CENTER FOR DRUG EVALUATION AND RESEARCH

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

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-982
NDA 20-936/S-008

GlaxoSmithKline
Attention: Susan Weill
Associate Director, U.S. Regulatory Affairs
1250 South Collegeville Road, P.O. Box 5089
Collegeville, Pennsylvania 19426

Dear Ms. Weill:

Please refer to your new drug application (NDA) dated and received April 22, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paxil CR (paroxetine hydrochloride) Controlled Release 12.5 and 25 mg Tablets.

We acknowledge receipt of your submissions dated December 18, 2001 and January 9, 2002. Your submission of December 18, 2001 constituted a complete response to our January 3, 2000 action letter.

We also acknowledge receipt of your labeling supplement #008 submitted to NDA 20-936 on January 25, 2002. We note that this supplement was submitted for an administrative purpose only.

This new drug application provides for the use of Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets for Panic Disorder.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). 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 copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-982." Approval of this submission by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until February 18, 2005. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

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

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

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

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81. We remind you that you must comply with the requirements for an approved NDA as set forth under 21 CFR 314.80 and 314.81. To comply with these regulations, all 7-day and 15-day alert reports, periodic adverse drug experience (ADE) reports, field alerts, annual reports, supplements, and other submissions should be addressed to NDA 20-936 for Paxil CR rather than NDA 20-982. In the future, no submissions should be made to NDA 20-982 except for final printed labeling as described earlier in this letter.

If you have any questions, call Melaine Shin, R.Ph., 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

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-982

APPROVABLE LETTER

NDA 20-982

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

Dear Mr. Kline:

Please refer to your new drug application (NDA) dated and received April 22, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paxil CR (paroxetine hydrochloride) Controlled Release 12.5 and 25 mg Tablets.

We also refer to your submission dated July 7, 1999 responding to our approvable letter dated March 10, 1999 and our Draft Labeling Proposal faxed to you August 17, 1999.

This application provides for the treatment of panic disorder.

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

CLINICAL

1. Labeling

   Accompanying this letter (Attachment) is the Agency's proposal for the labeling of Paxil CR for Panic Disorder. We believe it presents a fair summary of the information available on the benefits and risks of Paxil CR.

   We have proposed a number of changes to the draft labeling submitted in your July 7, 1999 submission. We will be happy to discuss these proposed changes in detail, and to discuss any disagreements you might have with any part of the proposed labeling format or content.

2. Safety Update

   Our assessment of the safety of Paxil CR is based on our review of all safety information provided in your original and subsequent submissions, with a cutoff date of 10-22-97. Under 21 CFR 314.50(d)(5)(vi)(b), we request that you provide a final safety update. If, as is likely, the amount of additional safety information available, either from new patients

or additional visits from ongoing patients, is small relative to what we already have, the safety update can focus on identifying any important new adverse events not previously reported. Consequently, rather than completely redoing the integrated safety summary, it may be preferable for you to submit a safety update of more limited scope, e.g., it might include a line listing of any patients meeting the following criteria and not previously reported in the original NDA: any deaths; any patients dropping out for adverse events; and any patients experiencing serious events (according to the definition used for classifying such patients in your original submission). Narrative summaries should be provided for patients who died, who had a serious event or who had an unexpected cause of dropout. In selected cases, we may ask for copies of case report forms. The Division will be happy to discuss with you more specifically what will be needed in the safety update.

3. Regulatory Status Update

Please provide any new information on the regulatory status of Paxil CR for the treatment of panic disorder worldwide. We require a review of the status of all actions with regard to this drug for this indication, either taken or pending before foreign regulatory authorities. Approval actions can be noted, but we ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. In addition, we ask that you provide us any current foreign labeling for Paxil CR for panic disorder, if appropriate, along with English translations when needed. It is only necessary to provide information that is more recent than that provided in your original April 22, 1998 submission.

4. World Literature Update

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

CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)

Please note that only the Crawley, UK facility establishment is being approved for drug product manufacturing.

BIOPHARMACEUTICS

Dissolution Specification

The following dissolution method and specification for both strengths of Paxil CR Tablets (12.5 mg and 25 mg), similar to the approved NDA 20-936, should be used.

Appartatus: USP II (paddles) 150 rpm

Dissolution Media	Time	Limit (%dissolved)
	2 hours	Not more than
	1 hour	NMT
	2 hour	Between
	4 hour	Between
	6 hour	NLT

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

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

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

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.
Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed for this indication until you have been notified in writing that the application is approved.

If you have any questions, please contact Ms. Melaine Shin, R.Ph., Regulatory Management Officer, at (301) 594-5511.

Sincerely yours,

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

ATTACHMENT

APPEARS THIS WAY ON ORIGINAL

cc:
Archival NDA 20-982
HFD-120/Div. Files
HFD-002/ORM

HFD-92/DDM-DIAB
HFD-120/M.Shin
HFD-120/RKatz/TLaughren/GDubitsky
HFD-120/RSeevers/RLostritto
HFD-710/KJin/KKoti
HFD-860/CSahajwalla
HFD-101/RTemple
DISTRICT OFFICE
HFD-40/DDMAC (with labeling)

Drafted by: MS/December 14, 1999
Revised : TPL/

filename: C:Wpfiles:NDA;PaxilCR:AE2.

APPROVABLE (AE)

NDA 20-982

MAR 10 1999

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

Dear Mr. Kline:

Please refer to your new drug application (NDA) dated and received April 22, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paxil CR (paroxetine hydrochloride) Controlled Release 12.5 and 25 mg Tablets.

We acknowledge receipt of your submissions dated May 27, June 30, July 2, and October 7, 1998. The User Fee goal date for this application is April 22, 1999.

This application provides for the treatment of panic disorder.

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

CLINICAL

1. Labeling

   Accompanying this letter (Attachment) is the Agency's proposal for the labeling of Paxil CR for Panic Disorder. We believe it presents a fair summary of the information available on the benefits and risks of Paxil CR.

   We have proposed a number of changes to the draft labeling submitted in your original April 22, 1998 submission. We will be happy to discuss these proposed changes in detail, and to discuss any disagreements you might have with any part of the proposed labeling format or content.

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rather than completely redoing the integrated safety summary, it may be preferable for you to submit a safety update of more limited scope, e.g., it might include a line listing of any patients meeting the following criteria and not previously reported in the original NDA: any deaths; any patients dropping out for adverse events; and any patients experiencing serious events (according to the definition used for classifying such patients in your original submission). Narrative summaries should be provided for patients who died, who had a serious event or who had an unexpected cause of dropout. In selected cases, we may ask for copies of case report forms. The Division will be happy to discuss with you more specifically what will be needed in the safety update.

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Please provide any new information on the regulatory status of Paxil CR for the treatment of panic disorder worldwide. We require a review of the status of all actions with regard to this drug for this indication, either taken or pending before foreign regulatory authorities. Approval actions can be noted, but we ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. In addition, we ask that you provide us any current foreign labeling for Paxil CR for panic disorder, if appropriate, along with English translations when needed. It is only necessary to provide information that is more recent than that provided in your original April 22, 1998 submission.

4. World Literature Update

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

CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)

Please note that only the Crawley, UK facility establishment is being approved for drug product manufacturing.

BIOPHARMACEUTICS

Dissolution Specification

The following dissolution method and specification for both strengths of Paxil CR Tablets (12.5 mg and 25 mg), similar to the approved NDA 20-936, should be used.

Appartatus: USP II (paddles) 150 rpm

Dissolution Media	Time	Limit (%dissolved)
[redacted]	2 hours	[redacted]
	1 hour	
	2 hour	
	4 hour	
	6 hour	[redacted]

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

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

Food and Drug Administration
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Rockville, Maryland 20857

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Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed for this indication until you have been notified in writing that the application is approved.

If you have any questions, please contact Ms. Melaine Shin, R.Ph., Project Manager, at (301) 594-5527.

Sincerely yours,

/S/

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

ATTACHMENT

cc:
Archival NDA 20-982
HFD-120/Div. Files
HFD-002/ORM
HFD-92/DDM-DIAB
HFD-120/M.Shin
HFD-120/RKatz/TLaughren/GDubitsky
HFD-120/RSeevers/~~RLostritto~~
HFD-710/KJin/KKoti
HFD-860/CSahajwalla/RYuan
HFD-101/RTemple
DISTRICT OFFICE
HFD-40/DDMAC (with labeling)

Drafted by: MS/March 1, 1999
Revised : TPL/3-2-99

filename: C:Wpfiles:NDA;PaxilCR:AE1.

APPROVABLE (AE)

**APPEARS THIS WAY
ON ORIGINAL**

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

APPEARS THIS WAY
ON ORIGINAL

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

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

/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

APPEARS THIS WAY
ON ORIGINAL

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
TABLE OF CONTENTS

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]

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[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.

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[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≤0.10)
* = significant (0.01<p≤0.05)
**= highly significant (p≤0.01)

[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.

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

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[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

rates of 1% and 1%) and placed in Table 2 under Urogenital System, with rates of 1% and 0%, respectively.

DOSAGE AND ADMINISTRATION/Panic Disorder

The proposed language is acceptable.

10.0 Conclusions

This application presents adequate data to support the sponsor's claim of the effectiveness of paroxetine CR in the treatment of panic disorder. While the clinical experience with Paxil CR is too limited to rule out infrequently or rarely occurring safety problems, the safety record of Paxil (IR) is reassuring and the clinical trials data with Paxil CR in depression and panic disorder do not suggest any problems unique to this formulation. Thus, paroxetine CR is expected to be reasonably safe for use as labeled.

11.0 Recommendations

From a clinical perspective, it is recommended that Paxil CR be approved for the treatment of panic disorder after agreement is reached on the labeling issues raised in section 9.0.

/S/

Gregory M. Dubitsky, M.D.
February 1, 1999

3-2-99
I agree that this NDA is approvable. See memo to file for more detailed comments.

/S/

TL, PDP

cc: NDA 20-982
HFD-120/Division File
HFD-120/TLaughren
/GDubitsky
/MShin

APPENDIX 5.0

CLINICAL DATA SOURCES

Table 5.1.1.1: Table of Studies	
Phase 1 Studies (Healthy Volunteers)	
569 (Germany)	Open-label, randomized, single dose, two treatment, replicate, four period crossover study of the bioequivalence of paroxetine CR tablets manufactured at two sites (Cidra and Crawley) in 80 healthy volunteers, ages 20-55; dose= 2x12.5 mg (25mg total).
Phase 3 Studies (Panic Disorder)	
494 (U.S.)	Randomized, double-blind, placebo-controlled, flexible dose study in 283 outpatients; dose=12.5 to 75mg once daily; 10 weeks duration.
495 (U.S.)	Randomized, double-blind, placebo-controlled, flexible dose study in 321 outpatients; dose=12.5 to 75mg once daily; 10 weeks duration.
497 (U.S./Canada)	Randomized, double-blind, placebo-controlled, flexible dose study in 285 outpatients; dose=12.5 to 75mg once daily; 10 weeks duration.

TABLE 5.1.1.2		
	Paroxetine CR	**Placebo**
Phase 1		
Single Dose	80	0
Phase 3		
494, 495, 497	444	445
Phase 1 + Phase 3 Combined		
Grand Total	524	445

TABLE 5.1.2.1 DEMOGRAPHIC CHARACTERISTICS: PHASE 3 STUDIES		
	Paroxetine CR (n=444)	**Placebo (n=445)**
Enumeration (%) by Age Group		
18-24	40 (9%)	54 (12%)
25-34	148 (33%)	129 (29%)
35-44	138 (31%)	137 (31%)
45-54	88 (20%)	92 (21%)
55-65	30 (7%)	32 (7%)
>65	0 (0%)	1 (<1%)
Age (yrs)		
Mean	37.57	37.82
Range	19-65	19-72
Gender		
Male	162 (36%)	194 (44%)
Female	282 (64%)	251 (56%)
Race		
White	380 (86%)	389 (87%)
Non-White	64 (14%)	56 (13%)
Weight (lbs)		
Mean	170	175
Range	93-435	98-383

Table 5.1.3.1: Number (Percentage) of Patients by Daily Dosage Level and Duration of Exposure to Each Level (Phase 3 Studies)

Days Exposure:	1-7		8-14		15-21		22-28		29-35		36-42		43-56		57-70		>70		Total	
Daily Dose Level (mg/d)	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Paroxetine CR																				
Dose Level																				
1 (12.5mg)	308	69.4	119	26.8	3	0.7	1	0.2	2	0.5	2	0.5	1	0.2	8	1.8	0	0	444	100.0
2 (25.0mg)	180	43.2	109	26.1	33	7.9	8	1.9	10	2.4	7	1.7	17	4.1	50	12.0	3	0.7	417	93.9
3 (37.5mg)	118	38.1	83	26.8	35	11.3	14	4.5	9	2.9	10	3.2	27	8.7	14	4.5	0	0	310	69.8
4 (50.0mg)	80	35.6	56	24.9	24	10.7	18	8.0	15	6.7	15	6.7	17	7.6	0	0	0	0	225	50.7
5 (62.5mg)	51	35.4	35	24.3	16	11.1	20	13.9	9	6.3	8	5.6	5	3.5	0	0	0	0	144	32.4
6 (75.0mg)	8	9.4	10	11.8	8	9.4	10	11.8	34	40.0	12	14.1	3	3.5	0	0	0	0	85	19.1
Placebo																				
1	311	69.9	127	28.5	4	0.9	0	0	0	0	1	0.2	0	0	2	0.4	0	0	445	100.0
2	221	51.0	112	25.9	36	8.3	14	3.2	5	1.2	8	1.8	8	1.8	28	6.5	1	0.2	433	97.3
3	171	45.1	106	28.0	36	9.5	13	3.4	13	3.4	13	3.4	21	5.5	6	1.6	0	0	379	85.2
4	123	41.1	88	29.4	30	10.0	17	5.7	20	6.7	12	4.0	9	3.0	0	0	0	0	299	67.3
5	94	41.4	72	31.7	23	10.1	11	4.8	10	4.4	15	6.6	2	0.9	0	0	0	0	227	51.0
6	7	4.5	31	19.7	12	7.6	13	8.3	60	38.2	32	20.4	2	1.3	0	0	0	0	157	35.3

Data Source: ISS Table 4.3.1 in Section 21.1

APPENDIX 7.2.1

STUDY 494: EFFICACY

Table 7.2.1.1
Study 494 Investigators

Investigator	Site	Institution	Location
Jeffrey T. Apter, MD	001	Princeton Biomedical Research	Princeton, NJ
Robert J. Bielski, MD	002	Institute for Health Studies	Okemos, MI
James D. Brenner, MD	003	Brenner Research Institute	Olympia, WA
Alexander Bystritsky, MD	004	University of California, Los Angeles	Los Angeles, CA
John S. Carman, MD	005	Carman Research	Atlanta, GA
Mukesh R. Dave, MD	006	Neuman Biomedical Research	Bryan, TX
Alan D. Feiger, MD	007	Peiger Health Research Center	Wheat Ridge, CO
Saul H. Helfing, MD	008	Hill Top Research, Inc.	Portland, OR
Eric Hollander, MD	009	Mt. Sinai School of Medicine	New York, NY
Carl A. Houck, MD	010	University of Alabama at Birmingham, School of Medicine	Birmingham, AL
James W. Jefferson, MD	011	Dean Foundation for Health, Research and Education	Madison, WI
Barbara L. Kennedy, MD, PhD	012	University of Louisville School of Medicine	Louisville, KY
Peter D. Lundborg, MD	013	Seattle Clinical Research Center, Inc.	Seattle, WA
Kevin B. Miller, MD Joan Busner, PhD Jeff Gill, PhD	014	St. Louis University, Health Sciences Center	St. Louis, MO
Dennis M. Pavlinac, MD	015	Private Practice	Oceanside, CA
William S. Rea, MD	016	Clinical Studies	Ft. Lauderdale, FL
Eric M. Reiman, MD	017	Good Samaritan Regional Medical Center, Samaritan Behavioral Health	Phoenix, AZ
Edward Sweizer, MD [a]	018	University PA Science Center	Philadelphia, PA
David V. Sheehan, MD, MBA	019	University of South Florida, College of Medicine	Tampa, FL
Richard C. Shelton, MD	020	Vanderbilt University	Nashville, TN
Ward T. Smith, MD	021	Pacific Northwest Clinical Research	Portland, OR
Murray B. Stein, MD, BSc (Med)	022	Univ. California San Diego Dept of Psychiatry	La Jolla, CA
Steven D. Targum, MD	023	Delaware Valley Clinical Studies Center	Philadelphia, PA
Peter M. Thompson, MD, MS	024	University of New Mexico Health Sciences Center	Albuquerque, NM
Madhukar H. Trivedi, MD	025	University of Texas, Southwestern Medical Center	Dallas, TX
Karen L. Weihs, MD	026	George Washington University Medical Center	Washington, DC
Charles H. Meredith, MD	027	Affiliated Research Institute	San Diego, CA
Patrick J. Donley, MD	028	Puget Sound Medical Research, a Subsidiary of Hill Top Research, Inc.	Tacoma, WA
Jeffrey S. Simon, MD	029	Northbrooke Research Center	Brown Deer, WI
Barnett M. Kaplan, MD	030	Private Practice	Renton, WA
Madelon Hanford, MD	031	Hanford Research Group	Cincinnati, OH
Jeffrey Mattes, MD	032	Psychopharmacology Research Associates of Princeton	Princeton, NJ
Larry M. Davis, MD	033	The Davis Psychiatric Clinic, Inc.	Indianapolis, IN

Source: Appendix A, Investigator CV
a Screening only patients

TABLE 7.2.1.2: STUDY 494 PATIENT DEMOGRAPHICS (ALL CENTERS)							
Treatment	ITT	Age (years)		Gender [n(%)]		Race [n(%)]	
		Mean	Range	Male	Female	White	Non-white
Paroxetine CR	139	38.1	19-63	58(42%)	81(58%)	117(84%)	22(16%)
Placebo	144	37.0	20-61	64(44%)	80(56%)	135(94%)	9(6%)

TABLE 7.2.1.3: STUDY 494 NUMBER OF ITT PATIENTS IN-STUDY OVER TIME						
	Baseline	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10
Paroxetine CR	139	118	113	108	104	103
Placebo	144	128	117	112	109	109

Table 7.2.1.4: Study 494
Full Panic Attacks
Response Rate Reduced to Zero Attacks
Adjusting for the Effect of Center Group Only
Excluding Center 033
Statistical Analysis presented at all Time Points
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons
	Paroxetine CR			Placebo			Paroxetine CR vs Placebo
	n	%	N	n	%	N	Odds Ratio (95% C.I.) p-value
Weeks 1 and 2	24	20.2%	119	34	26.8%	127	0.665 (0.363, 1.219) 0.187
Weeks 3 and 4	53	48.2%	110	42	36.5%	115	1.617 (0.944, 2.771) 0.080
Weeks 5 and 6	63	63.6%	99	52	49.1%	106	1.827 (1.040, 3.210) 0.036
Weeks 7 and 8	71	75.5%	94	57	55.3%	103	2.582 (1.393, 4.785) 0.003
Weeks 9 and 10	69	78.4%	88	61	59.2%	103	2.542 (1.332, 4.851) 0.005
Week 10 End Point	84	68.9%	122	66	50.4%	131	2.182 (1.303, 3.654) 0.003

Table 7.2.1.5: Study 494
Baseline and Change from Baseline in Total Number of Full Panic Attacks
Excluding Center 033
Intention to Treat Population

	Treatment Groups				Pairwise Comparisons	
	Paroxetine CR		Placebo		Paroxetine CR vs Placebo	
	Median (Min,Max)	N	Median (Min,Max)	N	Median (95% C.I.)	p-value
Baseline	5 (,)	122	5 (,)	128		
Weeks 1 and 2	-3 (,)	119	-2 (,)	124		
Weeks 3 and 4	-4 (,)	110	-3 (,)	113		
Weeks 5 and 6	-4 (,)	99	-3 (,)	105		
Weeks 7 and 8	-5 (,)	94	-3 (,)	102		
Weeks 9 and 10	-5 (,)	88	-3 (,)	102	-1 (-2, 0)	0.072
Week 10 End Point	-4 (,)	122	-3 (,)	128	-1 (-2, 0)	0.080

Table 7.2.1.6: Study 494
Baseline and Change from Baseline in CGI Severity of Illness Score
Excluding Center 033
Intention to Treat Population

	Treatment Groups				Pairwise Comparisons	
	Paroxetine CR		Placebo		Paroxetine CR vs Placebo	
	Median (Min,Max)	N	Median (Min,Max)	N	Median (95% C.I.)	p-value
Baseline	4 ( )	132	4 ( )	138		
Week 1	0 ( )	128	0 ( )	136		
Week 2	0 ( )	116	-1 ( )	125		
Week 3	-1 ( )	109	-1 ( )	120		
Week 4	-1 ( )	112	-1 ( )	116		
Week 5	-1 ( )	106	-1 ( )	108		
Week 6	-1 ( )	101	-1 ( )	110		
Week 8	-1 ( )	101	-1 ( )	109		
Week 10	-2 ( )	93	-1 ( )	104	0 (-1,0.0)	0.007
Week 10 End Point	-1 ( )	132	-1 ( )	138	0 (-1,0.0)	0.032

Table 7.2.1.7: Study 494
Summary Statistics for Baseline and Change from Baseline in Percentage of Time per Day with Anticipatory Anxiety
Adjusting for the Effect of Center Group Only
Excluding Center 033
Statistical Analysis presented at all Time Points
Intention to Treat Population

	Treatment Groups		Pairwise Comparisons	
	Paroxetine CR	Placebo	Paroxetine CR vs Placebo	
	Mean (s.e.) N	Mean (s.e.) N	Mean (95% C.I.)	p-value
Baseline	26.2 (2.01) 122	26.0 (2.03) 128		
Weeks 1 and 2	-3.5 (0.97) 119	-3.5 (0.95) 124	-0.0 (-2.67, 2.61)	0.980
Weeks 3 and 4	-9.2 (1.35) 109	-6.8 (1.34) 113	-2.4 (-6.09, 1.30)	0.202
Weeks 5 and 6	-11.5 (1.57) 99	-8.6 (1.54) 105	-3.0 (-7.19, 1.28)	0.170
Weeks 7 and 8	-12.6 (1.86) 94	-10.3 (1.82) 102	-2.2 (-7.20, 2.74)	0.377
Weeks 9 and 10	-14.9 (1.92) 88	-11.1 (1.80) 102	-3.9 (-8.96, 1.21)	0.135
Week 10 End Point	-13.7 (1.62) 122	-9.8 (1.59) 128	-4.0 (-8.35, 0.44)	0.078

Table 7.2.1.8: Study 494
Marks Sheehan Phobia Scale (MSPS)
Summary Statistics for Baseline and Change from Baseline in Total Fear Score
Adjusting for the Effect of Center Group Only
Statistical Analysis presented at all Time Points
Excluding Center 033
Intention to Treat Population

	Treatment Groups		Pairwise Comparisons
	Paroxetine CR	Placebo	Paroxetine CR vs Placebo
	Mean (s.e.) N	Mean (s.e.) N	Mean (95% C.I.) p-value
Baseline	43.0 (2.24) 114	43.5 (2.04) 126	
Week 6	-16.8 (2.21) 91	-13.6 (2.19) 97	-3.2 (-9.16, 2.68) 0.282
Week 10	-21.5 (2.34) 89	-17.8 (2.21) 101	-3.8 (-10.00, 2.48) 0.235
Week 10 End Point	-20.7 (2.03) 114	-15.0 (1.93) 126	-5.7 (-11.11, -0.26) 0.040

Table 7.2.1.9: Study 494
Marks Sheehan Phobia Scale (MSPS)
Summary Statistics for Baseline and Change from Baseline in Total Avoidance Score
Adjusting for the Effect of Center Group Only
Excluding Center 033
Statistical Analysis presented at all Time Points
Intention to Treat Population

	Treatment Groups		Pairwise Comparisons	
	Paroxetine CR	Placebo	Paroxetine CR vs Placebo	
	Mean (s.e.) N	Mean (s.e.) N	Mean (95% C.I.)	p-value
Baseline	15.1 (0.87) 114	15.3 (0.81) 125		
Week 6	-4.6 (0.90) 91	-4.8 (0.90) 96	0.1 (-2.29, 2.56)	0.910
Week 10	-6.9 (0.86) 89	-6.3 (0.81) 100	-0.7 (-2.98, 1.61)	0.557
Week 10 End Point	-6.8 (0.75) 114	-5.3 (0.72) 125	-1.5 (-3.52, 0.49)	0.139

APPENDIX 7.2.2

STUDY 495: EFFICACY

Table 7.2.2.1:
Study 495 Investigators

Investigator	Site	Institution	Location
Lawrence W. Adler, M.D.	001	Clinical Insights, Inc.	Glen Burnie, MD
Bernard D. Beitman, M.D.	002	University of Missouri	Columbia, MO
Jon Andrew Bell, M.D.	003	University of Colorado, School	Denver, CO
William J. Burke, M.D.	004	University of Nebraska	Omaha, NE
Larry M. Davis, M.D.	005	Davis Psychiatric Clinic, Inc.	Indianapolis, IN
Robert L. DuPont, M.D.	006	Institute for Behavior and	Rockville, MD
Donald Linklater England, M.D.	007	Peace Health Medical Group	Eugene, OR
James M. Ferguson, M.D.	008	Pharmacology Research Corp.	Las Vegas, NV
Jack Matthew Gorman, M.D.	009	Phobia Clinic, Hillside	Glen Oaks, NY
James T. Hartford, M.D.	010	Hartford Research Group	Dayton, OH
Jon Franklin Heiser, M.D.	011	Pharmacology Research	Newport Beach,
Amir H. Kalali, M.D.	012	UC-Irvine College of	Irvine, CA
Jeffrey A. Matles, M.D.	013	Psychopharmacology Research	Princeton, NJ
Charles B. Nemeroff, M.D.,	014	Emory University, Department	Atlanta, GA
William M. Patterson, M.D.	016	Birmingham Research Group	Birmingham, AL
Mark H. Pollack, M.D.	017	Massachusetts General	Boston, MA
Harvey Resnick, M.D.	018	R/D Clinical Research Inc.	Lake Jackson, TX
Murray Hal Rosenthal, D.O.	019	Behavioral and Medical	San Diego, CA
Steven K. Strawn, M.D.	020	Freedom Research	College Station,
Nicholas William Telew, M.D.	021	Oregon Center for Clinical	Eugene, OR
Richard Templeton, M.D.	022	Psychiatric Research Group	Annapolis, MD
Phebe Tucker, M.D.	023	University of Oklahoma	Oklahoma City,
Richard H. Weisler, M.D.	024	900 Ridgefield Drive, Suite	Raleigh, NC
Kenneth J. Weiss, M.D.,	025	Delaware Valley Research	King of Prussia,
Lorna P. Charles, M.D.	026	Southern NJ Medical Institute	Stratford, NJ
Lynn A. Cunningham, M.D.	027	Vine St. Clinical Research	Springfield, IL
Jack M. Stack, M.D.	028	Gratiot Community Hospital	Alma, MI
Susanna Goldstein, M.D.	030	Center for Psychobiology	New York, NY
Randall R. Stoltz, M.D.	031	GFI Pharmaceutical Services,	Evansville, IN

Source: Curriculum Vitae, Appendix A

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TABLE 7.2.2.2: STUDY 495 PATIENT DEMOGRAPHICS (ALL CENTERS)							
Treatment	ITT	Age (years)		Gender [n(%)]		Race [n(%)]	
		Mean	Range	Male	Female	White	Non-white
Paroxetine CR	158	37	19-62	53(34%)	105(66%)	146(92%)	12(8%)
Placebo	163	37	19-72	60(37%)	103(63%)	146(90%)	17(10%)

TABLE 7.2.2.3: STUDY 495 NUMBER OF ITT PATIENTS IN-STUDY OVER TIME						
	Baseline	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10
Paroxetine CR	158	135	124	114	107	106
Placebo	163	152	148	134	126	124

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Table 7.2.2.4: Study 495
Full Panic Attacks
Response Rate Reduced to Zero Attacks
Adjusting for the Effect of Center Group Only
Excluding Center 005
Statistical Analysis presented at all Time Points
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons	
	Paroxetine CR			Placebo			Paroxetine CR vs Placebo	
	n	%	N	n	%	N	Odds Ratio (95% C.I.)	p-value
Weeks 1 and 2	14	11.8%	119	22	16.3%	135	0.693 (0.334, 1.441)	0.327
Weeks 3 and 4	41	40.6%	101	49	38.6%	127	1.084 (0.633, 1.856)	0.768
Weeks 5 and 6	55	59.8%	92	48	44.4%	108	1.985 (1.104, 3.570)	0.022
Weeks 7 and 8	58	64.4%	90	60	56.1%	107	1.458 (0.811, 2.623)	0.208
Weeks 9 and 10	60	71.4%	84	55	55.6%	99	2.022 (1.084, 3.774)	0.027
70% End Point	68	53.1%	128	69	49.3%	140	1.177 (0.727, 1.907)	0.507
Week 10 End Point	73	57.0%	128	70	50.0%	140	1.325 (0.816, 2.149)	0.255

Table 7.2.2.5: Study 495
Baseline and Change from Baseline in Total Number of Full Panic Attacks
Excluding Center 005
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons Paroxetine CR vs Placebo			
	Paroxetine CR			Placebo						
	Median	(Min,Max)	N	Median	(Min,Max)	N	Median	(95% C.I.)		p-value
Baseline	7	(,)	123	5	(,)	136				
Weeks 1 and 2	-2	(,)	116	-2	(,)	132				
Weeks 3 and 4	-5	(,)	96	-3	(,)	124				
Weeks 5 and 6	-5	(,)	87	-3	(,)	105				
Weeks 7 and 8	-6	(,)	86	-3	(,)	106				
Weeks 9 and 10	-6	(,)	80	-3	(,)	98	-3	(-5,	-1)	<0.001
70% End Point	-5	(,)	123	-3	(,)	136	-2	(-3,	-1)	<0.001
Week 10 End Point	-5	(,)	123	-3	(,)	136	-2	(-4,	-1)	<0.001

Table 7.2.2.6: Study 495
Baseline and Change from Baseline in CGI Severity of Illness Score
Excluding Center 005
Intention to Treat Population

	Treatment Groups				Pairwise Comparisons		
	Paroxetine CR		Placebo		Paroxetine CR vs Placebo		
	Median (Min,Max)	N	Median (Min,Max)	N	Median (95% C.I.)	p-value	
Baseline	4 ( )	137	4 ( )	147			
Week 1	0 ( )	134	0 ( )	144			
Week 2	0 ( )	121	0 ( )	135			
Week 3	-1 ( )	119	-1 ( )	130			
Week 4	-1 ( )	101	-1 ( )	128			
Week 5	-1 ( )	101	-1 ( )	123			
Week 6	-2 ( )	91	-1 ( )	110			
Week 8	-2 ( )	95	-1 ( )	119			
Week 10	-2 ( )	85	-1 ( )	101	-1 (-1, -1)	<0.001	
70% End Point	-1 ( )	137	-1 ( )	147	0 (-1,0.0)	0.007	
Week 10 End Point	-2 ( )	137	-1 ( )	147	0 (-1,0.0)	0.004	

Table 7.2.2.7: Study 495

Summary Statistics for Baseline and Change from Baseline in Percentage of Time per Day with Anticipatory Anxiety
Adjusting for the Effect of Center Group Only
Excluding Center 005
Statistical Analysis presented at all Time Points
Intention to Treat Population

	Treatment Groups				Pairwise Comparisons	
	Paroxetine CR		Placebo		Paroxetine CR vs Placebo	
	Mean (s.e.)	N	Mean (s.e.)	N	Mean (95% C.I.)	p-value
Baseline	29.0 (2.10)	122	24.5 (1.79)	136		
Weeks 1 and 2	-2.9 (1.09)	115	-1.8 (1.01)	132	-1.1 (-3.97, 1.79)	0.457
Weeks 3 and 4	-9.9 (1.52)	96	-5.4 (1.33)	124	-4.5 (-8.43, -0.58)	0.025
Weeks 5 and 6	-14.5 (1.77)	87	-8.1 (1.60)	105	-6.3 (-10.93, -1.73)	0.007
Weeks 7 and 8	-15.9 (1.93)	86	-9.5 (1.71)	106	-6.4 (-11.36, -1.52)	0.011
Weeks 9 and 10	-17.4 (1.84)	80	-8.3 (1.64)	98	-9.0 (-13.78, -4.31)	<0.001
70% End Point	-13.1 (1.53)	122	-7.6 (1.45)	136	-5.5 (-9.60, -1.43)	0.008
Week 10 End Point	-14.1 (1.59)	122	-7.9 (1.51)	136	-6.1 (-10.38, -1.87)	0.005

Table 7.2.2.8: Study 495
Marks Sheehan Phobia Scale (MSPS)
Summary Statistics for Baseline and Change from Baseline in Total Fear Score
Adjusting for the Effect of Center Group Only
Statistical Analysis presented at all Time Points
Excluding Center 005
Intention to Treat Population

	Treatment Groups		Pairwise Comparisons	
	Paroxetine CR	Placebo	Paroxetine CR vs Placebo	
	Mean (s.e.) N	Mean (s.e.) N	Mean (95% C.I.)	p-value
Baseline	45.9 (2.19) 118	44.3 (2.00) 132		
Week 6	-15.0 (1.90) 80	-10.2 (1.75) 93	-4.8 (-9.75, 0.22)	0.061
Week 10	-22.9 (2.37) 82	-12.8 (2.16) 97	-10.1 (-16.32, -3.86)	0.002
Week 10 End Point	-19.3 (1.95) 118	-11.7 (1.84) 132	-7.7 (-12.87, -2.49)	0.004

Table 7.2.2.9: Study 495
Marks Sheehan Phobia Scale (MSPS)
Summary Statistics for Baseline and Change from Baseline in Total Avoidance Score
Adjusting for the Effect of Center Group Only
Excluding Center 005
Statistical Analysis presented at all Time Points
Intention to Treat Population

	Treatment Groups		Pairwise Comparisons
	Paroxetine CR	Placebo	Paroxetine CR vs Placebo
	Mean (s.e.) N	Mean (s.e.) N	Mean (95% C.I.) p-value
Baseline	16.4 (0.83) 118	15.3 (0.83) 132	
Week 6	-5.0 (0.77) 80	-2.8 (0.71) 93	-2.2 (-4.23, -0.19) 0.032
Week 10	-7.9 (0.87) 81	-4.0 (0.79) 97	-3.9 (-6.18, -1.61) <0.001
Week 10 End Point	-6.8 (0.71) 118	-3.8 (0.67) 132	-3.1 (-4.98, -1.18) 0.002

APPENDIX 7.2.3

STUDY 497: EFFICACY

Table 7.2.3.1:
Study 497 Investigators

Investigator	Site	Institution	Location
Ilgin Rastgi, M.D.	001	North East Ohio Health Services	Beachwood, OH
David Brown, M.D.	002	Community Clinical Research	Austin, TX
Joseph Baugher Beyer, M.D.	003	Clary Research Associates	New Castle, DE
Cal K. Cobb, M.D.	004	Hauser Clinic	Houston, TX
Alan Gelenberg, M.D. Pedro L. Delgado, M.D.	005	University of Arizona Health Science Center	Tucson, AZ
Eugene A. DuBoff, M.D.	006	Center for Behavioral Medicine	Denver, CO
James Mecham Ferguson, M.D.	007	Pharmacology Research Corporation	Salt Lake City, UT
Gregory Hantzer, M.D.	008	Miami Sinai Medical Center	Miami Beach, FL
Peter J. Holland, M.D., F.A.C.O.E.M., F.A.P.A.	009	Private Practice	*Boca Raton, FL*
Richard J. Kavanagi, M.D.	010	Allegheny University of the Health Sciences	Philadelphia, PA
Arifulla Khan, M.D.	011	Northwest Psychiatric Institute, Inc. PC	Kirkland, WA
Ronald P. Landblum, M.D.	012	St. Paul-Ramsey Medical Center	St. Paul, MN
Randall H. Leefelda, M.D.	013	Sutter Institute for Medical Research	Sacramento, CA
Robert Bruce Lydiard, Ph.D., M.D	014	Medical University of South Carolina	Charleston, SC
Dennis J. Murjack, M.D. John J. Murphy, M.D.	015	Southwestern Research Institute	Beverly Hills, CA
Frederick W. Reichert, M.D.	016	University of Utah Health Sciences Center	Salt Lake City, UT
Robert A. Rissenberg, M.D.	017	BioBehavioral Research Center	Decatur, GA
Peter C. Schram, M.D.	018	Menninger Clinic	Topeka, KS
JoAnne Santo, Ph.D. Leslie Seiden, M.D.	019	Center for Research in Anxiety, Inc.	New York, NY
George M. Simpson, M.D.	020	LAC - USC Medical Center	Los Angeles, CA
Harold David Udelman, M.D., F.A.P.A., P.A.P.M.	022	Psychiatric Research Network	Peoria, AZ
Dan L. Zimbroff, M.D.	023	Behavioral Medicine Center	Upland, CA
Pedro Melchor, M.D.	029	PharmaResearch, Inc.	Pinecrest, FL
Kenneth Neil Sokoloff, M.D. M.S.	031	Affiliated Research Institute	Santa Ana, CA
Shirvan Kazim Mahmud, M.B., Ch.B., F.R.C.P., L.M.C.C.	024	Private Practice	Saskatoon, Saskatchewan
Dr. Charles Henri Ragnar Lafreniere	025	Samson Lejeunesse Assoc.	Sillery, Quebec
Paul Stanley Morris, M.D.	026	Private Practice	Etobicoke, Ontario
Dr. Pierre Savard, Ph.D.	027	Private Practice	Montreal, Quebec
Peter G. Turner, M.B., Ch.B., F.R.C.P.C.	028	Private Practice	Burlington, Ontario

Source: Curriculum vitae, Appendix A

APPEARS THIS WAY
ON ORIGINAL

TABLE 7.2.3.2: STUDY 497 PATIENT DEMOGRAPHICS							
Treatment	ITT	Age (years)		Gender [n(%)]		Race [n(%)]	
		Mean	Range	Male	Female	White	Non-white
Paroxetine CR	147	38	20-65	51(35%)	96(65%)	117(80%)	30(20%)
Placebo	138	40	19-64	70(51%)	68(49%)	108(78%)	30(22%)

TABLE 7.2.3.3: STUDY 497 NUMBER OF ITT PATIENTS IN-STUDY OVER TIME						
	Baseline	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10
Paroxetine CR	147	130	120	117	105	103
Placebo	138	128	119	106	99	96

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Table 7.2.3.4: Study 497
Full Panic Attacks
Response Rate Reduced to Zero Attacks
Adjusting for the Effect of Center Group Only
Statistical Analysis presented at all Time Points
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons	
	Paroxetine CR			Placebo			Paroxetine CR vs Placebo	
	n	%	N	n	%	N	Odds Ratio (95% C.I.)	p-value
Weeks 1 and 2	29	22.8%	127	31	25.2%	123	0.895 (0.491, 1.629)	0.716
Weeks 3 and 4	51	43.6%	117	44	38.6%	114	1.203 (0.697, 2.079)	0.507
Weeks 5 and 6	69	63.9%	108	63	58.3%	108	1.330 (0.745, 2.375)	0.334
Weeks 7 and 8	74	73.3%	101	52	56.5%	92	2.154 (1.150, 4.036)	0.017
Weeks 9 and 10	68	70.1%	97	63	65.6%	96	1.224 (0.651, 2.302)	0.530
Week 10 End Point	84	62.7%	134	73	56.2%	130	1.362 (0.822, 2.257)	0.230

Table 7.2.3.5: Study 497
Baseline and Change from Baseline in Total Number of Full Panic Attacks
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons Paroxetine CR vs Placebo				
	Paroxetine CR			Placebo							
	Median	(Min,Max)	N	Median	(Min,Max)	N	Median	(95% C.I.			p-value
Baseline	5	( )	132	4	( )	130					
Weeks 1 and 2	-2	( )	125	-2	( )	123					
Weeks 3 and 4	-4	( )	115	-2.5	( )	114					
Weeks 5 and 6	-4	( )	106	-3	( )	108					
Weeks 7 and 8	-4	( )	99	-3	( )	92					
Weeks 9 and 10	-4	( )	95	-3	( )	96	-1	(-2,	0)		0.088
Week 10 End Point	-4	( )	132	-3	( )	130	-1	(-2,	0)		0.239

Table 7.2.3.6: Study 497
Baseline and Change from Baseline in CGI Severity of Illness Score
Intention to Treat Population

	Treatment Groups				Pairwise Comparisons	
	Paroxetine CR		Placebo		Paroxetine CR vs Placebo	
	Median (Min,Max)	N	Median (Min,Max)	N	Median (95% C.I.)	p-value
Baseline	4 ( )	144	4 ( )	136		
Week 1	0 ( )	142	0 ( )	136		
Week 2	0 ( )	128	0 ( )	122		
Week 3	-1 ( )	123	-1 ( )	120		
Week 4	-1 ( )	114	-1 ( )	116		
Week 5	-1 ( )	111	-1 ( )	110		
Week 6	-1 ( )	108	-1 ( )	110		
Week 8	-1 ( )	114	-1 ( )	101		
Week 10	-2 ( )	98	-1 ( )	96	0 (-1,0.0)	0.122
Week 10 End Point	-1 ( )	144	-1 ( )	136	0 (-1,0.0)	0.078

Table 7.2.3.7: Study 497

Summary Statistics for Baseline and Change from Baseline in Percentage of Time per Day with Anticipatory Anxiety
Adjusting for the Effect of Center Group Only
Statistical Analysis presented at all Time Points
Intention to Treat Population

	Treatment Groups		Pairwise Comparisons	
	Paroxetine CR	Placebo	Paroxetine CR vs Placebo	
	Mean (s.e.) N	Mean (s.e.) N	Mean (95% C.I.)	p-value
Baseline	25.6 (1.94) 132	27.4 (2.12) 130		
Weeks 1 and 2	-3.0 (1.11) 125	-2.6 (1.12) 123	-0.3 (-3.38, 2.71)	0.831
Weeks 3 and 4	-8.1 (1.21) 114	-4.0 (1.20) 114	-4.0 (-7.34, -0.72)	0.017
Weeks 5 and 6	-11.1 (1.45) 106	-8.1 (1.44) 107	-3.0 (-6.99, 0.95)	0.135
Weeks 7 and 8	-13.2 (1.68) 99	-9.3 (1.76) 92	-3.8 (-8.59, 0.90)	0.112
Weeks 9 and 10	-13.8 (1.76) 95	-10.1 (1.76) 96	-3.6 (-8.49, 1.22)	0.142
Week 10 End Point	-12.4 (1.50) 132	-8.7 (1.50) 130	-3.7 (-7.80, 0.41)	0.078

Table 7.2.3.8: Study 497
Marks Sheehan Phobia Scale (MSPS)
Summary Statistics for Baseline and Change from Baseline in Total Fear Score
Adjusting for the Effect of Center Group Only
Statistical Analysis presented at all Time Points
Intention to Treat Population

	Treatment Groups		Pairwise Comparisons	
	Paroxetine CR	Placebo	Paroxetine CR vs Placebo	
	Mean (s.e.) N	Mean (s.e.) N	Mean (95% C.I.)	p-value
Baseline	42.6 (2.25) 129	40.9 (1.94) 125		
Week 6	-14.9 (2.03) 87	-10.3 (2.11) 86	-4.6 (-10.32, 1.08)	0.112
Week 10	-19.1 (2.06) 89	-14.4 (2.07) 89	-4.7 (-10.38, 1.02)	0.107
Week 10 End Point	-19.6 (1.84) 129	-10.8 (1.86) 125	-8.7 (-13.81, -3.66)	<0.001

Table 7.2.3.9: Study 497
Marks Sheehan Phobia Scale (MSPS)
Summary Statistics for Baseline and Change from Baseline in Total Avoidance Score
Adjusting for the Effect of Center Group Only
Statistical Analysis presented at all Time Points
Intention to Treat Population

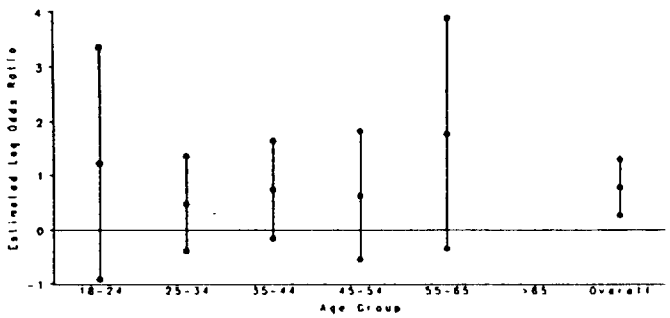
	Treatment Groups		Pairwise Comparisons
	Paroxetine CR	Placebo	Paroxetine CR vs Placebo
	Mean (s.e.) N	Mean (s.e.) N	Mean (95% C.I.) p-value
Baseline	15.4 (0.86) 128	15.2 (0.80) 125	
Week 6	-4.7 (0.87) 87	-3.1 (0.91) 85	-1.6 (-4.03, 0.86) 0.203
Week 10	-6.2 (0.79) 89	-4.4 (0.80) 88	-1.8 (-3.99, 0.39) 0.107
Week 10 End Point	-6.0 (0.68) 128	-3.3 (0.69) 125	-2.7 (-4.55, -0.79) 0.006

APPENDIX 7.3.1

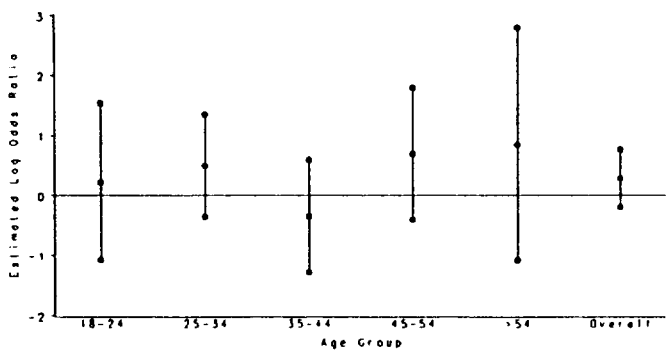
PREDICTORS OF RESPONSE

Figure 7.3.1.1 Natural Logarithm of Odds Ratio with 95% CI for Percentage Patients Free of Full Panic Attacks at Week 10 Endpoint by Age Group

Study 494 (excl. center 33)



Study 495 (excl. center 5)



Study 497

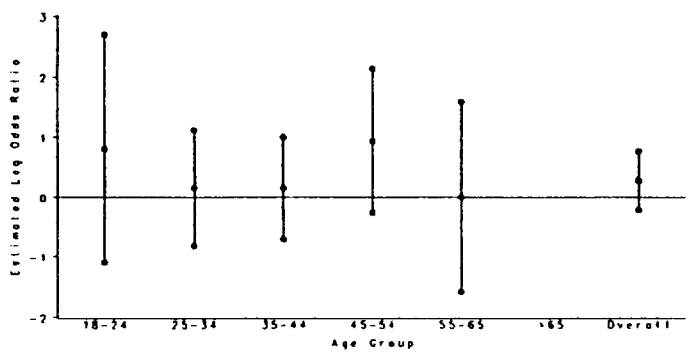
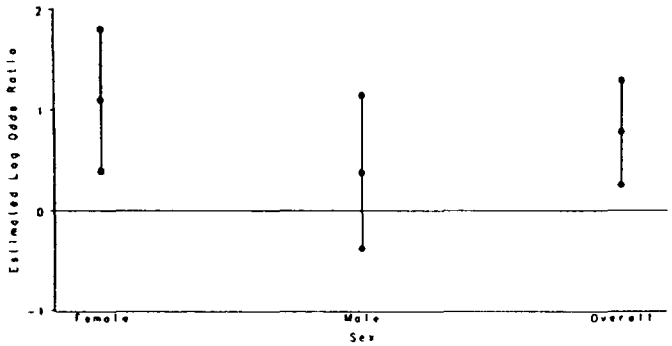
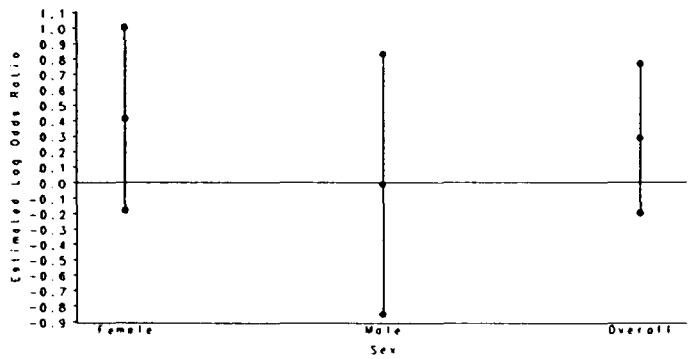


Figure 7.3.1.2 Natural Logarithm of Odds Ratio with 95% CI for Percentage Patients Free of Full Panic Attacks at Week 10 Endpoint by Gender

Study 494 (excl. center 33)



Study 495 (excl. center 5)



Study 497

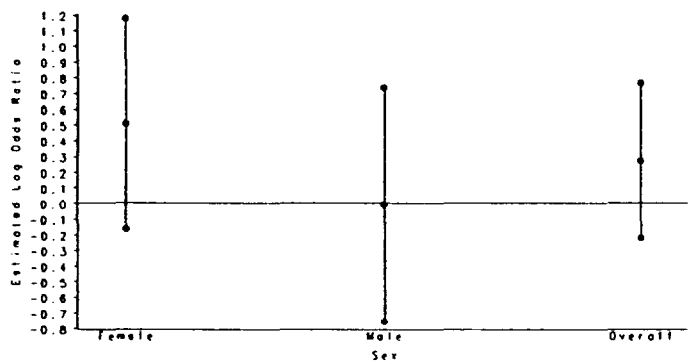
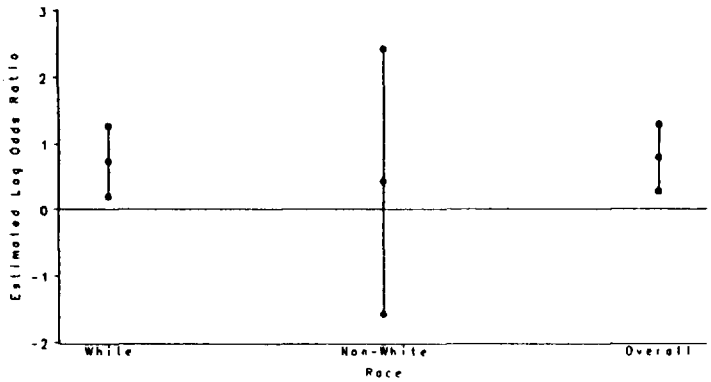
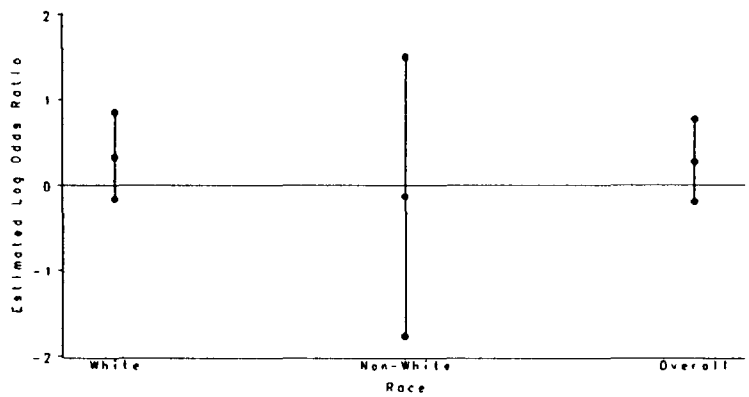


Figure 7.3.1.3 Natural Logarithm with 95% CI of Odds Ratio for Percentage Patients Free of Full Panic Attacks at Week 10 Endpoint by Race

Study 494 (excl. center 33)



Study 495 (excl. center 5)



Study 497

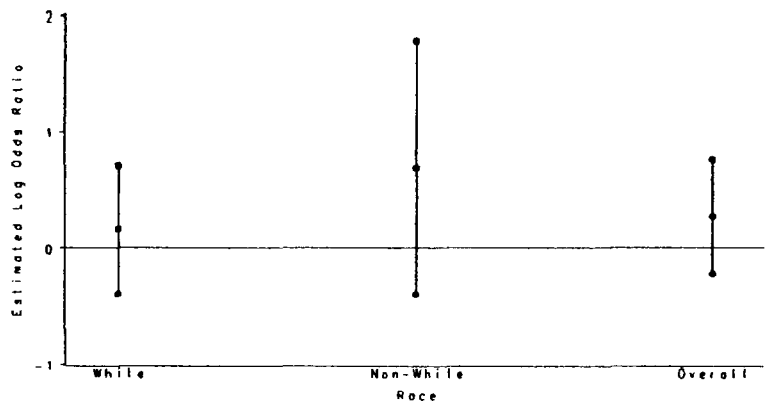
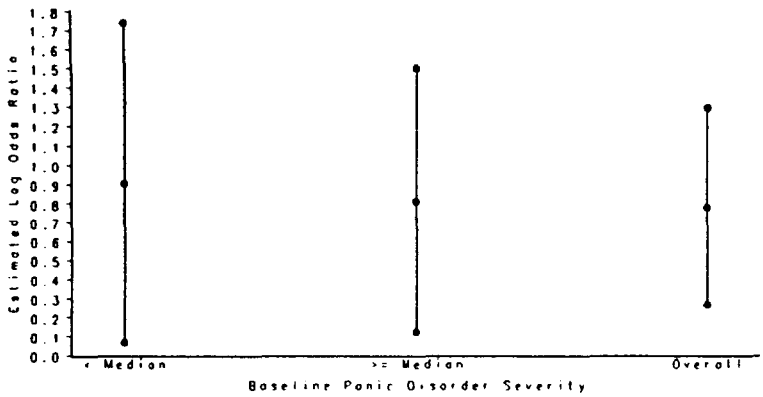
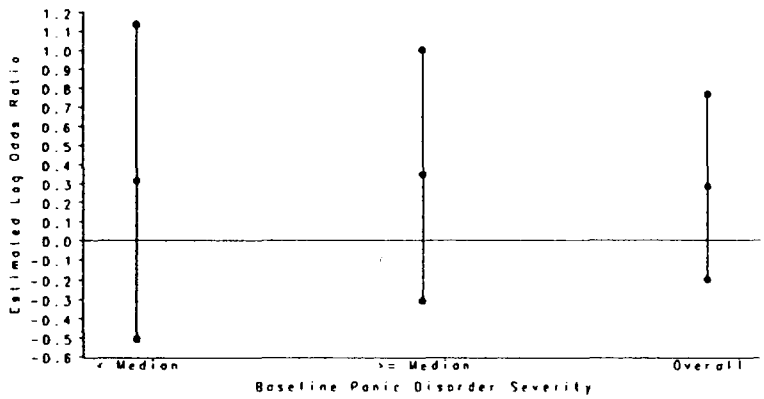


Figure 7.3.1.4 Natural Logarithm with 95% CI of Odds Ratio for Percentage Patients Free of Full Panic Attacks at Week 10 Endpoint by Severity of Panic Disorder at Baseline

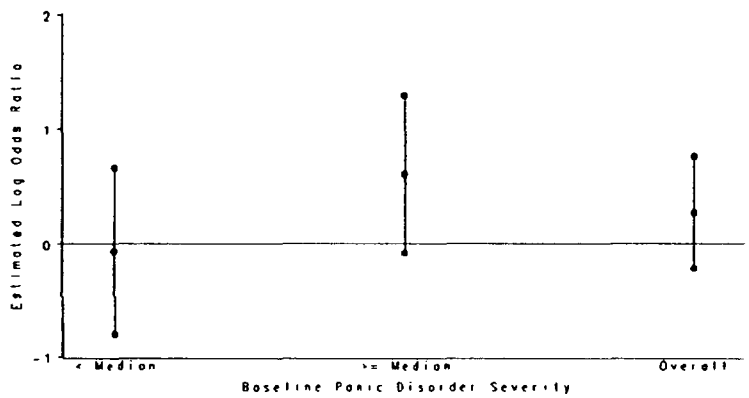
Study 494 (excl. center 33)



Study 495 (excl. center 5)



Study 497



APPENDIX 8.1

SAFETY FINDINGS

TABLE 8.1.2: Line Listing of Patients with Non-Fatal Serious Adverse Events (Studies 494, 495, and 497)					
Patient ID	**Age (yrs)**	**Sex**	**Dose at Onset (mg/day)**	**Day of Onset**	**Serious Event(s)**
Paroxetine CR					
494.021.00043	25	F	Unknown	Unknown	Ectopic pregnancy.
494.024.00345	48	F	Unknown	Unknown	Myoclonus.
494.027.00417	29	F	25	22	Acute anxiety reaction.
494.007.00024	29	F	Unknown	Unknown	Unintended pregnancy.
495.017.00934	22	F	Unknown	Unknown	Unintended pregnancy.
495.030.01095	33	M	37.5	37	Stab wound.
495.012.00994	33	M	25	43	Rhabdomyolysis.
495.028.01111	36	F	62.5	39	Depression.
497.004.01206	42	F	62.5	35	Unintended overdose.
497.002.02406	30	F	Unknown	Unknown	Unintended pregnancy.
Placebo					
494.022.00151	35	M	0	47	Agitation.
494.024.00518	21	F	0	Unknown	Unintended pregnancy.
494.025.00141	25	M	0	42	Arthritis.
495.009.00877	48	F	0	24	Traumatic bone fracture.
495.023.00968	42	F	0	37	Dyspepsia.
497.007.01428	21	F	0	~64	Unintended pregnancy.
494.027.00067	41	M	0	80	Kidney calculus (post-treatment).
497.004.01758	48	M	0	71	Pancreatitis (post-treatment)

TABLE 8.1.4.2: TREATMENT-EMERGENT ADVERSE EVENTS IN ≥1% OF PAROXETINE CR PATIENTS DURING THE TREATMENT PHASES OF STUDIES 494, 495, AND 497 [1,2]		
	% Reporting Event	
	Par CR (n=444)	Placebo (n=445)
Body as a Whole		
Asthenia	15%	10%
Abdominal Pain	6%	4%
Trauma[3]	5%	4%
Cardiovascular System		
Vasodilatation[4]	3%	2%
Digestive System		
Nausea	23%	17%
Dry Mouth	13%	9%
Diarrhea	12%	9%
Constipation	9%	6%
Decreased Appetite	8%	6%
Metabolic/Nutritional Disorders		
Weight Loss	1%	0%
Musculoskeletal System		
Myalgia	5%	3%
Nervous System		
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%

[1] Percentages are rounded to the nearest whole percent.
[2] Adverse events for which the paroxetine 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, vomiting.
[3] Various physical injuries.
[4] Mostly flushing.
[5] Mostly muscle tightness or stiffness.

TABLE 8.1.4.2: TREATMENT-EMERGENT ADVERSE EVENTS IN ≥1% OF PAROXETINE CR PATIENTS DURING THE TREATMENT PHASES OF STUDIES 494, 495, AND 497 [1,2]		
	% Reporting Event	
	Par CR (n=444)	Placebo (n=445)
Respiratory System		
Sinusitis	8%	5%
Yawning	3%	0%
Skin and Appendages		
Sweating	7%	2%
Special Senses		
Abnormal Vision[6]	3%	1%
Urogenital System		
Abnormal Ejaculation[7]	27%	3%
Impotence[7]	10%	1%
Female Genital Disorders[8,9]	7%	1%
Vaginitis[8]	1%	0%
Urinary Frequency	2%	1%
Urination Impaired	2%	0%

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[6] Mostly blurred vision.
[7] Based on the number of male patients.
[8] Based on the number of female patients.
[9] Mostly anorgasmia or difficulty achieving orgasm.

Table 8.1.4.5: Other Events Observed During Premarketing Panic Studies (494, 495, 497) with Paroxetine CR[10,11,12]
Body as a Whole
Abnormal laboratory value (+alprazolam on drug screen), accidental overdose, anaphylactoid reaction, cellulitis, chills, flu syndrome, malaise.
Cardiovascular System
Bradycardia, hemorrhage, hypertension, hypotension, palpitation, syncope.
Digestive System
Bruxism, digestive system disorder, dysphagia, eructation, gastroenteritis, gastrointestinal disorder, gingivitis, gum hyperplasia, increased salivation, liver function tests abnormal, melena, tooth disorder, ulcerative stomatitis.
Endocrine System
Testes disorder (testicular pain).
Hemic and Lymphatic System
Lymphadenopathy, purpura, thrombocytopenia.
Metabolic and Nutritional Disorders
Bilirubinemia, dehydration, generalized edema, hyperglycemia, hypokalemia, SGOT increased, SGPT increased, thirst, weight gain.
Musculoskeletal System
Arthralgia, arthritis, arthrosis, myopathy, myositis, tendinous disorder.
Nervous System
Alcohol abuse, amnesia, ataxia, convulsion, depersonalization, drug dependence, dystonia, emotional lability, hallucinations, hyperkinesia, hypesthesia, incoordination, lack of emotion, neuropathy, nystagmus, paralysis (facial weakness), paranoid reaction, withdrawal syndrome.
Respiratory System
Dyspnea, epistaxis, larynx disorder, pneumonia.
Skin and Appendages
Acne, alopecia, contact dermatitis, dry skin, eczema, fungal dermatitis, herpes simplex, photosensitivity, pruritis, rash, benign skin neoplasm, urticaria.

[10] Events listed in Table 8.1.4.2 are excluded.
[11] All events in this table were reported at a frequency between 1/100 and 1/1,000 within the pool of studies 494, 495, and 497 (N=444).
[12] Gender-specific event rates have been corrected for the number of males or females, as appropriate.

Special Senses
Ear pain, eye disorder, eye pain, keratoconjunctivitis, mydriasis, otitis externa, otitis media, photophobia, tinnitus, visual field defect.
Urogenital System
Albuminuria, amenorrhea, breast enlargement, breast pain, cystitis, dysuria, ectopic pregnancy, nocturia, pregnancy, prostate disorder, urinary retention, vaginal moniliasis.

Table 8.1.5.2 Predetermined Clinical Laboratory Values of Potential Clinical Concern

Hematology	
Hemoglobin - Male	≤ 115 gL
Hemoglobin - Female	≤ 95 gL
Hematocrit - Male	≤ 37%
Hematocrit - Female	≤ 32%
WBC	≤ 2.8 or ≥ 16.0 x109L
Lymphocytes	≥ 75%
Monocytes	≥ 15%
Basophils	≥ 10%
Eosinophils	≥ 10%
Platelets	≤ 75 or ≥ 700 x109L
Bands	≥ 10%
Segmented Neutrophils	≤ 15%
Blood Chemistry	
BUN (Blood Urea Nitrogen)	≥ 30 mgdL
Serum creatinine	≥ 2.3 mgdL
Total bilirubin	≥ 2.0 mgdL
SGOT (AST)	≥ 150 UL
SGPT (ALT)	≥ 165 UL
Alkaline phosphatase	≥ 390 UL
Chloride	≤ 90 or ≥118 mmolL
Potassium	≤ 3 or ≥ 6 mmolL
Sodium	≤ 126 or ≥ 156 mmolL

TABLE 8.1.5.3:
PROPORTIONS OF PATIENTS WITH LABORATORY VALUES OF POTENTIAL CLINICAL CONCERN
(STUDIES 494, 495, AND 497)

Test	Paroxetine CR			Placebo		
	N	n	%	N	n	%
↓Hemoglobin	444	1	<1%	445	0	0%
↓Hematocrit	444	2	<1%	445	2	<1%
↑Eosinophils	444	1	<1%	445	3	<1%
↓Platelets	444	1	<1%	445	1	<1%
↑Creatinine	444	0	0%	445	1	<1%
↑Bilirubin	444	1	<1%	445	1	<1%
↑AST	444	3	<1%	445	0	0%
↑ALT	444	4	<1%	445	0	0%
↓Chloride	444	1	<1%	445	0	0%

Key: N=total number of patients with test values.
n=number with values of potential clinical concern that emerged post-baseline.
%=(n/N)×100%.

Table 8.1.6.2: Vital Sign Values of Potential Clinical Concern

Systolic Blood Pressure	
Significant Increase	Increase of >= 40 mmHg from baseline
Significant Decrease	Decrease of >= 30 mmHg from baseline
Diastolic Blood Pressure	
Significant Increase	Increase of >= 30 mmHg from baseline
Significant Decrease	Decrease of >= 20 mmHg from baseline
Heart Rate	
Significant Increase	Increase of >= 30 bpm from baseline
Significant Decrease	Decrease of >= 30 bpm from baseline
Body Weight	
Significant Increase	Increase of >= 7% from baseline
Significant Decrease	Decrease of >= 7% from baseline

TABLE 8.1.6.3:
PROPORTIONS OF PATIENTS WITH VITAL SIGN MEASUREMENTS OF POTENTIAL CLINICAL CONCERN (STUDIES 494, 495, AND 497)

Sitting Diastolic BP (mmHg)

Treatment Group	Paroxetine CR		Placebo	
	N	%	N	%
Significant Increase	0	0.0	4	0.9
Significant Decrease	39	8.9	43	9.7
Number with Assessment	444	100.0	445	100.0

Sitting Systolic BP (mmHg)

Treatment Group	Paroxetine CR		Placebo	
	N	%	N	%
Significant Increase	1	0.2	5	1.1
Significant Decrease	19	4.3	20	4.5
Number with Assessment	444	100.0	445	100.0

Pulse (bpm)

Treatment Group	Paroxetine CR		Placebo	
	N	%	N	%
Significant Increase	10	2.3	17	3.8
Significant Decrease	7	1.6	8	1.8
Number with Assessment	444	100.0	445	100.0

Weight (lbs)

Treatment Group	Paroxetine CR		Placebo	
	N	%	N	%
Significant Increase	12	2.7	7	1.6
Significant Decrease	12	2.7	6	1.4
Number with Assessment	444	100.0	445	100.0

CENTER FOR DRUG EVALUATION AND RESEARCH

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

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA #	20-982
Applicant	SmithKline Beecham
Name of Drug	Paxil CR (paroxetine hydrochloride)
Indication	Panic Disorder with or without agoraphobia
Documents Reviewed	Volumes 1.001, 1.002, 1.041, 1.046, 1.049, 1.058, 1.065
Reviewer	Kallappa M. Koti (HFD-710)
Medical Officer	Dr. Greg Dubitsky

I. BACKGROUND AND INTRODUCTION

Panic Disorder is a significant public health issue worldwide. Its prevalence is estimated between 1.5 and 4.2%. It is estimated that up to 50% of patients with Panic Disorder also suffer from agoraphobia. Until the last several years, Panic Disorder has been treated primarily with benzodiazepines and tricyclic antidepressants etc. These medicines can produce a number of serious side effects. The need for effective and safe therapy for the treatment of Panic Disorder is paramount.

Paroxetine was first launched in the U.K. in 1991. It was approved for the treatment of depression in the U.S. in 1992, and more recently has been approved for the treatment of obsessive compulsive disorder and panic disorder. The immediate-release (IR) formulation of paroxetine has a favorable tolerability and overall safety profile. One of the most common side effects assocaited is that of nausea. It has been hypohesized that a reduction in the incidence of nausea could be achieved by controlling the rate and site of paroxetine absorption. A new formulation of paroxetine (paroxetine CR) was developed. Based upon the pharmacokinetic profile of paroxetine CR a decision was made to conduct Phase III studies with this formulation in panic disorder.

The Paroxetine Protocol 29060/494, 29060/495 & 29060/497 submitted by SmithKline Beecham is reviewed. The protocol deals with a multi-center, double-blind, placebo-controlled, flexible dosing identical t[illegible]. The term depression is defined as follows.
A major depressive episode implies a prominent and relatively persistent depressed mood or loss of interest or pleasure in usual activities, that usually interferes with daily functioning or causes clinically significant distress (nearly every day for at least 2 weeks); it should include at least 4 of the following symptoms: change in appetite or weight, change in sleep, psychomotor agitation or retardation, fatigue or loss of energy, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

II. THE PROTOCOL: OBJECTIVES AND DESIGN

Objectives

The primary objective of Study 494, 495 and Study 497, is to demonstrate the efficacy of the controlled release paroxetine in the treatment of panic disorder with or without agoraphobia among non-elderly people. The secondary objective of this study is to assess the safety of controlled release paroxetine in the treatment of panic disorder with or without agoraphobia among non-elderly people.

Study Design

Studies 494, 495 and 497 are identical trials. They are double-blinded, placebo-controlled, flexible dosing trials to evaluate the efficacy of controlled-release paroxetine.

The diagnosis of Panic Disorder is confirmed at Screening Visit. Patients with a minimal panic attack frequency were identified during a single-blind placebo run-in phase of two-weeks duration. Baseline is defined as Visit 3 that falls in week 3. At Baseline Visit patients were randomized in a balanced fashion to two treatments: flexible-doses of paroxetine controlled-release and placebo. The duration of the double-blind Treatment Phase is of 10 weeks. Post-Baseline Visits during the Treatment Phase are scheduled weekly at Week 1 through Week 6, then at Week 8 and Week 10. During the run-in phase, patients took one single-blind placebo capsule daily in the morning. During the double-blind Treatment Phase, the paroxetine CR daily dose level varied from 12.5 to 75 mg based upon the therapeutic response. During Week 1 and 2, dosing was fixed at levels 1 and 2 for all randomized patients, respectively, i.e., for paroxetine CR-treated patients, 12.5 mg per day during Week 1 and 25 mg per day during Week 2. Thereafter, increases in dosage increments of one dosage level (12.5 mg per day) were permitted if the patient's therapeutic response was deemed inadequate by the investigator. Dosage level increases were permitted no more frequently than every 7 days. One dosage level reduction, consequent to an adverse experience, was permitted after the Week 2 Visit. Patients requiring a dosage reduction prior to the Week 1 Visit were permitted to interrupt level 1 or level 2 dosing, respectively, for a maximum of two days.

Each visit during the Treatment Phase included the evaluations:
(i) Review and/or dispense panic inventory diary, (ii) Clinical Global Impressions, Global Improvement, (iii) Clinical Global Impressions, Severity of Illness, (iv) Hamilton anxiety total score (at Week 6 and Week 10 or early termination only), (v) MSPS fear and avoidance score (at Week 6 and Week 10 or early termination only) and (vi) adverse experience monitoring etc.

The Flow Chart of Patient Evaluations is in Table 1A. Table 1B provides the summary of patient populations.

Table 1A

Flow Chart of Patient Evaluation

	Screen Visit D -14	Run-in Visit D -7	Baseline Visit D 0	Week 1 2 3 4 5 6 8 10	Early Term	Taper-End Visit
Screen/Baseline Evaluations						
General Patient Information	X					
SCID-P	X					
Psychiatric and Medical history	X					
ECG Record	X	X				
Inclusion Criteria	X		X			
Patient Randomiz.			X			
Informed consent	X					
Effic. Evaluations						
Review/Disperse Panic Inv. Diary	X	X	X	X X X X X X X X	X	
CGI (Gl. Impr.)				X X X X X X X X	X	
CGI (Severity Ill.)			X	X X X X X X X X	X	
HAM-A			X	X X	X	
MSPS			X	X X	X	
Safety Evaluations						
Vital Signs etc.	X	X	X	X X X X X X X X	X	X
Misc. Records						
Dispence Medicine	X		X	X X X X X X X X[e]	X[e]	
Study Medication Record/Compliance	X		X	X X X X X X X X	X	X
Study Term Rec.				X[f]	X[f]	X

e: If patient entered Taper Phase; f: If patient did not enter Taper Phase

Table 1B

Summary of Patient Population by Study

	Paroxetine CR		Placebo		**Total**	
	n	**%**	**n**	**%**	**n**	**%**
Study 494						
ITT Population	139	100.0	144	100.0	283	100.0
Completing study	103	74.1	109	75.7	212	74.9
Study 495						
ITT Population	158	100.0	163	100.0	321	100.0
Completing study	105	65.5	123	75.0	228	71.0
Study 497						
ITT Population	147	100.0	138	100.0	285	100.0
Completing study	103	70.1	96	69.6	199	69.8
All Studies Combined						
ITT Population	444	100.0	445	100.0	889	100.0
Completing study	311	70.0	328	73.7	639	71.9

III. EFFICACY ASSESSMENTS

During the run-in and Treatment Phases, patients logged in daily diaries the number of panic attacks they experienced per day, and categorized each attack as to number of panic symptoms and whether the attack was situational or unexpected. Patients also recorded the percent of a 24-hour day they worried about attacks or going into a situation that might have brought on an attack, but an attack did not occur (anticipatory anxiety). These daily diaries were summarized in the CRF at every clinical visit and were combined into two-week periods for efficacy assessment for Weeks 1 and 2, Weeks 3 and 4, and Weeks 5 and 6; diaries for two-week dosing intervals, Week 7 and 8 and Weeks 9 and 10, were also summarized.

At the termination of the trial or at the time of early withdrawal, patients entered a two-week Taper Phase during which the dosage was reduced to 25 mg/day.

Overall, demographic characteristics were similar between treatment groups within a study and between studies. They are shown in Table 2.

Table 2
Summary of Demographic Characteristic by Study
ITT Population

Characteristic	Study 494		Study 495		Study 497	
	Par CR N=139	Placebo N=144	Par CR N=158	Placebo N=163	Par CR N = 147	Placebo N=138
Age	Years		Years		Years	
Mean (SD)	38.1 (10.1)	37.0 (10.2)	36.5 (10.1)	36.6 (10.7)	38.2 (10.4)	40.1 (10.7)
Min., Max.	19, 63	20, 61	19, 62	19, 72	20, 65	19, 64
Gender	n %	n %	n %	n %	n %	n %
Female	81 58.3	80 55.6	105 66.5	103 63.5	96 65.3	68 49.3
Male	58 41.7	64 44.4	53 33.5	60 36.8	51 34.7	70 50.7
Race	n %	n %	n %	n %	n %	n %
White	117 84.2	135 93.7	146 92.4	146 89.6	117 79.6	108 78.3
Black	8 5.8	4 2.8	7 4.4	8 4.9	19 12.9	14 10.1
Oriental	0 0.0	2 1.4	1 0.6	1 0.6	0 0.0	0 0.0
Other	14 10.1	3 2.1	4 2.5	8 4.9	11 7.5	16 11.6

Principal Efficacy Variables

Studies 494, 495 and 497 are identical trials. The following is true for all the three studies.

1. The percentage of patients who achieved zero full panic attack per two weeks at study endpoint (protocol-defined primary efficacy parameter);
2. The median change from baseline in total number of full panic attacks per two weeks at study endpoint;
3. The median change from baseline in CGI Severity of Illness score at study endpoint.

Secondary Efficacy Variables

The sponsor has considered several secondary efficacy variables. The medical officer asked this reviewer to look at the following three secondary variables.

1. Anticipatory anxiety change from baseline at study endpoint.
2. The Marks-Sheehan Phobia Scale Total Fear Score.
3. Change in Marks-Sheehan Phobia Scale total avoidance score.

IV. EFFICACY DATA ANALYSIS

Threre were no interim analyses. Statistical conclusions concerning the efficacy of paroxetine CR are made using data from each patient's last post-baseline assessment carried forward (LOCF) to Week 10 (study endpoint) of the ITT population. For statistical analysis small centers are combined to form a new character variable CENTGP as shown in Table 2 below. **A significant treatment by center group interaction was observed in the analysis of change from baseline in HAM-A total score.** On further investigation, center group 005 and 033 had a larger treatment effect favoring paroxetine CR than any other center group. Removal of center 033 from the analysis resulted in loss of the significant treatment by center group interaction. This center was also involved in significant treatment by center group interactions involving key efficacy parameters in an identical paroxetine CR study in panic disorder (Study 495). The results from both studies 494 and 495, for efficacy parameters involved in these interactions, consistently favored paroxetine CR over placebo at this center. Because of the consistent nature of treatment by center group interactions involving center 033 in studies 494 and 495, all patients enrolled in this center in Study 494 were excluded from efficacy but not safety analysis.

Table 3a: **Study 494 Center Groups**

CENTGP	# of Patients
001/007/009/013/014/015/027/029	75
002/004/005/006/021/022/025/033	62
003/012/016/019/020/023/024/031	79
008/010/011/017/026/028/030/032	73
Total	289

Table 3b: **Study 495 Center Groups**

CENTGP	# of Patients
001/002/005/018/ 028	64
003/009/013/026	49
004/012/016/020	36
006/017/019/024	41
007/023/025/027	47
008/010/014/030	44
011/021/022/031	46
Total	327

Table 3c: **Study 497 Center Groups**

CENTGP	# of Patients
001/004/009	38
002/015	26
003/005	15
006/018	14
007/025	17
008/012	16
010/014/017/029	44
011/013	19
016/022/027/028	35
019/020/027/028	28
024/031	13
Total	265

Categorical efficacy variables (i.e., responders based on zero full panic attacks, CGI Global Improvement) will be analyzed using logistic regression, allowing for center effects. The effect of adding treatment by center interaction into the model will be discussed. The effects of the covariates, age and baseline panic disorder severity, will be evaluated; other suitable covariates may also be investigated in additional analyses.
Adequacy of the model fit will be explored by inspecting plots of the Pearson residuals and deviance residuals. For each treatment group there is an odds of a patient being classed as a responder. The results will be presented in terms of odds ratios (i.e., the odds of the response on paroxetine relative to the odds of response on placebo). 95% confidence intervals for around the odds ratios will be provided.

Provided the underlying assumptions are satisfied, continuous efficacy (e.g., change from baseline in total number of full panic attacks) will be analyzed by analysis of variance and allowing for center effects. The effect of adding treatment by center interaction into the analysis will be assessed. The effects of the covariates, age and baseline panic disorder severity, will be evaluated; other suitable covariates may also be investigated in additional analyses. Results will be presented as the point estimate and 95% confidence interval for the difference between paroxetine and the placebo group. The assumptions of normality and homogeneity of variance will be assessed by inspection of normal probability plots and residual plots. If these assumptions are not met, appropriate non-parametric methods will be used.

The sponsor's results of LOCF data sets of Study 494 are reproduced in Table 4, Table 5.

Table 4
Study 494
Response to Treatment – Principal Efficacy Parameters
Excluding Center 033
Intention-To-Treat Population, Week 10 LOCF

Table 4a: **Percentage of Patients Free of Full Panic Attacks**

Paroxetine CR			Placebo			Pairwise Comparisons[a]	
n	%	N	n	%	N	Odds Ratio 95% CI	p-value
84	68.9	122	65	50.4	129	2.21 (1.289, 3.789)	0.004

[a] Statistical analysis adjusted for center group and covariates.

Table 4b: **Median Change from Baseline in Total Number of Full Panic Attacks**

Paroxetine CR				Placebo				Pairwise Comparisons	
med.	min	max	N	med.	min	max	N	median diff (95% CI)	p-value
-4	[redacted]		122	-3	[redacted]		128	-1 (-2, 0)	0.08

Table 4c: **Distribution of CGI Severity of Illness Scores**

CGI Severity of Illness Score	Paroxetime CR			Placebo			Pairwise Comaprisons[a]	
	n	%	N	n	%	N	Median Difference (95% CI)	p-value
normal, not at all ill	31	23.5	132	18	13.0	138		
borderline ill	28	21.2	132	35	25.4	138		
mildly ill	37	28.0	132	29	21.0	138		
moderately ill	27	20.5	132	37	26.8	138		
markedly ill	6	4.5	132	17	12.3	138		
severely ill	3	2.3	132	2	1.4	138		
among the most extremely ill	0	0.0	132	0	0.0	138		
Total	132	100	132	138	100	138	0 (-1, 0.0)	0.032

[a] Statistical analysis based on change from baseline in CGI Severity of Illness scores.

Table 5
Study 494
Response to Treatment – Additional Efficacy Parameters
Excluding Center 033
Intention-To-Treat Population, Week 10 LOCF

Parameter	Paroxetine CR			Placebo			Pairwise Comparison	
Mean Change from Baseline	**Mean**	**SE**	**N**	**Mean**	**SE**	**N**	**Mean Diff.[a] (95% CI)**	**p-value**
HAM-A total score	-10.0	0.86	115	-8.0	0.81	124	-2.0 (-4.1, 0.0)	0.052
% of day with anticipatory anxiety	-12.9	1.93	122	-9.2	1.82	128	-3.7 (-8.2, 0.7)	0.10
MSPS total fear score	-20.2	2.35	114	-15.2	2.21	124	-5.0 (-10.5, 0.5)	0.078
MSPS total avoidance score	-6.6	0.86	114	-5.4	0.81	123	-1.3 (-3.3, 0.8)	0.23
Median Change from Baseline	**Median**	**Min., Max.**	**N**	**Median**	**Min., Max.**	**N**	**Median Diff. (95% CI)**	**p-value**
Number of unexpected full panic attacks/2 wk	-1		122	-1		128	0 (0, 1)	0.56
Number of situational full panic attacks/2 wk	-3		122	-2		129	-1 (-2, 0)	0.003
Number of all panic attacks/2 wk	-11		122	-8		128	-3 (-6, 0)	0.021
Percentage of Patients	**n**		**N**	**n**		**N**	**Odds Ratio (95% CI)**	**p-value**
% with 1 or 2 on CGI Global Improvement item	94		132	72		136	2.30 (1.36, 3.90)	0.002

The sponsor's results of LOCF data sets of Study 495 and Study 497 are reproduced in Table 6 and Table 7, respectively.

Table 6
Study 495
Response to Treatment at Study Endpoint
(Week 10 LOCF Datasheet, Excluding Center 5)
Intention-to-Treat Population

	Paroxetine CR			Placebo			Pairwise Comparison	
Percentage of Patients	**n**	**%**	**N**	**n**	**%**	**N**	**Odds Ratio[a] (95% CI)**	**p-value**
% patients with zero full panic attacks	70	56.9	123	70	51.5	136	1.38 (.83, 2.32)	0.217
% with 1 or 2 on CGI Global Improvement item	82	61.7	133	60	42.0	143	2.31 (1.41, 3.78)	<.001
CGI Severity of Illness Score	**n**	**%**	**N**	**n**	**%**	**N**	**Median Diff (95% CI)**	**p-value**
normal, not at all ill	18	13.1	137	17	11.6	147		
borderline ill	35	25.5	137	15	10.2	147		

mildy ill	43	31.4	137	37	25.2	147		
moderately ill	22	16.1	137	52	35.4	147		
markedly ill	11	8.0	137	21	14.3	147		
severely ill	7	5.1	137	5	3.4	147		
among the most extremely ill	1	0.7	137	0	0.0	147		
Total	137	100	137	147	100	147	0 (-1, 0.0)	0.004
Median Change from Baseline in Frequency/2 Weeks	**Median**	**Min, Max**	**N**	**Median**	**Min, Max**	**N**	**Median Diff (95% CI)**	**p-value**
Full panic attacks	-5	-1 [illegible] 4	123	-3	[illegible]	136	-2 (-4, -1)	<.001
Situational full panic attacks	-2	-1	123	-2		136	-1 (-2.0, 0)	0.02
Unexpected full panic attacks	-2	-[illegible]	123	-1		136	-1 (-2.0, 0)	0.01
All panic attacks	-11	-1 [illegible]	123	-6		136	-4 (-8, -1)	<.001
Mean Change from Baseline	**Mean**	**SE**	**N**	**Mean**	**SE**	**N**	**Mean Diff [a] (95% CI)**	**p-value**
HAM-A total score	-9.4	0.86	112	-6.6	0.78	129	-2.7 (-4.7, -.76)	0.007
% of day with anticipatory anxiety	-14.7	1.89	122	-8.5	1.72	136	-6.2 (-10.49, -1.88)	0.005
MSPS total fear score	-19.9	2.35	114	-12.2	2.16	128	-7.7 (-13, -2.3)	0.005
MSPS total avoidance score	-7.1	0.86	114	-4.0	0.79	128	-3.0 (-5.0, -1.1)	0.003

Principal efficacy parameters are presented in italics.

[a] Statistical analysis adjusted for center group, age, gender, and baseline panic disorder severity.

[b] Statistical analyses based on change from baseline in CGI Severity of Illness scores.

Table 7

Study 497

Response to Treatment at Study Endpoint

(Week 10 LOCF Dataset)

Intention-to-Treat Population

	Paroxetine CR			**Placebo**			**Pairwise Comparison**	
Percentage of Patients	**n**	**%**	**N**	**n**	**%**	**N**	**Odds Ratio[a] (95% CI)**	**p-value**
% patients with zero full panic attacks	82	62.1	132	73	56.2	130	1.53 (0.89, 2.62)	0.127
% with 1 or 2 on CGI Global Improvement item	84	59.2	142	63	46.3	136	2.17 (1.29, 3.67)	<.004
CGI Severity of Illness Score	**n**	**%**	**N**	**n**	**%**	**N**	**Median Diff (95% CI)**	**p-value**
normal, not at all ill	27	18.8	144	15	11.0	136		
borderline ill	34	23.6	144	31	22.8	136		
mildy ill	36	25.0	144	31	22.8	136		
moderately ill	36	25.0	144	36	26.5	136		
markedly ill	8	5.6	144	19	14.0	136		
severely ill	3	2.1	144	4	2.9	136		
among the most extremely ill	0	0.0	144	0	0.0	147		
Total	144	100	144	136	100	136	0 (-1, 0.0)	0.004

Median Change from Baseline in Frequency/2 Weeks	Median	Min, Max	N	Median	Min, Max	N	Median Diff (95% CI)	p-value
Full panic attacks	-4		132	-3		130	-1 (-2, 0)	0.239
Situational full panic attacks	-2		132	-2		130	-1 (-1, 0)	0.066
Unexpected full panic attacks	-1		132	-2		130	0 (-1, 1)	0.980
All panic attacks	-9.5		132	-6		130	-3 (-6, 0)	0.028
Mean Change from Baseline	**Mean**	**SE**	**N**	**Mean**	**SE**	**N**	**Mean Diff [a] (95% CI)**	**p-value**
HAM-A total score	-9.4	0.86	112	-6.6	0.78	129	-2.7 (-4.83, -.53)	0.015
% of day with anticipatory anxiety	-11.5	1.72	132	-8.5	1.62	130	-3.0 (-7.33, -1.27)	0.166
MSPS total fear score	-18.6	2.14	127	-11.0	1.98	125	-7.6 (-12.87, -2.36)	0.005
MSPS total avoidance score	-5.8	0.80	126	-3.2	0.74	125	-2.5 (-4.53, -0.57)	0.012

Principal efficacy parameters are presented in italics.

[a] Statistical analysis adjusted for center group, age, gender, and baseline panic disorder severity.

[b] Statistical analyses based on change from baseline in CGI Severity of Illness scores.

V. SPONSOR'S CONCLUSIONS

The percentage of patients free of full panic attacks is the protocol-defined primary efficacy parameter. The following table shows the effect of Paroxetine CR on the percentage of patients free of full attacks for the three studies (Vol. 1.002, p. 127).

Table 8

Percentage of Patients Free of Full Panic Attacks Per Two Weeks
Studies 494, 495 and 497
ITT Population

Two Week Period	Paroxetine CR n	%	N	Placebo n	%	N	Paroxetine CR vs. Placebo[a] Odds Ratio (95 % CI)	p-value
Study 494 (Excluding Center 033)								
Week 10 Observed Case	69	78.4	88	60	58.8	102	2.85 (1.44, 5.61)	0.003
Week 10 Endpoint	84	68.9	122	65	50.4	129	2.21 (1.29, 3.79)	0.004
Study 495 (Excluding Center 005)								
Week 10 Observed Case	57	71.3	80	55	56.1	98	2.40 (1.22, 4.72)	0.012
Week 10 Endpoint	70	56.9	123	70	51.5	136	1.38 (0.83, 2.32)	0.217
Study 497								
Week 10 Observed Case	66	69.5	95	63	65.6	96	1.43 (0.72, 2.86)	0.306
Week 10 Endpoint	82	62.1	132	73	56.2	130	1.53 (0.89, 2.62)	0.127

[a] Statistical analysis adjusted for center group, age group, gender, and severity of panic disorder at baseline.

In Study 494, treatment with paroxetine CR resulted in a greater percentage of patients at Week 10 Endpoint who were free of full panic attacks compared to placebo. For patients who completed the 10-week Treatment Phase in Study 495, the odds of responding to paroxetine CR increased to 2.8-fold that of placebo.
Study 495 and 497 did not demonstrate a statistically or clinically significant effect of paroxetine CR on the percentage of patients free of full panic attacks at Week 10 Endpoint (Vol. 1.002, p. 126).
The overall interpretation of the results of Study 494 demonstrate that, treatment with paroxetine CR results in a significant decrease in the frequency of panic attacks (Vol. 1.041, p.07).

The following table shows the effects of paroxetine CR on the median change from baseline in the number of full panic attacks at Week 10 Endpoint and for observed cases at Week 10.
In study 495, treatment with paroxetine CR resulted in a significantly greater reduction in panic attack frequency compared to placebo, with the median difference being 2 full panic attacks for all patients (i.e., at Week 10 Endpoint), and 3 full attacks for patients who completed the 10-week Treatment Phase. Study 494 and 497 did not demonstrate a statistically significant effect of paroxetine CR on the change in number of full panic attacks at Week 10 Endpoint or at Week 10 for observed cases, although paroxetine CR was numerically superior to placebo.

Table 9
Median Baseline and Reductions from Baseline in Number of Full Panic Attacks Per Two Weeks
ITT Population

Two Week Period	Paroxetine CR Median	Min, Max	N	Placebo Median	Min, Max	N	Paroxetine CR vs. Placebo Median Diff (95 % CI)	p-value
Study 494 (Excluding Center 033)								
Baseline	5		122	5		128		
WK 10 OC	-5		88	-3		102	-1, (-2, 0)	0.072
LOCF Endpoint	-4		122	-3		128	-1, (-2, 0)	0.08
Study 495 (Excluding Center 005)								
Baseline	7		123	5		136		
WK 10 OC	-6		80	-3		98	-3, (-5, -1)	<0.001
LOCF Endpoint	-5		123	-3		136	-2, (-4, -1)	<0.001
Study 497								
Baseline	5		122	5		128		
WK 10 OC	-4		95	-3		96	-1, (-2, 0)	0.088
LOCF Endpoint	-4		132	-3		130	-1, (-2, 0)	0.239

Study 494 demonstrated significant effects of paroxetine CR on the change in CGI Severity of Illness score at Week 10 Endpoint, with the reductions for paroxetine CR being statistically superior to placebo (median difference between treatment groups=0, 95% confidence interval –1 to 0, p-value=0.032. See Table 3c). Compared to all treated patients (i.e., at Week 10 Endpoint), statistically significant improvement relative to

placebo was also noted for paroxetine CR-treated patients who completed the 10-week Treatment Phase (median difference=0, 95% confidence interval –1 to 0, p-value=0.007). Study 495 also demonstrated statistically significant effects of paroxetine CR on the changes in CGI Severity of Illness score at Week 10 Endpoint (median difference=0, 95% confidence interval –1 to 0, p-value=0.004, Table 5) and at Week 10 for observed cases (median difference=-1, 95% confidence interval –1 to –1, p-value<0.001), with the reductions for paroxetine CR being statistically superior to placebo. Study 497 did not demonsrtate statistically significant effects of paroxetine CR on change in CGI Severity of Illness score at Week 10 Endpoint and at Week 10 for observed cases, although reductions in score with paroxetine CR tended to be numerically superior to placebo.

Secondary Variables

1. Change in Percentage of Day Engaged in Anticipatory Anxiety

The following table presents a summary of the Baseline and mean change from Baseline in the percentage of day spent with anticipatory anxiety at study endpoint for ITT popoulation by 2-week period and treatment group for Study 495.

Table 10

Baseline and Mean Change from Baseline in Percentage of Day with Anticipatory Anxiety Excluding Center 005

Study 495: ITT Population

Two Week Period	Paroxetine CR			Placebo			Pairwise Comparison Paxil CR vs. Placebo	
	Mean	SE	N	Mean	SE	N	Mean (95% CI)	p-value
Baseline	29.0	2.10	122	24.5	1.79	136		
Weeks 9 and 10	-17.3	2.10	80	-8.8	1.86	98	-8.6 (-13.36, -3.80)	<.001
70% Endpoint	-13.6	1.82	122	-8.0	1.65	136	-5.6 (-9.79, -1.49)	0.008
Week 10 Endpoint	-14.7	1.89	122	-8.5	1.72	136	-6.2 (-10.49, -1.88)	0.005

The sponsor observed that at Week 10 Endpoint the mean reduction in percentage of day engaged in anticipatory anxiety from baseline is 14.7% in the paroxetine CR treatment group versus 8.5% in the placebo treatment group. The mean difference in reduction in percentage of day engaged in anticipatory anxiety of –6.2% for paroxetine CR relative to placebo is statistically significant (p = 0.005). At 70% Endpoint and at Week 10 OC, statistically significant differences in the mean reduction in percentage of day with anticipatory anxiety for paroxetine CR versus placebo were also obtained.

2. Change in Marks-Sheehan Phobia Scale Total Fear Score

The following are obtained from the data for Study 495. At Week 10 Endpoint the mean reduction in MSPS total score (Maximum total score, 140) from Baseline was 19.9 in the paroxetine CR treatment group versus 12.2 in the placebo treatment group. The mean difference in MSPS total fear score of –7.7 for paroxetine CR relative to placebo was statistically significant at p=0.005 (95% confidence interval of –13.0 to –2.3). Results obtained for the Week 10 observed cases data set were very similar to results obtained for the Week 10 Endpoint.

3. Change in Marks-Sheehan Phobia Scale Total Avoidance Score

The following is observed for Study 495. At Week 10 Endpoint the mean reduction in MSPS total avoidance score (Maximum total score, 56) from Baseline was 7.1 in the paroxetine CR treatment group versus 4.0 in the placebo treatment group. The mean difference in MSPS total avoidance score of –3.0 for paroxetine CR relative to placebo is statistically significant at p=0.003 (95% confidence interval of –5.0 to –1.1). Results obtained for the Week 10 OC data set were similar to results obtained for the Week 10 Endpoint.

VI. REVIEWER'S DATA ANALYSES AND COMMENTS

Demographic characteristics, as seen in Table 2 on page 4, were similar between treatment groups within a study and between studies. Proportions of white subjects in Study 494, 495 and 497 are 0.94, 0.90 and 0.78, respectively. Descriptive statistics for the total baseline full panic attacks are presented in Table 11 below..

Table 11

Total Baseline Full Panic attacks

	Parexotine CR					Placebo				
	N	Mean	SD	Min.	Max.	N	Mean	SD	Min.	Max.
Study 494	122	9.918	24.06			129	11.07	18.52		
Study 495	139	11.52	14.91			151	8.9	10.36		
Study 497	132	8.96	11.41			130	8.65	12.11		

ANALYSIS OF PROTOCOL DEFINED PRIMARY EFFICACY VARIABLE.

1. Main Results

The percentage of patients who achieved zero full panic attack per two weeks at study endpoint is the protocol-defined primary efficacy variable. It is analyzed using logistic regression without any covariates. That is, the model considered is

$$\text{Logit}(p) = \alpha + \beta_1 TRT,$$

where p is the probability of zero full panic attacks and TRT =1 for paroxetine and TRT = 0 for placebo. The results are:

Table 12

Logistic Model Response = Treatment

	LOCF			OC		
	Odds Ratio	p-value *	c	Odds Ratio	p-value *	c
[a]Study 494	2.177	0.0031	0.596	2.542	0.0045	0.612
[b]Study 495	1.245	0.3806	0.527	1.938	0.0388	0.580
Study 497	1.281	0.3262	0.531	1.192	0.5702	0.522

TRT=Treatment. *$H_0 : \beta_1 = 0$. [a] Center 033 is excluded. [b] Center 005 is excluded.

The value of c, the predictive power of the model, is moderate in all six analyses. Each study contains observations that either are not well explained by the model or are extreme points in the design space or cause instability in the coefficient of treatment. The results of Study 494 may be interpreted as follows.

Study 494 LOCF Week 10 endpoint data indicate that the odds of responding to paroxetine CR increased to 2.2-fold that of placebo. The model based estimates of proportions of patients with no full panic attacks under placebo and paroxetine CR are 0.504 and 0.688, respectively. For patients who completed the 10-week treatment in Study 494, the odds of responding to paroxetine CR increased to 2.54-fold that of placebo. The model based estimates of proportions of zero full panic attacks under placebo and Paroxetine CR are 0.588 and 0.784, respectively. For patients who completed the 10-week treatment in Study 495, the odds of responding to paroxetine CR increased to 1.25-fold that of placebo. The model based estimates of proportions of zero full panic attacks under placebo and Paroxetine CR are 0.56 and 0.71, respectively.

The results of the logistic regression analysis that includes Centers 033 and 005 are:

Table 13

Logistic Model Response = Treatment (No Center Excluded)

	LOCF			OC		
	Odds Ratio	p-value *	c	Odds Ratio	p-value *	c
[a]**Study 494**	2.387	0.0008	0.607	2.882	0.0011	0.626
[b]**Study 495**	1.878	0.0084	0.578	3.347	0.0001	0.643

*$H_0 : \beta_1 = 0$.

Inclusion of Center 005 in Study 495 OC data makes TRT highly significant (p-value = .0001). For patients who completed the 10-week treatment in Study 495, the odds ratio of responding to paroxetine CR increased to 3.3-fold that of placebo. In the Study 495-LOCF case, TRT turns out to be significant. These contradict the earlier results of the analysis without Center 005.

2. Subgroups, Interaction and Covariates

Since more than 90% of the patient populations in Study 494 and 495 are white, RACE is not considered as a factor in this study.

Sex

Table 14a and Table 14b contain sex-wise observed percentages of zero full panic attacks under the two treatment groups for Study 494 and Study 495, respectively. The difference between the percentages is also included.

Table 14a
Study 494
Observed Percentage of Zero Full Panic Attacks
Difference = Paxil CR - Placebo

Sex	Paroxetine CR	Placebo	Difference
Male	66.07 (n = 56)	53.45 (n = 58)	12.62 (n = 114)
Female	72.86 (n = 70)	45.95 (n = 74)	26.91 (n = 144)
Total	(n = 126)	(n = 132)	(n = 258)

Table 14b
Study 495
Observed Percentage of Zero Full Panic Attacks
Difference = Paxil CR - Placebo

Sex	Paroxetine CR	Placebo	Difference
Male	61.22 (n = 49)	42.11 (n = 57)	19.11 (n = 106)
Female	62.22 (n = 90)	48.94 (n = 94)	13.28 (n = 184)
Total	(n = 139)	(n = 151)	(n = 290)

There seems to be no difference in treatment effects between males and females.

Age-group
Age-group wise observed percentage of zero full panic attacks for Study 494 and Study 495 are shown in Table 15a and Table 15b, respectively. The difference = paroxetine-placebo of percentage is also shown.

Table 15a
Study 494
Observed Percentage of Zero Full Panic Attacks
Difference = Paxil CR – Placebo

Age-group	Paroxetine	Placebo	Difference
18-24	60.00 (n = 5)	30.77 (n = 13)	29.23 (n = 18)
25-34	67.39 (n = 46)	52.38 (n = 42)	15.01 (n = 88)
35-44	66.67 (n = 36)	47.83 (n = 46)	18.84 (n = 82)
45-54	76.67 (n = 30)	60.87 (n = 23)	15.80 (n = 53)
> 54	77.78 (n = 9)	37.50 (n = 8)	40.28 (n = 17)
Total	(n = 126)	(n = 132)	(n = 258)

Table 15b
Study 495
Observed Percentage of Zero Full Panic Attacks
Difference = Paxil CR – Placebo

Age-group	Paroxetine	Placebo	Difference
18-24	63.16 (n = 19)	40.91 (n = 22)	22.25 (n = 41)
25-34	65.85 (n = 41)	51.92 (n = 52)	13.93 (n = 93)
35-44	55.56 (n = 45)	47.37 (n = 38)	8.19 (n = 83)
45-54	66.67 (n = 27)	44.44 (n = 27)	22.23 (n = 54)
> 54	57.14 (n = 7)	33.33 (n = 12)	23.81 (n = 19)
Total	(n = 139)	(n = 151)	(n = 290)

It appears that paroxetine CR is effective in patients of all age-groups.

Center Effects

Center-wise observed percentages of zero full panic attacks for both treatment groups for study 494 are presented in Table 16 below. The difference between the percentages of treatment groups is also included. It may be noted that the significance of the effect of paroxetine CR is not attributed to any one or to a fewer number of centers.

Table 16
Study 494
Observed Percentage of Zero Full Panic Attacks
Difference = Paxil CR- Placebo

Center	Paroxetine % (n)	Placebo % (n)	Difference %
029	50.0 (2)	100.0 (1)	-50.00
012	66.67 (3)	100.0 (3)	-33.33
025	66.67 (3)	33.33 (3)	-33.33
024	60.0 (5)	75.0 (4)	-15.0
0.31	50.0 (2)	66.67 (3)	-16.67
005	66.68 (3)	66.67 (3)	00.00
009	100.0 (1)	100.0 (1)	00.00
013	50.0 (6)	50.0 (8)	00.00
028	75.0 (4)	75.0 (4)	00.00
030	100.0 (1)	100.0 (1)	00.00
010	00.0 (1)	- (0)	- --
016	66.67 (6)	57.14 (7)	09.53
026	50.0 (8)	40.0 (5)	10.0
001	85.71 (7)	71.43 (7)	14.28
004	75.0 (4)	59.0 (5)	15.0

007	75.0 (4)	60.0 (5)	15.0
017	40.0 (5)	25.0 (4)	15.0
023	50.0 (2)	33.33 (3)	16.67
027	50.0 (6)	33.33 (6)	16.67
020	100.0 (5)	80.0 (5)	20.0
008	77.78 (9)	54.55 (11)	23.23
032	75.0 (4)	50.0 (2)	25.0
011	100.0 (2)	66.67 (3)	33.33
002	100.0 (3)	60.0 (5)	40.00
019	66.67 (9)	22.22 (9)	44.45
003	50.0 (2)	0.0 (2)	50.00
015	100.0 (2)	33.33 (3)	66.67
006	75.0 (4)	0.0 (4)	75.00
021	75.0 (4)	0.0 (5)	75.00
022	100.0 (3)	25.0 (4)	75.0

ANALYSIS OF PROTOCOL DEFINED SECONDARY EFFICACY VARIABLES

This reviewer was requested by the medical officer to study the variables- (i) change in percentage of day engaged in anticipatory anxiety, (ii) change in MSPS total fear score, and (iii) change in MSPS total avoidance score. The treatment groups were compared using one-way analysis of variance. The results for Study 494 are summarized in the following table.

Table 17
p-values for ANOVA model y = TRT
Study 494

Response Variable y	**WK 10 LOCF**	**WK 10 OC**
Change in percentage of day engaged in anticipatory anxiety	0.0829	0.1936
Change in Marks-Sheehan Phobia Scale total fear score	0.1029	0.3702
Change in Marks-Sheehan Phobia Scale total avoidance score	0.3236	0.7363

Study 494 did not demonstrate a significant difference between paroxetine CR and placebo with respect to these three secondary efficacy variables. However, Study 495 showed that, for each one of the secondary efficacy variables, the mean difference (Paxil CR-Placebo) to be statistically significant. The 95% confidence intervals for the mean difference (Paxil CR-Placebo) and p-values of the one-way ANOVA model for Study 495 are as follows.

Table 18
95% Confidence Interval and p-values for ANOVA model y = TRT
Study 495

Response Variable y	**WK 10 LOCF**	**WK 10 OC**

Response Variable y	WK 10 LOCF	WK 10 OC
Change in percentage of day engaged in anticipatory anxiety	(-10.32, -7.796) 0.0052	(-13.86, -4.45) 0.0002
Change in Marks-Sheehan Phobia Scale total fear score	(-12.55, -2.04) 0.0067	(-16.28, -10.07) 0.0016
Change in Marks-Sheehan Phobia Scale total avoidance score	(-4.74, -2.82) 0.0043	(-6.1, -3.81) 0.0013

VII. OVERALL CONCLUSIONS

- In Study 494, treatment with paroxetine CR resulted in a significantly greater percentage of patients at Week 10 Endpoint who were free of full panic attacks compared to placebo.
- The results of Study 495 are supportive: The Study 495 OC data demonstrated a statistically significant effect of paroxetine CR on the percentage of patients free of full panic attacks. In addition, The results of Study 495 showed that paroxetine CR to be statistically significantly superior to placebo with respect to (i) change in percentage of day engaged in anticipatory anxiety, (ii) change in MSPS total fear score, and (iii) change in MSPS total avoidance score.
- Study 497 did not demonstrate a statistically significant effect of paroxetine CR on the percentage of patients free of full panic attacks at Week 10 Endpoint.

/S/
Kallappa M. Koti
Mathematical Statistician

Concur:
Dr. Kun Jin /S/

Dr. George Chi /S/

CC:
Arch. NDA 20-982
HFD 120
HFD-120 / Dr. Katz
HFD-120 / Ms. Homonnay
HFD-120 / Dr. Laughren
HFD-120 / Dr. Dubitsky
HFD-710 / Dr. Chi
HFD-710 / Dr. Jin
HFD-710 / Dr. Koti
HFD-710 / Chron

CENTER FOR DRUG EVALUATION AND RESEARCH

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

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

REC.
2/19/02
2:22 PM

NDA 20-982
Paxil® CR (paroxetine hydrochloride) Controlled-Release Tablets 12.5 and 25 mg For Panic Disorder

Approval Package

A. Table of Contents

B. Action Letter (AP letter)

C. Agreed AP Labeling/Comparison to AE labeling

D. AE Letter issued

E. Division Director's Memo

F. Group Leader's Memo

G. Medical Officer's Review

H. CMC Labeling Review

I. Correspondences (Labeling negotiations)

MEMORANDUM

DATE: February 14, 2002

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-982 & NDA 20-936/S-008

SUBJECT: Addendum to My 2/12/02 memo

In my 2/12/02 memo to NDA 20-982 & NDA 20-936/S-008, for the use of Paxil CR in patients with Panic Disorder, I stated that the issue of dissolution specifications, mentioned in our Approvable letter of 1/3/00, was not addressed in any of the reviews.

I was wrong on this point. In fact, Dr. Gurpreet Gill-Sangha, the chemistry reviewer, in her comprehensive CMC review dated 2/6/02, definitively dealt with this issue (page 8).

This memo is being written to correct the record.

Russell Katz, M.D.

APPEARS THIS WAY
ON ORIGINAL

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
2/14/02 08:23:11 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DATE: February 12, 2002

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-982 & NDA 20-936/S-008

SUBJECT: Action Memo for NDA 20-982 & NDA 20-936/S-008, for the use of Paxil CR (paroxetine hydrochloride) Controlled Release 12.5 mg and 25 mg Tablets in patients with Panic Disorder

NDA 20-982 & NDA 20-936/S-008, for the use of Paxil CR (paroxetine hydrochloride) Controlled Release 12.5 mg and 25 mg Tablets in patients with Panic Disorder, were submitted by GlaxoSmithKline on 4/22/98 and 1/25/02, respectively. NDA 20-982 was the subject of Approvable letters dated 3/10/99 and 1/3/00 (NDA 20-936/S-008 was submitted for administrative purposes only). The 1/3/00 Approvable letter requested labeling, a safety update, regulatory status and literature updates, and the adoption of certain specific dissolution specifications.

The sponsor responded to the 1/3/00 Approvable letter in a submission dated 12/18/01. This submission has been reviewed by Dr. Greg Dubitsky, medical officer, Dr. Tom Laughren, Psychiatric Drugs Team Leader, and Dr. Gurpreet Gill-Sangha, chemist. The review team recommends that the application be approved.

I agree. I have only one minor administrative point for the file.

As noted above, the 1/3/00 Approvable letter asked the sponsor to adopt specific dissolution specifications, and this issue is not addressed in the reviews. In fact, slightly modified dissolution specifications were adopted in an Approval letter dated 12/6/00 sent to NDA 20-936/S-005. This supplemental NDA was for the introduction of a new dosage strength CR tablet, 37.5 mg. This dissolution specification had previously been approved for the 12.5 and 25 mg tablets. The 12/6/00 Approval letter to NDA 20-936/S-005 definitively addressed the request in the 1/3/00 Approvable letter to NDA 20-982. Indeed, while the applications currently under consideration were submitted only for the 12.5 and 25 mg tablets, this action will include the 37.5 mg tablet as well.

For this reason, I will issue the attached Approval letter with appended labeling.

Russell Katz, M.D.

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
2/12/02 10:56:11 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

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: February 8, 2002

/S/

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

SUBJECT: Recommendation for Approval Action for Paxil CR (paroxetine controlled release tablets) for the treatment of panic disorder

TO: File NDA 20-982
[**Note:** This overview should be filed with the 12-18-01 response to the approvable action.]

This NDA was originally submitted 4-22-98, and an initial approvable letter was issued on 3-10-99. SKB responded with a 7-7-99 submission, including alternative labeling. They indicated that, as of that time, there were no new relevant clinical data to report, no foreign regulatory actions had been taken, and there were no relevant safety findings from the published literature. For completeness, they did report on the safety experience from 2 completed bioequivalence studies. The clinical information in that response was reviewed by Dr. Dubitsky (see 8-2-99 review), and we faxed the sponsor a slightly modified version of labeling on 8-17-99. Of note, we accepted most of the sponsor's proposed changes, and our disagreements were, in my view, minor. Apparently, our suggestion to delete certain terms from the Other Events table led to an extensive effort on the part of SKB to modify this section of Adverse Reactions, and when they had still not responded to our attempts to negotiate final labeling as the action date approached, we issued a second approvable letter on 1-3-00. That letter contained the same version of labeling we had faxed to the sponsor on 8-17-99, and in other respects was similar to the original approvable letter sent 3-10-99.

The sponsor finally responded to the 1-3-00 approvable letter with a 12-18-01 submission that included revised labeling, and statements in response to our requests for safety, regulatory status, and literature updates essentially indicating that there was nothing to report. The labeling included fairly minor changes relative to our 1-3-00 labeling, but did also include a number of changes that had been implemented in the intervening 2 years. Dr. Dubitsky has reviewed the revised labeling and negotiated final labeling regarding the few minor changes the sponsor had proposed (see his 1-11-02 review). I agree with this mutually agreed upon labeling, and, in my view, this NDA can now be approved.

cc:
Orig NDA 20-982 (Paxil CR/Panic Disorder)
HFD-120/Div File
HFD-120/TLaughren/RKatz/GDubitsky/MShin

DOC: MEMPXRPD.AP1

Shin, Melaine M

From: Dubitsky, Gregory M
Sent: Wednesday, February 06, 2002 10:52 AM
To: Shin, Melaine M
Cc: Laughren, Thomas P
Subject: NDA 20-982: Paxil CR for Panic Labeling

Hi Melaine,

The minor edits suggested by GSK look fine to me. So, it appears that we have reached agreement on labeling.

Attached is the final version of labeling. I have included a copy with shading to indicate additions to the approvable labeling (in case Tom wants to see these).

Thanks,

Greg

[redacted]
PAXILCR PAN
AP3.DOC

[redacted]
Shaded PAXILCR PAN
AP3.DOC

APPEARS THIS WAY
ON ORIGINAL

Shin, Melaine M

From: Susan.Weill@gsk.com
Sent: Thursday, January 31, 2002 3:42 PM
To: SHINM@cder.fda.gov
Subject: RE: Paxil CR (Panic) Adverse Event Labeling

Hi Melaine-
Sorry this was not addressed in the e-mail below.
Please refer to the fax cover of January 29, 2002, wherein we agreed to add "vasculitic syndromes (such as Henoch Schonlein purpura)" to the Postmarketing Reports section.
Thanks and apologies for the omission

Susan Weill
GlaxoSmithKline
U.S. Regulatory Affairs
610-917-6223 (phone)

"Shin, Melaine M" <SHINM@cder.fda.gov>

31-Jan-2002 15:20

To: "'Susan.Weill

cc:
Subject: RE: Paxil CR (Panic) Adverse Event Labeling

Hi Susan,

Do you also agree that we will add "vasculitic syndromes (such as Henoch Schonlein purpura)" to the Postmarketing Reports section since it wasn't mention in this e-mail.
Thanks,
Melaine

-----Original Message-----
From: Susan.Weill@sbphrd.com (mailto:Susan.Weill@sbphrd.com)
Sent: Thursday, January 31, 2002 3:04 PM
To: shinm@cder.fda.gov
Subject: FW: Paxil CR (Panic) Adverse Event Labeling

Hi Melaine-
Please see our comments below in bold font. Please let us know if you would also like a revised PI at this time.
Should you have any questions, I may be reached at 610-917-6223.
Thanks

Susan Weill
GlaxoSmithKline
U.S. Regulatory Affairs
610-917-6223 (phone)

	"Shin, Melaine M" <SHINM@cder.fda.gov> 30-Jan-2002 14:03	To: "'Susan.Weill cc: "Shin, Melaine M" Subject: FW: Paxil CR (Panic) Adverse Event Labeling

Hi Susan,

The following is the response from the Medical Officer for your earler faxed information. Please let me know if this proposal is acceptable. Also, I would appreciate your response to my earlier e-mail regarding CMC issues.
thanks,
Melaine

> -----Original Message-----
> From: Dubitsky, Gregory
> Sent: Wednesday, January 30, 2002 1:58 PM
> To: Shin, Melaine M
> Cc: Laughren, Thomas P
> Subject: Paxil CR (Panic) Adverse Event Labeling
>
> Hello Melaine,
>
> I have reviewed the FAX from GSK RE: the "Other Events" section of
> labeling for the Paxil CR for Panic NDA (20-982). Please inform the
> sponsor of the following proposal:
>
> 1) Regarding CNS Stimulation, over half of the verbatim terms subsumed by
> this COSTART term were "irritability" once akathisia was removed (see #2
> below). Hence, I recommend replacing CNS stimulation with
> "irritability." This will require a rewording of the preface to this
> section to indicate that some vague COSTART terms were replaced with more
> specific terms. Specifically, in the third paragraph of the preface, the
> phrase "those reported in terms so general as to be uninformative" in the
> third sentence should be removed. Then, the following should be added as
> the fourth sentence: "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."

Agree to replacement of "CNS Stimulation" with "Irritability". Also agree to the changes in the preface.

>
> 2) Akathisia should be subsumed by the term akathisia, not CNS

> stimulation. Given 6 reports of akathisia and a denominator of 760,
> akathisia should be added under Nervous System as an infrequent event.
>

"Akathisia" will replace the term"CNS Stimulation" and be added to the Other Events Observed During the Clinical Development of Paroxetine:Nervous System under the subcategory "also observed". Please note that per the algorithm used in this section of Adverse Events (described in paragraph 5 under this section) that for events that occurred with the IR product in clinical studies of depression, OCD, Panic, SAD and GAD labeling that frequencies are not listed. The subject events are for premarketing IR studies and thus fall into this "also observed" category. For clarity the revised section would read:

Nervous System: Infrequent were amnesia, ataxia, convulsion (Note: CR preferred term; moved from below), diplopia, dystonia, emotional lability, hallucinations, hypesthesia, hypokinesia, incoordination, neuralgia, neuropathy, nystagmus, paralysis, paranoid reaction, vertigo, withdrawal syndrome; also observed were abnormal gait, akathisia, akinesia, aphasia, choreoathetosis, circumoral paresthesia, , delirium, delusions, dysarthria, dyskinesia, euphoria, ex! trapyramidal syndrome, fasciculations, grand mal convulsion, hostility, hyperalgesia, i! rritability, libido increased, manic reaction, manic-depressive reaction, meningitis, myelitis, peripheral neuritis, psychosis, psychotic depression, reflexes decreased, reflexes increased, stupor, torticollis [b], trismus.

> 3) With respect to no specific verbatim term
> predominated. The variety of verbatim terms suggests no specific meaning
> that can generally be ascribed to this term. Thus, this term should be
> deleted.

Agree to delete

>
> 4) Regarding most of the verbatim terms fall under
> the rubric of an experience of tightness in the throat (i.e., throat
> tightness, lump in throat, throat constriction). Thus, this term should
> be replaced with "throat tightness."

Agree to replace ." with "throat tightness"

(IMAGE)

Table of Contents
NDA 20-982
Paxil® CR (paroxetine hydrochloride)
Controlled-Release Tablets 12.5 and 25 mg
For Panic Disorder

Approvable Package

MEMORANDUM

DATE: March 8, 1999

FROM: Acting Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-982

SUBJECT: Approvable Memo for NDA 20-982 for Paxil CR in Patients with Panic Attacks

On 4/22/98, SmithKline Beecham submitted NDA 20-982 for the use of Paxil CR for the treatment of patients with panic attacks. Paxil immediate release is approved for depression, OCD, and panic. Paxil CR is approved for depression. Both dosage forms are approved for once a day dosing.

The current supplement contains the results of 3 controlled trials of essentially identical design, in which patients were randomized to drug or placebo, and dosed according to a variable schedule in which doses started at 12.5 mg once a day, and could be titrated to a maximum daily single dose of 75 mg. Double blind treatment lasted for 10 weeks. The protocol specified primary outcome was a comparison of the proportion of patients in each group who had no full panic episodes during the last 2 weeks of double blind treatment. Other important variables included the median change from baseline in number of panic episodes and median change from baseline in CGI.

The data have been reviewed in detail by Dr. Dubitsky, medical officer (review dated 2/1/99) and Dr. Koti, statistician (review dated 2/25/99), and Dr. Laughren, Psychiatric Drugs Team Leader, has completed a summary of the pertinent findings. They all recommend that the application is approvable.

In brief, as Dr. Laughren describes, Study 494 yielded a clearly significant outcome on the primary analysis, and on analysis of the change from baseline in CGI. The analysis of the change from baseline in number of full panic attacks did not reach statistical significance, but was nearly so (p=0.08 for the LOCF analysis).

In Study 495, the LOCF analysis of the primary outcome was clearly not significant though numerically in favor of drug (p=0.26), but the OC analysis reached significance. Analysis of the change in number of attacks was clearly significant, as was the change from baseline in CGI.

Study 497 yielded no statistically significant outcomes on any of the 3 variables of interest.

Dr. Larry Davis contributed patients to Studies 494 and 495, but because there was a treatment by center interaction in Study 495 which was largely due to Dr. Davis' data, the

results described above were obtained with Dr. Davis' data removed. Specifically, in Study 495, he enrolled 16 Paxil patients and 15 placebo patients. All of the Paxil patients had 0 attacks, while none of the placebo patients were attack free. Because the same pattern was seen in his patients for Study 494, (although he enrolled only 4 Paxil and 3 placebo patients), his data was removed from the analysis of this study as well. Dr. Koti performed an analysis of the primary outcome in Study 495 with Dr. Davis' patient data included; it was highly statistically significant.

No important safety issues were identified in this application.

COMMENTS

The sponsor has submitted the results of 3 controlled trials, adequate by design, to establish the effectiveness of Paxil CR as a treatment for panic attacks. One of the trials provides clear support for effectiveness; a second trial (Study 495) is largely supportive, and Study 497 clearly is not.

As Dr. Laughren discusses, a single controlled trial yielding significance would have been considered sufficient to establish the effectiveness of Paxil CR as a treatment for patients with panic attacks, given the approval of the immediate release Paxil for the same indication (and given the relatively similar kinetics of the 2 products, which permit once a day dosing with both). The existence of other trials has the potential to complicate the matter, though, particularly given the less than consistent results seen. However, I agree with the review team that the data are sufficient to establish substantial evidence of effectiveness of Paxil CR in the treatment of panic attacks. Study 495 is essentially a "positive" study (indeed, if a strict Bonferroni correction were applied to the p-values obtained for the change from baseline in number of attacks and CGI, they would still reach statistical significance). It is not clear why Study 497 is clearly not positive, but the positive results for the other 2 studies establish, in my view, the effectiveness of the treatment.

Both Drs. Laughren and Dubitsky agree that it is appropriate for labeling to contain a statement describing the results of a study with the immediate release product demonstrating long term control of patients with panic attacks, because they believe that this result can reasonably be extrapolated to the CR preparation. I believe that this conclusion is based on the view that the different kinetics of the CR compared to the IR will not have a substantive effect on the effectiveness of the treatment in the long term, given that the CR is effective over a 10 week period, and, in any event, the kinetics are not extremely different (again, they are both dosed once a day). I am not completely convinced that long term control can be extrapolated from the IR data, because the difference in kinetics could possibly effect long term response, but the statement proposed makes clear that the prescriber should periodically reevaluate the long term usefulness of the CR. I agree, then, that the proposed statement is reasonable.

For the reasons stated above, I will issue the attached Approvable letter with draft labeling.

/S/

Russell Katz, M.D.

Cc:
NDA 20-982
HFD-120
HFD-120/Katz/Laughren/Dubitsky/Shin

APPEARS THIS WAY
ON ORIGINAL

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 2, 1999

/S/

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

SUBJECT: Recommendation for Approvable Action for Paxil CR (paroxetine controlled release tablets) for the treatment of panic disorder

TO: File NDA 20-982
[**Note:** This overview should be filed with the 4-22-98 original submission.]

1.0 BACKGROUND

Paroxetine is a selective serotonin reuptake inhibitor currently approved and marketed for depression in an immediate release formulation, i.e., Paxil (NDA 20-031, approved December, 1992) and also in the delayed and extended release formulation, i.e., Paxil CR (NDA 20-936, approved 2-16-99), proposed for panic disorder in this application. The immediate release formulation of paroxetine is also approved for OCD and panic disorder. Paxil CR is recommended for qd dosing, as is the immediate release formulation, Paxil. The recommended initial dose for Paxil CR in panic disorder is 12.5 mg/day, with increases up to a maximum dose of 75 mg/day as needed.

At the present time, there are only 4 drugs approved for the treatment of panic disorder in the US, i.e., alprazolam, clonazepam, Zoloft, and as noted, Paxil immediate release tablets.

SKB requested a meeting with the Division even prior to submission of an IND for the controlled release formulation, in order to seek feedback on their planned development program. Although they have not made comparative claims of superior safety in the NDAs subsequently submitted, it was clear at the 7-3-96 meeting that a major rationale for the new formulation was to develop a product less likely to induce nausea, by virtue of its delayed and then more gradual absorption, compared to the immediate release paroxetine. We emphasized the need for carefully conducted studies that would compare the CR and IR forms at equieffective points on the dose response curves for the two formulations. We also suggested that, rather than planning multiple studies for depression, they plan single studies for each of their currently approved indications, i.e., depression, OCD, and panic disorder. They did not accept our advice on either matter, and have not done studies that adequately

address the issue of comparative safety of the two formulations. Presumably they are satisfied with a simple claim of safety and effectiveness for depression and other indications for the CR formulation compared to placebo.

The sponsor submitted protocols for 3 panic disorder studies (494, 495, and 497) on 10-17-96 under

No preNDA meeting was held for this application.

Since the proposal is to use the currently approved Paxil CR controlled release tablets for this expanded population, there was no need for chemistry, pharmacology, or biopharmaceutics reviews of this supplement. The focus was on clinical data. The primary review of the efficacy and safety data was done by Greg Dubitsky, M.D., from the clinical group. Kallappa Koti, Ph.D., from the Division of Biometrics, also reviewed the efficacy data.

The original application for this expanded indication was submitted 4-22-98, and the application was considered adequate for filing on 6-16-98.

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

2.0 CHEMISTRY

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

3.0 PHARMACOLOGY

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

4.0 BIOPHARMACEUTICS

Paxil CR is intended for qd dosing. Paxil CR both delays dissolution with an enteric coat (about 4 hour absorption lag time) and slows the rate of absorption by the use of a polymeric matrix for dispersion (about 25% reduction in rate of absorption). Paxil CR is about 25% less available than Paxil IR; this difference is the basis for the 25% greater dosing of Paxil CR vs Paxil IR in the phase 2-3 clinical trials. The single and multiple-dose pharmacokinetics of Paxil CR have been characterized. There was a 31% reduction in peak to trough plasma level fluctuation for Paxil CR compared to Paxil IR. Although in single dose food studies there was a further delay in absorption with food, Cmax and AUC were unaffected in the steady state food study.

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

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of efficacy was based on the results of 3 randomized, multicenter, placebo-controlled, double-blind, parallel group, flexible-dose, 10-week trials in adult outpatients with a diagnosis of panic disorder with or without agoraphobia (DSM-IV). Patients could not have had another Axis I condition considered as the primary diagnosis within the preceding 6 months. In all studies, assignment was to Paxil CR or placebo (1:1), with treatment initiated at 12.5 mg/day for the first week, followed by dose increases at weekly increments of 12.5 mg, as needed for symptom control, to a maximum dose of 75 mg/day. Patients recorded information on panic attacks in daily diaries, and the protocol specified primary outcome for all three studies was the percentage of patients in each treatment group meeting a response criterion of zero full panic attacks at study endpoint. Secondary outcomes included (1) number of full panic attacks, (2) CGI severity, (3) percentage of time spent with anticipatory anxiety, and (4) the Marks-Sheehan Phobia Scale fear and avoidance scores. Logistic regression was used in the analyses of the primary outcome of percent responders based on zero full panic attacks. Change from baseline in CGI Severity scores was analyzed using the Wilcoxon rank sum test, and the other secondary outcomes were analyzed using analysis of variance. It should be noted that there was no prior agreement with the sponsor on what outcomes would be critical to deciding whether or not the results from a particular trial could be considered positive. Thus, I have focused on the outcomes that we have generally considered key in evaluating data for panic disorder studies, i.e., change from baseline in full panic attacks, percentage of patients achieving zero full panic attacks, and change from baseline in CGI severity scores.

5.1.2 Summary of Studies Pertinent to Efficacy Claims

5.1.2.1 Study 494

This was a US study involving 33 sites. There were approximately 140 patients per group, and the % completing to 10 weeks for Paxil CR and placebo was 74% & 76%, respectively. Patients had a mean age of roughly 38, were slightly more female than male, and were predominantly white. The mean dose for completers in the Paxil CR group was 48 mg/day.

In the LOCF analysis at 10 weeks, for median change from baseline in the number of full panic attacks, Paxil CR was numerically superior (-4 for Paxil CR vs -3 for placebo), but this difference did not achieve statistical significance (p=0.08). In the OC analysis at weeks 9-10, Paxil CR was again numerically superior but with a p-value that again missed statistical significance (p=0.07).

In the LOCF analysis at 10 weeks, for response based on % of patients achieving zero full panic attacks, Paxil CR was numerically superior (69% for Paxil CR vs 50% for placebo, yielding an odds ratio of 2.2), and this difference was statistically significanc (p=0.003). In the OC analysis at weeks 9-10, Paxil CR was again numerically superior with a statistically significant p-value (p=0.005). In the LOCF analysis at 10 weeks, for median change from baseline in the CGI Severity score, Paxil CR was statistically significantly superior to placebo (p=0.03). In the OC analysis at weeks 9-10, Paxil CR was again statistically significantly superior to placebo (p=0.007).

While the results are not entirely consistent, in my view, they are sufficient to consider this a positive study. Thus, I agree with Dr. Dubitsky's conclusion that this study is positive. Dr. Koti also considered this a positive study, based mostly on the results for the proportion of patients free of panic attacks at endpoint.

5.1.2.2 Study 495

This was a US study involving 29 sites. There were approximately 160 patients per group, and the % completing to 10 weeks for Paxil CR and placebo was 67% & 76%, respectively. Patients had a mean age of roughly 37, were slightly more female than male, and were predominantly white. The mean dose for completers in the Paxil CR group was 48 mg/day.

In the LOCF analysis at 10 weeks, for median change from baseline in the number of full panic attacks, Paxil CR was numerically superior (-5 for Paxil CR vs -3 for placebo), and this difference did achieve statistical significance (p<0.001). In the OC analysis at weeks 9-10, Paxil CR was again numerically superior with a p-value that achieved statistical significance (p=<0.001).

In the LOCF analysis at 10 weeks, for response based on % of patients achieving zero full panic attacks, Paxil CR was numerically superior (57% for Paxil CR vs 50% for placebo, yielding an odds ratio of 1.3); however, this difference was not statistically significant (p=0.26). In the OC analysis at weeks 9-10, Paxil CR was again numerically superior (71% for Paxil CR vs 55% for placebo, yielding an odds ratio of 2.0), with a statistically significant p-value (p=0.03).

In the LOCF analysis at 10 weeks, for median change from baseline in the CGI Severity score, Paxil CR was statistically significantly superior to placebo (p=0.004). In the OC analysis at weeks 9-10, Paxil CR was again statistically significantly superior to placebo (p=<0.001).

These results are are again sufficient, in my view, to consider this a positive study. Thus, I agree with Dr. Dubitsky's conclusion that this study is positive. Dr. Koti considered this study supportive since the results were statistically significant on the proportion of patients free of full panic attacks only in the OC analysis, and not in the LOCF analysis. However, the results on the other 2 variables I consider critical in interpreting this study were highly significant on both OC and LOCF analyses, and thus overcame, in my view, the inconsistency on the third outcome of interest.

5.1.2.3 Study 497

This was a US study involving 29 sites. There were approximately 140 patients per group, and the % completing to 10 weeks for Paxil CR and placebo was 70% for both groups. Patients had a mean age of roughly 39, were slightly more female than male, and were predominantly white. The mean dose for completers in the Paxil CR group was 51 mg/day.

In the LOCF analysis at 10 weeks, for median change from baseline in the number of full panic attacks, Paxil CR was numerically superior (-4 for Paxil CR vs -3 for placebo), but this difference did not achieve statistical significance (p=0.24). In the OC analysis at weeks 9-10, Paxil CR was again numerically superior but with a p-value that did not achieve statistical significance (p=0.08).
In the LOCF analysis at 10 weeks, for response based on % of patients achieving zero full panic attacks, Paxil CR was numerically superior (63% for Paxil CR vs 56% for placebo, yielding an odds ratio of 1.4); however, this difference was not statistically significant (p=0.23). In the OC analysis at weeks 9-10, Paxil CR was again numerically but not statistically significantly superior to placebo (p=0.53).

In the LOCF analysis at 10 weeks, for median change from baseline in the CGI Severity score, Paxil CR was not statistically significantly superior to placebo (p=0.08). In the OC analysis at weeks 9-10, Paxil CR was again not statistically significantly superior to placebo (p=0.12).

These results are are not sufficient, in my view, to consider this a positive study. Thus, I agree with Dr. Dubitsky's and Dr. Koti's conclusions that this study is negative. There was no active control arm to test the sensitivity of the study to detect a treatment effect.

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

Evidence Bearing on the Question of Dose/Response for Efficacy

There were no data in this development program pertinent to the issue of dose/response for the CR formulation, and there were also insufficient data pertinent to this issue in the original NDA for panic disorder for the immediate release product. Thus, one can at most recommend dosing patients in the ranges utilized and on the incremental schedule utilized in the trials supporting the effectiveness of this new formulation.

Clinical Predictors of Response

While there was a very limited potential for detecting subgroup interactions on the basis of demographics, severity of illness, or other covariates, there was no pattern of findings suggestive of any such interactions.

Size of Treatment Effect

One of the difficulties in assessing treatment effect size in panic disorder studies is that there is often a large placebo response. That was certainly the case here, even more so than for the Paxil immediate release program. Consequently, the drug placebo difference is not as quite as impressive for these data compared to those for the immediate release program, especially when looking at % responders based on zero full panic attacks, as Dr. Dubitsky has done. However, when looking at difference in change from baseline in the mean number of full panic attacks, the result is roughly the same for both programs, i.e., a difference between drug and placebo of roughly 1-2 panic attacks. This treatment effect is also comparable to what we have seen for the other drugs approved for the treatment of panic disorder.

Duration of Treatment

While there were no data in this development pertinent to duration of effect, there were data suggestive of longer-term effectiveness for panic disorder for the immediate release product, and it would not be unreasonable, in my view, to extrapolate from those data to the CR formulation.

5.1.3 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence from two trials to support the claim of effectiveness for Paxil CR in the treatment of panic disorder. While the third study was negative, I consider the data in the aggregrate sufficient to extend the anti-panic claim to this controlled release formulation of paroxetine.

5.2 Safety Data

Clinical Data Sources for Safety Review

The safety data for paroxetine CR were reviewed by Dr. Dubitsky. This original review was based on an integrated database with a cutoff date of 10-22-97 for the 1 phase 1 study (569: an open label PK study) and the 3 phase 2-3 studies (494, 495, 497; described under Efficacy Data) for this development program. The total paroxetine CR exposed sample consisted of n=80 normal volunteers in the single dose PK study and n=444 panic disorder patients in the 3 clinical studies. The demographics and dosing for the patients were previously summarized under Efficacy Data. Dr. Dubitsky has also very recently reviewed the paroxetine CR safety data for the Paxil CR depression program, consisting of n=371 normal volunteers and n=316 depressed patients.

Adverse Event Profile for Paroxetine CR

Given our extensive knowledge of the safety profile for immediate release paroxetine, and our recent review of paroxetine CR exposures in the Paxil CR depression program in a similar dose range to that proposed for the treatment of panic disorder, the focus in the safety review was on any differences

between the recognized safety profile for this drug, both in the immediate and controlled release formulations, in its approved indications from that observed in the panic disorder population.

Overall, the side effect profile of paroxetine CR in the panic disorder population was as expected for this SSRI and not obviously different from that of the immediate release product in the various populations in which it has been studied, including panic disorder, or from this same controlled release product in a depressed population. There were no new, unrecognized serious adverse events that could be considered related to paroxetine CR use or that would impact on the labeling of this product.

5.3 Clinical Sections of Labeling

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

6.0 WORLD LITERATURE

There were no published papers specifically concerning the CR formulation of paroxetine. We will ask for a literature update in the approvable letter.

7.0 FOREIGN REGULATORY ACTIONS

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

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

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

9.0 DSI INSPECTIONS

Although DSI did not conduct investigations specific to this application, they did check the list of investigators for those previously inspected and classified as VAI-3 or worse. Only 1 investigator, Dr. Cal Cohn, was in that category. He is on the "restricted" list, but the requirement for third party verification has apparently been met. Consequently, there was no need to exclude data from this investigator.

10.0 LABELING AND APPROVABLE LETTER

10.1 Final Draft of Labeling Attached to Approvable Package

Our proposed draft of labeling is attached to the approvable letter. As noted, we have modified the sponsor's draft dated 4-22-98.

10.2 Foreign Labeling

Paxil CR is not marketed anywhere at this time.

10.3 Approvable Letter

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

11.0 CONCLUSIONS AND RECOMMENDATIONS

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

cc:
Orig NDA 20-982 (Paxil CR/Panic Disorder)
HFD-120/Div File
HFD-120/TLaughren/RKatz/GDubitsky/MShin

DOC: MEMPXRPD.AE1

OFFICES OF DRUG EVALUATION
ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST

NDA #_20982__
Drug _Paxil CR (paroxetine HCL) controlled-release 12.5 & 25mg Tablets DATE_ 04/22/98____
Applicant_SmithKline Beecham___CSO_Melaine Shin__/Phone_x 4-5527_____
User Fee Goal Date:_04/22/99_____

Arrange package in the following order:	Check or Comment
1. ACTION LETTER with supervisory signatures	AP_____AE__X__ NA_____
Are there any Phase 4 commitments?	Yes_____ No___X_____
2. Have all disciplines completed their reviews?	Yes___X____ No_____
If no, what review(s) is/are still pending?	_____
3. Completed copy of this CHECKLIST in package	Chem/Ther Types__3S___
4. LABELING (package insert and carton and container labels).	Draft_____
(If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.)	Revised Draft_____X_____ Final_____
5. PATENT INFORMATION	____X_____
6. EXCLUSIVITY CHECKLIST	____X_____
7. PEDIATRIC PAGE	____X_____
8. DEBARMENT CERTIFICATION (Copy of applicant's certification for all NDAs submitted on or after June 1, 1992).	__X____
9. Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES	__Memo___
If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status. If no audits were requested, include a memo expaining why.	
10. REVIEWS:	
DIVISION DIRECTOR'S MEMO (If more than 1 review for any discipline, separate reviews with a sheet of colored paper. Any conflicts between reviews must have resolution documented)	_____X_____
GROUP LEADER'S MEMO	_____X_____
MEDICAL REVIEW	_____X_____
SAFETY UPDATE REVIEW	_____N/A_____
STATISTICAL REVIEW	_____X_____
BIOPHARMACEUTICS REVIEW	_____X_____
PHARMACOLOGY REVIEW (Include pertinent IND reviews)	_____Memo_____
Statistical Review of Carcinogenicity Study(ies)	_____N/A_____
CAC Report/Minutes	_____N/A_____
CHEMISTRY REVIEW	_____X_____
Labeling and Nomenclature Committee Review Memorandum	_____X_____
Date EER completed __8/4/98___ (attach signed form or CIRTS printout) FUR needed __n/a___ FUR requested _n/a___	OK__X___ No_____
Have the methods been validated?	Yes (attach)_____ No__X___
Environmental Assessment Review / FONSI	Review __n/a____ FONSI_n/a___
MICROBIOLOGY REVIEW	_____n/a_____
What is the status of the monograph?	_____
11. CORRESPONDENCE, MEMORANDA OF TELECONS, and FAXes	_____X_____
12. MINUTES OF MEETINGS	_____X_____
Date of End-of-Phase 2 Meeting	___n/a_____
Date of pre-NDA Meeting	___n/a_____
13. ADVISORY COMMITTEE MEETING MINUTES or, if not available, 48-Hour Info Alert or pertinent section of transcript.	Minutes_____ Info Alert_____ Transcript_____ No mtg__X___
14. FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS	_____n/a_____
15. If approval letter, has ADVERTISING MATERIAL been reviewed?	Yes_____ No__n/a_____
If no and this is an AP with draft labeling letter, has advertising material already been requested?	Yes, documentation attached_____ No, included in AP ltr _____
16. INTEGRATED SUMMARY OF EFFECTIVENESS	_____X_____
17. INTEGRATED SUMMARY OF SAFETY	_____X_____

revision: 3/7/96

Paxil® CR (paroxetine hydrochloride)
Controlled-Release Tablets

ITEM 13/14 - PATENT INFORMATION

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

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

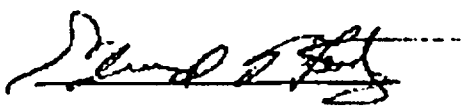
(continued on next page)

Paxil® CR (paroxetine hydrochloride) Controlled-Release Tablets

4 839 177	June 13, 2006	Drug Product	Jagotec AG, Hergiswill, Switzerland	Parkhurst, Oliff & Berridge
5 422 123	June 6, 2012	Drug Product	Jagotec AG, Hergiswill, Switzerland	Birch, Stewart, Kolasch & Birch

The undersigned declares that Patent No's 4 839 177 and 5 422 123 cover the formulation, composition and/or method of use of paroxetine hydrochloride controlled release formulation. This product is the subject of this application for which approval is being sought:

SmithKline Beecham

By: 

Edward T. Lentz
Vice President & Director
Corporate Intellectual Property - US

APPEARS THIS WAY
ON ORIGINAL

Trade Name Paxil CR Generic Name: Paroxetine HCL Controlled Release 12.5&25mg Tablets

Applicant Name: SmithKline Beecham HFD - 120
Approval Date If Known _____

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 question about the submission.

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

b) Is it an effectiveness supplement?

YES /___/ NO /_X_/

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

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 /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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 8.

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 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES /_X_/ NO /___/

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

NDA# 20-031 Paxil (paroxetine HCL) Immediate Release 10, 20, 30, and 40mg Tablets

NDA# 20-936 Paxil CR (paroxetine HCL) Controlled Release 12.5 and 25mg Tablets

2. Combination product.

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

YES /___/ NO /_X_/

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 8. IF "YES" GO TO PART III.

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

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

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

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

(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 8:

(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 # 494

Investigation #2, Study # 495

Investigation #3, Study # 497

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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:

_____ _____

_____ _____

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 investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

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 # 494
Investigation #2,	Study # 495
Investigation #3,	Study # 497

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

_____ YES /_X_/ NO /___/ Explain: _____

Investigation #2

_____ YES /_X_/ NO /___/ Explain: _____

Investigation #3

_____ YES /_X_/ NO /___/ Explain: _____

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

Investigation #1

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

Investigation #2

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

APPEARS THIS WAY
ON ORIGINAL

(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: _____

_____

/S/ 3/9/99

Signature of preparer Date

Title: CSO/PM

/S/ 3/9/99

Signature of ~~Office~~/ Date

Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

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ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

Mr 3/9/99

NDA/BLA Number:	20982	**Trade Name:**	PAXIL CR (PAROXETINE HCL) TABS 12.5MG
Supplement Number:		**Generic Name:**	PAROXETINE HCL TABS 12.5MG
Supplement Type:		**Dosage Form:**	CRT
Regulatory Action:	AE	**Proposed Indication:**	Panic Disorder, with or without agoraphobia

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? NO

What are the INTENDED Pediatric Age Groups for this submission? N/A

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

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

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
3/5/99 Since the diagnosis of panic disorder generally would not be made in pediatric patients, there is no need for pediatric information in labeling re: this diagnosis and no need for a phase 4 commitment to conduct studies in pediatric patients with this disorder.

Studies are ongoing (studies being conducted on the immediate release formulation, NDA 20-031)

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, LANA CHEN

/S/ 3/5/99

Signature Date

DEBARRMENT STATEMENT

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

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **NDA 20982/000**
Stamp: **22-APR-1998** Regulatory Due: **22-APR-1999**
Applicant: **SKB PHARMS**
1250 SOUTH COLLEGEVILLE RD
COLLEGEVILLE, PA 194260989

Priority: **3S** Org Code: **120**
Action Goal: District Goal: **21-DEC-1998**
Brand Name: **PAXIL CR (PAROXETINE HCL) TABS 12.5/25MG**
Established Name:
Generic Name: **PAROXETINE HCL TABS 12.5/25MG**
Dosage Form: **CRT (CONTROLLED RELEASE TABL**
Strength: **12.5,25,37.5,50 MG**

FDA Contacts:

A. HOMONNAY WEIKEL	**(HFD-120)**	**301-594-5535**	**, Project Manager**
R. LOSTRITTO	**(HFD-570)**	**301-594-5564**	**, Review Chemist**
R. SEEVERS	**(HFD-120)**	**301-594-2850**	**, Team Leader**

Overall Recommendation:

ACCEPTABLE on 04-AUG-1998 by M. EGAS (HFD-322) 301-594-0095

Establishment: **9612240**
SMITHKLINE BEECHAM
MANOR RD WEST RH10 2QJ
CRAWLEY, ENGLAND - WEST SUSS
DMF No:
AADA No:

Profile: **TCT** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **04-AUG-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment: **9610449**
SMITHKLINE BEECHAM CHEMICA
AYRSHIRE, SCOTLAND
, IRVINE, UK
DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **07-MAY-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
DRUG SUBSTANCE RELEASE TESTER

APPEARS THIS WAY
ON ORIGINAL

Consult #841 (HFD-120)

PAXIL CR paroxetine hydrochloride controlled release tablets

There were no look-alike/sound-alike conflicts noted or misleading aspects found in the proposed proprietary name.

The Committee has no reason to find the proposed proprietary name unacceptable.

/S/ 9/9/97, Chair
CDER Labeling and Nomenclature Committee

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

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

DATE: February 22, 1999
FROM: Alfreda Burnett, HFD-344
TO: Melaine Shin, HFD-120
SUBJECT: NDA 20-982: Paxil CR (paroxetine HCl)
Panic Disorder

On April 22, 1998 SmithKline Beecham submitted NDA 20-982 for Paxil CR for the treatment of Panic Disorder. Paxil is already an approved drug product, this NDA covers a new formulation and new indication. DSI does not routinely assign inspections of new formulations or new indications. We have reviewed the list of investigators for those previously inspected and classified as VAI-3 or worse.

C [redacted] A requirement of this restriction is that there be third party verification of subject identification. The sponsor has submitted verification of subject identification. The data from his site can be used to support the approval requests for this NDA.

/s/ Alfreda Burnett

APPEARS THIS WAY
ON ORIGINAL

E L E C T R O N I C M A I L M E S S A G E

Date: 04-Nov-1998 11:20am EST
From: Anna Marie Homonnay
HOMONNAYA
Dept: HFD-120 WOC2 4025
Tel No: 301-594-5535 FAX 301-594-3839

D: Alfreda Burnett (BURNETTA)

ubject: FWD: re: NDA 20-982/Paxil CR/Panic

lfreda,

nstead of calling, I think it's better if I forward you our request with egards to DSI. Please let me know if you have anymore questions.

nna Marie

APPEARS THIS WAY
ON ORIGINAL

E L E C T R O N I C M A I L M E S S A G E

Date: 04-Nov-1998 09:30am EST
From: Anna Marie Homonnay
HOMONNAYA
Dept: HFD-120 WOC2 4025
Tel No: 301-594-5535 FAX 301-594-3839

O: Greg Dubitsky (DUBITSKYG)

C: Thomas Laughren (LAUGHREN)

ubject: re: NDA 20-982/Paxil CR/Panic

reg,

SI called today to check which of the clinical trials would be considered
ore pivotal than the other since they are planning to choose to inspect one?

hanks,

nna Marie

Request for Audit

DATE: October 27, 1998

FROM: Division of Neuropharmacological Drug Products, HFD-120.

SUBJECT: Request for Study-Oriented Audits for sNDA

TO: DSI Staff: Alfreda Burnett

Please refer to a correspondence to Dr. Robert Young dated May 27, 1998, from SmithKline Beecham Pharmaceuticals regarding NDA 20-982 for Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets in the treatment of Panic Disorder.

Please audit any sites as necessary. The due date of this application is 4/22/99. If you should have any questions, please contact: Ms. Anna M. Homonnay-Weikel, Project Manager at (301) 594-5535.

DUPLICATE

SmithKline Beecham
Pharmaceuticals

May 27, 1998

Anna M. Homonnay-Weikel
Project Manager

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

Agency Request for Information

[illegible] AMENDMENT
NCBM

Dear Anna,

Reference is made to NDA 20-982 for Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets in the treatment of Panic Disorder.

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

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

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

Sincerely,

Thomas F. Kline
Manager
US Regulatory Affairs

Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets

for Panic Disorder

NDA 20-982

List of Investigators (and No. of Patients): Alphanumeric by Protocol

For clinical studies 29060/494, 495 and 497

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
STUDY 494					
Apter, Jeffrey T., M.D. Princeton Biomedical Research 256 Bunn Drive Suite 6 Princeton, NJ 08540 *and* Princeton Biomedical Research Axelrad Building 809 River Rd (Rt 9) Lakewood, NJ 08701	United States	494/001	8	8	16

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Bielski, Robert J., M.D. Institute for Health Studies 26105 Orchard Lake Rd. Suite 301 Farmington Hills, MI 48334 *and* Institute for Health Studies 825 Parchment Dr., S.E. Grand Rapids, MI 49546 *and* Institute for Health Studies 4084 Okemos Road Suite C Okemos, MI 48864	United States	494/002	4	5	9
Bremner, James D., M.D. Bremner Research Institute, Inc. 1021 West 4th - Suite G Olympia, Washington 98502	United States	494/003	2	2	4
Bystritsky, Alexander, M.D. University of California, Los Angeles 300 UCLA Medical Plaza, Suite 2200 Los Angeles, CA 90095	United States	494/004	4	5	9
Carman, John S., M.D. Carman Research 4015 South Cobb Drive Suite 245 Smyrna, GA 30080	United States	494/005	3	3	6

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Dave, Mahesh R., M.D. Sciman Biomedical Research, Inc. 1303 Memorial Drive Bryan ,Texas 77802 *and* Sciman Biomedical Research, Inc. 2901 E. 29th Street, Suite 117 Bryan, Texas 77802	United States	494/006	4	4	8
Feiger, Alan, P.C., M.D. Feiger Health Research Center 3003 E. Third Avenue Denver, CO 80206 *and* Feiger Health Research Center 3555 Lutheran Pkwy, Suite 320 Wheat Ridge, CO 80033	United States	494/007	4	5	9
Helfing, Saul H., M.D. Hill top Research 5331 SW Macadam Avenue, Suite 210 Portland, OR 97201	United States	494/008	12	12	24
Hollander, Eric, M.D. Department of Psychiatry, Box 1230 Mount Sinai School of Medicine One Gustave L. Levy Place New York, NY 10029	United States	494/009	2	2	4

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Houck, Carl A., M.D. University of Alabama at Birmingham Department of Psychiatry/Clinical Research Professional Arts Building, Suite 302 1025 18th Street South Birmingham, AL 35205	United States	494/010	1	0	1
Jefferson, James W., M.D. Dean Foundation for Health, Research and Education 8000 Excelsior Drive, Suite 302 Madison, WI 53717-1914	United States	494/011	2	4	6
Kennedy, Barbara L., M.D., Ph.D. Department of Psychiatry and Behavioral Sciences School of Medicine University of Louisville Louisville, KY 40202	United States	494/012	3	4	7
Londborg, Peter D., M.D. Seattle Clinical Research Center, Inc. Cabrini Medical Tower 901 Boren Ave., Suite 1800 Seattle, WA 98104	United States	494/013	8	8	16

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Miller, Kevin, M.D. St. Louis University Health Sciences Center Department of Psychiatry 1221 South Grand Blvd. St. Loius, MO 63104 *(Co-Investigator with Joan Busner, Ph.D. and Jeff Gall, M.D.* Busner, Joan, Ph.D. St. Louis University Health Sciences Center Department of Psychiatry 1221 South Grand Blvd. St. Loius, MO 63104 *(Co-Investigator with Kevin Miller, M.D.* Gall, Jeff, M.D. St. Louis University Health Sciences Center Department of Psychiatry 1221 South Grand Blvd. St. Loius, MO 63104 *(Co-Investigator with Kevin Miller, M.D.)*	United States	494/014	3	4	7
Pavlinac, Dennis M., M.D. 3907 Waring Road, Suite 3 Oceanside, CA 92056	United States	494/015	3	3	6
Rea, William S., M.D. Clinical Studies, Fort Lauderdale 108 N.E. 1st Street Fort Lauderdale, FL 33301	United States	494/016	6	7	13

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Reiman, Eric M., M.D. Good Samaritan Regional Medical Center Samaritan Behavioral Health 925 E. McDowell Road - 4th Floor Phoenix, AZ 85006	United States	494/017	5	4	9
Schweizer, Edward, M.D. Mood & Anxiety Disorders Section University Science Center 3600 Market Street Philadelphia, PA 19104-2649	United States	494/018	0	0	0
Sheehan, David V., M.D. University of South Florida College of Medicine, Dept. of Psychiatry 3515 E. Fletcher Ave. Tampa, FL 33613-4788	United States	494/019	10	10	20
Shelton, Richard C., M.D. Vanderbilt University Medical Center 2200 Village at Vanderbilt 1500 21st Ave, South Nashville, TN 37212	United States	494/020	5	6	11
Smith, Ward T., M.D. Pacific Northwest Clinical Research Center 9495 S.W. Locust, Suite E Portland, OR 97223 *and* Pacific Northwest Clinical Research Center 2212 Lloyd Center Portland, OR 97232	United States	494/021	5	5	10

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Stein, Murray B., M.D. UCSD Department of Psychiatry Anxiety & Traumatic Stress Disorders Program 8950 Villa La Jolla Dr., Ste #2243 La Jolla, CA 92037	United States	494/022	3	4	7
Targum, Steven D., M.D. Philadelphia Medical Institute 1015 Chestnut St., Suite 1303 Philadelphia, PA 19107 *and* Crozer-Chester Medical Center Old Main President's Blvd. Upland, PA 19013	United States	494/023	2	4	6
Thompson, Peter M., M.D. University of New Mexico Health Sciences Center Department of Psychiatry, Research Office/Lab 943 Stanford Drive NE. Medical Bldg. 6 Albuquerque, NM 87131-5326	United States	494/024	6	6	12
Trivedi, Madhukar H., M.D. University of Southwestern Medical Center St. Paul POB I, Suite #520 5959 Harry Hines Blvd. Dallas, TX 75235-9101	United States	494/025	3	3	6

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Weihs, Karen, M.D. Clinical Psychiatric Research Center George Washington University Medical Center Ross Hall R,. 730 2300 eye Street, N.W. Washington, DC 20037	United States	494/026	8	7	15
Merideth, Charles H., M.D. Affiliated Research Institute 8880 Rio San Diego Drive, Suite 1090 San Diego. CA 92108	United States	494/027	7	7	14
Donley, Patrick J., M.D. Puget Sound Medical Research A Division of Hill Top Research, Ltd. 6210 75th St. West, Suite A200 Tacoma, WA 98467	United States	494/028	4	4	8
Simon, Jeffrey S., M.D. Northbrooke Research Center 4600 West Schroeder Drive Brown Deer, WI 53223	United States	494/029	2	1	3
Kaplan, Barnett, M.D. Rainer Clinical Research Center 4033 Talbot Road South, #500 Renton, WA 98055 *and* Southlake Professional Group 1400 Talbot Road South, #203 Renton, WA 98055	United States	494/030	1	1	2

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Hartford, Madelon, M.D. Hartford Research Group 3120 Burnet Avenue Suite 103 Cincinnati, OH 45229	United States	494/031	3	3	6
Mattes, Jeffrey A., M.D. Psychopharmacology Research Association of Princeton Princeton Professional Park 601 Ewing St., Ste A-12 Princeton, NJ 08540	United States	494/032	4	4	8
Davis, Larry M., M.D. Broad Ripple MedCheck 1091 Broad Ripple Avenue Indianapolis, IN 46220 *and* Davis Clinic, P.C. 1431 North Delaware Street Indianapolis, IN 46202	United States	494/033	4	3	7

APPEARS THIS WAY
ON ORIGINAL

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
STUDY 495					
Adler, Lawrence W., M.D. Clinical Insights, Inc. 1600 Crain highway South, Suite 601 Glen Burnie, MD 21061 *(Co-Investigator with Marc Hertzman, M.D.)* *and* Clinical Research Center 1600 Crain Highway South, Suite 410 Glen Burnie, MD 21061 *(Co-Investigator with Marc Hertzman, M.D.)* Hertzman, Marc, M.D. Clinical Research Center 1600 Crain Highway South, Suite 410 Glen Burnie, MD 21061 *(Co-Investigator with Lawrence W. Adler, M.D.)* *and* Clinical Insights, Inc. 1600 Crain highway South, Suite 601 Glen Burnie, MD 21061	United States	495/001	6	7	13

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Beitman, Bernard D., M.D. University of Missouri-Columbia University School of Medicine One Hospital Drive Columbia, MO 65212 *(Co-Investigator with Lee Ann Kelley, M.D.)* Kelley, Lee Ann M.D. University of Missouri-Columbia University School of Medicine One Hospital Drive Columbia, MO 65212 *(Co-Investigator with Bernard D Beitman, M.D.)*	United States	495/002	3	3	6
Bell, Jon, M.D. University of Colorado Health Sciences Center Anxiety and Mood Disorders Clinic C-261-72 4200 E. 9th Avenue Denver, CO 80262	United States	495/003	4	4	8
Burke, William, M.D. Psychopharmacology Research Center University of Nebraska Medical Center 600 South 42nd Street Omaha, NE 68198-5575	United States	495/004	2	4	6

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Davis, Larry M., M.D. Davis Clinic, P.C. 1431 North Delaware Street Indianapolis, IN 46202 *and* Broad Ripple MedCheck 1091 Broad Ripple Ave. Indianapolis, IN 46220	United States	495/005	16	16	32
DuPont, Robert, M.D. Institute for Behavior and Health 6191 Executive Blvd. Rockville, MD 20852	United States	495/006	2	1	3
England, Donald L., M.D. PeaceHealth Medical Group 1162 Williamette Street Eugene, OR 97401	United States	495/007	8	8	16
Depriest, Michael, M.D. Pharmacology Research Corporation 516 south 6th Street, Suite 100 Las Vegas, NV 89104 *(Co-Investigator with James M. Ferguson, M.D.)* Ferguson, James M., M.D. Pharmacology Research Corporation 516 south 6th Street, Suite 100 Las Vegas, NV 89104 *(Co-Investigator with Michael Depriest, M.D.)*	United States	495/008	3	3	6

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Gorman, Jack, M.D. Phobia Clinic, Hillside Hospital Long Island Jewish Medical Center 75-59 263rd Street Glen Oaks, NY 11004 *(Co-Investigator with Laszlo Papp, M.D.)* Papp, Laszlo, M.D. Phobia Clinic, Hillside Hospital Long Island Jewish Medical Center 75-59 263rd Street Glen Oaks, NY 11004 *(Co-Investigator with Jack Gorman, M.D.)*	United States	495/009	5	5	10
Hartford, James T., M.D. Hartford Research Group 273 Regency Ridge Dayton, OH 45459	United States	495/010	12	12	24
Heiser, Jon F., M.D. Pharmacology Research Institute 1000 Dove Street, Suite 200 Newport Beach, CA 92660-2814 *and* 3505 Long Beach Blvd., Suite 2F Long Beach, CA 90807-3947	United States	495/011	2	1	3

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Kalali, Amir, M.D. The Irvine Clinical Research Center 16259 Laguna Canyon Road Irvine, CA 92618 *(Co-Investigator with Sid Rosenblatt, M.D.)* Rosenblatt, Sid, M.D. The Irvine Clinical Research Center 16259 Laguna Canyon Road Irvine, CA 92618 *(Co-Investigator with Amir Kalali, M.D.)*	United States	495/012	8	8	16
Mattes, Jeffrey A., M.D. Psychopharmacology Research Association of Princeton Princeton Professional Park 601 Ewing Street, Suite A-12 Princeton, NJ 08540	United States	495/013	12	13	25
Nemeroff, Charles B., M.D., Ph.D. Emory University Department of Psychiatry & Behavioral Sciences 1701 Uppergate Drive, Room 126 Atlanta, GA 30322 *(Co-Investigator with Philip T. Ninan, M.D.)* Ninan, Philip T, M.D. Emory University Department of Psychiatry & Behavioral Sciences 1701 Uppergate Drive, Room 126 Atlanta, GA 30322 *(Co-Investigator with Charles B. Nemeroff, M.D., Ph.D.)*	United States	495/014	1	2	3

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Patterson, William M., M.D. Birmingham Research Group, Inc. 2120 Lynngate Drive Birmingham, AL 35216	United States	495/016	5	6	11
Pollack, Mark H., M.D. Massachusetts General Hospital ACC-815, 15 Parkman Street Boston, MA 02114	United States	495/017	3	4	7
Resnick, Harvey, M.D. 321 E. Phillips Road Angleton, TX 77515 *and* 135 Oyster Creek Drive Suites S & W Lake Jackson, TX 77566 *and* 201 Oak Drive South Suites 102, 107 & 204 Lake Jackson, TX 77566 *and* 52 Flag Lake Plaza Lake Jackson, TX 77566 *and* 106 Circle Way Lake Jackson, TX 77566	United States	495/018	5	4	9
Rosenthal, Murray H., D.O. 9449 Balboa Avenue Suite 205 San Diego, CA 92123	United States	495/019	8	8	16

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Strawn, Steven K., M.D. Freedom Research, Inc. 1303 FM 2818 East College Station, TX 77840	United States	495/020	2	1	3
Telew, Nicholas W., M.D. OCCI 132 East Broadway Suite 332 Eugene, Oregon 97401 *and* Mental Health Match 175 West B Street Building B Springfield, Oregon 97401 *and* Oakway Internal Medicine 495 Oakway Road Eugene, Oregon 97401	United States	495/021	14	13	27
Templeton, Richard K., M.D. The Psychiatric Research Group 110 Annapolis Street Annapolis, MD 21401	United States	495/022	4	5	9
Tucker, Phebe, M.D. University of Oklahoma Health Science Center Department of Psychiatry 920 Stanton L. Young Blvd. (5SP520) Oklahoma City, OK 73104	United States	495/023	5	5	10

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Weisler, Richard H., M.D. Duke University Medical Centre Ervin Drive Durham, North Carolina 27709 *and* 900 Ridgefield Drive, Suite 320 Raleigh, North Carolina 27609	United States	495/024	9	6	15
Weiss, Kenneth J., M.D. 722 E. Butler Pike Ambler, PA 19002 *and* 400 Market Street P.O. Box 1990 Camden, NJ 08101 *and* 2792 Egypt Road Audubon, PA 19403 *and* Suburban Psychiatric Assoc. 600 N. Jackson Street Media, PA 19063 *and* Delaware Valley Research Assoc. 133 Ivy Lane King of Prussia, PA 10406	United States	495/025	9	9	18
Charles, Lorna, M.D. Southern New Jersey Medical Institute 9 East Laurel Road Stratford, NJ 08084	United States	495/026	4	3	7

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Cunningham, Lynn A., M.D. Vine Street Clinic 301 No. Sixth St., Suite 330 Springfield, IL 62701 *and* Clinical Research Associates of Edwardsville 1121 University Drive Edwardsville, IL 62025	United States	495/027	1	2	3
Stack, Jack M., M.D. Gratiot Community Hospital 300 Warwick Alma, MI 48801	United States	495/028	2	2	4
Goldstein, Susanna, M.D. Center for Psychobiology 65 Central Park West, # 1BR New York, NY 10023	United States	495/030	5	6	11
Stoltz, Randall R., M.D. GFI Pharmaceutical Services, Inc. 800 St. Mary's Drive Evansville, IN 47714	United States	495/031	3	4	7

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
STUDY 497					
Bastini, Bijan, M.D. North East Ohio Health Services One Commerce Park Square 23200 Chagrin Blvd., Suite 400 Beachwood, OH 44122 *and* Portage Path CMHC 340 South Broadway St. Akron, OH 44308	United States	497/001	1	1	2
Brown, David, M.D. Community Clinical Research, Inc. 4411 Medical Parkway Austin, Texas 78756	United States	497/002	8	7	15
Bryer, Joseph, M.D. Clary Research Associates, P.A. 575 South duPont Highway New Castle, DE 19720	United States	497/003	3	3	6
Cohn, Cal K., M.D. The Cohn Center 7777 Southwest Freeway Suite 1036 Houston. TX 77074	United States	497/004	16	16	32

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Delgado, Pedro, M.D. University of Arizona Health Science Center 1501 N. Campbell Ave. Tucson, AZ 85724 *(Co-Investigator with Alan Gelenberg, M.D.)* Gelenberg, Alan, M.D. University of Arizona Health Science Center 1501 N. Campbell Ave. Tucson, AZ 85724 *(Co-Investigator with Delgado, Pedro, M.D.)*	United States	497/005	6	7	13
DuBoff, Eugene A., M.D. Center for Behavioral Medicine 4704 Harlan Street Suite 430 Denver, CO 80212	United States	497/006	6	4	10
Ferguson, James M., M.D. Pharmacology Research Corporation Commerce Park 448 East 6400 South, Suite 350 Salt Lake City, Utah 84107	United States	497/007	7	7	14
Haefner, Gregory, M.D. Wein Center (1st Floor MRI Building) Mount Sinai Medical Center 4300 Alton Road Miami Beach, FL 33140	United States	497/008	5	6	11
Holland, Peter J., M.D. 7280 W. Palmetto Park Road #203 Boca Raton, FL 33433	United States	497/009	5	4	9

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Kavoussi, Richard J., M.D. Allegheny University of the Health Sciences EPPPI Room 250A 3200 Henry Avenue Philadelphia, PA 19129	United States	497/010	2	2	4
Khan, Arifulla, M.D. Hambleton Professional Building 10126 NE 132nd Suite B Kirkland, WA 98034	United States	497/011	8	7	15
Landbloom, Ronald, M.D. St. Paul-Ramsey Medical Center 640 Jackson Street St. Paul, MN 55101	United States	497/012	4	3	7
Leefeldt, Randall Henshaw, M.D. Sutter Institute for Medical Research 2801 K Street, Suite 505 Sacramento, CA 95816 *and* Sutter Community Clinic - Fruitridge 1740 Fruitridge Road Sacramento, CA 95822	United States	497/013	2	2	4
Lydiard, R. Bruce, M.D., Ph.D. Medical University of South Carolina 171 Ashley Avenue Charleston, South Carolina 29425	United States	497/014	7	7	14

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Murphy, John J., M.D. 820 W. Service Avenue West Corina, CA 91790 *(Co-Investigator with Dennis J. Munjack, M.D.)* Munjack, Dennis J., M.D. 820 W. Service Avenue West Corina, CA 91790 *(Co-Investigator with Murphy, John J., M.D.)*	United States	497/015	6	6	12
Reimherr, Fred W., M.D. Department of Psychiatry University of Utah Health Sciences Center Mood Disorders Clinic 50 North Medical Drive Salt Lake City, UT 84132	United States	497/016	3	4	7
Riesenberg, Robert A., M.D. BioBehavioral Associates 625 DeKalb Industrial Way Decatur, GA 30033	United States	497/017	12	9	21
Schram, Peter, M.D. Menninger Clinic 5800 SW Sixth Avenue PO Box 829 Topeka, KS 66601-0829	United States	497/018	2	3	5

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Seiden, Leslie M.D. Center for Research in Anxiety, Inc. 133 East 91st Street New York, New York 10128 *(Co-Investigator with JoAnne Santo, Ph.D.)* Santo, JoAnne, Ph.D. Center for Research in Anxiety, Inc. 133 East 91st Street New York, New York 10128 *(Co-Investigator with Leslie Seiden, M.D.)*	United States	497/019	7	8	15
Simpson, George M., M.D. LAC + USC Medical Center Psychiatric Outpatient Clinic 1937 Hospital Place Los Angeles, CA 90033	United States	497/020	0	1	1
Udelman, Harold D., P.C., M.D. 45 E. Osborn Road Phoenix, AZ 85012	United States	497/022	4	4	8
Zimbroff, Dan L., M.D. Behavioral Medicine Center Loma Linda University Med. Center 1710 Barton Road Redlands, CA 92373	United States	497/023	7	6	13
Kukha-Mohamad, S., M.D. 515-750 Spadina Cresent East Saskatoon, SK S7K 3H3	Canada	497/024	4	3	7
La Jeunesse, Charles, M.D. Management Pharmaco-Medical (MPM) 1134 Chemin St-Louis Sillery, Quebec G1S 1E5	Canada	497/025	2	3	5

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Morris, Paul, M.D. Toronto Centre for Behavioral Medicine Inc. 1243 Islington Ave. #608 Toronto, Ontario, Canada M8X 1Y9	Canada	497/026	2	0	2
Savard, Pierre, M.D., Ph.D. Hospital du Care-Coeur de Montreal 1575 Henri-Bourssa O. Montreal, Canada H3M 3A9	Canada	497/027	4	5	9
Turner, Peter G., M.D. Mood and Anxiety Disorders Clinic 3155 Harvester Rd., Suite 310 Burlington, Ontario L7N 3V2 *and* 30 Plains Road Burlington, Ontario L7T 2C6	Canada	497/028	7	8	15
Melchor, Pedro, M.D. 2348 N. 7th Street Miami, FL 33125 *and* Community Mental Health Center 1469 N.W. 36 St. Miami, FL 33142	United States	497/029	5	4	9

NAME	COUNTRY	PROTOCOL / CENTER NUMBER	Paxil CR No. of patients randomized	Placebo No. of patients randomized	Total number of patients randomized
Sokolski, Kenneth N., M.D. Affiliated Research Institute 801 N. Tustin Avenue, Suite 501 Santa Ana, CA 92705 *and* Dr. Rosenfeld's Office 24022 Calle De La Plata Suite 540 Laguna Hills, CA 92653	United States	497/031	4	4	8

SmithKline Beecham
Pharmaceuticals

ORIGINAL

October 7, 1998

NDA 20-982
Paxil® CR (paroxetine hydrochloride) Controlled-Release Tablets

Paul D. Leber, M.D., Director
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products (HFD-120)
Food and Drug Administration
Woodmont II, 4th Floor
1451 Rockville Pike
Rockville, Maryland 20852

FDA Request for Information

Dear Dr. Leber:

Reference is made to our New Drug Application for Paxil® CR (paroxetine hydrochloride) Controlled-Release Tablets, NDA 20-982 for treatment of panic disorder. Reference is also made to the request by the biopharm reviewer, Dr. Rae Yuan, for additional information regarding a bioavailability study submitted in NDA 20-982.

Submitted herein, per Dr. Yuan's request, are diskettes containing individual patient plasma concentration data for bioequivalence study 29060/569 submitted in the aforementioned NDA. Please note the EXCEL file contains four worksheets; CIDRA DOSE 1, CIDRA DOSE 2, CRAWLEY DOSE 1 and CRAWLEY DOSE 2. These correspond to Tables B.1 to B.4, respectively, in Appendix B of the study report, where explanatory footnotes for *flagged* data in the EXCEL file can be found.

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

Sincerely,

Thomas F. Kline
Manager
U.S. Regulatory Affairs

SmithKline Beecham
Pharmaceuticals

ORIGINAL

July 2, 1998

NDA 20-982
Paxil® CR (paroxetine hydrochloride) Controlled-Release Tablets

Paul D. Leber, M.D., Director
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products (HFD-120)
Food and Drug Administration
Woodmont II, 4th Floor
1451 Rockville Pike
Rockville, Maryland 20852

FDA Request for Information

Dear Dr. Leber:

Reference is made to our New Drug Application for Paxil® CR (paroxetine hydrochloride) Controlled-Release Tablets, NDA 20-982 for treatment of panic disorder. Reference is also made to the June 19, 1998 fax from the Division's medical reviewers requesting additional information regarding this application.

Submitted herein, in duplicate, are SB's responses to the aformentioned request. For your convenience, each question is duplicated in Attachment 1 and is followed by the respective response. Attachments 2 and 3 contain the adverse event thesaurus sorted by verbatim and preferred terms respectively; Attachment 4 contains the relative risk data tables and, finally, hardcopy printouts of the requested P-values are provided in Attachment 5.

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

Sincerely,

Thomas F. Kline
Manager
U.S. Regulatory Affairs

SmithKline Beecham
Pharmaceuticals

ORIGINAL

June 30, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

JUL 06 1998

RECEIVED HFD-120

NDA 20-982
Paxil® CR (paroxetine hydrochloride) Controlled-Release Tablets

Paul D. Leber, M.D., Director
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products (HFD-120)
Food and Drug Administration
Woodmont II, 4th Floor
1451 Rockville Pike
Rockville, Maryland 20852

FDA Request for Information: SAS Datasets

Dear Dr. Leber:

Reference is made to our New Drug Application for Paxil® CR (paroxetine hydrochloride) Controlled-Release Tablets, NDA 20-982 for panic disorder. Reference is also made to the June 3, 1998 Fax from the statistical reviewer Sue-Jane Wang, Ph.D. requesting SAS datasets and other information regarding this application.

Submitted herein, per Dr. Wang's request, are diskettes containing the SAS transport files for the primary and secondary efficacy variables for each of the three principal studies, 494, 495 and 497. Two copies are provided for the NDA file and a third set is provided as a desk copy for Dr. Wang. Please refer to the enclosed instructions on downloading the respective files.

In addition to the diskettes provided in Attachment 1, descriptions of the datasets are provided in Attachment 2; the first 20 observations from studies 494, 495 and 497 are provided in Attachments 3 –5 respectively; Attachment 6 contains the requested annotated CRF containing the variable names used in the data files; and Attachment 7 contains the "Reporting and Analysis Plan" describing the algorithms used for derivation of the various datasets.

Regarding a hardcopy of the program, please note that since this consists of approximately 15,000 pages, a hardcopy is not provided in this submission. The code

for the efficacy parameters are contained within the ".SAS" files. There is one program for each variable, i.e. 10 efficacy source code files for each study, and are listed on page 000006.

Finally, as we discussed at our teleconference, a table of contents for the case report forms submitted in the NDA were provided electronically to the Division as "N0290936\CRF\CRFTOC.PDF".

Should you have any questions, or need any additional information, please don't hesitate to contact me at (610) 917-5970.

Sincerely,

Thomas F. Kline
Manager
U.S. Regulatory Affairs

APPEARS THIS WAY ON ORIGINAL

FAX'd 6/19/98

MEMORANDUM

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

FROM: Food and Drug Administration
Center for Drug Evaluation and Research/ORM/ODEI
Division of Neuropharmacological Drug Products
HFD-120
Psychiatric Drug Products Group
5600 Fishers Lane
Rockville, MD 20857

DATE: June 19, 1998

SUBJECT: NDA 20-982
Request for Information

We request that you respond to the following items in order to assist us in reviewing your New Drug Application for Paxil CR in the treatment of panic disorder.

1) We note some large differences between the sizes of the intent-to-treat populations for studies 494, 495, and 497 as displayed in Table 3 of the ISE (vol. 1.31, page 44) and the N's shown for the endpoint (LOCF) efficacy analyses in the study reports, with the former being larger than the latter. For example, in considering the LOCF N's for mean change from baseline in the number of full panic attacks in the Paxil CR treatment group for studies 494 and 495 (vol. 1.8, page 106 and vol. 1.16, page 106, respectively), the following discrepancies are apparent:

	ITT N ISE Table 3	LOCF N Study Reports
Study 494	139	126
Study 495	158	139

It is unclear why the LOCF N's are much smaller than the ITT number of patients. Please explain these differences.

2) The protocols for studies 494, 495, and 497 indicate that the primary measure of efficacy would be the proportion of patients who attained zero panic attacks. However, the ISE now indicates that you are considering this variable as well as a) the mean change from baseline in the number of full panic attacks and b) the mean change from baseline in the CGI severity score as primary efficacy variables. Please provide your rationale for modifying the primary measures of efficacy.

3) For each primary and secondary efficacy variable, please provide the p-values for the drug/placebo comparisons at each assessment point during these studies for the observed cases datasets. For studies 494 and 495, this should include analyses that excluded center 33 and center 5, respectively.

4) Please provide a copy of the adverse event thesaurus that was used to code verbatim terms to preferred terms. We ask that this be done in two formats, one indexed by verbatim term and one by preferred term.

5) Please perform an analysis of the effects of demographic variables (age, gender, race) on the incidence of common and likely drug-related adverse events, i.e. those events reported in at least 5% of the Paxil CR patients and at a rate at least twice the placebo rate, within the pool of studies 494, 495, and 497. We ask that you use the following methodology; we have used gender as an example. For the identified adverse events, calculate the relative risks for male patients (RRm) and for female patients (RRf) with reference to placebo and compute the respective 95% confidence intervals within this study pool. Next, determine the ratios of the relative risks for females to males (RRf/RRm). Then, using the Mantel-Haenszel method, compute odds ratios for each subgroup and also a common odds ratio with the 95% confidence interval. Finally, test the homogeneity of the odds ratios between subgroups for each selected adverse event using the Breslow-Day Chi-Square and provide p-values. Please submit the results as shown in the two attached tables. Similar analyses should be carried out for age and race effects for these same adverse events.

Your timely response to these requests is very much appreciated. Should questions arise, please contact Dr. Dubitsky at (301)594-5543.

/S/

Gregory M. Dubitsky, M.D.
Medical Reviewer
Psychiatric Drug Products Group

/S/

Thomas P. Laughren, M.D.
Group Leader
Psychiatric Drug Products Group

cc: HFD-120/GDubitsky
TLaughren
AHomonnay

Attachment: Two tables.

ATTACHMENT

RELATIVE RISKS AND CONFIDENCE INTERVALS FOR SELECTED STUDY EVENTS									
Adverse Events	MALES				FEMALES				RR = RRf ÷ RRm
	Paxil CR (n=) N (%)[3]	Placebo (n=) N (%)	RRm[1]	95% C.I.	Paxil CR (n=) N (%)	Placebo (n=) N(%)	RRf[2]	95% C.I.	

ODDS RATIOS BY GENDER FOR SELECTED ADVERSE EVENTS						
Adverse Event	Odds Ratios[4]		Common Odds Ratio[5]	95% C.I.	Breslow-Day[6]	
	Males	Females			χ^2	p-value

[1] RRm = relative risk for male patients (Paxil CR/placebo).
[2] RRf = relative risk for female patients (Paxil CR/placebo).
[3] N = number of patients with the event and % = (N ÷ n) × 100%.
[4] Odds ratios computed with reference to placebo patients.
[5] Common odds ratio computed using the Mantel-Haenszel method.
[6] Breslow-Day test for homogeneity of the odds ratios.

facsimile
TRANSMITTAL

To: Thomas Kline
Sponsor: SmithKline Beecham
Fax #: (610) 917-7665
Re: Electronic Data Requirements for Statistics
Date: 6/4/98
Pages: (including cover sheet) 3

From the desk of...

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

TO: Thomas Kline
Manager
U.S. Regulatory Affairs
SmithKline Beecham Pharmaceuticals

FAX:

FROM: Sue-Jane Wang, Ph.D.
Mathematical Statistician
Division of Biometrics I, CDER, FDA

Date: June 3, 1998

RE: Electronic Data Request for NDA# 20-982: Paxil CR Tablets

Dear Mr. Kline,

Please submit the following for NDA#20-982 statistical review and evaluation:

1) Documentation of data files per protocol, including formats of coding and explanation of coding. When derived variables are used, please provide the algorithms used for derivation.

2) Annotated Case Report Form (CRF with variable names used in the SAS data files)

3) Listing of Case Report Form

Diskettes (1 diskette per trial), including

1) SAS macro files (Please include those files for your primary efficacy endpoint and for your secondary efficacy endpoints analyses).

2) Datasets

A). Please submit an electronic data file that includes
- Basic patients identification;
- Baseline AEDs therapy at screen;
- Relevant information for early discontinuation assessment: date of screen, date of randomization, early withdrawal (Y/N), date of withdrawal or date of trial completion, date last seen if different from date of withdrawal, reason of discontinuation;
- Demographic variables;
- Efficacy related information: baseline medical history, baseline measurements (individual items and total measurement if applicable), date of baseline measurements collected, final measurements (individual items and total measurement if applicable), date of final measurements collected for the primary and secondary efficacy variables, indicators of ITT, LOCF, OC, retrieved dropout analysis,

etc.
This file should contain one record per patient.

B). Please submit an electronic data file that includes raw data:
- Basic patients identification;
- For each visit, the primary and secondary efficacy measurements including date or week of each visit, visit #; etc.
- For each visit, the individual items (e.g., all panic attacks includes full panic attacks, full situational panic attacks, etc.) which constitute the primary and secondary efficacy variables. This file should contain one visit per record.

1) Hardcopy of program
2) Output of contents
3) Print out of first 20 obs.

Please provide each type of file separated by trials. The SAS system *.sd2 files or transport files *.xpt are fine.

Thank you.

SmithKline Beecham
Pharmaceuticals

ORIGINA

May 27, 1998

Anna M. Homonnay-Weikel
Project Manager

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

NCBM

Agency Request for Information

Dear Anna,

Reference is made to NDA 20-982 for Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets in the treatment of Panic Disorder.

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

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

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

Sincerely,

Thomas F. Kline
Manager
US Regulatory Affairs

1250 S. Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989. Telephone (610) 917 7000. Fax (610) 917 7707

The f. are on \\cdwtal\2c

SmithKline Beecham
Pharmaceuticals

DUPLICATE

May 20, 1998

NDA 20-982
Paxil® CR (paroxetine hydrochloride) Controlled-Release Tablets

Paul D. Leber, M.D., Director
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products (HFD-120)
Food and Drug Administration
Woodmont II, 4th Floor
1451 Rockville Pike
Rockville, Maryland 20852

CORRESP

CENTER FOR DRUG EVALU AND RESEARCH

MAY 22 1998

RECEIVED HFD.

General Correspondence: Electronic Files

Dear Dr. Leber:

Reference is made to our New Drug Application for Paxil® CR (paroxetine hydrochloride) Controlled-Release Tablets, NDA 20-982 for the treatment of panic disorder.

Submitted herein, per the Divison's request, are CDs containing the aforementioned New Drug Application in PDF format. Also provided, for reviewer convenience, and as an optional installation, is a —— based review tool to assist the respective reviewers. If the Division chooses to utilize this review tool, SB would be glad to assist in its installation and provide individual reviewer training.

Please refer to page 000005 for a brief set of instructions regarding the PDF installation on your network. Should you have any questions, please don't hesitate to contact me at (610) 917-5970.

Sincerely,

Thomas F. Kline
Manager
U.S. Regulatory Affairs

OCT - 6 1998

MEETING MINUTES

Date: June 16, 1998
NDA: 20-982
Location: Woodmont II, Conference Room E
Sponsor: SmithKline Beecham Pharmaceuticals
Drug: Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets
Indication: Panic Disorder
Meeting Type: 45 Day Filing Meeting
Participants:

Paul Leber, M.D.
Tom Laughren, M.D.
Greg Dubitsky, M.D.
Bob Seevers, Ph.D.
Rick Lostritto, Ph.D.
Sue Jane Wang, Ph.D.
Rae Yuan, Ph.D.
Anna M. Homonnay-Weikel, R.Ph. (Project Manager)
Alfreda Burnetta (DSI)

BACKGROUND:

SmithKline Beecham Pharmaceuticals has submitted an efficacy supplement for panic disorder. It has been assigned a new NDA number pending approval of NDA 20-936 for Paxil CR in the treatment of Depression (per the 'Bundling Policy). The application consists of three clinical studies and statistical analyses. The pharmacology/toxicology and chemistry, manufacturing, and controls sections reference previously submitted NDA 20-936 and approved NDA 20-031.

DISCUSSION:

CLINICAL

- The application appears to be fileable.

STATISTICAL

- The application appears to be fileable. The firm has submitted the requested datasets.

CONCLUSION:

The application appears on its face to be acceptable for filing.

Minutes prepared by: /S/
Anna M. Homonnay-Weikel, R.Ph.
Project Manager

cc: Orig NDA & Div File

C:\WPFILES\NDA\PAXIL\20982.FM

APPEARS THIS WAY
ON ORIGINAL