

CENTER FOR DRUG EVALUATION AND RESEARCH

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

APPROVAL LETTER



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.

Apparatus: 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 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 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)

**APPEARS THIS WAY
ON ORIGINAL**

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

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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

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CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)

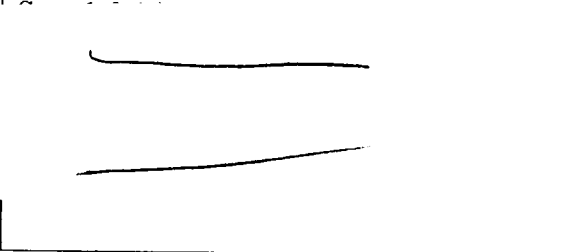
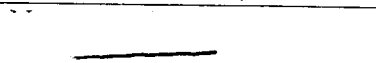
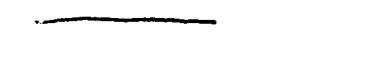
Please note that only the Crawley, UK facility establishment is being approved for drug product manufacturing.

BIOPHARMACEUTICS

Dissolution Specification

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Appartatus: USP II (paddles) 150 rpm

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

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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,

A handwritten signature in black ink, appearing to read 'RS', is written over the typed name.

Russell Katz, M.D.
Acting 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 *ms*

HFD-120/RKatz/TLaughren/GDubitsky

HFD-120/RSeEVERS/~~Roberto~~ M.Zarita

HFD-710/KJin/KKoti *su seougi*

HFD-860/CSahajwalla/R Yuan *Rly*

HFD-101/R Temple

DISTRICT OFFICE

HFD-40/DDMAC (with labeling)

3-5-99

3/4/99

RHS 3/3/99

m2 3/3/99

3/2/99

3/3/99

SI

Drafted by: MS/March 1, 1999

Revised : TPL/3-2-99

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

APPROVABLE (AE)

**APPEARS THIS WAY
ON ORIGINAL**