CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-982
20-936/S-008

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data
NDA #20-982

Sponsor:	GlaxoSmithKline
Drug:	Paroxetine HCl CR Tablets
Indication:	Panic Disorder
Material Submitted:	Response to 1-3-00 Approvable Letter
Correspondence Date:	December 18, 2001
Date Received:	December 18, 2001

I. Background

This NDA provides for the use of Paxil Controlled-Release Tablets (Paxil CR) for the treatment of panic disorder.

Approvable letters were forwarded to the sponsor on March 10, 1999, and January 3, 2000. The last letter stated that the following clinical issues would need to be addressed before the application could be approved:

1) agreement on labeling.
2) final safety update to encompass data collected since 10-22-97.
3) worldwide regulatory status update.
4) world literature update.

This submission contains GSK's responses to the above issues.

Please note that this submission was provided in electronic format only and is located in the Electronic Document Room at \\CDSESUB1\N20982\N_000\2001-12-18.

II. Clinical Data

A. Labeling

The sponsor is proposing labeling that is essentially identical to the Agency labeling which was attached to the last approvable letter. However, they have made revisions to incorporate recently approved safety statements from the labeling for Paxil (IR) tablets and oral suspension.

Also, changes related to the recently approved 37.5mg tablet and in the appearance of the 12.5 and 25mg tablets are included and should be reviewed by the chemistry team.

Specific changes to the clinical sections of our last approved labeling are reviewed below. Additionally, in accordance with the currently approved labeling for Paxil (IR), the general terms "depression" and "depressed" have been replaced with the more specific reference to "major depressive disorder" throughout labeling.

These changes are acceptable to this reviewer unless otherwise noted below.

INDICATIONS AND USAGE
There is an added reference to CLINICAL PHARMACOLOGY regarding the one-year study in depression conducted with Paxil (IR).

CONTRAINDICATIONS
A contraindication with thioridazine has been added.

WARNINGS
A new section describing the potential interaction with thioridazine has been added.

PRECAUTIONS
Suicide
A precautionary statement concerning the risk of suicide in psychiatric disorders other than major depression has been added.

Discontinuation of Treatment with Paxil CR
This new section regarding potential discontinuation phenomena has been added.

Use in Patients with Concomitant Illness
A paragraph regarding narrow angle glaucoma has been added.

In the second sentence of that paragraph, the word "have" should be inserted immediately prior to the word "been."

Drug Interactions
Thioridazine
A reference to CONTRAINDICATIONS and WARNINGS has been added.

Drugs Metabolized by Cytochrome P450IID6
A paragraph regarding the risk of serious ventricular arrhythmias and sudden death with elevated thioridiazine levels has been added.

Drugs Metabolized by Cytochrome P450IIIA4
Two typographical errors were corrected: the word "activity" has been added after P450IIIA4 in the second sentence and "in vitro" has been replaced by "in vivo" in the last sentence.

ADVERSE REACTIONS
Male and Female Sexual Dysfunction with SSRI's
Data regarding the incidence of sexual adverse events in controlled clinical trials were placed in a table.

Other Events Observed During the Clinical Development of Paroxetine
In the prefatory text, the recently approved indications for Paxil (IR) have been added, i.e., generalized anxiety disorder and posttraumatic stress disorder.

Changes were made to the listing of adverse event terms we had proposed, generally based on one of the following reasons:

- some nonspecific terms were subsumed under more meaningful terms (see Table C of the submission for a list of these terms).
- certain terms were added due to the approval of S-026 and S-029 to NDA 20-031 (Paxil treatment of GAD and PTSD, respectively).

Modifications to this listing were reviewed by the undersigned and were found to be acceptable except for the following.

In our proposal, we had requested that the sponsor either delete the following four nonspecific terms or subsume them under more informative terms: oropharynx disorder, drugged feeling, male genital disorder, and CNS stimulation.

The sponsor contends that it is not reasonable to subsume or delete these terms and, hence, they have been retained in the sponsor's current proposal. No further explanation was offered. The rationale behind this stance is unclear

and should be explained by the sponsor. Otherwise, it is recommended that these terms be deleted.

Postmarketing Reports
The listing of adverse events in this subsection was revised to add events which were inserted into Paxil (IR) labeling since our approvable letter for this NDA and to delete the statement regarding reports of discontinuation-related events, since this information is now included in a new subsection under PRECAUTIONS.

OVERDOSAGE
Human Experience
This subsection was revised to align it with currently approved labeling for Paxil (IR).

DOSAGE AND ADMINISTRATION
Discontinuation of Treatment with Paxil CR
This new subsection was added in accordance with currently approved labeling for Paxil (IR).

B. Safety Update

The sponsor states that no clinical studies of Paxil CR in panic disorder have been conducted beyond those submitted in the supplemental application.

C. Worldwide Regulatory Status Update

The sponsor indicates that no marketing applications for Paxil CR have been submitted to any country other than the U.S.

D. World Literature Update

GSK performed a systematic search of the worldwide literature for articles relating to the use of Paxil CR in the treatment of panic disorder. This search covered the period from the time of submission of the supplemental application to the time of this response. The search was conducted by Clinical Information Analysts from GSK's Information Management group. The following databases were utilized: Derwent WPI, CAPLUS, Medline, Embase, Biosis, Derwent Drug File, Scisearch, and IPA.

The sponsor states that this search revealed no new findings to report with respect to the safety of Paxil CR.

III. Conclusions and Recommendations

From a clinical perspective, this NDA may be approved upon resolution of the following two labeling issues:

1) under PRECAUTIONS/Use in Patients with Concomitant Illness, the word "have" should be inserted immediately prior to the word "been" in the second sentence of the paragraph regarding acute angle closure glaucoma.

2) under ADVERSE REACTIONS/Other Events Observed During the Clinical Development of Paroxetine, the sponsor should provide a reasonable rationale for retaining the following four nonspecific terms in this adverse event listing: oropharynx disorder, drugged feeling, male genital disorder, and CNS stimulation. Otherwise, these terms should be deleted.

Gregory M. Dubitsky, M.D.
January 11, 2002

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cc: NDA #20-982
HFD-120 (Div. File)
HFD-120/GDubitsky
/TLaughren
/MShin

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/s/

Greg Dubitsky
1/11/02 05:09:06 PM
MEDICAL OFFICER

Electronic Format Only. No hardcopy.

Thomas Laughren
1/14/02 02:37:52 PM
MEDICAL OFFICER
Once agreement is reached on final labeling, this NDA can be approved.--TPL

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REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA #:	20-982
Sponsor:	SmithKline Beecham
Clock Date:	April 22, 1998

Drug Name

Generic Name:	Paroxetine hydrochloride controlled-release tablets
Trade Name:	Paxil CR

Drug Categorization

Pharmacological Class:	Selective Serotonin Reuptake Inhibitor
Proposed Indication:	Panic Disorder
NDA Classification:	3 S
Dosage Forms:	12.5 and 25 mg tablets
Route:	Oral

Reviewer Information

Clinical Reviewer:	Gregory M. Dubitsky, M.D.
Completion Date:	February 1, 1999

NDA 20-982:
PAXIL CR FOR PANIC DISORDER
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1.0 Materials Utilized for Review

1.1 Materials from the NDA/IND

This review involved an examination of the following items:

NDA VOLUME (S)	SUBMISSION DATE	MATERIAL
1.1	4/22/98	Cover letter, index, proposed labeling.
1.2	"	Foreign marketing.
1.6	"	Compliance audits.
1.7-1.14	"	Study Report: 494
1.15-1.23	"	Study Report: 495
1.24-1.30	"	Study Report: 497
1.31	"	Integrated Summary of Efficacy
1.32-1.38	"	Integrated Summary of Safety
# pending	7/2/98	Response to request for information.

In addition, sponsor provided a Computer Assisted New Drug Application (CANDA) which was utilized extensively during the review process. The CANDA encompassed electronic case report tabulations and case report forms as well as folio views of the hardcopy version with hypertext links to supporting data.

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

494.012.00115 495.010.01069
494.008.01830 497.026.01526

Also, narrative summaries were examined for all patients in studies 494, 495, and 497 who were randomized to paroxetine CR and who experienced an adverse experience classified as serious.

1.2 Related Reviews and Consultations for the NDA

A statistical review of the efficacy data was conducted by Dr. Kallappa Koti of the Division of Biometrics I.

The Division of Scientific Investigations was consulted to perform routine compliance inspections for this NDA.

No other consultations were obtained.

There are no plans to convene a meeting of the Psychopharmacological Drugs Advisory Committee for this NDA.

2.0 Background

2.1 Indication

Paroxetine is a selective serotonin reuptake inhibitor (SSRI) that was approved as the immediate release formulation for the treatment of panic disorder in 1996. The sponsor has developed a controlled-release (CR) formulation of paroxetine and has conducted studies to demonstrate the efficacy and safety of this product in the treatment of panic disorder, which forms the basis of this NDA. Although the CR formulation, like the immediate release Paxil, requires only once daily administration, it possesses a delayed absorption characteristic which, in theory, could reduce the incidence of nausea which frequently accompanies the early course of treatment with SSRI's and, consequently, improve tolerance and compliance.

Only three other agents are approved in the U.S. for the treatment of panic disorder: two benzodiazepines (alprazolam and clonazepam) and another SSRI (sertraline). Paroxetine CR may be superior to the benzodiazepines by virtue of the cognitive disturbance, sedation, and addictive potential associated with the latter. Sertraline is not marketed as a controlled release formulation and shares a common adverse event profile with other SSRI's, particularly nausea early in treatment. Paroxetine CR may be superior to sertraline in this regard.

2.2 Important Information from Related IND's and NDA's and from Pharmacologically Related Compounds

All marketed SSRI's are presumed to have the potential of producing serious, sometimes fatal, reactions when used in combination with monoamine oxidase inhibitors (MAOI's). This risk is adequately labeled for all these products currently.

The marketed SSRI's differ in their potential to inhibit various isozymes of the cytochrome P450 system. Paroxetine is a potent inhibitor of P450 2D6 and therefore caution is warranted when paroxetine is co-administered with drugs metabolized by this isozyme.

2.3 Administrative History

The Division met with the sponsor on 7/3/96 to discuss the clinical development plans for a modified-release formulation of paroxetine, then called Paxil [redacted], [1] with the intention of eventually replacing the marketed immediate release Paxil with the [redacted] product for the treatment of depression, panic disorder, and OCD. We informed the sponsor that, although efficacy could not be extrapolated from the immediate release Paxil to [redacted] we would likely consider one positive RCT as adequate evidence of efficacy in each of these three conditions. Also, we explained that any comparative safety/tolerance claims (e.g., less nausea with the [redacted] would have to be based on a study design which assured a fair comparison between the [redacted] (for example, with respect to dosing). However, if they elected not to pursue such comparative claims, a simple flexible dose study would be sufficient. Subsequently, it became clear that the sponsor had chosen the latter option.

An application to conduct a U.S. investigation of a controlled-release formulation of paroxetine in depression was received on 7/23/96 and assigned [redacted] The SRD meeting took place on 8/15/96 and it was decided to allow the sponsor to proceed with this trial. The sponsor also planned to conduct Phase 3 trials in panic disorder and OCD as well as a series of pharmacokinetic studies in normal volunteers.

On 10/17/96, SB submitted protocols to conduct three studies of [redacted] in panic disorder (494, 495, and 497). These three trials form the core of this application.

No pre-NDA meeting for this NDA was held.

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[1] At some subsequent point, based on recommendations from our Labeling and Nomenclature Committee, the sponsor changed the name of this compound from [redacted] to Paxil CR.

A 9/9/97 consultation response from the Labeling and Nomenclature Committee indicated that the name "Paxil CR" was acceptable.

This NDA was submitted on 4/2/98 and was considered fileable on 6/16/98.

2.4 Proposed Labeling

Paxil CR is indicated for the treatment of panic disorder. Safety and effectiveness in the pediatric population have not been established.

Paxil CR is contraindicated in patients taking MAOI's. At least 14 days should elapse between discontinuation of an MAOI and starting Paxil CR therapy; likewise, 14 days should pass after stopping Paxil CR before starting an MAOI.

Paxil CR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (Pregnancy Category C).

Co-administration of Paxil CR with drugs metabolized by cytochrome P450 2D6 should be approached with caution since paroxetine may significantly inhibit the activity of this isozyme.

Paxil CR tablets should not be chewed or crushed and should be swallowed whole. It should be taken as a single daily dose, usually in the morning.

For the treatment of panic disorder, the recommended starting dose for most patients is 12.5 mg/day. Dose increases should occur in 12.5 mg/day increments, up to a maximum of 75 mg/day. Dose changes should occur at intervals of at least one week.

In elderly or debilitated patients and for patients with severe renal or hepatic impairment, the recommended starting dose is 12.5 mg/day, with increases to a maximum of 50 mg/day if indicated.

2.5 Foreign Marketing

The controlled release formulation of paroxetine has never been marketed, nor have any marketing applications been submitted to any foreign regulatory authorities.

3.0 Chemistry, Manufacturing, and Controls

Rik Lostritto, Ph.D., is the chemistry reviewer for this application. At this time, there are no outstanding chemistry deficiencies for the controlled release formulation.

4.0 Animal Pharmacology and Toxicology

No new non-clinical information was submitted with this application.

5.0 Description of Clinical Data Sources

5.1 Primary Development Program

5.1.1 Study Type and Design/Patient Enumeration

At the time of this NDA submission, paroxetine controlled release (CR) had been studied in a total of 17 clinical trials: 11 Phase 1 studies and 6 Phase 3 studies. Ten of the Phase 1 studies and 3 of the Phase 3 studies had been submitted to NDA 20-936 (paroxetine CR for depression) and were discussed in the clinical review of that NDA; these studies will not be further mentioned in this review. This application contains the reports of the remaining one Phase 1 study in normal volunteers (569) and three Phase 3 trials in outpatients with panic disorder (494, 495, and 497).

Study 569 was an open-label, randomized, four period crossover study in 80 volunteers to demonstrate the bioequivalence of paroxetine CR tablets manufactured at two sites (Cidra and Crawley).

Studies 494, 495, and 497 are of identical design: 10 week, randomized, double-blind, placebo-controlled, parallel group studies with flexible dosing in the range 12.5-75 mg once daily. The intent-to-treat population for the pool of these three studies consists of 889 patients, 444 treated with paroxetine CR and 445 with placebo. This

pool comprises the integrated safety database for this application, with a cut-off date of 10/22/97.

Appendix 5.0 summarizes information for the four clinical studies addressed in this NDA: Table 5.1.1.1 displays the study design characteristics and Table 5.1.1.2 provides an enumeration of the study participants. In all, 524 subjects received at least one dose of paroxetine CR.

5.1.2 Demographics

Of the 80 subjects in study 569, 57 were male and 23 were female. Subjects were in the age range 20-55 years, with a mean age of 33 years.

Appendix 5.0, Table 5.1.2.1, displays the demographic characteristics of the Phase 3 study pool. No patients were under the age of 19 and only one patient, who received placebo, was over 65; the mean age was about 38 years old. Over half of the patients were female and the vast majority were white.

5.1.3 Extent of Exposure

Subjects in study 569 received a total of four doses of paroxetine CR, each dose consisting of two 12.5mg tablets and each separated by at least 7 days. Two doses utilized tablets manufactured at the Cidra site and two used tablets made at Crawley.

Appendix 5.0, Table 5.1.3.1, is an enumeration of Phase 3 study patients by dose level and exposure duration.[2] Each cell in this table provides the number of patients exposed to the indicated dose level for the specified total duration. Thus, patients are counted in multiple cells (i.e., once for each dose level received) and durations do not necessarily represent continuous periods of exposure. Percentages are based on the total number of patients at each dose level.

Within the pool of Phase 3 studies, 49 patients received the maximum dose of paroxetine CR (75 mg/day) for a total duration of at least 4 weeks.

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[2] This table was electronically copied from the sponsor's CANDA.

5.2 Secondary Source Data

5.2.1 Non-IND Studies

Study 569 was not conducted under the IND for paroxetine CR
This investigation was done in Germany.

5.2.2 Post-Marketing Experience

The controlled release formulation of paroxetine has never been marketed in any country.

5.2.3 Literature

At the time of this NDA submission, no information about paroxetine CR had been published.

6.0 Human Pharmacokinetics

The pharmacokinetic characteristics of controlled release paroxetine were described in detail in my clinical review of NDA 20-936.

At this time, study 569 is still under review by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB).

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7.0 Efficacy Findings

7.1 Overview of Studies Pertinent to Efficacy

The demonstration of the efficacy of paroxetine CR in the treatment of panic disorder is based on three multicenter, randomized, double-blind, placebo-controlled, parallel group studies of 10 weeks duration: 494, 495, and 497.

No other studies which address the antipanic efficacy of paroxetine CR have been submitted to this NDA. Immediate release paroxetine (Paxil) was approved for this indication in 1996.

7.2 Summary of Studies Pertinent to Efficacy

One important issue involving two of these three studies will be mentioned at this point. A significant treatment by center group interaction was observed for 5 of the 11 efficacy parameters in study 495 at week 10 in the endpoint (LOCF) analysis, plus the protocol-defined primary efficacy parameter at Week 10 for the observed cases (OC) dataset. The major contributor to these interactions was center 005, where Larry M. Davis, M.D., was the principal investigator. This center was relatively large (16 patients in paroxetine CR and 15 in placebo of the evaluable ITT population) with 100% response rate (reduction to zero attacks) in the paroxetine CR group, and 100% non-response in the placebo group. This same investigator also participated in Study 494. In this latter study, this center (033) contributed 4 patients on paroxetine CR and 3 patients on placebo and again the pattern of response was 100% response rate in the paroxetine CR group and 100% non-response in the placebo group. Although there was no evidence of a treatment by center group interaction in study 494 for the primary efficacy parameter, this pattern of response was not seen typically at other centers. Thus, the analyses of efficacy discussed in this review exclude patients from center 005 in Study 495 and center 033 in Study 494.

Also, for purposes of succinctness, features common to these three studies will be described below. This is followed by a discussion of information specific to each trial.

Objectives

The primary objective of these studies was to demonstrate the efficacy of paroxetine CR in the treatment of panic disorder. The secondary objective was to evaluate the safety of paroxetine CR in this condition.

Population

Inclusion criteria for these three studies were:

- outpatient with a primary diagnosis of DSM-IV panic disorder with or without agoraphobia (based on SCID-P).
- at least two full panic attacks during the two-week, single blind placebo run-in phase.
- age at least 18 but not greater than 65 years.

Important exclusion criteria were:

- another Axis I condition as a primary or dominant diagnosis within 6 months.
- DSM-IV criteria for substance abuse or dependence within 6 months.
- previously unresponsive to paroxetine for panic disorder.
- current formal psychotherapy or psychoanalysis.
- ECT within the previous 3 months.
- use of other psychotropics within 14 days of baseline or lithium or depot neuroleptics within 12 weeks of baseline.
- emergence of benzodiazepine withdrawal symptoms during placebo run-in.
- use of an investigational drug within the longer of 5 half-lives or 30 days of this study.

Design

These trials were multicenter, randomized, double-blind, placebo-controlled, flexible dose, parallel group studies. The diagnosis of panic disorder was established at screening, which was followed by a 2 week single blind placebo run-in.

At the end of run-in, eligible patients were randomized in a 1:1 ratio to receive either paroxetine CR or placebo for a 10-week treatment phase. Paroxetine was administered in six dosage levels:

- level 1 = 12.5 mg/d
- level 2 = 25 mg/d
- level 3 = 37.5 mg/d
- level 4 = 50 mg/d
- level 5 = 62.5 mg/d
- level 6 = 75 mg/d

Paroxetine CR therapy was started at level 1 for the first week, then increased to level 2 for the second week. Thereafter, dosage adjustments were made at the investigator's discretion, with a maximum rate of increase of 12.5 mg/day every seven days.

At the end of the 10 week treatment phase or at early withdrawal, patients entered a 2 week taper phase during which the dosage was gradually reduced to level 2 under double-blind conditions.

Efficacy Assessments

Clinic visits during treatment occurred at weeks 1, 2, 3, 4, 5, 6, 8, and 10.

During the run-in and treatment phases, patients documented the number of panic attacks experienced each day in daily diaries; each attack was categorized by the number of panic symptoms and whether the attack was situational or unexpected. They also recorded the percentage of a 24 hour day during which they worried about attacks or going into a situation that might have provoked an attack (i.e., anticipatory anxiety). These diaries were summarized in the CRF at each visit and were combined into 2 week periods for purposes of efficacy analysis (weeks 1/2, 3/4, 5/6, 7/8, and 9/10).

The protocol-specified primary efficacy variable for all three studies was the percentage of patients achieving zero full panic attacks at study endpoint.[1]

[1] Study endpoint was specified as the timepoint of primary interest for purposes of statistical comparisons. For all efficacy variables other than diary data, the study endpoint was the patient's Week 10 assessment where this exists, or in the case of early withdrawals, the last valid on-treatment assessment for each individual variable. For variables relating to panic attacks and anticipatory anxiety, study endpoint was defined as the last 2 week period for which there was valid diary data.

There were a number of secondary efficacy measures, to include the mean change from baseline to endpoint in:

- the number of full panic attacks.[2]
- the CGI severity score.
- the percentage of time spent with anticipatory anxiety.
- the Marks-Sheehan Phobia Scale (MSPS) fear and avoidance scores.

These latter variables have been considered important in assessing antipanic efficacy in the past and were also considered in evaluating the data from each study.

The CGI was rated at each visit, while the MSPS was administered only at weeks 6 and 10.

It is also notable that serum and urine screening for benzodiazepines was conducted at baseline and at weeks 6 and 10 or at premature termination in all three studies.

Statistical Analysis Plan

The intention-to-treat (ITT) population consisted of all patients who were randomized to study medication, received at least one dose of randomized treatment, and had at least one valid on-therapy assessment. Please noted that ITT patients with missing values for full situational or full unexpected panic attacks or those having less than 10 days with evaluable diary data for any 2 week time period were excluded from analyses for affected variables since these data were deemed incomplete for that period. For this reason, in addition to the exclusion of one center from studies 494 and 495 as discussed above, the number of evaluable patients is generally considerably less than the number of ITT patients.

Paroxetine CR was compared with placebo at study endpoint using two-tailed statistical tests with a significance level of 5%.

Centers were combined to form groups with a minimum of eight patients at Week 10 per center group before model fitting. This was accomplished by combining centers with the smallest numbers of patients with those having the

[2] A full panic attack is defined as having 4 or more of the DSM-IV symptoms present.

largest numbers until every center group consisted of at least eight patients at Week 10. By protocol, the method of grouping centers was to be established prior to unblinding of the study.

The protocol-specified analysis for each efficacy variable is described below. This review will focus on these analyses. Categorical efficacy parameters (responders based on zero full panic attacks) were analyzed using logistic regression, adjusting for center effects only. For each treatment group, the odds of a patient being classed as a responder was calculated. The results were presented in terms of odds ratios (i.e., the odds of the response on paroxetine relative to the odds of response on placebo) with 95% confidence intervals around the odds ratios.

Ordered categorical variables (change from baseline in CGI severity of illness) were analyzed using a Wilcoxon rank sum test with no adjustment for center group or covariates. Results were reported in terms of the median change from baseline.

Continuous efficacy parameters were analyzed by analysis of variance, adjusting for center effects only. Results were presented as the point estimate and 95% confidence interval for the difference between paroxetine CR and the placebo group. The underlying assumptions of normality and homogeneity of variance were tested by inspection of normal probability plots and residual plots. If these were found to be satisfied the modeling process was continued. For continuous variables where the assumptions of normality and homogeneity of variance did not hold, a nonparametric approach was adopted; these data were analyzed using the Wilcoxon Rank Sum test with no adjustment for center group or covariates. In fact, for all three studies, it was discovered that assumptions of normality did not hold true for variables involving numbers of panic attacks. Thus, changes from baseline in the number of full attacks were analyzed using the non-parametric Wilcoxon Rank Sum Test and, consequently, mean changes in the number of full panic attacks are reported in terms of medians, not means.

For variables analyzed by ANOVA or logistic regression, the statistical model adjusted for treatment, center, and the following covariates: sex, age and baseline panic disorder severity. The treatment by center group interaction was

assessed and if non-significant ($p \geq 0.1$) was dropped from the model. Each covariate by treatment interaction was then assessed separately for statistically significance ($p < 0.10$). If the covariate-by-treatment interaction was non-significant ($p \geq 0.1$) it was dropped from the model.

7.2.1 Study 494

Investigators

Thirty-three investigators conducted this study in the U.S. Investigators and sites are listed in Appendix 7.2.1, Table 7.2.1.1.[3]

Baseline Demographics

Demographic characteristics are summarized for all centers in Appendix 7.2.1, Table 7.2.1.2. Age and gender distributions were comparable between groups. There was a slightly higher proportion of non-whites in the paroxetine CR group compared to placebo (16% vs. 6%).

Baseline Severity of Illness

Both the paroxetine CR and placebo groups (excluding center 33) had a median of 5 full panic attacks in the two weeks preceding baseline. A comparison of treatment groups at baseline in terms of the distribution of CGI severity of illness scores revealed no major differences.

Patient Disposition

Of the 454 patients screened for this study, 289 were randomized. The other 165 failed entrance criteria. Six of the 289 randomized patients had no on-treatment safety or efficacy data and were excluded from the ITT. The remaining 283 patients comprised the ITT: 139 paroxetine CR and 144 placebo patients.

An enumeration of all ITT patients in-study over time is displayed in Appendix 7.2.1, Table 7.2.1.3. Study completion rates were not much different between groups: 74% (103/139) for paroxetine CR and 76% (109/144) for placebo.

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[3] This table was electronically copied from the sponsor's CANDA.

Dosing Information

For all patients completing treatment and randomized to drug, the mean (median) dose of paroxetine CR at week 10 was 47.7 (50.0) mg/day.

Concomitant Medication

There were no major differences between treatment groups in terms of the proportions of ITT patients using various concomitant medication during the study.

Chloral hydrate was permitted by protocol for insomnia during the trial. Other psychotropics were disallowed. Two placebo patients were identified as protocol violators because of prohibited psychotropic medication use.[4] It is very unlikely that this use would bias the study results in favor of paroxetine CR.

Efficacy Results

Efficacy data displays may be found in Appendix 7.2.1, Tables 7.2.1.4 - 7.2.1.9.[5]

With respect to the protocol-identified primary measure of efficacy, i.e., the percentage of patients achieving zero full panic attacks at weeks 9/10 in the endpoint (LOCF) analysis, paroxetine CR was clearly superior to placebo: 68.9% vs. 50.4%, odds ratio = 2.182, p= 0.003. This held true for the OC dataset at weeks 9/10, with 78.4% of paroxetine CR and 59.2% of placebo patients achieving zero full attacks (odds ratio = 2.542, p = 0.005).
Also, paroxetine CR was statistically superior to placebo from weeks 5/6 onward.

Other variables considered by this reviewer to be supportive are discussed below.

The median change from baseline in the number of full panic attacks was greater for paroxetine CR than placebo in the endpoint analysis, although the difference was not statistically significant (-4 vs. -3, median difference -1, p=0.080). OC results at weeks 9/10 were similar.

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[4] Patients 494.007.00020 and 494.033.01899; both patients used alprazolam during the trial.
[5] These tables were electronically copied from the sponsor's CANDA.

The median change from baseline in CGI severity of illness scores was significantly greater for paroxetine CR than for placebo (LOCF median difference between groups = 0, 95% CI (-1, 0.0), p = 0.032). OC results were highly significant (p = 0.007).

Mean changes in the percentage of time spent with anticipatory anxiety were not significantly different between groups in either LOCF (p=0.078) or OC analysis (p=0.135) at week 10.

The mean changes in the MSPS total fear scores were significantly larger for paroxetine CR than for placebo at endpoint (mean difference between groups = -5.7, p = 0.040). OC results were not significant.

Mean changes in the MSPS total avoidance scores were somewhat larger for paroxetine CR but not statistically superior to placebo in either LOCF or OC analyses.

Conclusions

It would have been reassuring to find more consistency across the supportive variables examined in assessing the antipanic efficacy of paroxetine CR in this trial. Nonetheless, paroxetine CR was clearly superior to placebo on the primary efficacy measure as well as on the CGI severity of illness rating, with a trend toward statistical superiority in terms of the change in number of full panic attacks. Based on these findings, I feel that this study provides reasonably convincing evidence of a therapeutic effect.

7.2.2 Study 495

Investigators

Investigators and sites for this U.S. study are listed in Appendix 7.2.2, Table 7.2.2.1.[6]

Baseline Demographics

Demographic characteristics are summarized for all centers in Appendix 7.2.2, Table 7.2.2.2. Age, gender, and race distributions were comparable between groups.

[6] This table was electronically copied from the sponsor's CANDA.

Baseline Severity of Illness

Paroxetine CR patients had a slightly larger median number of full panic attacks in the 2 week period preceding baseline compared to placebo (7 vs. 5)(excluding center 5). A comparison of treatment groups at baseline in terms of the distribution of CGI severity of illness scores revealed no major differences.

Patient Disposition

Of the 479 patients screened for this study, 328 were randomized. The other 151 failed entrance criteria. Seven of the 328 randomized patients did not take at least one dose of study drug and were excluded from the ITT. The remaining 321 patients comprised the ITT: 158 paroxetine CR and 163 placebo patients.

An enumeration of all ITT patients in-study over time is displayed in Appendix 7.2.2, Table 7.2.2.3. Study completion rates were not very different between groups: 67% (106/158) for paroxetine CR and 76% (124/163) for placebo.

Dosing Information

For all patients completing treatment and randomized to drug, the mean (median) dose of paroxetine CR at week 10 was 48.0 (50.0) mg/day.

Concomitant Medication

There were no major differences between treatment groups in terms of the proportions of ITT patients using various concomitant medication during the study.

Chloral hydrate was permitted by protocol for insomnia during the trial. Other psychotropics were disallowed. Two paroxetine CR and five placebo patients were identified as protocol violators because of prohibited psychotropic medication use.[7] This use was reviewed and was not judged as likely to bias the efficacy results in favor of paroxetine CR.

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[7] Paroxetine CR patients 495.019.00745 and 495.019.00750; placebo patients 495.009.00877, 495.012.01001, 495.019.02133, 495.030.01093, and 495.012.01127.

Efficacy Results

Efficacy data displays may be found in Appendix 7.2.2, Tables 7.2.2.4 - 7.2.2.9.[8]

With respect to the protocol-identified primary measure of efficacy, i.e., the percentage of patients achieving zero full panic attacks at endpoint (weeks 9/10 LOCF), paroxetine CR was numerically, but not statistically, superior to placebo: 57.0% vs. 50.0%, odds ratio = 1.325, p= 0.255. In the OC analysis at weeks 9/10, paroxetine CR was superior to placebo, with 71.4% of paroxetine CR and 55.6% of placebo patients achieving zero full attacks (odds ratio = 2.022, p = 0.027). Paroxetine CR was also statistically superior to placebo at weeks 5/6 (p=0.022) (OC analysis).

The difference in response to paroxetine CR between the Week 10 OC dataset and Week 10 LOCF may be explained by a greater number of non-responding patients withdrawing from the paroxetine CR group relative to placebo.

Other variables considered by this reviewer to be supportive are discussed below.

The median change from baseline in the number of full panic attacks was significantly greater for paroxetine CR than placebo in the LOCF analysis (-5 vs. -3, median difference -2, p<0.001). OC results were equally significant.

The median change from baseline in CGI severity of illness scores was significantly greater for paroxetine CR than for placebo (LOCF median difference between groups = 0, 95% CI (-1, 0.0), p = 0.004). OC results were also highly significant (p<0.001).

Mean changes in the percentage of time spent with anticipatory anxiety were highly significantly different between groups in both LOCF and OC analyses at week 10.

Mean changes in the MSPS total fear scores and total avoidance scores were significantly larger for paroxetine CR than for placebo in both LOCF and OC analyses.

[8] These tables were electronically copied from the sponsor's CANDA.

Conclusions

The failure of paroxetine CR to achieve statistical superiority on the primary efficacy variable must be viewed in the context of the robust findings favoring drug on other relevant variables, especially the mean change in panic attack frequency and CGI severity of illness.

Overall, I am compelled to conclude that convincing evidence of antipanic efficacy has been demonstrated in this study.

7.2.3 Study 497

Investigators

Thirty-two principal investigators conducted this study at 29 sites in the U.S. and Canada. Investigators and sites are listed in Appendix 7.2.3, Table 7.2.3.1.[9]

Please note that , is considered by the Division of Scientific Investigations to be restricted.[10] Previously, his data were considered acceptable to support the approval of an NDA after third party verification of subject identification from his site. Since this study is considered negative for reasons that will be presented below, such verification is not considered critical for the approval of this NDA.

Baseline Demographics

Demographic characteristics are summarized in Appendix 7.2.3, Table 7.2.3.2. Age and race distributions were comparable between groups. There was a higher proportion of females in the paroxetine CR group compared to placebo (65% vs. 49%).

Baseline Severity of Illness

The paroxetine CR group had a median of 5 full panic attacks in the two weeks preceding baseline compared to 4 in the placebo group. A comparison of treatment groups at

[9] This table was electronically copied from the sponsor's CANDA.
[10]

baseline in terms of the distribution of CGI severity of illness scores revealed no major differences.

Patient Disposition

Of the 483 patients screened for this study, 293 were randomized. The other 190 failed entrance criteria. Eight of the 293 randomized patients had no on-treatment safety or efficacy data and were excluded from the ITT. The remaining 285 patients comprised the ITT: 147 paroxetine CR and 138 placebo patients.

An enumeration of all ITT patients in-study over time is displayed in Appendix 7.2.3, Table 7.2.3.3. Study completion rates were essentially the same for each group: 70% (103/147) for paroxetine CR and 70% (96/138) for placebo.

Dosing Information

For all patients completing treatment and randomized to drug, the mean (median) dose of paroxetine CR at week 10 was 51.2 (50.0) mg/day.

Concomitant Medication

There were no major differences between treatment groups in terms of the proportions of ITT patients using various concomitant medications during the study.

Chloral hydrate was permitted by protocol for insomnia during the trial. Other psychotropics were disallowed. Four paroxetine CR and seven placebo patients were identified as protocol violators because of prohibited psychotropic medication use.[11] Most of these patients had positive benzodiazepine screens. Of particular concern are the four paroxetine CR patients: two had therapeutic serum levels of alprazolam detected on drug screening, one had a therapeutic level of alprazolam and also took imipramine on days 4-6, and one took alprazolam on day 8 before dropping out on day 9. Since alprazolam is recognized as an effective antipanic agent, any improvement in these patients will be confounded by their concomitant alprazolam

[11] Paroxetine CR patients: 497.008.01593, 497.009.01448, 497.014.01575, and 497.029.01740; placebo patients: 497.004.01773, 497.004.02459, 497.017.01277, 497.018.01234, 497.029.01732, 497.029.01739, and 497.031.01741.

use. Since the known benzodiazepine use appears to be balanced between the treatment groups or possibly favoring placebo over drug (3% (4/132) of the paroxetine CR and 5% (6/130) of the placebo patients), this potential source of bias is not considered a major concern.

Efficacy Results

Efficacy data displays may be found in Appendix 7.2.3, Tables 7.2.3.4 - 7.2.3.9.[12]

With respect to the protocol-identified primary measure of efficacy, i.e., the percentage of patients achieving zero full panic attacks at endpoint (weeks 9/10 LOCF), paroxetine CR was numerically, but not statistically, superior to placebo: 62.7% vs. 56.2%, odds ratio = 1.362, p= 0.230.

This was also true for the OC dataset at weeks 9/10, with 70.1% of paroxetine CR and 65.6% of placebo patients achieving zero full attacks (odds ratio = 1.224, p = 0.530). By-visit OC data revealed that paroxetine CR was superior to placebo only at weeks 7/8, where the response rates were 73.3% and 56.5%, respectively (p=0.017). Between the week 7/8 and week 9/10 visits, the drug response rate dropped slightly and the placebo rate increased substantially.

Other variables considered by this reviewer to be supportive are discussed below.

The median change from baseline in the number of full panic attacks was greater for paroxetine CR than placebo in the LOCF analysis, though the difference was not statistically significant (-4 vs. -3, median difference -1, p=0.239). OC results at weeks 9/10 for this variable trended toward statistical significance (p=0.088).

The median changes from baseline in CGI severity of illness scores were not significantly different between groups in either the LOCF or OC analyses, although the LOCF analysis trended toward significance (p=0.078).

Mean changes in the percentage of time spent with anticipatory anxiety trended toward being significantly

[12] These tables were electronically copied from the sponsor's CANDA.

different in the LOCF analysis at weeks 9/10 (p=0.078) but were not significantly different in the OC analysis at this timepoint.

Mean changes in the MSPS total fear scores were significantly larger for paroxetine CR than for placebo (-19.6 vs. -10.8, p=<0.001). OC results were not significant.

Likewise, mean changes in the MSPS total avoidance scores were significantly larger for paroxetine CR relative to placebo (-6.0 vs. -3.3, p=0.006). OC results were not significant.

Conclusions

This study failed to show a pattern of significant differences between paroxetine CR and placebo that could be interpreted as convincing evidence of antipanic efficacy.

Since an active comparator was not employed in this trial to assess assay sensitivity, this trial is considered negative. In terms of the primary efficacy variable (percentage of patients reduced to zero attacks), the poor results in this study may be attributable to a smaller drug effect and a larger placebo effect compared to study 494, which was positive. The reason for this difference is not clear.

7.3 Summary of Data Pertinent to Important Clinical Issues

7.3.1 Predictors of Response

The sponsor conducted an analysis of the influence of various demographic (age, sex, race) and baseline severity subgroups on efficacy findings in studies 494, 495, and 497, separately. This section will present the results of this analysis, using the natural logarithm of the drug:placebo odds ratio for the percentage of patients free of full panic attacks at endpoint, the primary measure of efficacy in these studies. Note that analyses for studies 494 and 495 exclude data from centers 33 and 5, respectively, due to interaction concerns discussed above. Results are presented graphically in Appendix 7.3.1.[13]

[13] Graphs were electronically copied from the sponsor's CANDA.

Appendix 7.3.1, Figure 7.3.1.1, presents data based on age subgroups for these trials. The wide 95% confidence intervals at the two extreme age groups are due to the relatively small numbers of patients in these groups. Visual inspection reveals no major consistent effect of age on efficacy.

Appendix 7.3.1, Figure 7.3.1.2, depicts efficacy as a function of gender subgroup. The natural log of the odds ratio was greater than zero among females in all three studies but, among males, only in study 494. However, any gender difference must be inferred with caution due to the width and overlapping nature of the confidence intervals.

Appendix 7.3.1, Figure 7.3.1.3, displays data based on race subgroups (white and non-white). Confidence intervals for the non-white group are comparatively wide due to the small number of patients in this group in all three studies. No clear effect of race on efficacy can be concluded from these data.

Baseline severity of illness subgroups were defined by the median number of full panic attacks at baseline: patients were then classified as having greater than or equal to the median number of attacks or less than the median. Appendix 7.3.1, Figure 7.3.1.4, shows no consistent effect of baseline severity group on efficacy.

Visual inspection of logarithmic plots is not a very sensitive method of detecting differences or trends across groups. Also, it may have been reasonable to pool these three identical trials in lieu of examining each separately for these analyses. Nonetheless, for the purpose of detecting very large differences, the method employed is satisfactory.

Additionally, age group, gender, and baseline frequency of full panic attacks were used as covariates in the statistical analysis of the percentage of patients free of full panic attacks, the protocol-defined primary efficacy parameter. No treatment-by-covariate interaction was observed in studies 494, 495, and 497 for this efficacy parameter at week 10 (LOCF). Thus, based on this examination, there was no statistical evidence supporting a difference in efficacy of paroxetine CR due to age, gender, or baseline panic disorder severity.

In sum, there is insufficient evidence to infer an effect of age, gender, race, or baseline severity on efficacy.

7.3.2 Size of Treatment Effect

Treatment effect size was examined in terms of the percentage of patients who were free of full panic attacks at endpoint. Results are summarized below in Table 7.3.2 for the studies 494, 495, and 497. Also displayed are the corresponding effect sizes observed in the three positive short-term studies of immediate release paroxetine in the treatment of panic disorder (studies 120, 108, and 187 in NDA 20-031, S-009).

TABLE 7.3.2:
TREATMENT EFFECT SIZE AS EXPRESSED BY THE PROPORTION OF PATIENTS FREE OF FULL PANIC ATTACKS AT ENDPOINT

Study	Paroxetine (IR or CR)	Placebo	Difference (Drug-Placebo)
494	69%	50%	19%
495	57%	50%	7%
497	63%	56%	7%
120	76%	44%	32%
108	33%	14%	19%
187	51%	32%	19%

It must be borne in mind that paroxetine CR beat placebo on this variable only in study 494; study 495 is considered positive by virtue of the strong findings on the secondary variables and study 497 is negative. The 19% difference observed in 494 is identical to the difference observed in the two of the three trials with immediate release paroxetine that provided support for the approval of that NDA. Thus, the effect observed in study 494 is considered to be clinically relevant.

7.3.3 Choice of Dose

No fixed dose trials of paroxetine CR in panic disorder have been conducted and, thus, no definitive conclusions can be drawn regarding dose-response.

Study 120 was a fixed dose study of immediate release paroxetine that examined doses of 10, 20, and 40 mg/day versus placebo in the treatment of panic disorder. In this trial, only the 40mg group produced a significant

difference over placebo. Also, in the other two immediate release studies discussed above (108 and 187), the mean paroxetine dose for completers at endpoint was about 40 mg/day. Interestingly, under steady state conditions, 40mg of immediate release paroxetine has been shown to exhibit bioavailability similar to 50mg of controlled release paroxetine,[14] which approximates the mean doses among completers in the flexible dose studies 494, 495, and 497.

In the key studies of this NDA, dosing for paroxetine CR began at 12.5 mg/day for the first week of treatment, and all patients were increased to 25 mg/day during the second week. After week 2, patients could have their dosage increased in 12.5 mg increments every 7 days to a maximum dose of 75 mg daily based upon the investigator's judgment regarding therapeutic efficacy and tolerability. This is consistent with the dosing instructions proposed by the sponsor for labeling.

7.3.4 Duration of Treatment

No study addressing the long-term efficacy of paroxetine CR in panic disorder has been completed. However, long-term maintenance effects were demonstrated for immediate release paroxetine in a 3 month double-blind extension to study 120 in which short-term responders were randomized to paroxetine (10, 20, or 40 mg/day) or placebo.[15] Patients randomized to paroxetine were significantly less likely to relapse than patients randomized to placebo (relapse rates of 4.7% vs. 29.7%, respectively; p=0.002).

The sponsor argues that the results of this study should be extrapolated to the CR formulation on the basis of the following considerations: 1) approximately equal steady state bioavailability of the CR and IR formulations at daily doses in a 5:4 ratio, 2) identical pharmacokinetic profiles of these formulations once absorbed, and 3) demonstrated acute efficacy for paroxetine CR in panic disorder. This argument is reasonable and extrapolation seems acceptable.

7.4 Conclusions Regarding Efficacy

The sponsor has provided evidence from two adequate, well-controlled studies that supports the claim of short-term

[14] See study 474 submitted to NDA 20-936.
[15] Designated as study 222.

efficacy for the use of paroxetine CR in panic disorder (studies 494 and 495).

Study 497 failed to convincingly demonstrate the superiority of paroxetine CR over placebo in this condition.

The results of all three studies are summarized in Table 7.4 below.

TABLE 7.4: SUMMARY OF EFFICACY RESULTS (STATISTICAL SIGNIFICANCE OF DRUG/PLACEBO DIFFERENCES AT WEEK 10)

Variable	Dataset	Study		
		494[16]	495[17]	497
% patients with zero full attacks	LOCF	**	ns	ns
	OC	**	*	ns
mean Δ in number of full attacks	LOCF	tr	**	ns
	OC	tr	**	tr
mean Δ in CGI severity score	LOCF	*	**	tr
	OC	**	**	ns
mean Δ in anticipatory anxiety	LOCF	tr	**	tr
	OC	ns	**	ns
mean Δ in MSPS fear score	LOCF	*	**	**
	OC	ns	**	ns
mean Δ in MSPS avoidance score	LOCF	ns	**	**
	OC	ns	**	ns.

Codes: ns= not significant ($p>0.10$)
tr= trend ($0.05<p\leq0.10$)
* = significant ($0.01<p\leq0.05$)
**= highly significant ($p\leq0.01$)

[16] Excluding center 33.
[17] Excluding center 5.

8.0 Integrated Review of Safety

8.1 Methods and Findings for Safety Review

Given the U.S. approval of immediate release paroxetine for three separate indications (depression, OCD, and panic disorder), the extensive worldwide safety experience with immediate release paroxetine, the pharmacokinetic properties of controlled release paroxetine, and the pending approval of paroxetine CR for the treatment of depression,[1] this review will be much briefer than would be the case for a new molecular entity.

This safety assessment will focus on the more significant adverse events associated with the use of paroxetine CR in the treatment of panic disorder (i.e., deaths, non-fatal events classified as serious, and events leading to discontinuation). Also, the common adverse event profile will be examined and, finally, potentially clinically significant changes in laboratory and vital sign ECG measures will be addressed. ECG's were not performed during these studies.

The pool of studies 494, 495, and 497 comprises the integrated safety database for this review.

The report of study 569, a bioequivalence study in 80 volunteers, was also submitted with this NDA. There were no deaths, serious non-fatal adverse experiences, or dropouts due to adverse events in this single dose Phase 1 study. No other safety data from this investigation will be presented in this review.

8.1.1 Deaths

There were no deaths reported from studies 494, 495, or 497 as of the safety cutoff date (10/22/97).

8.1.2 Other Serious Adverse Events

A serious non-fatal adverse experience was defined as any event which was life threatening, permanently or temporarily disabling or incapacitating, resulted in hospitalization, prolonged a hospital stay, or was associated with congenital abnormality, cancer or overdose

[1] See NDA 20-936.

(either accidental or intentional). In addition, a non-fatal serious adverse experience was defined as any experience which the investigator regarded as serious or which would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the drug.

There were 18 patients with non-fatal serious adverse events in the integrated database as of the safety cutoff date: of these, 10 had received paroxetine CR and 8 received placebo. Information for these patients is summarized in Appendix 8.1, Table 8.1.2.

Narrative summaries were examined for the 10 paroxetine CR patients with adverse experiences classified as serious. The only clinically remarkable event that might be drug related was a case of rhabdomyolysis, which will be discussed in section 8.4.1.

8.1.3 Dropouts

8.1.3.1 Overall Pattern of Dropouts

Table 8.1.3.1 displays the numbers (percentages) of patients in the pool of studies 494, 495, and 497 who completed the entire study, including taper phase, and who dropped out, categorized by reason for dropout.

A total of 70% of paroxetine CR and 74% of placebo patients completed the 10 week treatment phase. The most common reason for dropout in the drug group was an adverse experience, whereas in the placebo group adverse experiences, lack of efficacy, and lost to follow-up were all equally frequent reasons for premature discontinuation.

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Table 8.1.3.1: Enumeration (Percentages) of Completers and Premature Terminations by Reason *		
	Par CR (n=444)	Placebo (n=445)
Completed	310 (70%)	328 (74%)
Dropout due to:		
Adverse Event	52 (12%)	28 (6%)
Lack of Efficacy	12 (3%)	28 (6%)
Protocol Violation	13 (3%)	20 (5%)
Lost to Follow-up	35 (8%)	25 (6%)
Other Reasons	22 (5%)	16 (4%)

* Percentages may not total 100% due to rounding.

8.1.3.2 Dropouts due to Adverse Experiences

During the 10 week treatment phases of studies 494, 495, and 497, a total 11% (50/444) of paroxetine CR and 6% (25/445) of placebo patients dropped out due to adverse events. Table 8.1.3.2 depicts the proportions of patients who dropped out during the 10 week treatment phase due to various adverse events for those events leading to dropout in at least 1% of paroxetine CR patients.

Table 8.1.3.2: Proportions of Patients Dropping Out due to Adverse Events for Events Leading to Dropout in at Least 1% of Paroxetine CR Patients *		
Body System/Event	Paroxetine CR (n=444)	Placebo (n=445)
Body as a Whole		
Asthenia	1%	0%
Headache	1%	<1%
Digestive System		
Nausea	3%	<1%
Nervous System		
Insomnia	2%	0%
Agitation	1%	<1%

* All adverse events leading to a patient's dropout are enumerated. Thus, patients may be counted more than once.

Other events that led to dropout in less than 1% of the paroxetine CR patients, along with the number of those

patients dropping out for each, are as follows: dizziness and somnolence (4); abdominal pain (3); diarrhea, dry mouth, myalgia, anxiety, concentration impaired, confusion, depression, hypertonia, tremor, and unintended pregnancy (2); and infection, malaise, tachycardia, vasodilatation, bruxism, dyspepsia, flatulence, melena, hypokalemia, myopathy, alcohol abuse, amnesia, convulsion, depersonalization, drug dependence, emotional lability, hallucinations, incoordination, libido decreased, nervousness, paresthesia, yawning, rash, sweating, urticaria, abnormal vision, photophobia, abnormal ejaculation, and ectopic pregnancy (1).

Among these, the only event worthy of mention is a convulsion that occurred in one patient. This patient will be discussed in section 8.4.2.

8.1.4 Adverse Events

8.1.4.1 Establishing Appropriateness of Adverse Event Categorization and Preferred Terms

An adverse experience included any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, and/or laboratory changes occurring in any phase of the studies, whether associated with study drug or placebo and whether or not considered drug-related. This included an exacerbation of pre-existing condition or events, intercurrent illnesses, drug interaction or the significant worsening of the disease under investigation.

At each clinic visit in Studies 494, 495 and 497, all adverse experiences were recorded after either being observed by the investigative staff or reported by the patient spontaneously in response to a non-leading question. Adverse experiences were coded using the World Health Organization (WHO) disease codelist, and were then mapped to the ADECS (COSTART based) classification to give a body system and preferred term.

The sponsor provided a thesaurus for the coding of all adverse events in the safety database.[2] This listing was examined to assess the adequacy of coding. There are a number of preferred terms that are too general to be

[2] See the 7/2/98 submission to this NDA.

clinically useful (e.g., female genital disorders, which encompasses orgasmic complaints). For those terms appearing in the table of adverse reactions in labeling, clarification should be accomplished with footnotes.

Otherwise, no important deficiencies were found.

8.1.4.2 Common, Drug-Related Adverse Events

Appendix 8.1, Table 8.1.4.2 presents the proportions of patients who experienced various treatment-emergent adverse events for those events reported in at least 1% of paroxetine CR patients within the integrated safety database. Events occurring during taper are excluded.

Based on this table, the following adverse events are considered common and probably drug-related (i.e., occurring in at least 5% of paroxetine CR patients at an incidence at least twice that in the placebo group) (listed in order of decreasing frequency in the paroxetine CR group):

abnormal ejaculation, somnolence, impotence, libido decreased, tremor, sweating, and female genital disorders (generally anorgasmia or trouble achieving orgasm).

These events are typical of those observed previously with paroxetine and other SSRI's.

8.1.4.3 Effects of Gender and Race on Adverse Event Reporting Incidence

For the above common, drug-related events, the sponsor performed an analysis of the effects of gender and race on reporting rates in the pool of studies 494, 495, and 497. Since there was only one patient over the age of 65 years, no analysis of age was performed. These analyses involved statistical comparisons of the (drug:placebo) odds ratios between gender and race subgroups.

The only statistically significant finding was for decreased libido in race subgroups, which was much more frequently associated with drug among white patients compared to non-white patients (odds ratio = 3.29 among white and 0.42 among non-white patients, p=0.017). The clinical meaning of this finding is unknown.

8.1.4.4 Dose-Relatedness

The potential relationship between adverse event incidence and dose could not be reasonably evaluated from these three flexible dose studies. Study PAR 09, submitted in support of the original paroxetine NDA 20-031, used fixed doses the immediate release formulation (10, 20, 30, and 40 mg/day) and did reveal evidence of dose-dependency for some of the more common adverse events with paroxetine IR, such as nausea, somnolence, sweating, and abnormal ejaculation.

8.1.4.5 Other Events Observed During Premarketing GAD Studies with Effexor XR

Events other than those listed in Table 8.1.4.2 (Appendix 8.1) that were reported in association with paroxetine CR treatment in studies 494, 495, and 497 are presented, by body system and preferred term, in Table 8.1.4.5 in Appendix 8.1.

8.1.5 Laboratory Data

8.1.5.1 Laboratory Assessments

In studies 494, 495, and 497, routine chemistry and hematology laboratory tests were conducted at screening and at week 10 of the treatment phase (or at early termination).[3]

8.1.5.2 Analyses of Laboratory Data

Clinical laboratory values were evaluated by examining the proportion of patients in each treatment group with values outside predetermined limits for potential clinical concern that emerged during treatment. Criteria for values of potential concern are specified in Appendix 8.1, Table 8.1.5.2.[4]

8.1.5.3 Results of Laboratory Data Analyses

Appendix 8.1, Table 8.1.5.3 displays the proportions of paroxetine CR and placebo patients who experienced a treatment-emergent laboratory test result of potential

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[3] H/H, WBC with diff, platelet count, electrolytes (Na^+, K^+, and Cl^-), alkaline phosphatase, BUN, creatinine, AST, ALT, bilirubin, and U/A for blood and protein.

[4] This table was electronically copied from the sponsor's CANDA.

clinical concern. There was a statistically significant difference[5] for only one variable, ALT. Elevated liver enzymes will be discussed further in section 8.4.3.

8.1.6 Vital Sign Data

8.1.6.1 Vital Sign Assessments

Measurement of vital signs (sitting blood pressure and heart rate, and weight) was performed at every clinic visit[6] during Studies 494, 495 and 497.

8.1.6.2 Analyses of Vital Sign Data

This review will focus on the sponsor's identification of patients from the pool of studies 494, 495, and 497 who had at least one vital sign measurement of potential clinical concern according to predetermined criteria listed in Appendix 8.1, Table 8.1.6.2.[7]

8.1.6.3 Results of Vital Sign Data Analyses

Appendix 8.1, Table 8.1.6.3 displays the proportions of patients in each treatment group had experienced a vital sign measurement of potential clinical concern.[8]

For most variables, the placebo incidence of measurements of potential concern exceeded those for drug. Only for significant changes in weight was the paroxetine CR incidence higher than placebo; however, none of these differences were statistically significant.[9]

8.2 Adequacy of Patient Exposure and Safety Assessments

The patient exposure and safety assessments in the integrated safety database, complemented by experience with the use of immediate release paroxetine in the treatment of panic disorder, are deemed to be sufficient to adequately address the safety of paroxetine CR in the treatment of panic disorder.

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[5] Based on a two-tailed Fishers exact test with α=0.10.
[6] That is, at baseline; weeks 1, 2, 3, 4, 5, 6, 8, and 10; end of taper; and at early termination for dropouts.
[7] This table was electronically copied from the sponsor's CANDA.
[8] This table was electronically copied from the sponsor's CANDA.
[9] Based on a two-tailed Fishers exact test with α=0.10.

8.3 Assessment of Data Quality and Completeness

Case report forms for four randomly selected patients who dropped out due to adverse events were reviewed to audit the completeness and accuracy of adverse event data in the corresponding narrative summaries and line listings.[10] No discrepancies were detected.

An appreciable number of patients in both the drug and placebo groups were lost to follow-up (8% and 6% of the safety ITT, respectively). However, given previous safety data in support of paroxetine CR (NDA 20-936), extensive safety experience with the immediate release formulation, and the relatively small safety database in this application, it is unlikely that this loss of data would change conclusions about the safety of paroxetine CR. Overall, there were no indications that data was less than reasonably complete and accurate.

8.4 Summary of Serious Adverse Events Considered Possibly Drug-Related

8.4.1 Rhabdomyolysis

There was a case of rhabdomyolysis in this database:

Patient 495.012.00994 was a 33 y.o. white male had taken paroxetine CR for 43 days when, at a dose of 25 mg/day, he presented to the hospital with paroxysmal muscle cramping and dizziness after working under extreme stress. A preliminary diagnosis of heat exhaustion was made but he was subsequently discovered to have severe hypokalemia, elevated CPK and CPK MB isozymes, and rhabdomyolysis. He was admitted and received potassium supplementation, but later that day signed out against medical advice. He was readmitted the next day complaining of muscle aches. Potassium levels were normal on day 45. He was discontinued from this study on day 47 after a positive alprazolam blood level was found. He had apparently concealed alprazolam and diazepam use from the study site.

It is difficult to discern the etiology of this event with reasonable certainty. Drugs, such as neuroleptics, have been implicated in rhabdomyolysis and symptoms suggestive of neuroleptic malignant syndrome, which can include

[10] Patients are identified in section 1.1.

rhabdomyolysis, have been reported in association with SSRI's, usually when MAOI's are taken with an SSRI. The Micromedex Adverse Reactions Index lists no SSRI's as causing rhabdomyolysis. This event was apparently not accompanied by other feature of NMS, such as fever, muscle rigidity, vital sign abnormalities, or acute mental status changes. It is notable, though, that this patient had been treated with thioridazine for panic disorder prior to the study and it is conceivable that he surreptitiously took thioridazine during the study. Assuming that "working under extreme stress" means extreme physical exertion, excessive muscular exertion is judged to be more likely causative than paroxetine CR for this event.

8.4.2 Seizure

One patient dropped out after a seizure:

Patient 495.013.00607 was a 44 y.o. white female had received paroxetine CR for 59 days when, at a dose of 62.5 mg/day, she experienced a witnessed tonic-clonic seizure of 15 minutes duration during which she bit her lip. Her dose of paroxetine CR had been reduced about two weeks before this event. There were no concomitant medications and she stopped taking the study drug two days later. She had been evaluated for a seizure about six months prior but an extensive work-up was unremarkable. She was referred for a neurological evaluation but no results were available.

In premarketing studies with immediate release paroxetine, seizures were reported in 0.1% of paroxetine-treated patients. The etiology in this case is not clear but paroxetine CR may have been a causative factor.

Another patient (494.027.00417) experienced six episodes of "fainting" over a 1-2 hour period on day 22 of the study. These episodes, which were witnessed by her mother, were described as her eyes rolling to the top of her head, the right side of her mouth twitching, and subsequent sleep followed by awakening with no memory of the experience. She was taken to the emergency room, where a neurological examination and laboratory tests were essentially unremarkable. Medication was continued for four more days before the patient dropped out due to difficulty with memory and concentration which began on day 26. A CT scan and EEG, completed over the next week, were both normal. There was no past history of seizures. The investigator

attributed these events to an acute anxiety reaction. A classification of the episodes on day 22 as seizures is questionable.

8.4.3 Elevated Liver Transaminases

The criterion for a significant elevation in ALT (SGPT) was met by 0.9% of paroxetine CR vs. 0.0% of placebo patients (p=0.062) in the pool of studies 494, 495, and 497. There was also a larger percentage of drug patients with significant elevations in AST (SGOT) compared to placebo (0.7% vs. 0.0%, respectively). Essentially, four paroxetine CR patients contributed to these findings.[11] Most of these elevations were in the range of three- to five-fold the upper limits of normal. One patient (495.03.00948) also experienced a two-fold elevation in total bilirubin, although none of these patients exhibited jaundice. All transaminase and bilirubin abnormalities decreased substantially following discontinuation of paroxetine CR and no patient progressed to more severe liver pathology, such as hepatic failure or necrosis. The mean changes from baseline to week 10 in liver enzymes were larger for the paroxetine CR group than for placebo:

	Paroxetine CR	Placebo
AST (U/L)	+2.29	+0.05
ALT (U/L)	+2.53	-1.74

Based on scatterplots of baseline vs. week 10 values for AST and ALT, the larger changes in the drug group appear to be attributable to large changes in a few patients.[12]

In placebo-controlled premarketing trials with immediate release paroxetine, drug patients exhibited abnormal values on liver function tests at rates no greater than those in the placebo group. However, worldwide postmarketing surveillance for paroxetine has revealed several cases of substantial LFT elevations, to include a few cases of significant liver pathology (such as fatal liver necrosis). As a result of these reports, the Division Safety Group was consulted in April 1996 to evaluate the risk of liver failure with SSRI's. This examination did not suggest a unique hepatotoxic effect of the SSRI's and no significant

[11] Patients 495.03.00948, 495.05.02114, 495.14.01007, and 497.05.01421.
[12] Figures 4 and 5 in the ISS.

difference between the SSRI's with respect to crude reporting rates of serious hepatic events.[13]

The findings in this database add no new information to the safety experience with paroxetine with respect to hepatic effects and are not judged to represent a significant hazard associated with paroxetine CR.

8.5 Conclusions Regarding Safety

This safety review revealed no findings that would preclude the approval of paroxetine CR for the treatment of panic disorder or merit prominent discussion in the labeling of paroxetine CR.

9.0 Labeling Review

Information in the proposed labeling, submitted 4/22/98, pertaining to the use of Paxil CR for depression, as well as other general information regarding Paxil CR (e.g., pharmacokinetic information), is currently being addressed under NDA 20-936 (Paxil CR for depression). It is expected that NDA 20-936 will be approved prior to this NDA and, thus, the labeling for NDA 20-936 will be the base labeling for this NDA. Therefore, the labeling review discussed below will focus only those sections of labeling directly relevant to the use of Paxil CR in panic disorder.

CLINICAL PHARMACOLOGY/Clinical Trials/Panic Disorder

It is suggested that the results for the key panic attack variables be specifically cited. I recommend that the second paragraph in this section be split into two paragraphs, the first providing results from study 494 and the second from study 495:

"Study 1 was a 10-week flexible-dose study comparing paroxetine controlled-release (12.5 to 75 mg daily) and placebo. At endpoint, 69% of patients receiving paroxetine controlled-release were free of panic attacks, compared to 50% of placebo-treated patients.

[13] Drugs examined were paroxetine, sertraline, fluvoxamine, fluoxetine, and venlafaxine. This evaluation was completed by James Knudsen, M.D., Ph.D., on July 23, 1996, under the supervision of the Safety Group Leader, Greg Burkhart, M.D., M.S.

In Study 2, also a 10-week flexible dose study comparing paroxetine controlled-release (12.5 to 75 mg daily) to placebo, there was a significant reduction in the number of full panic attacks for patients treated with Paxil CR compared to placebo-treated patients at endpoint. Median decreases from baseline in the number of full panic attacks during the last two weeks of the study were 5 in the paroxetine controlled-release group and 3 in the placebo group."

For sake of full disclosure, it could be argued that both variables (percentage reduced to zero attacks and mean change in the number of full attacks) should be described for both studies, even though statistical significance was not achieved for the former in Study 2 and for the latter in Study 1. Since this would add considerably to the verbiage, may be confusing to clinicians, and is not critical to our conclusion that the drug was efficacious in both studies, I have chosen not to include this information.

INDICATIONS AND USAGE/Panic Disorder

The proposed language is acceptable.

ADVERSE REACTIONS/Incidence in Controlled Clinical Trials/Panic Disorder

A few minor changes to Table 2 are in order:

Some adverse event terms, which seem too general to be useful, should be clarified in footnotes to better convey the nature of the experiences: vasodilatation, abnormal vision, abnormal ejaculation, and female genital disorders.

It is preferable to list adverse events within each body system in descending order of incidence and not in alphabetical order, as proposed by the sponsor.

Generally, I would prefer to round the figure "0.4" to the whole number "0" (and not "1"). Therefore, the placebo incidence rates for the following events should be 0% (not 1%): abnormal vision and urination impaired. For the same reason, the adverse event *vaginitis*, with paroxetine CR and placebo incidence rates of 1.1% and 0.4%, respectively, should be removed from the footnote (which assumed rounded