacy based on a positive outcome in all three studies based on the VAS MOOD; however, given our policy of looking at all of the symptoms in a disorder unless there are compelling reasons not to, we asked the sponsor to submit and analyze data on the VAS total scores.

The following tables reflect the analysis of the three studies with respect to VAS total. Study 688 fails on the LOCF analysis of the VAS total score however, studies 677 and 689 show a statistically significant improvement in VAS total scores in the LOCF analyses at both 12.5 and 25-mg doses. Study 688 showed differences in treatment response that were in the same directions as studies 677 and 689 and showed statistical improvement in the 25-mg OC analysis. Even though there is no active control, a dose response is seen and therefore this represents a failed study as opposed to a negative study.

LOCF and OC Analysies on VAS Tootal Score (ITT Population) by Treatment Cycle

Study #		L.S mean change from baseline in VAS Total Score		
	Treatment group	**Treatment Cycle 1**	**Treatment Cycle 2**	**Treatment Cycle 3**
		LOCF Analysis		
677	Parox CR 25 mg	-312.09	-304.48	-328.44
	Parox CR 12.5 mg	-259.97	-274.37	-302.04
	Placebo	-164.23	-188.85	-225.44
	P-values			
	Parox 25 Vs. placebo	<.0001	.0019	.0037
	Parox 12.5 Vs. placebo	.0065	.0252	.0357
		OC Analysis		
	Parox CR 25 mg	-306.76	-300.55	-353.91
	Parox CR 12.5 mg	-260.78	-277.37	-331.53
	Placebo	-172.54	-216.68	-246.11
	P-values			
	Parox 25 Vs. placebo	.0001	.0375	.0096
	Parox 12.5 Vs. placebo	.0136	.1372	.0446
		LOCF Analysis		
689	Parox CR 25 mg	-270.70	-337.37	-343.96
	Parox CR 12.5 mg	-229.11	-289.47	-298.41
	Placebo	-163.33	-192.41	-220.20
	P-values			
	Parox 25 Vs. placebo	<.0001	<.0001	<.0001
	Parox 12.5 Vs. placebo	.0391	.0011	.0109
		OC Analysis		
	Parox CR 25 mg	-265.11	-381.67	-335.03
	Parox CR 12.5 mg	-233.88	-304.50	-324.07
	Placebo	-170.12	-201.42	-247.86
	P-values			
	Parox 25 Vs. placebo	.0035	.0004	.0145
	Parox 12.5 Vs. placebo	.0504	.0016	.0245
		LOCF Analysis		
688	Parox CR 25 mg	-280.34	-285.80	-300.61
	Parox CR 12.5 mg	-226.79	-265.22	-288.08
	Placebo	-176.56	-208.95	-241.76
	P-values			
	Parox 25 Vs. placebo	.0019	.0166	.0599
	Parox 12.5 Vs. placebo	.1081	.0638	.1179
		OC Analysis		
	Parox CR 25 mg	-290.44	-316.09	-335.25
	Parox CR 12.5 mg	-221.80	-283.14	-302.89
	Placebo	-164.74	-196.41	-250.28
	P-values			
	Parox 25 Vs. placebo	.0002	.0003	.0055
	Parox 12.5 Vs. placebo	.0668	.0047	.0728

5.2 Safety
As Dr. Brugge states in her review that the overall safety results appear to show that Paxil CR® is adequately safe to treat patients with PMDD as proposed. The dose range of 12.5-25mg/day is on the low end of the approved dose ranges for paroxetine's other approved indications; therefore, one does not expect to see a greater amount or different quality of adverse events in this population than the depressed and panic patient populations. This data supports this assumption.

5.3 Clinical Sections of Labeling
Clinical sections of draft labeling are attached to the approvable package. As a summary, I recommend that the [ ] (see section 3.0 of this memo). The labeling in the Clinical Trials section was changed to reflect the new primary efficacy variable of VAS-total and the resultant two positive studies instead of three.

6.0 WORLD LITERATURE
The sponsor did an appropriate literature search. According to Dr. Brugge, no unexpected or unlabeled adverse events were reported in this review.

7.0 FOREIGN REGULATORY ACTIONS
I am not aware of any foreign regulatory actions regarding the use of Paxil CR® in PMDD

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING
We decided not to take this supplement to the PDAC.

9.0 DSI INSPECTIONS
Ni Khin performed DSI inspection. The inspection of one of the three sites is pending. The Bergeron site in Canada was partially audited and what was examined was acceptable; however, the review of this site is incomplete. Data from the other two sites was acceptable.

10.0 APPROVABLE LETTER
An approvable letter acknowledging our decision and draft labeling is attached to this approvable action package.

11.0 CONCLUSIONS AND RECOMMENDATIONS
I recommend that the Division take an approvable action on supplement SE1-011 (Paxil CR® for the treatment of PMDD). In order to reach approval, the sponsor would need to concur with our changes in draft labeling.

I agree with Dr Brugge that the VAS-total scale is a more appropriate measure than the VAS-MOOD scale as a basis for approval for Paxil CR® for the treatment of PMDD. The Division now has a policy of approving drugs in this class for PMDD based on scales that reflect all of the symptoms of the disorder. In the past there have been cases where oral contraceptives that

were studied for the treatment of PMDD were scrutinized using the VAS-MOOD; however, this was because these drugs were expected to effect the physical symptoms. It was feared that the effects on the physical symptoms would drive any potential difference from placebo. This is not the case with the SSRIs. SSRIs are expected to elevate mood in patients who feel depressed or irritable and it is not intuitive that SSRIs would improve physical symptoms. Therefore, physical as well as mood symptoms should be considered together as a basis for approval for treatment of PMDD with drugs in this class.

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/s/

Paul Andreason
3/20/03 04:12:16 PM
MEDICAL OFFICER

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: August 19, 2003

FROM: Paul J. Andreason, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation of Approval for Paxil CR for the Treatment of Pre-menstrual Dysphoric Disorder- Supplement SE1-011

TO: File, NDA 20-936 SE1-011
[Note: This memo should be filed with the June 27, 2002 original submission of this NDA.]

BACKGROUND

The Division took an Approvable (AE) action on NDA 20-936 SE1-011 (Paxil CR for the treatment of PMDD) on April 11, 2003. On July 8, 2003 the sponsor submitted a complete response to the Division's AE action letter. In that response, the Sponsor provided a safety update and revised draft labeling that was reviewed by Karen Brugge, MD, who was the primary clinical reviewer.

REVIEW OF RESPONSE

I concur with Dr. Brugge that the safety update did not reveal any new adverse events that were not identified in the primary review for this supplement. I concur with Dr. Brugge that the following sentences should be replaced in the Precautions section:

> Adverse events while discontinuing therapy with *Paxil CR* were not systemically evaluated in 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.

The sponsor has agreed to include this in final labeling along with the other changes that we proposed in the AE action letter of April 11, 2003. I do not agree with Dr. Brugge that the 25-mg and 12.5-mg treatment groups should be listed separately in the adverse event narrative for discontinuation symptoms. Though as she states correctly, there appears to still be a dose dependent effect even with the short taper, the study was not a systematic evaluation of discontinuation and the splitting of the groups implies more precision than was actually possible. I believe that the text as suggested by the Sponsor clearly reflects the evidence of adverse effects of discontinuation even with the taper phase. It suggests that the taper phase should probably be longer and this is more than likely the clinically correct course of action.

RECOMMENDATIONS AND CONCLUSIONS

I recommend that the Division issue the attached Approval (AP) action letter with the attached final product labeling for supplement SE1-011.

Though not a matter of action at this point the Sponsor should explain why subject 717.404.31580, who was listed as a withdrawal due to myocardial infarction was not considered a serious adverse event, since myocardial infarction is a life-threatening condition that requires emergency medical treatment.

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/s/

Paul Andreason
8/19/03 11:59:10 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-936/S-011

CHEMISTRY REVIEW(S)

CHEMIST REVIEW
OF **SUPPLEMENT**

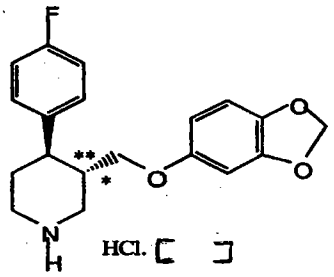
1. ORGANIZATION: HFD-120
2. NDA: **20-936**
3. SUPPLEMENT NUMBER **SE1-011**
letter date: June 26, 2002
stamp date: June 28, 2002
4. AMENDMENTS/REPORTS/DATES:
5. RECEIVED BY CHEMIST: July 1, 2002

6. APPLICANT NAME & ADDRESS: Smithkline Beecham Pharmco Puerto Rico, Inc. d/b/a GlaxoSmithKline
One Franklin Plaza, Philadelphia, PA 19101

7. NAME OF DRUG: Paxil® Controlled Release Tablets

8. NONPROPRIETARY NAME: Paroxetine hydrochloride

9. CHEMICAL NAME/STRUCTURE: (-)*trans*-4R-(4′-fluorophenyl)-3S-[(3′,4′-methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate



10. DOSAGE FORM(S): Tablet
11. POTENCY: 12.5, 25 and 37.5 mg
12. PHARMACOLOGICAL CATEGORY: Depression, Panic Disorder, Premenstrual Dysphoric Disorder
13. HOW DISPENSED: X (R_X) _____ (OTC)
14. RECORDS & REPORTS CURRENT: X Yes _____ No

SUPPLEMENT PROVIDES FOR: Use of Paxil® CR tablets for treatment of premenstrual dysphoric disorder as a new indication in addition to depression and panic disorder.

COMMENTS: There are no changes to the drug substance and drug product as referred in approved NDA 20-936. The package insert information for DESCRIPTION and HOW SUPPLIED sections also remains unchanged from the current package insert. A categorical exclusion to the environmental analysis requirements is granted in accordance with 21 CFR 25.31 (b). Based on all the information provided, this supplement is recommended for approval from a CMC perspective.

CONCLUSIONS & RECOMMENDATIONS: APPROVAL

Cc:
NDA 20-936/SE1-011
HFD-120/Division File
HFD-120/GGill-Sangha/TOliver/DBates
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Chemistry Review

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/s/

Gurpreet Gill-Sangha
2/20/03 03:49:19 PM
CHEMIST

Updated review

Thomas Oliver
2/21/03 09:17:58 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-936/S-011

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

NDA:	20-936 Supplemental
DRUG NAME:	Paxil (Paroxetine hydrochloride) Tablets
INDICATION:	Premenstrual Dysphoric Disorder
SPONSOR:	GlaxoSmithkline
STATISTICAL REVIEWER:	Ohidul Siddiqui
DATE OF DOCUMENT:	June 26, 2002

DISTRIBUTION:

HFD-120 Doris Bates, Ph.D. Project Manager
Karen Brugee, M.D., Clinical Reviewer
Thomas Laughren, M.D., Team Leader
Russell Katz, M.D., Director

HFD-710 Kun Jin, Ph.D., Team Leader
George Chi, Ph.D., Director

HFD-700 Charles Anello, Sc. D., Deputy Director

TABLE OF CONTENTS

EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

The sponsor submitted results of three adequate and well-controlled clinical trials to support the efficacy of paroxetine in the treatment of PMDD, diagnosed according to DSM-IV criteria. The LOCF endpoint ANCOVA analyses on the primary efficacy measure luteal phase VAS total score demonstrated the efficacy of paroxetine CR 25 mg and 12.5 mg over placebo across two studies during which subjects were treated for up to three complete menstrual cycles. The clinician rated outcome measure, the CGI global improvement scale showed a clinically relevant and statistically significant benefit of both paroxetine CR doses over placebo in all three studies. The statistical findings of this NDA demonstrated that paroxetine 25 mg and 12.5 mg were both effective for the treatment of PMDD patients.

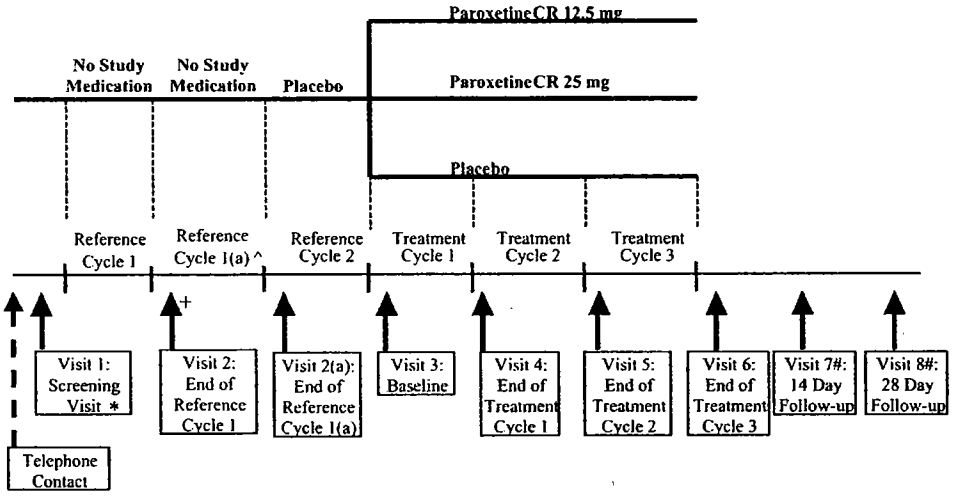
INTRODUCTION

The sponsor submitted results of three identical randomized, double-blind, placebo-controlled, fixed-dose trials (Studies 677, 689 and 688) to demonstrate the efficacy and safety of paroxetine CR for the treatment of Premenstrual Dysphoric Disorder (PMDD). These studies were carried out in the United States (Study 677), Canada/United States (Study 689) and Europe/South Africa (Study 688).

Figure 1 lists an overview of the study design. The studies enrolled female subjects with a diagnosis of PMDD according to DSM-IV criteria. Following an initial screening visit, subjects fulfilling a preliminary diagnosis for PMDD (DSM-IV criteria A to C) recorded their symptoms on a daily basis for up to three menstrual cycles (reference cycles), using visual analogue scales, to confirm the diagnosis (DSM-IV criterion D). Subjects were required to meet the protocol defined VAS entry criteria for two consecutive menstrual cycles in order to confirm the diagnosis. Subjects who failed to meet the VAS entry criteria during reference cycle 1 were, at the investigator's discretion, entered into an additional reference cycle 1(a) rather than be excluded from the study at this point. Subjects received no medication during reference cycle 1 or 1(a). Following reference cycle 1 or 1(a), eligible subjects entered reference cycle 2 during which they received single-blind placebo medication.

At the end of reference cycle 2 (baseline visit), subjects with a diagnosis of PMDD according to DSM-IV criteria A to D (confirmed based on their daily VAS ratings) were randomized into the double-blind treatment phase of the study. Subjects were randomized in a 1:1:1 ratio to receive daily treatment with paroxetine CR 25mg, paroxetine CR 12.5mg or placebo for up to three double-blind treatment cycles. Figure 1 illustrates the details of the reference cycle, treatment cycle of the studies.

Figure 1: Study Design (for Studies 677, 689 and 688)



* The Screening Visit was carried out in the follicular phase prior to reference cycle 1. It was scheduled to take place at least seven days after premenstrual symptoms from the previous cycle had ended.
+ Reference and treatment cycle visits took place in the follicular phase (between days 1 to 3) of the next reference or treatment cycle.
^ Subjects who did not qualify for inclusion in the study on the basis of their reference cycle 1 diary scores could, at the discretion of the investigator, enter an optional reference cycle 1(a) rather than being withdrawn from the study.
# For those subjects who entered the extension study (711), follow-up visits took place following three additional double-blind treatment cycles in the study.

Inclusion and exclusion Criteria

The inclusion and exclusion criteria for the three protocols were identical with regard to demographic and clinical characteristics. Subjects meeting all of the inclusion criteria and none of the exclusion criteria were eligible for entry into the studies. Some of the important inclusion criteria are: (I) Female out-patients aged between 18 and 45 years, (ii) Regular menstrual cycles (duration between 22 and 35 days), (iii) Diagnosis of PMDD, (iv) PMDD present for at least the past year during which symptoms present in at least 9 out of 12 menstrual cycles, (v) A baseline (Visit 3: end of reference cycle 2) Clinical Global Impression (CGI) - Severity of Illness score of >=3, (vi) Use of an adequate non-hormonal form of contraception. Methods such as IUD, tubal ligation, and double barrier contraception (any two of diaphragm /spermicidal foam/ condom) were acceptable. The uses of oral contraceptives or systemic contraception (e.g. Norplant, Depo Provera) were not acceptable.

The some of the important exclusion criteria are: (i) Subjects who fulfilled DSM-IV criteria for any Axis 1 disorder (other than PMDD or specific phobias) in the 6 months prior to screening, (ii) Subjects with diagnosed gynecological disease (e.g. uterine fibroids, ovarian, uterine or cervical carcinoma, or endometriosis), (iii) Subjects with a

baseline Montgomery Asberg Depression Rating Scale (MADRS) score of >=10 during the follicular phase of the menstrual cycle (i.e. at Visit 1), (iv) Subjects with a significant risk of suicide, (v) Subjects taking any ongoing medications that could affect the subject's PMDD symptomatology, (vi) Subjects who received any previous adequate treatment with an SSRI for premenstrual symptoms, (vii) Subjects with a history of hypersensitivity or adverse reaction to paroxetine or other SSRIs.

Primary Efficacy Variable

The protocol specified primary measure of efficacy was the change from baseline in the mean luteal phase VAS-Mood score at the treatment cycle 3 LOCF endpoint. The mean luteal phase VAS score for each symptom was the mean of the last five days of the menstrual cycle, calculated for each subject. The VAS-Mood score was defined as the mean of luteal phase VAS scores for the four core PMDD symptoms: irritability, tension, depressed mood and affective liability.

Division of Neuropharmacological Drug Products (DNDP) strongly recommend the sponsor to change the primary outcome to the luteal phase VAS total score, encompassing all 11 symptoms of PMDD, rather than the four-item VAS Mood score alone. The Division also informed the sponsor that DNDP will focus on the luteal phase VAS total score in the efficacy assessment and in any regulatory consideration of data derived from this NDA,

Secondary Efficacy Variables

The studies included several secondary efficacy variables. Some of the variables are: (i) Change from baseline in the mean luteal phase VAS physical symptoms score at treatment cycle 3 LOCF endpoint where mean luteal phase score was the mean VAS physical symptom scores of the last 5 days of the menstrual cycle, calculated for each subject; (ii) proportion of responders at the treatment cycle 3 LOCF endpoint, where response is defined as a 50% reduction from their baseline luteal phase VAS-Mood score; (iii) proportion of responders at treatment cycle 3 LOCF endpoint, where response is defined as a mean luteal phase VAS-Mood score of less than or equal to their baseline mean follicular phase VAS-Mood score; (iv) change from baseline in area under the curve (AUC) for treatment cycles 1-3 in daily luteal phase VAS-Mood scores adjusted for the total number of luteal days; (v) change from baseline in the CGI-Severity of Illness score at the treatment cycle 3 LOCF endpoint; (vi) the proportion of subjects who scored 1 (very much improved) or 2 (much improved) on the CGI-Global Improvement item at the treatment cycle 3 LOCF endpoint.

Among the secondary measures, DNDP felt that a clinician-rated global measure of clinical status, such as the Clinical Global Impression (CGI) scale might be an important secondary measure for PMDD indication. Therefore, in this review, CGI-Global Improvement scale will be reviewed as a secondary outcome measure.

Data Analysis Method

All analyses were carried out using data generated from the intent-to-treat (ITT) population, which consisted of all subjects who were randomized, had taken at least one dose of double-blind study medication, and for whom at least one post-baseline assessment was available. Statistical inferences concerning the efficacy of paroxetine CR were drawn from this population at the protocol defined treatment cycle 3 endpoint, using the LOCF dataset. Observed cases dataset at the Treatment Cycle 3 endpoint (OC) was also analyzed.

DNDP defined primary variable, change from baseline in the luteal phase VAS total score at treatment cycle 3 LOCF, was analyzed using parametric analysis of covariance (ANCOVA). The model on which inference was based included terms for treatment group, center group, baseline score, and age. The protocol defined primary variable, change from baseline in the mean luteal phase VAS-Mood score at treatment cycle 3 LOCF was also analyzed using the same ANCOVA model. In both models, the interactions of treatment with center group and age were assessed separately.

All hypothesis tests were two sided. For the primary efficacy variable, hypothesis tests used a nominal 5% level of statistical significance and significance levels were adjusted for two treatment comparisons using Hochberg's modification to the Bonferroni inequality.

The secondary categorical efficacy variable, the proportion of subjects who scored 1 (very much improved) or 2 (much improved) on the CGI-Global Improvement item at the treatment cycle 3 LOCF endpoint was analyzed using logistic regression. The model included treatment group, center group, and age. The ITT population was analyzed for the secondary efficacy variables. No adjustments were made for multiple treatment comparisons; hypothesis tests used a 5% level of significance. The interaction of treatment with the other main effects was not assessed for the secondary efficacy variable.

Multiple Comparison/Multiplicity

There were two comparisons of interest: paroxetine CR 25 mg versus placebo, and paroxetine CR 12.5 mg versus placebo. For the primary efficacy variable, adjustments comparisons using Hochberg's modification to the Bonferroni inequality were made to the significance level to reduce the incidence of spurious results and thereby protect the validity of the inferences between each dose of paroxetine CR and placebo. As the analysis of the secondary variable was to provide supportive evidence only, no adjustment was made to the significance level for these variables.

Subgroup Analysis

No subgroup analyses were carried out for any of the three trials. Among the subgroup factors age, gender and race, age has been included as a covariate in all of the efficacy

analyses while the population is exclusively female so there are no gender subgroups. Since the vast majority of the clinical trial population (94.6%) was Caucasian with relatively small numbers of Non-Caucasian subjects, a subgroup analysis would not be of value.

Handling Missing Data

For each subject, missing data for a rating scale at a particular visit was handled as follows:

Last Observation Carried Forward

To account for missing data, the LOCF method was used, i.e. the last available on-therapy observation for a subject is used 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 intermediate visit within the study period, e.g., a subject may only have scores for treatment cycles 1 and 3; in this case the value for treatment cycle 1 was carried forward in the LOCF analysis of the treatment cycle 2. 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. For each subject, missing data within rating scales were handled as follows:

VAS Individual Symptom Items

For each of the individual VAS items a mean score for the luteal phase was only calculated if scores were available for at least 4 of the 5 designated days.

VAS Total Score
Calculating the VAS Total score:
For each subject, a mean luteal phase score for each of the 11 VAS-Mood items for a given menstrual cycle, was calculated only if scores were available for four or five of the designated 'luteal' days within that cycle. If data were missing for no more than 1 day within the last 5 days of the menstrual cycle (representing the luteal phase), then the mean was calculated on the remaining non-missing daily scores [mean = (sum of non-missing scores)/(number of days with non-missing data)]. A VAS total score for the luteal phase was calculated as [VAS total score=(Mean of the available items)*11]. In each of the studies, majority of the subjects had mean score on each of the 11 VAS items. A few subjects had missing response only on one item.

VAS-Mood Score
Calculating the VAS-Mood score:

For each subject, a mean luteal phase score for each of the four core VAS-Mood items (depressed mood, tension, irritability and affective lability as captured from the Visual Analogue Scales) for a given menstrual cycle, was calculated only if scores were

available for four or five of the designated 'luteal' days within that cycle. If data were missing for no more than 1 day within the last 5 days of the menstrual cycle (representing the luteal phase), then the mean was calculated on the remaining non-missing daily scores [mean = (sum of non-missing scores)/(number of days with non-missing data)]. A VAS-Mood total score for the luteal phase was calculated only if mean scores were available for three or four of the individual items (depressed mood, tension, irritability and affective lability) within that phase.

Table 1: Patients baseline characteristics by treatment groups of each of the three studies (ITT Population).

Study No.	Treatment Group (N)	Mean Age (years)	Race (% of White)	Baseline Mean VAS-Mood Score	Baseline Mean VAS Total Score
677	Parox CR 25 mg (111)	35.9	88.3	54.5	566.3
	Parox CR 12.5 mg (95)	35.2	91.6	60.3	622.1
	Placebo (107)	34.9	86.9	53.9	567.8
689	Parox CR 25 mg (120)	36.5	96.7	51.5	527.5
	Parox CR 12.5 mg (115)	36.4	93.9	55.1	585.1
	Placebo (124)	35.8	93.5	52.6	559.4
688	Parox CR 25 mg (117)	36.7	100	48.0	506.7
	Parox CR 12.5 mg (123)	37.1	98.4	55.1	564.7
	Placebo (118)	36.5	100	57.9	585.0

Table 2. Percentages of withdrawn patients in the double-blind treatment phase by reason (ITT Population)..

	Study 677			Study 689			Study 688		
	P25 mg	P12.5 mg	PBO	P25 mg	P12.5 mg	PBO	P25 mg	P12.5 mg	PBO
Randomized ITT (N)	111	95	107	120	115	124	117	123	118
Total Completers (%)	64.9	73.7	73.8	68.3	77.4	77.4	74.4	78.9	76.3
Total Withdrawn (%)	35.1	26.3	26.2	31.7	22.6	22.6	25.6	21.1	23.7
Adverse event (%)	13.5	9.5	6.5	16.7	10.4	7.3	16.2	10.6	5.9
Protocol Deviation(%)	9.0	3.2	6.5	4.2	1.7	4.0	3.4	4.9	5.1
Other Reasons (%)	5.4	6.3	3.7	2.5	4.3	6.5	2.6	0.8	4.2
Lack f Efficacy (%)	0.9	4.2	4.7	-	2.6	2.4	1.7	4.1	5.1
Lost to follow-up (%)	6.3	3.2	4.7	8.3	3.5	2.4	1.7	0.8	3.4

P25 mg=Paroxetine CR 25mg, P12.5 mg= Paroxetine CR 12.5mg, PBO=Placebo

Table 3. Percentages of subjects remained in each treatment Cycle (ITT Population).

Study #	Treatment group (N)	Baseline (%)	Treatment Cycle 1 (%)	Treatment Cycle 2 (%)	Treatment Cycle 3 (%)
677	Parox CR 25 mg (111)	100	85.6	73.0	60.4
	Parox CR 12.5 mg (95)	100	93.7	84.2	69.5
	Placebo (107)	100	91.6	83.2	72.9
689	Parox CR 25 mg (120)	100	88.3	78.3	65.0
	Parox CR 12.5 mg (115)	100	89.6	83.5	77.4
	Placebo (124)	100	95.2	87.1	75.0
688	Parox CR 25 mg (117)	100	82.1	76.9	73.5
	Parox CR 12.5 mg (123)	100	93.5	87.8	75.6
	Placebo (118)	100	95.8	86.4	69.5

Table 4. LOCF and OC analyses on VAS Total Score (ITT population) by treatment cycle

Study #	L.S mean change from baseline in VAS Total Score			
	Treatment group	Treatment Cycle 1	Treatment Cycle 2	Treatment Cycle 3
	LOCF Analysis			
677	Parox CR 25 mg	-312.09	-304.48	-328.44
	Parox CR 12.5 mg	-259.97	-274.37	-302.04
	Placebo	-164.23	-188.85	-225.44
	P-values			
	Parox 25 Vs. placebo	<.0001	.0019	.0037
	Parox 12.5 Vs. placebo	.0065	.0252	.0357
	OC Analysis			
	Parox CR 25 mg	-306.76	-300.55	-353.91
	Parox CR 12.5 mg	-260.78	-277.37	-331.53
	Placebo	-172.54	-216.68	-246.11
	P-values			
	Parox 25 Vs. placebo	.0001	.0375	.0096
	Parox 12.5 Vs. placebo	.0136	.1372	.0446
	LOCF Analysis			
689	Parox CR 25 mg	-270.70	-337.37	-343.96
	Parox CR 12.5 mg	-229.11	-289.47	-298.41
	Placebo	-163.33	-192.41	-220.20
	P-values			
	Parox 25 Vs. placebo	<.0001	<.0001	<.0001
	Parox 12.5 Vs. placebo	.0391	.0011	.0109
	OC Analysis			
	Parox CR 25 mg	-265.11	-381.67	-335.03
	Parox CR 12.5 mg	-233.88	-304.50	-324.07
	Placebo	-170.12	-201.42	-247.86
	P-values			
	Parox 25 Vs. placebo	.0035	.0004	.0145
	Parox 12.5 Vs. placebo	.0504	.0016	.0245
	LOCF Analysis			
688	Parox CR 25 mg	-280.34	-285.80	-300.61
	Parox CR 12.5 mg	-226.79	-265.22	-288.08
	Placebo	-176.56	-208.95	-241.76
	P-values			
	Parox 25 Vs. placebo	.0019	.0166	.0599
	Parox 12.5 Vs. placebo	.1081	.0638	.1179
	OC Analysis			
	Parox CR 25 mg	-290.44	-316.09	-335.25
	Parox CR 12.5 mg	-221.80	-283.14	-302.89
	Placebo	-164.74	-196.41	-250.28
	P-values			
	Parox 25 Vs. placebo	.0002	.0003	.0055
	Parox 12.5 Vs. placebo	.0668	.0047	.0728

Table 5. LOCF and OC analyses on Primary measure VAS-Mood Score (ITT population) by treatment cycle

Study #	L.S mean change from baseline in VAS-Mood Score			
	Treatment group	Treatment Cycle 1	Treatment Cycle 2	Treatment Cycle 3
	LOCF Analysis			
677	Parox CR 25 mg	-34.77	-34.76	-35.94
	Parox CR 12.5 mg	-30.04	-30.02	-32.56
	Placebo	-18.38	-20.85	-23.84
	P-values			
	Parox 25 Vs. placebo	<.0001	.0002	.0005
	Parox 12.5 Vs. placebo	.0009	.0171	.0149
	OC Analysis			
	Parox CR 25 mg	-34.77	-34.23	-38.28
	Parox CR 12.5 mg	-30.04	-29.78	-35.23
	Placebo	-18.38	-22.09	-24.87
	P-values			
	Parox 25 Vs. placebo	<.0001	.0033	.0008
	Parox 12.5 Vs. placebo	.0009	.0653	.0109
	LOCF Analysis			
689	Parox CR 25 mg	-30.92	-36.32	-35.87
	Parox CR 12.5 mg	-25.29	-30.77	-30.80
	Placebo	-16.61	-19.73	-23.29
	P-values			
	Parox 25 Vs. placebo	<.0001	<.0001	<.0001
	Parox 12.5 Vs. placebo	.0064	.0002	.0126
	OC Analysis			
	Parox CR 25 mg	-30.92	-35.98	-35.99
	Parox CR 12.5 mg	-25.29	-31.70	-32.64
	Placebo	-16.61	-19.64	-25.03
	P-values			
	Parox 25 Vs. placebo	<.0001	<.0001	.0012
	Parox 12.5 Vs. placebo	.0064	<.0001	.0178
	LOCF Analysis			
688	Parox CR 25 mg	-32.52	-32.96	-33.28
	Parox CR 12.5 mg	-25.93	-28.38	-30.38
	Placebo	-17.10	-21.93	-25.75
	P-values			
	Parox 25 Vs. placebo	<.0001	.0013	.0187
	Parox 12.5 Vs. placebo	.0067	.0447	.1229
	OC Analysis			
	Parox CR 25 mg	-32.52	-34.73	-35.01
	Parox CR 12.5 mg	-25.93	-30.69	-32.99
	Placebo	-17.10	-21.44	-27.90
	P-values			
	Parox 25 Vs. placebo	<.0001	.0001	.0190
	Parox 12.5 Vs. placebo	.0067	.0041	.0800

Table 6. Summary Of Logistic Regression for % of Subjects Responding† on the CGI-Global Improvement (ITT LOCF Population)

Study#	Treatment	% Responder	Odd Ratio*	Pairwise Comparison P-value
677	Parox CR 25 mg vs placebo	70.5 vs 49.0	2.88	<0.001
	Parox CR 12.5 mg vs placebo	65.9 vs 49.0	1.93	0.038
689	Parox CR 25 mg vs placebo	73.3 vs 44.7	3.87	<0.001
	Parox CR 12.5 mg vs placebo	62.1 vs 44.7	2.11	0.010
688	Parox CR 25 mg vs placebo	71.6 vs 41.6	3.94	<0.001
	Parox CR 12.5 mg vs placebo	61.4 vs 41.8	2.30	0.003

*The odds ratio represents the odds of improving with paraxetine relative to placebo.

† A responder was defined as having a score of 1 (very much improved) or 2 (much improved) at endpoint. Logistic model was adjusted for center group and age.

SPONSOR'S FINDINGS

Demographics and Other Baseline Characteristics

Table 1 summarizes the demographic characteristics of the ITT population by treatment groups. Within each study, the demographic characteristics of the three treatment groups were similar with respect to mean age, race, weight, height and BMI. The patients' characteristics were also similar across the three studies. In each study, majority of the patients were white. In studies 677 and 689, the baseline VAS total score was higher in the paroxetine CR 12.5 mg group compared to the scores for paroxetine CR 25 mg group and the placebo group.

Number of Subjects Present at the study endpoint

Table 2 lists a summary of the numbers of patients completed the study in each treatment group. The percentages of patients completing the studies were well balanced for the paroxetine CR 12.5mg and placebo groups, but there were fewer completers in the CR 25mg group. The same trend was also true at the treatment cycles 1 & 2 [Table 3]. The number of subjects who withdrew prematurely was higher in the paroxetine CR 25 mg treatment group. The primary reason for early withdrawal in both of the paroxetine CR groups was adverse event. Adverse event and protocol deviation were the most common reasons for withdrawal in the placebo group. The proportion of subjects withdrawing because of an adverse event was highest in the paroxetine CR 25 mg group and lowest in the placebo group. The number of subjects who withdrew prematurely because of a lack of efficacy was lower for the paroxetine CR 25 mg group compared to the paroxetine CR 12.5 mg group and placebo group.

Primary Efficacy Results

Table 4 lists the LOCF and OC analyses on the change from baseline in VAS total score (the DNDP defined primary efficacy measure). Primary inferences were based on treatment differences between the paroxetine CR 25 mg and 12.5 mg groups and placebo for the covariate adjusted model (center group, baseline VAS total score and age) at the treatment cycle 3 LOCF endpoint.

In study 677, a statistically significant difference in adjusted change from baseline to treatment cycle 3 LOCF endpoint was demonstrated in favor of paroxetine CR 25 mg versus placebo [adjusted mean difference =103.00 (=-328.44-(-225.44)), p =0.003]. A statistically significant difference was also demonstrated in favor of paroxetine CR 12.5 mg versus placebo [adjusted mean difference =76.60 (=-302.04-(-225.44)), p = 0.035]. There were no significant interactions between treatment and any of the covariates. Based on adjustments comparisons using Hochberg's modification to the Bonferroni inequality to the significance level, both paroxetine CR 25 mg and 12 mg are statistically significantly efficacious, as compared to placebo. The results of the OC analyses at each treatment cycle were also similar to the corresponding LOCF results.

In study 689, a statistically significant difference in adjusted change from baseline to treatment cycle 3 LOCF endpoint was demonstrated in favor of paroxetine CR 25 mg versus placebo [adjusted mean difference =123.76 (= -343.96-(-220.20)), p <0.001]. A statistically significant difference was also demonstrated in favor of paroxetine CR 12.5 mg versus placebo [adjusted mean difference = 78.21 (=-298.41-(-220.20)), p = 0.0109]. There were no significant interactions between treatment and any of the covariates. Based on adjustments comparisons using Hochberg's modification to the Bonferroni inequality to the significance level, both paroxetine CR 25 mg and 12 mg are statistically significantly efficacious, as compared to placebo. The results of the OC analyses at each treatment cycle were also similar to the corresponding LOCF results.

In study 688, paroxetine was not statistically significantly different from placebo at the treatment cycle 3 LOCF endpoint. The p-values for paroxetine 25 mg vs. placebo, and paroxetine 12.5 mg vs. placebo were .0599 and .1179, respectively. Based on the p-values, the study 688 was a failed study.

Table 5 lists the LOCF and OC analyses on the change from baseline in VAS-Mood score (the protocol defined primary efficacy measure). Primary inferences were based on treatment differences between the paroxetine CR 25 mg and 12.5 mg groups and placebo for the covariate adjusted model (center group, baseline VAS-Mood score and age) at the treatment cycle 3 LOCF endpoint.

In study 677, a statistically significant difference in adjusted change from baseline to treatment cycle 3 LOCF endpoint was demonstrated in favor of paroxetine CR 25 mg versus placebo [adjusted mean difference = -12.10, p <0.001]. A statistically significant difference was also demonstrated in favor of paroxetine CR 12.5 mg versus placebo [adjusted mean difference = -8.72, p = 0.015]. There were no significant interactions

between treatment and any of the covariates. Based on adjustments comparisons using Hochberg's modification to the Bonferroni inequality to the significance level, both paroxetine CR 25 mg and 12 mg are statistically significantly efficacious, as compared to placebo. The results of the OC analyses were also similar to the results of the treatment cycle 3 LOCF endpoint analyses.

In study 689, a statistically significant difference in adjusted change from baseline to treatment cycle 3 LOCF endpoint was demonstrated in favor of paroxetine CR 25 mg versus placebo [adjusted mean difference = -12.58, p <0.001]. A statistically significant difference was also demonstrated in favor of paroxetine CR 12.5 mg versus placebo [adjusted mean difference = -7.51, p = 0.012]. There were no significant interactions between treatment and any of the covariates. Based on adjustments comparisons using Hochberg's modification to the Bonferroni inequality to the significance level, both paroxetine CR 25 mg and 12.5 mg are statistically significantly efficacious, as compared to placebo. The results of the OC analyses were also similar to the results of the treatment cycle 3 LOCF endpoint analyses.

In study 688, a statistically significant difference in adjusted change from baseline to treatment cycle 3 LOCF endpoint was demonstrated in favor of paroxetine CR 25 mg versus placebo [adjusted mean difference = -7.53, p <0.018]. Paroxetine CR 12.5 was not statistically significantly (p=.1229) different from placebo at the treatment cycle 3 LOCF endpoint. Based on adjustments comparisons using Hochberg's modification to the Bonferroni inequality to the significance level, only paroxetine CR 25 mg is statistically significantly efficacious, as compared to placebo. The results of the OC analyses were also similar to the results of the treatment cycle 3 LOCF endpoint analyses.

Secondary Efficacy Results

Percent of patients responding on the CGI-Global Improvement

Table 6 lists the summary of logistic regression results on the responders on CGI-Global Improvement. In study 677, there were 67/95 (70.5%), 56/85 (65.9%) and 48/98 (49.0%) responders on the CGI global improvement scale for the paroxetine CR 25mg, CR 12.5mg and placebo treatment groups, respectively. The odds of being a responder at the treatment Cycle 3 LOCF endpoint (odds ratio=2.88, p<0.001) indicated a statistically significant benefit of paroxetine CR 25mg over placebo. The odds of being a responder on paroxetine CR 12.5mg compared to placebo at the treatment Cycle 3 LOCF endpoint (odds ratio=1.93, p=0.038) also indicated a statistically significant benefit of CR 12.5mg over placebo.

In study 689, there were also more paroxetine CR than placebo responders at the Treatment cycle 3 LOCF endpoint (74/101 (73.3%), 64/103 (62.1%) and 51/114 (44.7%) for the paroxetine CR 25mg, CR 12.5mg and placebo treatment groups, respectively). The odds of response indicated a statistically significant benefit of paroxetine CR 25mg compared to placebo at the treatment cycle 3 LOCF endpoint (odds ratio=3.87, p<0.001). The odds of response also indicated a statistically significant benefit of paroxetine CR

12.5mg compared to placebo at the treatment cycle 3 LOCF endpoint (odds ratio=2.11, p=0.010).

In study 688, the number of responders was once again greater for the two paroxetine CR treatment groups than for placebo at the treatment cycle 3 LOCF endpoint (68/95 (71.6%), 70/114 (61.4%) and 47/113 (41.6%) for the paroxetine CR 25mg, 12.5mg and placebo treatment groups respectively). The odds of response indicated a statistically significant benefit of paroxetine CR 25mg compared to placebo at the treatment cycle 3 LOCF endpoint (odds ratio=3.94, p<0.001). The odds of response also indicated a statistically significant benefit of paroxetine CR 12.5mg compared to placebo at the treatment cycle 3 LOCF endpoint (odds ratio=2.30, p=0.003).

Reviewer's Analysis and Comments

This reviewer was able to reproduce the sponsor's reported results of each of the three studies. Among the three studies, studies 677 and 689 were positive studies with respect to the significant efficacy of paroxetine CR 25 mg and 12.5 mg for treating PMDD patients. Paroxetine 25 mg and 12.5 mg were both statistically significantly different from placebo based on luteal phase VAS total score, as well as based on the luteal phase VAS-MOOD score. Based on the luteal phase VAS total score, study 688 was a failed study. Based on the luteal phase VAS-MOOD score, paroxetine 25 mg was efficacious as compared to placebo in study 688.

Reviewer's Overall Conclusion

The efficacy of paroxetine CR 25 mg and 12.5 mg in the treatment of PMDD, diagnosed according to DSM-IV criteria, was demonstrated across two identical, well designed, placebo controlled studies during which subjects were treated for up to three complete menstrual cycles.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-936/S-011

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 20-936 SUPPL # 011

Trade Name Paxil CR

Generic Name paroxetine hydrochloride controlled-release tablets

Applicant Name GlaxoSmithKline HFD- 120

Approval Date August 28, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

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

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

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

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

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

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

YES /_X_/ NO /___/

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

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

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name

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

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

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

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

NDA # 20-936 Paxil CR (paroxetine hydrochloride) controlled-release tablets

NDA # 20-885 Paxil(paroxetine hydrochloride) capsules

NDA # 20-031 Paxil(paroxetine hydrochloride) tablets

NDA # 20-710 Paxil(paroxetine hydrochloride) suspension

2. Combination product. N/A

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing anyone of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

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

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /__X__/ NO /___/

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

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /__/

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

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

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

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /__X__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 677

Investigation #2, Study # 688

Investigation #3, Study # 689

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /__X__/

Investigation #2 YES /___/ NO /__X__/

Investigation #3 YES /___/ NO /__X__/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

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

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /_X__/

Investigation #3 YES /___/ NO /_X__/

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

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

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

Investigation #_1_, Study # 677

Investigation #_2_, Study # 688

Investigation #_3_, Study # 689

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of

the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 51,171 YES /_X_/ NO /___/ Explain:

Investigation #2

IND # 51,171 YES /_X_/ NO /___/ Explain:

Investigation #3

IND # 51,171 YES /_X_/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? N/A

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /__X_/

If yes, explain: _____

_____

_____

Signature of Preparer Date
Title:

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

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

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/s/

Richardae Taylor
9/10/03 03:06:53 PM

Russell Katz
9/23/03 08:17:58 AM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 20-936 Supplement Type (e.g. SE5): SE1 Supplement Number: 011

Stamp Date: June 26, 2002 Action Date: August 28, 2003

HFD 120 Trade and generic names/dosage form: Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets

Applicant: GlaxoSmithKline Therapeutic Class: Serotonin reuptake inhibitor (SSRI)

Indication(s) previously approved: Major depressive disorder
Panic disorder

— Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Premenstrual Dysphoric Disorder

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.

X No: Please check all that apply: ___Partial Waiver __X__Deferred ___Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval

- ☐ Formulation needed
- ☐ Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- X Other: Pediatric Rule currently in litigation.

Date studies are due (mm/dd/yy): _____

, studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- ☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

:tion D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
?1-594-7337

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/s/

Richardae Taylor
9/9/03 03:37:06 PM

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 20-936
SPONSOR: GLAXOSMITHKLINE
DRUG: PAXIL CR
MATERIAL SUBMITTED: REQUEST FOR DEFERRAL OF PEDIATRIC STUDIES
DATE SUBMITTED: 12-13-02
DATE RECEIVED: 12-16-02

This letter requests a deferral of pediatric development for the indication of PMDD in adolescents. The sponsor is requesting deferral of the study requirements under the Pediatric Rule until the pending supplement for adult PMDD is approved.

Reviewer comment: The Pediatric Rule was voided by the US District Court for the District of Columbia on 10-17-02. Accordingly, I suggest advising the sponsor that no formal deferral from this Division is needed at this point in time.

Andrew D. Mosholder, M.D., M.P.H.
Medical Officer, HFD-120

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/s/

Andy Mosholder
12/27/02 06:22:30 PM
MEDICAL OFFICER

Thomas Laughren
12/28/02 11:46:09 AM
MEDICAL OFFICER

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: March 13, 2003

TO: Doris Bates, Ph.D., Regulatory Project Manager
Karen Brugge, M.D., Medical Officer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Antoine El-Hage, Ph.D., Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
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/SE1-011

APPLICANT: GlaxoSmith Kline

DRUG: Paxil CR (paroxetine hydrochloride controlled release) Tablets

THERAPEUTIC CLASSIFICATION: Type S, Standard Review

INDICATION: Premenstrual Dysphoric Disorder (PMDD)

CONSULTATION REQUEST DATE: August 19, 2002

ACTION GOAL DATE: April 25, 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 Premenstrual Dysphoric Disorder (PMDD).

The NDA submission included the results from two identical protocols #29060/677 and 29060/689 entitled "A double-blind, placebo-controlled, 3-arm fixed dose study of paroxetine CR continuous treatment (12.5mg and 25mg/day) for Premenstrual Dysphoric Disorder." The study was a multicenter, randomized, double-blind, placebo-controlled, fixed dose, three-arm parallel group study to assess the efficacy and safety of continuous treatment with 12.5mg and 25mg o.d. doses of paroxetine CR versus placebo in subjects with a diagnosis of PMDD according to the DSM-IV criteria. Female subjects aged between 18 and 45 years fulfilling a preliminary diagnosis of PMDD (DSM-IV criteria A to C) at screening visit completed daily symptom visual analogue scales (VAS) for up to three consecutive menstrual cycles (reference cycles) to confirm diagnosis of PMDD. To satisfy the DSM-IV Criterion D, the VAS entry criteria stipulated that during two consecutive reference cycles the subject's mean luteal phase score must rate at least 200% higher (i.e. worse) on one, or at least 100% higher on two or more of the four core symptoms (irritability, depressed mood, tension or affective lability) compared to their mean follicular phase score. Subjects were required to meet the protocol defined VAS entry criteria for two consecutive menstrual cycles. Those subjects who failed to meet the protocol defined VAS entry criteria during reference cycle 1 were entered into an additional reference cycle 1(a) at the investigator's discretion. Subjects received no medication during reference cycle 1 [and 1(a) if applicable].

Subjects eligible to enter reference cycle 2 received single-blind placebo medication once daily throughout reference cycle 2. At the end of reference cycle 2, subjects meeting all screening and baseline eligibility criteria were randomized in a 1:1:1 ratio to receive one of three treatments (paroxetine CR 25 mg, paroxetine CR 12.5 mg or placebo) once daily for up to three treatment cycles. The primary efficacy variable was the change in mean luteal phase VAS-Mood Score from baseline at treatment cycle 3.

Inspection assignment was issued for two domestic sites: Drs. Corder and Grant for Protocol 677 and one Canadian site: Dr. Bergeron for Protocol 689.

II. RESULTS (by site):

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
Corder	Oklahoma City	OK	09-11-2002	11-20-2002	VAI
Grant	Chesterfield	MO	09-11-2002	12-26-2002	NAI
Bergeron*	Hull	Quebec	08-22-2002	03-03-2003	pending

* findings based on Form FDA 483 Inspectional Observations only; EIR still pending

CORDER, M.D., Ph.D

At this clinical site, 98 subjects were screened; 28 subjects were randomized (26 subjects per IRB closing report) and 20 subjects completed the study. Discontinuation reasons included protocol violation, lost to follow-up, adverse event (back surgery), and withdrawal of consent.

An audit of records for 11 randomized subjects was conducted. Inspection noted minor discrepancies between drug accountability records and progress notes regarding the amount of drug returned for subject 12750 (treatment cycle 3) and subject 12755 (reference cycle 2 & treatment cycle 3). For subject 12724, the drug accountability record was not created and maintained as the drug was dispensed and returned. Instead, it was reconstructed from the progress notes. The medication record showed that the start/stop dates of each treatment cycle was slightly different than which was recorded in the progress notes. All subjects who participated in the study signed the consent form. Overall, data appear acceptable.

GRANT, M.D.

At this clinical site, 72 subjects were screened; 24 subjects were randomized to receive either Paxil CR (12.5 or 25 mg/day) or Placebo for treatment of PMDD; 18 subjects completed the study. Discontinuation reasons included lost to follow up, non-compliance, adverse event (intercurrent illness), or lack of efficacy.

An audit of records from 18 subjects who completed the study was conducted. The inspection revealed no major problems. The inspection also reviewed the dates of the signed informed consent documents for subjects who had laboratory tests performed and began recording information in the Reference Cycle Diaries and did not note any discrepancies. Data appear acceptable.

BERGERON, M.D., Ph.D.

At this site, 70 subjects were randomized and 59 subjects completed the study. An audit of 20 subjects (6 subjects from placebo, 6 subjects from 12.5 mg paroxetine and 8 subjects from 25 mg paroxetine group) was conducted. According to the FDA Form 483 Inspectional Observation, two diary pages dated the same (5/29/00) showed different scores for subject 17954 during reference cycle; and there was a missing page in the diary dated 5/30/01 for subject 17669 during reference cycle 2. Overall, data seem acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As stated above, there was minor drug accountability discrepancy at Dr. Corder and record keeping issue at Dr. Bergeron site. Overall, the data from these sites appear acceptable for use in support of this NDA supplement.

Note: Should the EIR and exhibits from the audit of Dr. Bergeron, 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.

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

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

cc:
NDA 20-936/SE1-011
Division File
HFD-45/Program Management Staff (electronic copy)
HFD-47/c/r/s
HFD-47/El-Hage
HFD-47/Khin
HFD-47/Friend
HFD-45/RF

rd: NK: 03/13/03

O:\NK\CIS\NDA20936SE1011 PaxilCR PMDD CIS.DOC

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/s/

Ni Aye Khin
3/14/03 09:10:00 AM
MEDICAL OFFICER

This clinical inspection summary (DSI-paper version) was initialed and concurred by Dr. A. El-Hage on 3/13/03.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Bates

Kenneth E. Grant, M.D.
Mercy Health Research
1585 Woodlake Drive, Suite 200
Chesterfield, Missouri 63017

DEC 21 2002

Dear Dr. Grant:

Between October 30 and November 5, 2002, Ms. Pamela L. Vega, representing the Food and Drug Administration (FDA), conducted an investigation and met with Dr. [redacted] your subinvestigator, to review your conduct of a clinical investigation [protocol #29060/677 entitled: "A double-blind, placebo-controlled, 3-arm fixed dose study of paroxetine CR continuous treatment (12.5mg and 25mg/day) for Premenstrual Dysphoric Disorder"] of the investigational drug Paxil CR (paroxetine controlled- release) Tablets, performed for GlaxoSmithKline. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies 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 Vega 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,

for Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

cc:
[redacted] M.D.
Mercy Health Research
1585 Woodlake Drive, Suite 200
Chesterfield, Missouri 63017

FEI: 3003780956
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/SE1-011
HFD-120 Review Div.Dir. Katz
HFD-120 MO Brugge
HFD-120 PM Bates
HFD-47 c/r/s GCP File #10773
HFD-47 MO Khin
HFD-47 CSO Friend
HFR-SW350 Kan-DO DIB Woleske
HFR-SW350 Bimo Monitor Montgomery
HFR-SW350 Field Investigator Vega
GCF-1 Seth Ray

r/d:NK:12/27/02
reviewed:AEH:12/27/02
f/t:ml:12/31/02

O:\NK_Letters\Grant.nai.doc

Reviewer Note to Rev. Div. M.O.

- At this clinical site, 72 subjects were screened; 24 subjects were randomized to receive either Paxil CR (12.5 or 25 mg/day) or Placebo for treatment of PMDD; 18 subjects completed the study. Discontinuation reasons included lost to follow up, non-compliance, adverse event (intercurrent illness), or lack of efficacy.
- An audit of records from subjects who completed the study was conducted.
- The inspection revealed no major problems.
- The inspection also reviewed the dates of the signed informed consent documents for subjects who had laboratory tests performed and began recording information in the Reference Cycle Diaries and did not note any discrepancies.
- Data appear acceptable.

DSI CONSULT: Request for Clinical Inspections

Date: August 19, 2002

To: Ni Aye Khin, GCPB Reviewer/HFD-47

Through: Joanne Rhoads, M.D., Director, DSI, HFD-45
Russell Katz, M.D., Director, HFD-120

From: Doris J. Bates, Ph.D., Regulatory Project Manager, HFD-120

Subject: **Request for Clinical Inspections**
NDA 20-936/S-011
GlaxoSmithKline
Paxil CR (paroxetine) 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.

The Supplement provides for the following new indication: the use of Paxil CR in the treatment of Premenstrual Dysphoric Disorder (PMDD)

Indication	Protocol #	Site (Name and Address)	Number of Subjects
PMDD	689	Richard Bergeron, MD, PhD Pierre Janet Hospital Hull, Quebec, Canada	70
PMDD	677	Clinton N. Corder, PhD, MD COR Clinical Research, LLC Oklahoma City, OK, USA	26
PMDD	677	Kenneth E. Grant, MD Mercy Health Research Chesterfield, MO, USA	23

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):

__X__ There are insufficient domestic data

____ 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) **December 23, 2002**. We intend to issue an action letter on this application by (action goal date) **April 23, 2003**.

Should you require any additional information, please contact Doris J. Bates, Ph.D..

Concurrence: (if necessary)

Thomas P. Laughren, MD, Medical Team Leader

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/s/

Doris Bates
8/20/02 05:16:38 PM
Dr. Laughren is signing for both himself and Dr. Katz, who is out of the office at this time.

Thomas Laughren
8/21/02 08:10:13 AM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA	Efficacy Supplement Type SE-	Supplement Number
Drug:	Applicant:	
RPM:	HFD-	Phone #
Application Type: ( ) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	( ) Standard ( ) Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	
❖ Special programs (indicate all that apply)	( ) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	( ) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes ( ) No
• This application is on the AIP	( ) Yes ( ) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	( ) Verified
❖ Patent	
• Information: Verify that patent information was submitted	( ) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ ( ) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	
General Information	
❖ Actions	
• Proposed action	( ) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	

❖ Advisory Committee Meeting	
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	
❖ Demographic Worksheet *(NME approvals only)*	
❖ Statistical review(s) *(indicate date for each review)*	
❖ Biopharmaceutical review(s) *(indicate date for each review)*	
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ CAC/ECAC report	

7/2/02

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-936 / S-011

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

Dear Mr. Whitman:

We acknowledge receipt on July 10, 2003 of your July 8, 2003 resubmission to your supplemental new drug application for PAXIL® CR (paroxetine hydrochloride) Controlled-Release Tablets.

We consider this a complete, Class 1 response to our April 11, 2003 approvable action letter. Therefore, the user fee goal date for this submission is September 10, 2003.

If you have any questions, please call the undersigned, at (301) 594-2850.

Sincerely,

{See appended electronic signature page}

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Doris Bates
7/23/03 04:49:47 PM

Bates, Doris J

From: Bates, Doris J
Sent: Wednesday, July 23, 2003 4:11 PM
To: Andreason, Paul J; Bates, Doris J
Cc: Brugge, Karen
Subject: NDA 20-936 / S-011 Resubmission Completeness Assessment

This e-mail documents that, as discussed between Drs. Brugge and Andreason and Drs. Andreason and Bates, the 8 July 2003 resubmission, received 10 July 2003, is a complete Class I response. The resubmission is considered to be clinical (labeling) only and as of this date no consult reviews were considered necessary. The goal date for acting on this resubmission is therefore two months, i.e., 10 September 2003.

The recently identified pediatric suicidality issue was discussed in the context of adolescent PMDD. To date, the Division has deferred requesting studies for this drug in adolescent PMDD. The issue wil be revisited when more information is available related to the pediatric depression indication; until that time, this deferral decision will hold.

This submission is already on the Division planning calendar with a 10-SEP-03 goal date. The firm will be notified of the decision, submission class, and goal date via secure e-mail. A copy of this e-mail will be placed in DFS as the official minutes of today's discussion.

Doris J. Bates, Ph.D.
for the review team

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/s/

Doris Bates
8/10/03 02:58:38 PM

Minutes of Meeting
NDA 20-936 / SE1-011: PAXIL CR (paroxetine) Tablets, 12.5, 25, 37.5 mg
GlaxoSmithKline: Premenstrual Dysphoric Disorder
Supplemental NDA Filing Meeting

DATE: August 15, 2002 (3:00 – 3:15 p.m.) **LOCATION:** WOC II Rm. 4034
PARTICIPANTS: R. Katz, T. Laughren, K. Brugge, O. Siddiqui, L. Stockbridge, B. Friend, D. Bates
ADDITIONAL CONTRIBUTORS: T. Oliver, K. Jin, B. Rosloff, G. Gill-Sangha, L. Fossom

Background: Paroxetine is currently approved for MDD, OCD, Panic Disorder, Social Anxiety Disorder, and Generalized Anxiety Disorder. The controlled-release dosage form, Paxil CR, is presently approved for MDD and panic disorder.

Summary: The supplemental NDA is an all-electronic submission and was found fileable in all disciplines. It is classified 6S (approved chemical entity, new indication, standard priority). The action due date is April 23, 2003. This action will require Dr. Katz' signature. All reviews should be completed by late December 2002 – early January 2003.

Discussion: *CMC:* Drs. Oliver and Gill-Sangha have informed the RPM that the submission is fileable for CMC; only the request for categorical exclusion (EA) and the CMC-related portions of labeling require CMC review.

Pharm/Tox: Drs. Rosloff and Fossom have informed the RPM that the submission is fileable for P/T. The labeling includes added information in the [redacted]; this is the only area in which P/T review is needed.

Clin Pharm/Biopharmaceutics: There is no new information for this discipline, and no review needed.

Clinical: The submission is fileable for clinical. The supplement includes three fixed-dose, three treatment cycle studies. Discrepancies have been noted in the financial disclosure information, which will be followed up as a review issue. See following section re DSI audit.

DSI: A DSI audit will be performed for two US sites and one Canadian site (Center 136-Dr. Bergeron; N = 70, utilized protocol 689). A consult request will be submitted for the Canadian inspection.

Statistics: The submission is fileable for statistics.

DDMAC: No filing issues were identified by DDMAC.

NDA 20-936 / S-011: PAXIL CR (paroxetine)
Filing Meeting, August 15, 2002

Regulatory / Project Management (with Post Meeting Notes): All team members have EDR access. User Fees were paid prior to supplement submission. The firm has not previously requested a deferral of the requirement for pediatric studies; the acknowledgement letter for the supplement will note this omission and request that it be addressed. There are no pediatric studies in the submission.

There were no objections to filing the supplemental NDA. It was officially filed as of this date. The GSK contact person, Mr. Matthew Whitman, was telephoned and informed of the filing decision immediately following the meeting.

Doris J. Bates, Ph.D.
RPM

Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drugs Group

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/s/

Doris Bates
1/16/03 08:33:53 AM

Thomas Laughren
1/16/03 08:44:49 AM

Bates, Doris J

From: Bates, Doris J
Sent: Monday, October 28, 2002 11:25 AM
To: 'Matt.Whitman-1@gsk.com'
Subject: RE: sNDA 20-936 SE1-011 Paxil CR for PMDD

Good morning, Matt.

I am attaching a 'cybermemo' - it is equivalent to a telefax and can be considered an official communication. Our clinical and statistical reviewers recently discussed the statistical approach we will take to the review of S-011, and based on this discussion we wanted to (a) inform you of the approach itself and (b) ask for some additional information, mostly datasets, to help in our analysis.

Please feel free to contact me if you have questions about the attachment. I suggest e-mail as the best route since I am working on several other interactive projects and it may be difficult to reach me by phone...

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research
FDA

TELEFAX / CYBER MEMO

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

DATE:	October 28, 2002
TO:	Matthew Whitman
FROM:	Doris J. Bates, Ph.D.
SUBJECT:	**Statistical Questions and Comments / Request for Additional Data**
	NDA 20-936/S-011, Paxil CR (paroxetine hydrochloride) Controlled Release Tablets

Please refer to the above cited supplemental NDA. As noted in the e-mail accompanying this transmission, our statistical review team has the following comments and requests for additional data at this time: Please note that these comments refer to the three studies numbered 677, 688, and 689; responses, including additional data, should be provided respective to each of these studies.

1. Statistical inferences concerning our review of the efficacy of PAXIL CR will be drawn from the ITT population, at the protocol defined treatment cycle 3 endpoint, using the LOCF dataset.

2. We will be analysing, as primary variable, change from baseline in the mean luteal phase VAS-total score (that is, the sum of all 11 symptoms rated via Visual Analogue Scale), at treatment cycle 3. We will use the LOCF dataset and analyse this variable as a dependent measure, using parametric analysis of covariance. The ANCOVA model will include terms for treatment group, center group, baseline score (VAS-total) and age.

3. Please provide Observed Case Analysis datasets for all three referenced studies, at Treatment Cycles 1, 2, and 3.

4. Please assess, for all three referenced studies, the interaction of treatment with each of the other main effects included in the model from your principal analysis.

5. Please provide the following additional information for each referenced study:
   a. A SAS exportable dataset including PID, CENTER GROUP, VISIT, VAS-TOTAL SCORE, AGE, and TRX_0.
   b. A statement of your approach to the handling of missing items from the 11-item VAS total scores.

If you have any questions, please feel free to contact me directly at 301-594-2850 or via e-mail at batesd@cder.fda.gov,

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/s/

Doris Bates
10/28/02 01:11:41 PM
CSO

Placed in DFS as an NDA teleconference because there is no category for supplement teleconferences. Transmitted to firm via secure e-mail as per date/time of message to Mr. Whitman.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-936/S-011

PRIOR APPROVAL SUPPLEMENT

GlaxoSmithKline
Attention: Matthew Whitman, Associate Director US Regulatory Affairs
One Franklin Place
PO Box 7929
Philadelphia, PA 19101-7929

Dear Mr. Whitman:

This letter acknowledges that 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™ (paroxetine hydrochloride) Controlled-Release Tablets

NDA Number: 20-936 Supplement number: S-011

Date of supplement: June 26, 2002 Date of receipt: June 26, 2002

As you were previously notified by telephone on August 15, 2002, your supplemental application has been filed as of that date, in accordance with 21 CFR 314.101(a).

Please note that, in accordance with 21 CFR 314.55, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens must contain an assessment of the safety and effectiveness of the product in pediatric patients, unless this requirement is waived or deferred. As also discussed in the August 15, 2002 teleconference, we have noted that this supplemental application does not address the pediatric study requirements [which in this case would apply to adolescent females aged 12 – 17 years]. Please submit your pediatric drug development plan, or a request for either a waiver or deferral if you consider either one appropriate, within 120 days from the date of this letter.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857-1706

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Document Room 4008
1451 Rockville Pike
Rockville, Maryland 20852-1448

If you have any questions, please call the undersigned, at (301) 594-2850.

Sincerely yours,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Doris Bates
8/27/02 03:19:55 PM