

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020936

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

DAVID

NDA 20-936

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

OCT 9 1998

OCT 9 1998

Dear Mr. Kline:

Please refer to your pending New Drug Application dated and received December 19, 1997, submitted pursuant to 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 January 26, February 18, April 21, May 4, June 10, June 11, June 17, and August 12, 1998. The User Fee goal date for this application is December 19, 1998.

We have completed our review of your application, and it is approvable. Before the 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. 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 December 19, 1997 submission, and amended in your April 21, 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.

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. 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 drop-out. 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 worldwide. We require a review of the status of all actions with regard to this drug, 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, if appropriate, along with English translations when needed.

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. 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. 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)

1. We note that you have not responded to the CMC deficiencies conveyed in an Agency letter dated August 12, 1998. Final approval of this application will be contingent upon the resolution of these deficiencies.
2. The stability data to date only support an expiration date of one year for both the 12.5 and 25 mg tablets. Additionally, please note that only the _____ facility establishment is being approved for manufacturing.

BIOPHARMACEUTICSDissolution Specification

The Division of Pharmaceutical Evaluation I (Office of Clinical Pharmacology and Biopharmaceutics) requests that you agree to the following dissolution method and specification for both strengths of Paxil CR Tablets (12.5 mg and 25 mg):

Apparatus: USP II (paddles) 150 rpm

Dissolution Media	Time	Limit (% dissolved)
Step 1: 0.1 M HCL (750 mL) for 2 hours	2 hours	
Step 2: pH 7.5 Tris buffer containing 60 mmol Tris, 90 mmol NaCl (1000 mL) for 7 hours	1 hour	
	2 hours	
	4 hours	
	6 hours	

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 one 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 such action FDA may take action to withdraw the application.

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 may not be legally marketed until you have been notified in writing that the application is approved.

NDA 20-936

Page 4

If you have any questions, please contact Mr. Paul David, R.Ph., Project Manager, at (301) 594-5530.

Sincerely yours,

LSI 10/9/95

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

ATTACHMENT

39 PAGES

DRAFT

LABELING



PAUL DAVID
DESK COPY

SmithKline Beecham
Pharmaceuticals

December 18, 1998

NDA 20-936

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

Response to FDA Approvable Letter

Dear Dr. Leber:

Reference is made to our New Drug Application for Paxil® CR (paroxetine hydrochloride) Controlled-Release Tablets, NDA 20-936, for the treatment of depression and to your letter of October 9, 1998 indicating that NDA 20-936 is approvable.

Submitted herein, is SmithKline Beecham's response to the aforementioned approvable letter for NDA 20-936. Regarding item 1 of the October 9th letter, please refer to SB's draft labeling proposal provided in Attachment 1 of this submission (a diskette containing an electronic version is also included). In response to items 2 - 4, i.e. a safety update, regulatory status update and world literature update respectively, please note that no additional clinical studies in depression have been conducted with this controlled-release formulation of paroxetine, and that, to date, no marketing applications for Paxil CR have been submitted to any country other than the United States, thus there is no information to report regarding a regulatory status update. Also note that a systematic search of the worldwide literature confirms the fact that there are no new findings with respect to the safety of Paxil CR.

Regarding the clinical experience for Paxil CR for other indications, please refer to SB's application for panic disorder, i.e. NDA 20-982, submitted to FDA April 22, 1998. Specifically, the Integrated Safety Summary is located in volume 1.032, page 000013 of NDA 20-982. In addition to the aforementioned clinical trials in panic

000001

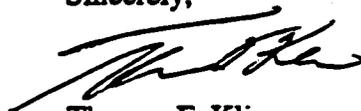
disorder, SB initiated a further Phase I bioequivalence study for Paxil CR in normal subjects. For completeness, individual narratives of those subjects who experienced a serious adverse event or who withdrew from this study due to an adverse event, are provided as Attachment 2 of this submission. Supporting labeling data containing a comprehensive adverse event listing, and individual patient narratives from our elderly study 487 are provided in Attachments 3 and 4 respectively.

In response to the labeling issue pertaining to citation of sexual side effects, please refer to SB's position piece in Attachment 5 which contains a critical review of the referenced publication cited in the Agency's proposed draft labeling.

Finally, SB's response to the Chemistry, Manufacturing and Controls issues raised in the Agency's letter of August 12, 1998 was submitted to the Division on November 19, 1998; and regarding Biopharmaceutics Dissolution Specifications, please refer to Attachment 6.

For your convenience, a copy of your October 9, 1998 letter is provided on page 000007, and a Table of Contents for this submission is provided on page 000006. Please do not hesitate to contact me at (610) 917-5970 if you have any questions or require any additional information.

Sincerely,



Thomas F. Kline

Manager

U.S. Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR
AN ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
 Expiration Date: April 30, 2000
 See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT SmithKline Beecham Pharmaceuticals		DATE OF SUBMISSION December 18, 1998	
TELEPHONE NO. (Include Area Code) (610) 917-5970		FACSIMILE (FAX) Number (Include Area Code) (610) 917-7665	
APPLICANT ADDRESS (Number, Street, City, State, County, and ZIP Code or Mail Code and U.S. License number if previously issued): 1250 S. Collegeville Road P.O. Box 5089 Collegeville, PA 19426		AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 20-936			
ESTABLISHED NAME (e.g., Proper Name, USP/USAN name) Paxil®		PROPRIETARY NAME (trade name) IF ANY paroxetine hydrochloride	
CHEMICAL/BIOCHEMICAL BLOOD PRODUCT NAME (if any) (-) trans-4R-(4'-Fluorophenyl)-3S-[3',4' methylenedioxyphenoxy)methyl] piperidine hydrochloride hemihydrate		CODE NAME (if any)	
DOSAGE FORM: Tablet	STRENGTHS: 12.5mg, 25mg	ROUTE OF ADMINISTRATION: Oral	
PROPOSED INDICATIONS FOR USE Depression			

APPLICATION INFORMATION

APPLICATION TYPE (check one)			
<input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)		<input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)	
<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)			

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE			
<input checked="" type="checkbox"/> 505 (b) (1)	<input type="checkbox"/> 505 (b) (2)	<input type="checkbox"/> 507	

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION			
Name of Drug		Holder of Approved Application	

TYPE OF SUBMISSION (check one)			
<input type="checkbox"/> ORIGINAL APPLICATION	<input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION	<input type="checkbox"/> RESUBMISSION	
<input type="checkbox"/> PRESUBMISSION	<input type="checkbox"/> ANNUAL REPORT	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT	<input type="checkbox"/> SUPAC SUPPLEMENT
<input type="checkbox"/> EFFICACY SUPPLEMENT	<input type="checkbox"/> LABELING SUPPLEMENT	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT	<input type="checkbox"/> OTHER

REASON FOR SUBMISSION Response to FDA Approvable Letter			
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PROPOSED MARKETING STATUS (check one)			
<input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx)		<input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)	

NUMBER OF VOLUMES SUBMITTED <u>1</u>	THIS APPLICATION IS	<input checked="" type="checkbox"/> PAPER	<input type="checkbox"/> PAPER AND ELECTRONIC	<input type="checkbox"/> ELECTRONIC
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ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substances and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (Check all that apply)

1.	Index		
2.	Labeling (check one)	<input type="checkbox"/> Draft Labeling	<input type="checkbox"/> Final Printed Labeling
3.	Summary (21 CFR 314.50 (c))		
4.	Chemistry section		
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)		
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)		
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)		
5.	Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)		
6.	Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)		
7.	Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))		
8.	Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)		
9.	Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)		
10.	Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)		
11.	Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)		
12.	Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)		
13.	Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))		
14.	A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))		
15.	Establishment description (21 CFR Part 600, if applicable)		
16.	Debarment certification (FD&C Act 306 (k) (1))		
17.	Field copy certification (21 CFR 314.50 (k) (3))		
18.	User Fee Cover Sheet (Form FDA 3397)		
X	19. OTHER (Specify)	Response to FDA Approvable Letter	

CERTIFICATION

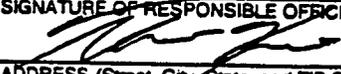
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by the FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to, the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge, are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Thomas Kline Manager, U.S. Regulatory Affairs	DATE December 18, 1998
ADDRESS (Street, City, State, and ZIP Code) 1250 S. Collegeville Road P.O. Box 5089 Collegeville, PA 19426	Telephone Number (610) 917-5970	

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Washington, DC 20201

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FORM FDA 356h (7/87)

000004

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000005

NDA 20-936
Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets

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February 3, 1999

NDA 20-936

Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets

Russell Katz, M.D., Acting Director
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Division of Neuropharmacological
Drug Products (HFD-120)
Document Control Room
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

General Correspondence

Dear Doctor Katz:

Reference is made to our New Drug Application for PAXIL[®] CR (paroxetine hydrochloride) Controlled-Release Tablets, NDA 20-936

In response to the draft labeling Faxed to SmithKline Beecham (SB) on January 28, 1999 regarding the aforementioned NDA, please note that SB accepts FDA's proposed labeling except for (1) deletion of proposed 3A4 Contraindication/Precaution statements, and (2) addition of the description of laboratory findings with the immediate-release paroxetine formulation.

Firstly, regarding 3A4 drug interactions, SmithKline Beecham has conducted a comprehensive review of the paroxetine worldwide safety database, comprising both clinical trial experience and spontaneous reports, and we have not identified any documented cases of QT interval prolongation, ventricular tachycardia, Torsades dePoint or ventricular fibrillation when paroxetine was coadministered with astemizole, cisapride and/or pimozide. As a consequence of this lack of clinical data, SB therefore, does not believe labeling revisions for Paxil, particularly with regards to a Contraindication, are warranted at this time. SB, of course, will continue to monitor all safety reports involving paroxetine, and will pursue labeling revisions as appropriate.

Secondly, with regards to the subsection "Liver Function Tests", we propose that a clarifying paragraph be added to put the experience with paroxetine controlled-release into a more meaningful context to prescribers. This reflects wider clinical experience, and would be more consistent with other similar sections of the labeling which also describe data with the immediate-release formulation. Specifically, our proposed wording originates from the labeling for Paxil Tablets and Oral Suspension, and is: "In placebo-controlled clinical trials with the immediate release formulation of paroxetine, patients exhibited abnormal values on liver function tests at no greater rate than that seen in placebo-treated patients."

Finally, regarding the cross-validation methods and the dissolution specifications, please note that SB does accept the methods and dissolution specifications for the Crawley produced tablets as proposed by the Agency in the October 1998 approvable letter.

For your convenience, only the respective pages affected by the above revisions, are attached. No changes are requested of the remaining sections of the labeling.

Please do not hesitate to contact me at (610) 917-5970 should you have any questions regarding this submission.

Sincerely,



Thomas Kline
Manager,
U.S. Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

**Revised Labeling Text for Paxil CR (paroxetine hydrochloride)
Controlled-Release Tablets.**

Note: Changes from the FDA proposed labeling, as presented in the January 28, 1999 FAX to SB, are described on the following pages. The sections affected are:

- (i) "Contraindications"
- (ii) Drugs Metabolized by Cytochrome P450III A4, and
- (iii) Liver Function Tests

Please also note that strike-through font indicates deleted text, while double underline font indicates proposed additional text. The remainder of the labeling text is unchanged from the aforementioned FAX.

**APPEARS THIS WAY
ON ORIGINAL**

29 Pages

DRAFT

LABELING

David

NDA 20-936

JAN 5 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:

We acknowledge receipt of your amendment dated December 18, and received December 21, 1998, submitted to your new drug application (NDA) for Paxil CR (paroxetine hydrochloride) Controlled-Release 12.5 and 25 mg Tablets.

This amendment contains additional information submitted in response to our October 9, 1998 approvable letter.

We consider this a major amendment under 21 CFR 314.60 of the regulations and it constitutes a full response to our letter. Therefore, the primary goal date under the FDA Modernization Act of 1997 (FDAMA) is February 21, 1999.

If you have any questions, please contact Mr. Paul David, R.Ph., Regulatory Project Manager, at (301) 594-5530.

Sincerely yours,

/S/ 1/5/99

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

EXCLUSIVITY SUMMARY for NDA # 20-936 SUPPL # _____

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

Applicant Name SmithKline Beecham HFD-120

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA? YES / 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 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

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

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

YES /___/ NO /_X_/

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

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

1. Single active ingredient product.

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

YES / X / NO / /

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

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

NDA # _____

NDA # _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety

and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /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 9. IF "YES," GO TO PART III.

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

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

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

YES /_X_/ NO /___/

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

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

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

YES / X / NO / ___ /

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

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data

would not independently support approval of the application?

YES /___/ NO /_X_/

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

YES /___/ NO /___/

If yes, explain: _____

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

YES /___/ NO /_X_/

If yes, explain: _____

- ⊙ 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 # 449

Investigation #2, Study # 487

Investigation #3, Study # _____

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

redemonstrate something the agency considers to have been demonstrated in an already approved application.

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

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

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

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

APPEARS THIS WAY
ON ORIGINAL

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

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

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

Investigation #1__, Study #_449_____

Investigation #2__, Study #_487_____

Investigation #__, Study # _____

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

substantial support will mean providing 50 percent or more of the cost of the study.

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

Investigation #1 |
|
IND # _____ YES /X_/ | NO /___/ Explain: _____
|
| _____
|
| _____

Investigation #2 |
|
IND # _____ YES /X_/ | NO /___/ Explain: _____
|
| _____
|
| _____

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

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

Investigation #2 |

YES /___/ Explain _____

!
!
!
!
!
!

NO /___/ Explain _____

**APPEARS THIS WAY
ON ORIGINAL**

- 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 / /

If yes, explain: _____

TS/ _____ 9-20-98
 Signature of preparer Date
 Title: Project Manager

IS/ _____ 10/9/98
 Signature of Division Director Date

cc:
 Archival NDA 20-936
 HFD-120/Division File
 HFD-120/PDavid
 HFD-85/Mary Ann Holovac

APPEARS THIS WAY
 ON ORIGINAL

Form OGD-011347
 Revised 8/7/95; edited 8/8/95; revised 8/25/98

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 20-936 Supplement # _____ Circle one: SE1, SE2, SE3, SE4, SE5, SE6

HFD-120 Trade and generic names/dosage form: Paxil CR (paroxetine HCL) Controlled-Release Tablets Action: AP AE NA

Applicant: SmithKline Beecham Therapeutic Class: 3S

Indication(s) previously approved: None

Pediatric information in labeling of approved indication(s) is: adequate _____ inadequate X

Proposed indication in this application: treatment of depression

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? X Yes (Continue with questions) _____ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

____ Neonates (Birth-1month) _____ Infants (1month-2yrs) X Children (2-12yrs) X Adolescents (12-16 yrs)

- _____ 1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
- _____ 2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children and adolescents but not neonates). Further information is not required.
- X 3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.
- _____ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- _____ b. A new dosing formulation is needed, however, the sponsor is either not willing to provide it or is in negotiations with FDA.
- X c. The applicant has committed to doing such studies as will be required.
- X (1) Studies are ongoing (studies being conducted on the immediate release formulation, NDA 20-031)
- _____ (2) Protocols were submitted and approved.
- _____ (3) Protocols were submitted and are under review.
- _____ (4) If no protocol has been submitted, attach memo describing status of discussions.
- _____ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
- _____ 4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.
- _____ 5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? _____ Yes X No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from _____ (e.g., medical review, medical officer, team leader).

/S/
Signature of Preparer and Title

9-20-98
Date

cc: Orig NDA/BLA # 20-936
HFD-120/Div File
NDA/BLA Action Package
HFD-006/KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

NDA 20-936

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

AUG 12 1998

Dear Mr. Kline:

Please refer to your New Drug Application for Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets.

Reference is also made to telephone conversations dated April 7, and 24, 1998, between Ms. Deborah Zuber, of your firm, and Dr. Mona Zarifa, of this Agency.

We have completed our review of the chemistry and manufacturing section of your submission and, as previously conveyed in the aforementioned telephone conversations, we have the following comments and information requests:

1. The regulatory specifications/methods for the drug product should include a chiral identity test.
2. We note that you only provided one copy of the Method Validation package. The copy does not include sample assignments for the FDA validating laboratories and the references to the analytical methods in the list of specifications do not correspond to those in the descriptions and validation reports. Please complete the Method Validation package and submit three copies
3. Please submit a description and validation data for the degradation profile gradient HPLC method mentioned in Vol.5 p.108. Also, please demonstrate that the present assay method is specific for all potential degradants including the paroxetine-lactose adducts. These changes should also be included in the amended method validation package.
4. The dissolution method uses USP Apparatus II at 150 rpm. It is unusual to use a speed higher than considering the high rate of dissolution of the tablets in the testing media. Please explain.
5. The available stability results to date do not support an expiration date beyond one year for the 12.5 mg and 25 mg tablets and 9 months for the 37.5 mg and 50 mg tablets. Any proposal for an expiry date extension should be supported by actual stability data.

6. Due to the controlled release nature of this drug product, the labeling section needs an additional precautionary statement to ensure proper administration. A statement such as
:" may be added to the container label."
7. You have provided specifications for packaging components. However, it is not clear if you perform all tests on acceptance. Please specify the acceptance tests to be performed on these components.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions concerning these comments, please contact Mr. Paul David, Project Manager, at (301) 594-5530.

Sincerely yours,

/S/

Robert H. Seevers, Ph.D.
Chemistry Team Leader , Psychiatric Drugs
for the Division of Neuropharmacological
Drug Products, (HFD-120)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

David

NDA 20-936

JUN 10 1998

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 for Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets.

Reference is also made to a meeting between the Agency and representatives from SmithKline Beecham dated February 11, 1998, to discuss issues related to the biopharmaceutic review of this application.

We acknowledge receipt of your submission dated February 18, 1998, providing for your version of meeting minutes from the aforementioned meeting

We have completed our review of your meeting minutes, and we believe that they accurately reflect the proceedings of the meeting.

If you have any questions concerning these comments, please contact Mr. Paul David, Project Manager, at (301) 594-5530.

Sincerely yours,

/S/

6/11/98

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

David

NDA 20-936

JAN 6 1998

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:

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

Name of Drug Product: Paxil CR (paroxetine hydrochloride) Controlled-Release 12.5 mg, 25 mg, 37.5 mg, and 50 mg Tablets

Therapeutic Classification: Standard

Date of Application: December 19, 1997

Date of Receipt: December 19, 1997

Our Reference Number: 20-936

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 17, 1998 in accordance with 21 CFR 314.101(a).

If you have any questions, please contact Paul David, R.Ph., Project Manager, at (301) 594-5530.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

/S/

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

MEMORANDUM OF TELEPHONE CONVERSATION

Dates of Calls: February 3 & 5, 1998
NDA #: 20-936
Drug Name: Paxil CR
Sponsor: SmithKline Beecham
Point of Contact: Thomas Kline
Phone #: 610-917-5970
Subject of Call: Request for coding dictionary.

Mr. Kline, of SKB U.S. Regulatory Affairs, was telephonically contacted by the undersigned on February 3, 1998, for information regarding the location of the adverse event coding dictionary that was used for this NDA safety database. He acknowledged that such a dictionary was not submitted but that he would arrange to have one forwarded to me after consulting with colleagues.

Additionally, he was asked if a literature search had been done to identify published studies involving this formulation of paroxetine. He stated that no information on this formulation has been published to date.

Mr. Kline was recontacted on February 5, 1998, to follow-up on my request for a coding dictionary. He indicated that such a listing was available, indexed by verbatim term. I asked if a listing indexed by preferred term could be provided as well. He indicated that listings sorted each way could be provided within the next two weeks and that he would send them as an amendment to the NDA.

I thanked him and the conversation was terminated.

/S/

Gregory M. Dubitsky, M.D.
February 5, 1998

cc: HFD-120/GDubitsky
/TLaughren
/PDavid

SB
SmithKline Beecham
Pharmaceuticals

ORIGINAL

February 18, 1998

NDA 20-936

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)
Document Control Room 10B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

CENTER FOR DRUG EVALUATION
AND RESEARCH

NEW CONTROL

FEB 23 1998

RECEIVED HFD-120

General Correspondence: Draft Meeting Minutes

Dear Dr. Leber:

Reference is made to our New Drug Application for Paxil® CR (paroxetine hydrochloride) Controlled-Release Tablets, NDA 20-936. Reference is also made to the teleconference of ~~February 11, 1998 between representatives of SmithKline Beecham Pharmaceuticals and FDA~~ to discuss issues related to the biopharm review of NDA 20-936.

Submitted herein are SB's draft meeting minutes of the aforementioned teleconference. Please confirm if these accurately reflect the Division's interpretation of the issues as discussed at the meeting.

As emphasized at the teleconference, it's extremely critical that SB be informed of the Division's position regarding acceptability of our manufacturing site transfer bioequivalence study No. 539, as described in issue 2 of the minutes.

We are very grateful for your arranging the teleconference, and appreciate your awareness of the urgency of this matter. 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

000001

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR
AN ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER
NDA 20-936

APPLICATION INFORMATION

NAME OF APPLICANT

SmithKline Beecham Pharmaceuticals

DATE OF SUBMISSION

February 18, 1998

TELEPHONE NO. (Include Area Code)

(610) 917-5970

FACSIMILE (FAX) Number (Include Area Code)

(610) 917-7665

APPLICANT ADDRESS (Number, Street, City, State, County, and ZIP Code or Mail Code and U.S. License number if previously issued):

1250 S. Collegeville Road
P.O. Box 5089
Collegeville, PA 19426

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) NDA 20-936

ESTABLISHED NAME (e.g., Proper Name, USP/USAN name)

Paroxetine Hydrochloride

PROPRIETARY NAME (trade name) IF ANY

CHEMICAL/BIOCHEMICAL BLOOD PRODUCT NAME (if any)

(-) trans-4R-(4'-Fluorophenyl)-3S-[3',4' methylene-dioxphenoxy)
methyl] piperidine hydrochloride hemihydrate

CODE NAME (if any)

BRL-29060

DOSAGE FORM:

Tablet

STRENGTHS:

12.5mg, 25mg, 37.5mg, 50mg

ROUTE OF ADMINISTRATION:

Oral

PROPOSED INDICATIONS FOR USE

Depression

APPLICATION INFORMATION

APPLICATION TYPE

(check one)

NEW DRUG APPLICATION (21 CFR 314.50)

ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

505 (b) (1)

505 (b) (2)

507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug

Holder of Approved Application

TYPE OF SUBMISSION

(check one)

ORIGINAL APPLICATION

AMENDMENT TO A PENDING APPLICATION

RESUBMISSION

PRESUBMISSION

ANNUAL REPORT

ESTABLISHMENT DESCRIPTION SUPPLEMENT

SUPAC SUPPLEMENT

EFFICACY SUPPLEMENT

LABELING SUPPLEMENT

CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one)

PRESCRIPTION PRODUCT (Rx)

OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED

THIS APPLICATION IS

PAPER

PAPER AND ELECTRONIC

ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (Check all that apply)

1.	Index
2.	Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
3.	Summary (21 CFR 314.50 (c))
4.	Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
5.	Nondclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
6.	Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
7.	Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
8.	Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
9.	Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
10.	Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
11.	Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
12.	Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
13.	Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
14.	A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
15.	Establishment description (21 CFR Part 600, if applicable)
16.	Debarment certification (FD&C Act 306 (k) (1))
17.	Field copy certification (21 CFR 314.50 (k) (3))
18.	User Fee Cover Sheet (Form FDA 3397)
19.	OTHER (Specify) General; Correspondence

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by the FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to, the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.87, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge, are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Thomas F. Kline Manager, U.S. Regulatory Affairs	DATE February 18, 1998
--	---	---------------------------

ADDRESS (Street, City, State, and ZIP Code) 1250 S. Collegeville Road P.O. Box 5089 Collegeville, PA 19426	Telephone Number (610) 917-5970
---	------------------------------------

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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000004

Minutes of February 11, 1998 Teleconference

A teleconference was held February 11, 1998 between representatives of SmithKline Beecham Pharmaceuticals and FDA to discuss issues related to the biopharm review of NDA 20-936, Paxil (paroxetine hydrochloride) Controlled-Release Tablets. The following individuals participated:

FDA: Gregory Dubitsky, Medical Reviewer; Ruihua Yuan, Biopharm Reviewer; Mr. Chandahas Sahajwalla, Biopharm Team Leader, and Project Manager; Mr. Paul David

SB: Stella Jones, Vice President, U.S. Regulatory Affairs; Thomas Kline, Manager, U.S. Regulatory Affairs; Colin Broom, Vice President and Director CNS/GI, Clinical R&D; Barry Zussman, Department of Drug Metabolism and Pharmacokinetics; Martha L Hyneck, Department of Drug Metabolism and Pharmacokinetics; David P Elder, Pharmaceutical Development; Nevine Zariffa, Statistician; Kate Howland, Statistician; Deborah Zuber, U.S. Regulatory Affairs, CMC

Background:

NDA 20-936 for Paxil (paroxetine hydrochloride) Controlled Release Tablets, 12.5 mg, 25 mg. was submitted to FDA on December 19, 1997.
The application identified as the proposed manufacturing site

Reference was also made to SB's submission of September 29, 1997, (Serial Number 018) to IND for controlled-release paroxetine, wherein SB provided a briefing document and a request for a meeting with the Division to discuss several issues pertaining to the transfer of the manufacturing site for this product.

2. Acceptability of Bioequivalence Study 539

Making reference to SB's briefing document of September 29, 1997, Nevine Zarriffa described SB's position regarding the interpretation of a bioequivalence study, i.e. study 539, comparing 25 mg tablets manufactured , versus 25 mg tablets produced in

Dr. Sahajwalla remarked that the Division has not yet fully reviewed these data, and thus was not prepared to comment, at this time, on the acceptability of this study. Stella Jones stressed the extreme urgency of this matter to SB's commercial development of the product. She emphasized that a timely response from the Agency is critical and, inquired about the possibility of the Division concluding their review and agreeing to meet with SB within the next two weeks. Paul David agreed that the briefing document, (which stands alone from the Item 6 section of NDA 20-936 to lessen the reviewer's burden) would be reviewed in great detail. However, he could not commit to a two-week timeframe for another meeting. It was understood that Mr. David

would contact T. Kline as soon as possible regarding the completion of the review.

3. Alternate Statistical Approaches

Marty Hyneck asked the Agency's view on the use of adaptive designs for evaluating bioequivalence studies. Nevine Zariffa made specific reference to attachment 2 of the September 29th briefing document, and inquired about the Division's acceptance of such adaptive design approaches for these studies. Specific reference was made to page 000025 of the document. It was pointed-out that such a design, i.e. no stopping rule, is commonly accepted by statisticians. It is proposed that variability is examined while a study is ongoing and the size of the trial increased if necessary. This would allow an increase of the original sample size in the event variability was higher than anticipated. Mr. Sahajwalla, again, mentioned that the Division is not prepared to answer this question, but promised to review the briefing document in more detail. It was suggested by Mr. David, and agreed by SB, to submit a draft protocol to the paroxetine controlled-release IND for full Agency consideration. Mr. Sahajwalla mentioned that there is precedence for these types of analyses being acceptable to FDA and that the proposed analyses should be described in the protocol. For example, the Agency has agreed to designs with 72 subjects as the target sample size and based on the analysis of the first 36 subjects, recalculated the required sample size accordingly.

4. Use of Draft Guidance Documents

Marty Hyneck inquired about the Division's opinion on use of Agency draft guidance documents, specifically in regards to the need for conducting BE studies in both fed and fasted states. Reference was made to the "Guidance for Industry, Food-Effect Bioavailability and Bioequivalence Studies", issued October 1997. Dr. Sahajwalla reminded SB that such a document, as standard procedure, would go through several stages of comments and revisions and may not necessarily reflect the Agency's final position. Therefore, at this time, SB would not be expected to comply with these draft guidelines.

5. Possible Tablet Color Change

As a future consideration, Deborah Zuber raised the possibility of SB pursuing a color change to the existing Paxil CR tablets and inquired about the regulatory requirements for supporting such a change. She made reference to several conversations with the Agency's Office of Pharmaceutical Science, in which they informed SB that the color change will fall outside of SUPAC MR guidelines and thus recommended that this issue be raised with the

Division. Specifically, she asked the Division's opinion on the need to conduct new bioavailability studies when the comparative dissolution profiles show equivalence. As this was a new issue for discussion, the Division was not prepared to answer, however, Paul David suggested that this question be formally submitted to the paroxetine controlled-release IND for full Agency consideration.

6.

7. Possible Amendment to the NDA

T. Kline raised the possibility of SB amending the NDA with as an alternate manufacturing site. He inquired about the impact of such an amendment and, for example, if the review clock for NDA 20-936 would be extended. Mr. David replied that, while SB could indeed amend the file, he could not be certain of the impact on the review clock. He mentioned that the Division's goal is to complete the NDA review well in advance of the final User Fee deadline for this application, and thus the potential effect on the review timing is unknown at this time.

MEMORANDUM

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

DATE: February 5, 1998

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

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

TO: File NDA 20-936
[Note: This overview should be filed with the 12-18-98 response to our 10-9-98 approvable letter.]

SKB's 12-18-98 response to our 10-9-98 approvable letter represented a complete response to all the issues raised in our letter. Dr. Dubitsky reviewed the responses to clinical issues in a 1-7-99 review, including labeling, a safety update, a regulatory status update, and a literature update. There were no new safety findings revealed in either the safety update or literature update that would impact on the labeling or an approval action for this NDA. To our knowledge, Paxil CR is still not approved elsewhere for any indications.

The differences in labeling were rather minor, and we have been able to readily reach agreement with SKB on final labeling. We have agreed to delay the inclusion of our recommended contraindications of Paxil CR with 3 drugs cleared by 3A4, until Pfizer, and other SSRI manufacturers, have an opportunity to fully address the questions regarding such an action.

To my knowledge, the CMC and biopharmaceutics issues noted in the 10-9-98 letter have been resolved.

Thus, I recommend that we issue the attached approval letter with the mutually agreed upon final labeling (PAXILCR DEP AP2.DOC).

cc:
Orig NDA 20-936 (Paxil CR)
HFD-120/Div File
HFD-120/TLaughren/RKatz/GDubitsky/PDavid

DOC: MEMPXDRP.API

MEMORANDUM

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

DATE: September 30, 1998

FROM: Thomas P. Laughren, M.D. /S/
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 depression

TO: File NDA 20-936
[Note: This overview should be filed with the 12-19-97 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). NDA 20-936 is for a delayed and extended release formulation of paroxetine, i.e., Paxil CR, in 12.5, 25

Paxil CR is recommended for qd dosing, as is the immediate release formulation, Paxil. The recommended initial dose for Paxil CR is 25 mg/day, with increases up to a maximum dose of 62.5 mg/day as needed.

IND for paroxetine controlled release was originally submitted 7-23-96. Several critical meetings were held during the development of paroxetine controlled release:

7-3-96: PreIND Meeting:

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 NDA 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 of the CR formulation compared to placebo.

7-11-97: PreNDA Meeting:

This meeting was focused primarily on the format and content of the planned NDA. However, we did revisit several issues discussed previously, i.e., the need for adequately designed studies to support comparative safety claims, the issue of support for multiple efficacy claims, and our concern about the CR name for a product dosed qd as is the case for the IR formulation.

Since this NDA involved a new formulation of paroxetine, it necessitated reviews by all disciplines. The clinical review of safety and efficacy data was conducted by Greg Dubitsky, M.D., from the clinical group, and the statistical review of efficacy data was conducted by Japo Choudhury, Ph.D. from the biometrics group.

The original NDA 20-936 for Paxil CR was submitted 12-19-97.

We decided not to take Paxil CR to the PDAC.

2.0 CHEMISTRY

While several minor CMC issues need resolution prior to final approval, I am not aware of any substantive issues that would preclude approval. The proposed name has been accepted by the nomenclature committee.

3.0 PHARMACOLOGY

I am not aware of any substantive pharmacology/toxicology issues that would preclude approval.

4.0 BIOPHARMACEUTICS

Paxil CR is intended for qd dosing. Paxil CR both delays dissolution with an enteric coat dispersion () and the rate of absorption by the use of a polymeric matrix for Paxil CR is about available than Paxil IR; this difference is the basis for the dosing of Paxil CR vs Paxil IR in the phase 2-3 clinical trials.

10 in vivo biopharmaceutics studies were reported on in this NDA, including 2 early studies to select the best performing prototype, and 8 additional studies for dose proportionality (472), food effect (473, 563, 564), steady state comparison of Paxil CR 50 mg and Paxil IR 40 mg (474), and 2

bioequivalence studies (539, 480). 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.

Apparently the sponsor is seeking marketing only of the 12.5 and 25 mg strengths.

Labeling has been modified to incorporate new information for Paxil CR.

The approvable letter will include dissolution specifications.

To my knowledge, there are no biopharmaceutics issues that would preclude the approvability of Paxil CR.

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 placebo-controlled trials in depressed outpatients, including 2 in adults (448 & 449) and 1 in elderly patients (487). The identified primary outcome measure for these studies was change from baseline for HAMD-17 total score. Our focus in these studies was on change from baseline for the following outcomes: HAMD total score; HAMD Item 1; CGI Severity.

5.1.2 Summary of Studies Pertinent to Efficacy Claims

5.1.2.1 Study 448

This was a randomized, double-blind, parallel group, 12-week study (22 US sites) comparing paroxetine CR (25 to 62.5 mg/day), paroxetine IR (20 to 50 mg/day), and placebo in depressed adult outpatients meeting DSM-IV criteria for MDD. There were approximately 100 patients per group with the % completing to 12 weeks ranging from 67-73%. The mean doses for completers in the active drug groups were as follows: CR (50 mg/day); IR(40 mg/day).

Overall, the results from this study consistently favored paroxetine CR over placebo, and less strongly favored paroxetine IR over placebo, on all outcomes. However, there was a significant treatment by center interaction, with one center largely affecting the overall positive outcome. When analyzed without this center, paroxetine CR was superior to placebo only on HAMD Item 1. While the explanation for this outcome remains unclear, Dr. Dubitsky considered the pattern of response in the 1 very positive center unusual considering the typical antidepressant trial. Thus, he considered the

analysis without the unusually positive center to be the appropriate analysis, and concluded, on the basis of the marginal outcome (for both paroxetine CR and IR), that this was a failed study. Dr. Choudhury reached the same conclusion, and I also agree that this cannot be considered a positive study in support of the antidepressant effectiveness of Paxil CR.

5.1.2.2 Study 449

This was a randomized, double-blind, parallel group, 12-week study (20 US sites) comparing paroxetine CR (25 to 62.5 mg/day), paroxetine IR (20 to 50 mg/day), and placebo in depressed adult outpatients meeting DSM-IV criteria for MDD. There were approximately 100 patients per group with the % completing to 12 weeks ranging from 67-75%. The mean doses for completers in the active drug groups were as follows: CR (47 mg/day); IR(37 mg/day).

Overall, the results from this study consistently favored paroxetine CR over placebo on all outcomes, but surprisingly did not demonstrate a statistically significant superiority for paroxetine IR over placebo. Since there was concern about the integrity of results from 1 of the sites, an analysis was conducted involving all results except those from that site, and the results were essentially the same. Both Drs. Dubitsky and Choudhury considered this a positive study, and I agree.

5.1.2.3 Study 487

This was a randomized, double-blind, parallel group, 12-week study (31 Canadian and US sites) comparing paroxetine CR (12.5 to 50 mg/day), paroxetine IR (10 to 40 mg/day), and placebo in depressed elderly (≥ 60) outpatients meeting DSM-IV criteria for MDD. There were approximately 100 patients per group with the % completing to 12 weeks ranging from 76-78%. The mean doses for completers in the active drug groups were as follows: CR (31 mg/day); IR(27 mg/day).

Overall, the results from this study consistently favored both paroxetine CR and paroxetine IR over placebo on all outcomes. Both Drs. Dubitsky and Choudhury considered this a positive study, and I agree.

5.1.3 Comment on Other Important Clinical Issues Regarding Paxil CR

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 the immediate release product. Thus, one can at most recommend dosing patients in the ranges 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

While it is difficult to assess treatment effect size based on HAMD scores, the effect sizes observed in these trials were comparable to what we have observed for other recently approved antidepressant drugs.

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 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 to support the claim of an antidepressant effect for Paxil CR.

5.2 Safety Data

Clinical Data Sources for Safety Review

The safety data for paroxetine CR, including the original submission and several amendments (2-11-98; 2-18-98; 4-21-98) in response to our requests for additional information, were reviewed by Dr. Dubitsky. This original review was based on databases with a cutoff date of 10-15-97 for phase 1 studies and 9-22-97 for phase 2-3 studies, for both routine data and also deaths and other serious adverse event reporting.

The development program for paroxetine CR consisted of 13 studies, including 10 phase 1 studies and the 3 phase 2-3 efficacy studies previously summarized. 371 normal volunteers were exposed to paroxetine in phase 1 studies, and 316 depressed patients were exposed to paroxetine in phase 2-3 studies. Phase 1 subjects were predominantly young, M:F roughly 1, and almost all white. The phase 1 exposures were roughly half single dose, and for the remainder, the mean exposure was for 7 days and the most commonly used paroxetine CR dose was 30 mg/day. For phase 2-3 studies, the mean age was 40 in the 2 adult studies and 70 in the elderly study. There was a 2:1 F:M ratio in the adult studies and roughly 1:1 ratio in the elderly study. Patients in the phase 2-3 studies were also predominantly white. The phase 2-3 studies were relatively short-term (12 weeks). The actual dose levels utilized in the phase 2-3 studies were summarized previously under "Efficacy."

Adverse Event Profile for Paroxetine CR

Given our extensive knowledge of the safety profile for immediate release paroxetine, the safety review focused on patients and subjects exposed to paroxetine CR in the 13 studies comprising the database for this supplement. Overall, the side effect profile of paroxetine CR was as expected for an SSRI and not obviously different from that of the immediate release product. There were no new, unrecognized serious adverse events that could be considered related to paroxetine CR use.

There was 1 study (452) that specifically addressed the question of differential nausea for the IR and CR forms. This study involved 3 days of treatment in normal volunteers with the following: paroxetine 30 mg/day IR; paroxetine 30 mg/day CR (enteric coated); paroxetine 30 mg/day CR (non-enteric coated); placebo. The risk of nausea was as follows:

paroxetine 30 mg/day IR	59%
paroxetine 30 mg/day CR (enteric coated)	40%
paroxetine 30 mg/day CR (non-enteric coated)	49%
placebo	13%

While suggestive of a differential risk of nausea, these data are not sufficient to support a claim of an advantage for the CR form, and no such claim was sought by SKB.

5.3 Clinical Sections of Labeling

We have modified the clinical and biopharmaceutics 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 in the approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take Paxil CR to the PDAC.

9.0 DSI INSPECTIONS

In response to our 2-9-98 consult to DSI regarding this NDA, they chose the option of not doing any inspections. However, very late in the review cycle (8-21-98), they belatedly raised a concern about Cal Cohn, M.D., an investigator for study 449, one of the 2 positive studies upon which an approval action would depend. Alfreda Burnett of DSI indicated in an 8-21-98 e-mail that Dr. Cohn is on the "Assurance List" as of 4-17-91, and that we can accept data from his site only if it has been "third party verified." This recommendation was made despite the fact that we have a 2-24-97 memo from Robert Young, M.D. of DSI indicating that, since Dr. Cohn submitted an acceptable plan in response to FDA's notice of violation, his data could be accepted. In any case, DSI offered the option of the sponsor, SKB, validating the patients at Dr. Cohn's site, and we have forwarded to DSI SKB's statement of validation. While we await a response from DSI on the acceptability of this validation, I recommend that we proceed with an approvable action, pending the final resolution of this matter.

10.0 LABELING AND APPROVABLE LETTER

10.1 Final Draft of Labeling Attached to Approvable Package

Our proposed draft of labeling is attached to the approvable letter. As noted, we have modified the sponsor's draft dated 12-19-97.

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 depression. 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.