CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-936/S002

Trade Name: Paxil CR

Generic Name: (paroxetine hydrochloride)

Sponsor: SmithKline Beecham Pharmaceuticals

Approval Date: August 17, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-936/S002

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-936/S002

APPROVAL LETTER

NDA 20-936/S-002

SmithKline Beecham Pharmaceuticals
Attention: Deborah E. Zuber, R.Ph.
Assistant Director, Regulatory Affairs
1250 S. Collegeville Road, P.O. Box 5089
Collegeville, PA 19426-0989

Dear Ms. Zuber:

Please refer to your supplemental new drug application dated April 17, received April 19, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets.

We additionally acknowledge receipt of your amendment dated July 31, 2000.

This supplemental new drug application provides for the following revisions:

1. A revision of your commercial drug product image from a two-toned bilayered enteric coated tablet to a colored (b) (4) film coated enteric coated tablet to be manufactured at your Cidra, Puerto Rico establishment facility.
2. A change in your commercial tablet core thickness in-process manufacturing control for the 12.5 mg tablet only.
3. A revision of the dissolution method and specifications to the following:

   Apparatus: USP II (paddle) at 150 rpm
   Dissolution Media: Step 1: 0.1 N HCl (750 mL) for 2 hours
   Step 2: pH 7.5 Tris Buffer (1000 mL) containing 50 mmol Tris
   Specifications: Step 1 (In 0.1 N HCl): 2 Hours – NMT (b) (4) dissolved
   Step 2 (In 0.05 M Tris Buffer at pH 7.5):
   1 hour – NMT (b) (4) % dissolved
   2 hours – between (b) (4) % dissolved
   4 hours – between % dissolved
   6 hours – NLT (b) (4) % dissolved
4. A revision of the **HOW SUPPLIED** and **DESCRIPTION** sections of labeling to reflect the new commercial image.

We have completed the review of this supplemental application, as amended, and all of the above changes are approved effective on the date of this letter except for your proposed dissolution methods and specifications.

We have the following requests and comments:

Clinical Pharmacology and Biopharmaceutics

Our Office of Clinical Pharmacology and Biopharmaceutics concurs with your proposed revisions to reduce the ionic strength to 50 mmol Tris and eliminate the (b) (4) as originally approved) in Step 2 as well as change the 2 hours specification in Step 2 from (b) (4) % to (b) (4) %. Additionally,

for the 4 hour time point in Step 2, there was no individual value below (b) (4)% from 11 clinical and/or bio-batches tested and only one tablet was under (b) (4) for all other available batches (b) (4) batches). Therefore, the specification change from (b) (4)% to (b) (4)% cannot be granted. However, we believe that the dissolution data suggest that the specification at the 4 hour time point in Step 2 of (b) (4)% would be more appropriate.

Therefore, we are approving the following dissolution method and specifications:

Apparatus:	USP II (paddle) at 150 rpm
Dissolution Media:	Step 1: 0.1 N HCl (750 mL) for 2 hours
	Step 2: pH 7.5 Tris Buffer (1000 mL) containing 50 mmol Tris
Specifications:	Step 1 (In 0.1 N HCl): 2 Hours – NMT 10% dissolved
	Step 2 (In 0.05 M Tris Buffer at pH 7.5):
	1 hour – NMT (b) (4)% dissolved
	2 hours – between (b) (4)% dissolved
	4 hours – between (b) (4)% dissolved
	6 hours – NLT (b) (4)% dissolved

Chemistry and Manufacturing

1. We are requesting that you adopt the approved specifications, as stated under the Clinical Pharmacology and Biopharmaceutics section of this letter, for both drug product specifications and stability protocol.

2. We acknowledge your commitment (page 445, April 17, 2000 submission) to monitor tablet hardness on drug product stability. Please update all documents including stability protocol and COA to reflect the measurement of tablet hardness in accordance with your stated commitment.

We note your agreement to adopt the revised specifications for dissolution specifications, drug product specifications, and stability protocol in a telephone conversation on August 17, 2000 between Mr. Paul David of this Agency and yourself.

The final printed labeling (FPL) must be identical to the draft labeling submitted on July 31, 2000.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-936/S-002." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane

Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely,

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

cc:
Archival NDA 20-936
HFD-120/Div. File
HFD-120/P.David
HFD-120/R.Katz/T.Laughren/G.Dubitsky
HFD-120/R.Seevers/R.Lostritto/G.Gill-Sangha
HFD-860/R.Baweja/H.Zhao
DISTRICT OFFICE

Rd:7/28/00pd
Rev: 8/8/00pd
Ft:8/8/00pd
filename:PAXIL/CR/NDA/SCM-002 APPROVAL LETTER.DOC

APPROVED (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-936/S002

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data
NDA #20-936

Sponsor:	SmithKline Beecham Pharmaceuticals
Drug:	Paxil CR
Indication:	Depression
Material Submitted:	Draft Labeling for SCM-002 (New Commercial Image)
Correspondence Date:	July 31, 2000
Date Received:	August 1, 2000

This submission contains draft labeling reflecting a supplemental application to change, among other things, the commercial image (appearance) for the 12.5mg and 25mg Paxil CR tablets.[1] Specifically, these dosage forms are being changed from bilayer (two color) tablets to tablets of uniform color.

The only relevant clinical concern derives from the fact that the CR tablets will be the same color as the near-equivalent immediate release (IR) strengths: the 12.5mg CR tablet and the 10mg IR tablet will both be yellow; the 25mg CR tablet and the 20mg IR tablet will both be pink. The potential for confusion between these formulations may be increased.

However, there will remain two important differences between the CR and IR tablets: 1) the CR tablets are round and the IR tablets are oval; 2) the CR tablets are imprinted with "Paxil CR" and the strength and the IR tablets with "Paxil" and the strength. In my opinion, these differences are reasonably sufficient to mitigate the possibility of confusing the CR and IR formulations. Additionally, any confusion that might arise is unlikely to have a major impact in terms of clinical safety or efficacy, since the expected serum concentrations for each formulation are not vastly different and paroxetine does not have a narrow therapeutic index.

From a clinical standpoint, this supplement may be approved.

---

[1] This supplement is being reviewed by Dr. Gurpreet Gill-Sangha of the Office of New Drug Chemistry.

Gregory M. Dubitsky, M.D.
August 9, 2000

cc: NDA #20-936
HFD-120 (Div. File)
HFD-120/GDubitsky
/TLaughren
/PDavid

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-936/S002

CHEMISTRY REVIEW(S)

CHEMIST REVIEW OF **SUPPLEMENT**	1. ORGANIZATION: HFD-120
	2. NDA: **20-936**
	3. SUPPLEMENT NUMBER **SCM002**
	letter date: April 17, 2000/July 31, 2000
	stamp date: April 19, 2000/August 1, 2000
	4. AMENDMENTS/REPORTS/DATES:
	5. RECEIVED BY CHEMIST: August 4, 2000/August 9, 2000
6. APPLICANT NAME & ADDRESS	Smithkline Beecham Pharmaceuticals 1250 S. Collegeville Road, PO Box 5089, PA 19426-0989
7. NAME OF DRUG:	Paxil® Controlled Release Tablets
8. NONPROPRIETARY NAME:	Paroxetine hydrochloride
9. CHEMICAL NAME/STRUCTURE:	(-)trans-4R-(4'-fluorophenyl)-3S-[3',4'-methylenedioxyphenoxymethyl]-piperidine hydrochloride hemihydrate
10. DOSAGE FORM(S):	Tablet
11. POTENCY:	12.5 mg, 25 mg
12. PHARMACOLOGICAL CATEGORY:	Depression
13. HOW DISPENSED:	X (Rx) (OTC)
14. RECORDS & REPORTS CURRENT:	X Yes No

SUPPLEMENT PROVIDES FOR: Additional manufacturing and controls data for Paxil® CR tablets manufactured at Cidra, PR facility for inclusion of the color coating process and proposes changes in dissolution method and specifications.

COMMENTS:
N20-936/SCM001 was approved on July 2, 1999 for site change to Cidra, PR for drug product manufacture of "original image" tablets. However, additional color coating step for "new commercial image" was not approved at the Cidra, PR site (b) (4)

CONCLUSIONS & RECOMMENDATIONS:
N20-936 is recommended for **APPROVAL** for Cidra, PR site to perform the colored (b) (4) film coating for the "new commercial image" of Paxil® CR tablets 12.5 mg and 25 mg. In addition, refer to the Biopharm and chemistry review for comments on changes to the dissolution method and specifications.

19. REVIEWER NAME	SIGNATURE	DATE COMPLETED
Gurpreet Gill-Sangha, Ph.D. Review Chemist, HFD-120		
Robert H. Seevers, Ph.D. Chemistry Team Leader, HFD-120		

Cc:
NDA 20-936/SCM002
HFD-120/Division File
HFD-120/GGill-Sangha
HFD-120/RLostritto
HFD-120/RSeevers
HFD-120/PDavid

File: C:\data\My Documents\data gill\supplement NDA\20-936rik\SCM002.doc

4 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 20-936 S002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-936/S002

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

/14-1 COMPLETED JUL 31 2000

JUL 27 2000

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Submission Dates: 4/17/2000

NDA:	20-936/SCM-002
Name of Drug:	Paxil (Paroxetine HCl) Controlled Release 12.5 and 25 mg Tablets
Indication of Drug:	Depression
Type of Submission:	CMC Manufacturing Supplement
Sponsor:	SmithKline Beecham, Collegeville, PA
Reviewer:	Hong Zhao, Ph.D.

Introduction

This supplement requests for the approval of the additional colored (b) (4) film coating for Paxil CR manufactured at Cidra, PR. This submission also requests for the approval of a revision to the approved drug product dissolution method and specifications.

Current Dissolution Method and Specifications

In the FDA approval letter of October 9, 1998 for Paxil Controlled release tablets (NDA 20-936), the sponsor was requested to adopt the following dissolution method and specifications:

Apparatus:	USP II (paddle) at 150 rpm
Dissolution media:	Step 1: 0.1 N HCl (750 mL) for 2 hours Step 2: pH 7.5 Tris Buffer containing (b) (4) mmol Tris, (b) (4)
Specifications:	In 0.1 HCl (b) (4) hours- NMT (b) (4) dissolved In 0.06 M Tris Buffer at pH 7.5: 1 hour- NMT (b) (4) dissolved 2 hours- between (b) (4) dissolved 4 hours- between (b) (4) dissolved 6 hours- NLT (b) (4) dissolved.

Changes of Dissolution Method and Specifications Proposed by Sponsor

Change of Dissolution Method

The sponsor encountered analytical problems with this approved method which resulted in artefactually fast release attributable to the high ionic strength of the media causing (b) (4) of the (b) (4) matrix. This had been discussed in the originally submission for this NDA and the sponsor had given a commitment to re-develop and cross-validate a new lower ionic strength method. The sponsor's response of December 18, 1998 stated that the dissolution method was acceptable, with the provision that the ionic strength of the method be reduced. The method has been slightly modified as a result of several 'burst' release profiles observed during stability testing, which were attributed to the ionic strength of the Tris buffer being too high. The modification is achieved by elimination of (b) (4) and the use of 50 mmol Tris, rather than the (b) (4) mmol Tris utilized in the original method for the Step 2 medium. The rest of the methodology remains unchanged.

This modified method (i.e., reduced ionic strength) has been cross-validated for Paroxetine (b) (4) Geomatrix® Controlled Release Tablet formulations of strength 12.5, 25, 37.5 (b) (4) and the mean data and ranges are listed below:

Strength	12.5mg	25mg	37.5mg	(b) (4)
Batch	*520050*	*515550*	*565540*	
1 hr Original			(b) (4)	
Modified				
2 hr Original				
Modified				
4 hr Original				
Modified				
6 hr Original				
Modified				
f_2	**66**	**74**	**63**	

The dissolution results obtained using the modified method comply with the specifications proposed by the sponsor (see next section) and were comparable to the data generated using the original method on selected batches of each of the (b) (4) strengths (12.5, 25, 37.5 (b) (4) using f_2 similarity factors.

Change of Dissolution Specifications

Supplement S-001 approved on July 2, 1999 provides Cidra as an alternate manufacturer of the two-toned bilayered (original commercial image) enteric coated tablet. The sponsor has conducted bioequivalence studies for both strengths 12.5 mg and 25 mg tablets from Crawley and Cidra manufacturing facilities. The dissolution specification that was approved was identical to that contained in the original NDA.

The addition of a colored (b) (4) film coating, also the subject of this submission, was compared to the approved dissolution specification. Results show a high frequency of having to progress to stage II and III testing. The approved Cidra 12.5 mg and 25 mg tablets (original commercial image) also showed a high frequency of stage II and III level testing (see below):

Site	Cidra		Crawley	
Strength	12.5mg	25mg	12.5mg	25mg
Batch#	M97049 (b) (4)	M97052 (b) (4)	M96285 (b) (4)	M96175 (b) (4)
	Dissolution Data (% dissolved) (Range)			
2 hrs				(b) (4)
4 hrs				

* represents the number of tablets failed the current specification.

Taking into account the use of these tablets in the bioequivalence studies and the frequency of progression to stage II and III testing, the sponsor proposes changes in specifications for the Step 2 testing from (b) (4)% to (b) (4)% for the 2 hours point and from (b) (4)% to (b) (4)% for the 4 hours point.

Dissolution Data Supporting Color Image Change

Methods

According to SUPAC MR guidance, the information needed to support a color image change is the dissolution data using 3 different media of the two stage testing. Comparative dissolution profiles (versus the currently approved enteric coated tablets) were performed in four different media (0.1 N HCl, pH 4.5 tris buffer, pH 6.8 Tris buffer, water and pH 7.5 Tris buffer) on one batch each of the 12.5 mg and 25 mg tablets that were colored (b) (4) film coated at SB Cidra, facility. In all cases the USP enteric resistance test <724> was performed prior to dissolution testing in the four different media. Final dissolution profile data for supporting color image change were generated using the USP dissolution apparatus II method (paddle) at 150 rpm in:

1) 750 ml of 0.1 N hydrochloric acid for two hours, followed by
2) 1000 ml of pH 7.5 0.05 M Tris buffer or pH 6.8 Tris buffer for up to seven hours (reported up to 6 hours).

Results

There was no evidence of any drug release from any of the batches after 2 hours testing in 0.1 N HCl demonstrating that the integrity of the enteric coat was unaffected by the presence or absence of an additional colored (b) (4) film coat. As was anticipated, the presence of the enteric coat ensured that there was no evidence of any drug release from any of the batches tested in water or pH 4.5 Tris buffer. Therefore, in these cases the similarity factors were not calculated. The comparative dissolution profile data and similarity factor values for new image vs. old image in pH 6.8 Tris buffer and pH 7.5 Tris buffer are shown below:

	1 hr	2 hrs	4 hrs	6 hrs	f_2
		pH 6.8 Tris Buffer (b) (4)			
12.5 mg Original Image X105-9PCRT1	(b) (4)				
12.5 mg New Image X602-9PCRT					57
25 mg Original Image X205-9PCRT1					
25 mg New Image X703-9PCRT					71
		pH 7.5 Tris Buffer (b) (4)			
12.5 mg Original Image X105-9PCRT1	(b) (4)				
12.5 mg New Image X602-9PCRT					91
25 mg Original Image X205-9PCRT1					
25 mg New Image X703-9PCRT					92

Summary

- There was no evidence of any drug release from any of the batches after 2 hours testing in 0.1 N HCl; demonstrating that the integrity of the enteric coat was unaffected by the presence or absence of an additional colored (b) (4) film coat.
- The presence of the enteric coat ensured that there was no evidence of any drug release from any of the batches tested in water or pH 4.5 Tris buffer.
- For the remaining media (pH 6.8 and pH 7.5 Tris buffer), dissolution profiles are comparable (f_2>50) between the additional colored (b) (4) film coated tablets and the currently approved tablets (without additional colored (b) (4) film coating).

Comment 1
There was no significant different between the release profiles of the colored (b) (4) film coated tablet and the currently approved enteric coated tablet for either strength of the product in all media tested. This demonstrates that product performance is unaffected by the presence or absence of an additional colored (b) (4) film coat.

Comment 2
The dissolution results obtained using the modified method (i.e., reduced ionic strength for the dissolution medium) were comparable to the data generated using the original method on selected batches of each of the (b) (4) strengths (12.5, 25, 37.5 (b) (4) using f_2 similarity factors.

Comment 3
Dissolution data from clinical and/or bio-batches support the proposed change of specification in 2 hours from (b) (4)% to (b) (4)%. For 4 hours point, there was no individual value below (b) (4)% from 11 clinical and/or bio-batches tested and only one tablet was under (b) (4) for all other available batches (b) (4) batches). Therefore, the specification change from (b) (4)% to (b) (4)% cannot be granted. The dissolution data suggest that the specification of (b) (4)% in 4 hours is appropriate.

Recommendation
Since dissolution data demonstrate that product performance is unaffected by the presence or absence of an additional colored (b) (4) film coat, the approval of the additional colored (b) (4) film coating for Paxil CR 12.5 and 25 mg tablets manufactured at Cidra, PR can be granted. The sponsor is requested to adopt the following dissolution method and specifications for Paxil CR tablets:

Apparatus:	USP II (paddle) at 150 rpm
Dissolution media:	Step 1: 0.1 N HCl (750 mL) for 2 hours
	Step 2: pH 7.5 Tris Buffer (1000 ml) containing 50 mmol Tris,
Specifications:	In 0.1 N HCl: 2 hours- NMT (b) (4)% dissolved
	In 0.05 M Tris Buffer at pH 7.5:
	1 hour- NMT (b) (4)% dissolved
	2 hours- between (b) (4)% dissolved
	4 hours- between % dissolved
	6 hours- NLT (b) (4)% dissolved.

Please convey this Recommendation to the sponsor.

Hong Zhao, Ph.D. Hong Zhao 7/26/2000

RD/FT Initialed by Raman Baweja, Ph.D. R. Baweja 7/27/00

cc: NDA 20-936/SCM-002 (Paxil, Paroxetine SR Tablets), HFD-120, HFD-860 (Zhao, Baweja, Mehta), Central Documents Room (CDR-Biopharm)

2.0 Validation of the UV Dissolution Methodology

2.1 Cross Validation Exercise for Tris Buffer Stage

For each tablet strength, dissolution testing was performed on 12 replicates from the same batch of Paroxetine Geomatrix® tablets as specified in the original method and the reduced ionic strength method. The results for each sample are shown in Tables 1-8.

Table 1: Results for the (b) (4) Dissolution (Original Method)
12.5 mg - Batch 520050

	Stage I	Stage II	Mean
(b) (4)			(b) (4)

Table 2: Results for the (b) (4) Dissolution (Modified Method)
12.5 mg - Batch 520050

	Stage I	Stage II	Mean
(b) (4)			(b) (4)

Table 3: Results for the (b) (4) Dissolution (Original Method)
25 mg - Batch 515550

	Stage I	Stage II	Mean
(b) (4)	(b) (4)	(b) (4)	(b) (4)

Table 4: Results for the (b) (4) Dissolution (Modified Method)
25 mg - Batch 515550

	Stage I	Stage II	Mean
(b) (4)	(b) (4)	(b) (4)	(b) (4)

Table 5: Results for the (b) (4) Dissolution (Original Method)
37.5 mg - Batch 565540

	Stage I	Stage II	Mean
(b) (	(b) (4		(b) (4)

I
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Table 6: Results for the (b) (4) Dissolution (Modified Method)
37.5 mg - Batch 565540

	Stage I	Stage II	Mean
(b) (4)			(b) (4)

(b) (4)

1
4 of 4

2.2 Calculation of f_2 Similarity Factor for the UV Dissolution Method

All of the results from the dissolution profiles obtained from the reduced ionic strength method were compared those from the original dissolution method using the following SUPAC equation, that defines a similarity factor (f_2) :

$$f_2 = 50 \text{ LOG } \{[1 + 1/n \Sigma^{n}_{t=1} (R_t - T_t)^2]^{-0.5} \text{ x } 100\}$$

where R_t and T_t are percent dissolved at each time point for the Reference and Test profiles respectively. An f_2 value between 50 and 100 confirms that the two dissolution profiles are equivalent [3].

For each tablet strength 12 replicate dissolution analyses were performed. Samples were analysed and the results were used to determine the f_2 similarity factor for the cross-validation between the original method and reduced ionic strength method, (b) (4)

Table 9: f_2 Similarity Factors for the UV Dissolution Method

Sample		f_2
12.5 mg	Batch 520050	66
25 mg	Batch 515550	74
37.5 mg	Batch 565540	63
		(b) (4)

Comparison of the profiles using the SUPAC similarity factor (f_2) demonstrate that the profiles obtained are equivalent as f_2 values are within the range of 50 and 100.

Batches of Paroxetine CR Tablets Utilized in Bioequivalence Studies

Cidra 12.5	Cidra 25	Crawley 12.5	Crawley 25
(b) (4)			

Appendix IV
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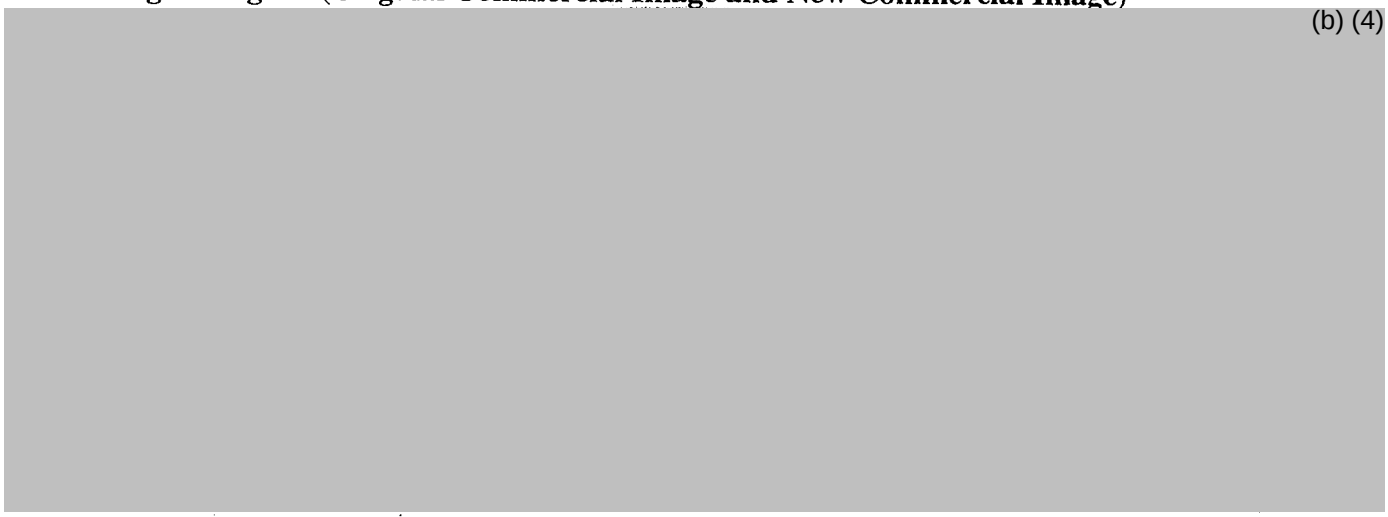
Table 1 Manufacturing Details for Paroxetine CR Tablets 12.5 and 25mg Strengths (Original Commercial Image and New Commercial Image)

(b) (4)



III

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Table 2 Comparative Dissolution Data for 12.5mg Paroxetine CR Tablets in (b) (4) New Commercial Image, X602-9PCRT versus Original Commercial Image, X105-9PCRT1

Storage Condition		Enteric Resistance (% Claim	Cumulative Dissolution % Claim Dissolved After:

(b) (4)

Table 3 Comparative Dissolution Data for 12.5mg Paroxetine CR Tablets in pH 4.5 Tris. Buffer (New Commercial Image, X602-9PCRT versus Original Commercial Image, X105-9PCRT1)

Storage Condition		Enteric Resistance (% Claim	Cumulative Dissolution % Claim Dissolved After:

(b) (4)

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4 of 10

Table 4 Comparative Dissolution Data for 12.5mg Paroxetine CR Tablets in pH 6.8 Tris. Buffer (New Commercial Image, X602-9PCRT versus Original Commercial Image, X105-9PCRT1)

Storage Condition		Enteric Resistance (% Claim	Cumulative Dissolution % Claim Dissolved After:

(b) (4)

Table 5 Comparative Dissolution Data for 12.5mg Paroxetine CR Tablets in pH 7.5 tris. Buffer (New Commercial Image, X602-9PCRT versus Original Commercial Image, X105-9PCRT1)

Storage Condition		Enteric Resistance (% Claim	Cumulative Dissolution % Claim Dissolved After:

(b) (4)

Table 6 Comparative Dissolution Data for 25mg Paroxetine CR Tablets in (b) (4) (New Commercial Image, X703-9PCRT versus Original Commercial Image, X205-9PCRT1)

Storage Condition		Enteric Resistance (% Claim	Cumulative Dissolution % Claim Dissolved After:

(b) (4)

Table 7 Comparative Dissolution Data for 25mg Paroxetine CR Tablets in pH 4.5 Tris. Buffer (New Commercial Image, X703-9PCRT versus Original Commercial Image, X205-9PCRT1)

Storage Condition		Enteric Resistance (% Claim	Cumulative Dissolution % Claim Dissolved After:

(b) (4)

8 of 10

Table 8 Comparative Dissolution Data for 25mg Paroxetine CR Tablets in pH 6.8 Tris. Buffer (New Commercial Image, X703-9PCRT versus Original Commercial Image, X205-9PCRT1)

Storage Condition		Enteric Resistance (% Claim Dissolved)	Cumulative Dissolution % Claim Dissolved After:

(b) (4)

Table 9 Comparative Dissolution Data for 25mg Paroxetine CR Tablets in pH 7.5 Tris. Buffer (New Commercial Image, X703-9PCRT versus Original Commercial Image, X205-9PCRT1)

Storage Condition		Enteric Resistance (% Claim	Cumulative Dissolution % Claim Dissolved After:

(b) (4)

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Paroxetine Dissolution Data

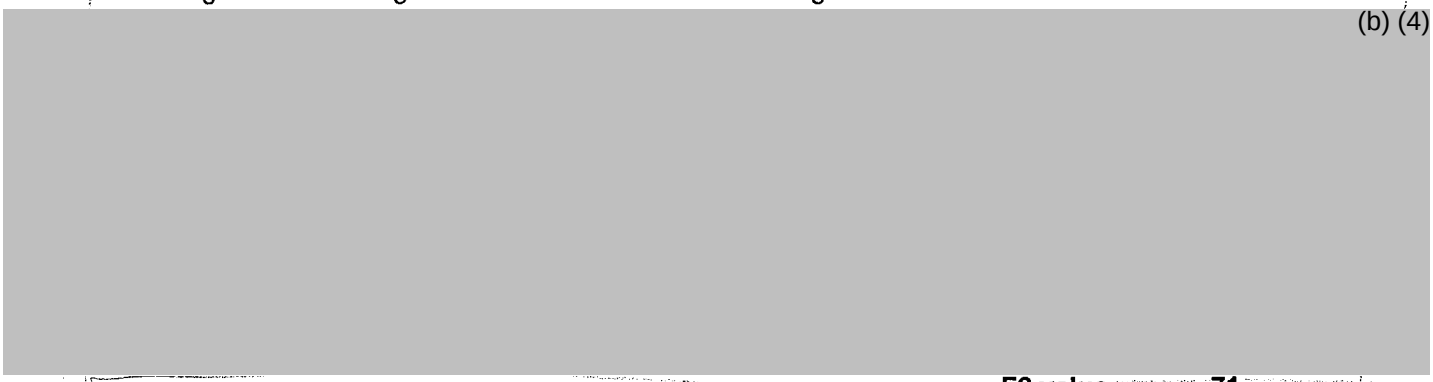
USP App 2, 1000 ml pH 6.8 Tris Buffer, 100 rpm, 1-6 hrs

(b) (4)

F2 value **57**

25 mg New Image X602-9PCRT Old Image X105-9PCRT1

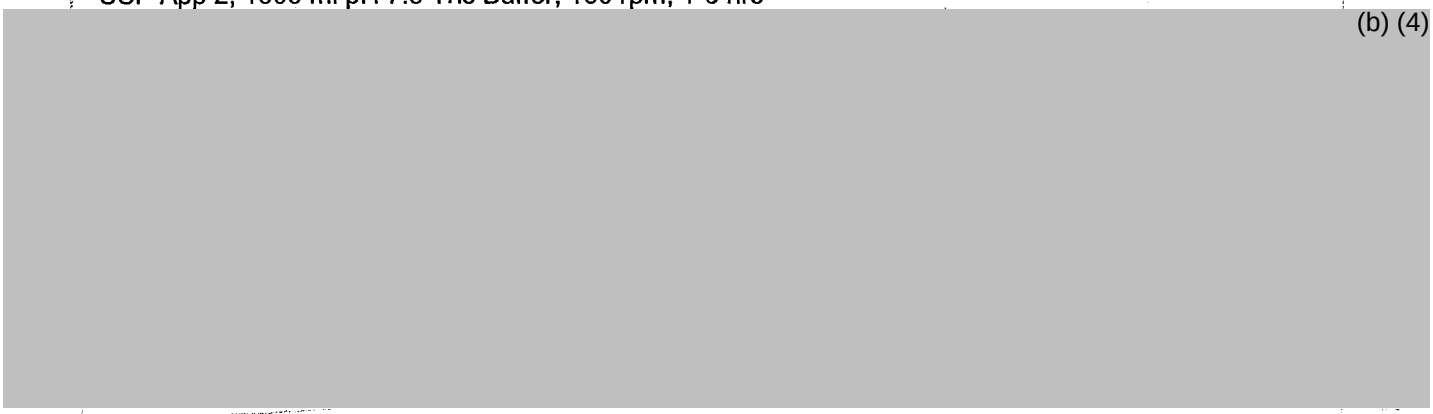
(b) (4)



F2 value **71**

USP App 2, 1000 ml pH 7.5 Tris Buffer, 100 rpm, 1-6 hrs

(b) (4)



F2 value **91**

25 mg New Image X602-9PCRT Old Image X105-9PCRT1

(b) (4)

F2 value **92**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-936/S002

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

AUG 16 2000

MEMORANDUM

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

DATE: August 16, 2000

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

SUBJECT: Recommendation for Approval Action for CMC Changes for Paxil CR (paroxetine) 12.5 & 25 mg strength tablets

TO: File NDA 20-936/S-002
[Note: This memo should be filed with the 4-17-00 original submission.]

Paxil CR is an approved drug product, for the treatment of depression, currently available in 12.5 and 25 mg tablet strengths. This supplement provides for (1) a change in the drug product image from a two-toned bilayered enteric coated tablet to a colored (b) (4) film coated enteric coated tablet, to be manufactured only at the Cidra, PR site, (2) a change in the tablet core thickness in-process manufacturing control for the 12.5 mg tablet, (3) revised dissolution method and specifications, and (4) revisions in the Description and How Supplied sections of labeling.

There was no requirement for in vivo bioequivalence data for this supplement. The dissolution data provided were reviewed by Dr. Hong Zhao from Biopharmaceutics. She concluded that the supplement can be approved, however, with a slightly different dissolution method and specifications than proposed by the sponsor.

The CMC data provided in this supplement were reviewed by Dr. Gill-Sangha from Chemistry. While I have not yet seen her completed review, it is my understanding that the supplement can be approved from a chemistry standpoint. One remaining issue to be resolved is the inspection. Apparently, Compliance had originally indicated that the inspection has not been done, however, the sponsor has apparently been able to produce an inspection report from Compliance indicating that the insection has been done and it satisfactory. The details are yet to be worked out.

The only clinical question for this supplement is whether or not confusion might result from the fact that the new CR tablets will be the same color as the near equivalent IR tablets. Dr. Dubitsky from the clinical group has considered this question and concluded that there are sufficient differences in the tablets (also differ in shape and both have adequate markings) that it is not likely to be a problem.

Furthermore, he notes that, even if they were to be confused, the amount of drug substance contained in each is comparable.

Recommendation

Thus, I agree with the recommendations of all reviewers that this supplement can be approved, with our slightly different proposed dissolution method and specifications, assuming the inspection issue can be finally resolved.

cc:
Orig NDA 20-936/S-002
HFD-120/DivFile
HFD-120/TLaughren/RKatz/PDavid

DOC: NDA20936.02

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	REQUEST FOR CONSULTATION Dr. Baweja DELIVERED MAY 0 1 2000
TO (Division/Office) **HFD-860/Biopharmaceutics**	FROM: **HFD-120/NEUROPHARMACOLOGY**

Date	IND No.	NDA No.	TYPE OF DOCUMENT	DATE OF DOCUMENT
4/28/00		**20-936/SCM-002**	**CMC Manufacturing Supplement**	**4/17/00**

Name of Drug **Paxil (Paroxetine HCl) Controlled Release 12.5 and 25 mg Tablets**	Classification of Drug : **Depression**

Name of Firm **SmithKline Beecham** Desired Completion Date: **8/1/00** ←

REASON FOR REQUEST

1. General

☐NEW PROTOCOL	☐PRE-NDA MEETING	☐RESPONSE TO DEFICIENCY LETTER
☐PROGRESS REPORT	☐END OF PHASE 2 MEETING	☐FINAL PRINTED LABELING
☐NEW CORRESPONDENCE	☐RESUBMISSION	☐LABELING REVISION
☐DRUG ADVERTISING	☐SAFETY/EFFICACY	☐ORIGINAL NEW CORRESPONDENCE
☐ADVERSE REACTION REPORT	☐PAPER NDA	☐FORMULATIVE REVIEW
☐MANUFACTURING CHANGE/ ADDITION	☐CONTROL SUPPLEMENT	☐OTHER (SPECIFY BELOW)
☐MEETING PLANNED BY		

III. BIOPHARMACEUTICS

☐DISSOLUTION	☐DEFICIENCY LETTER RESPONSE
☐BIOAVAILABILITY STUDIES	☐PROTOCOL-BIOPHARMACEUTICS
☐PHASE IV STUDIES	☐IN-VIVO WAIVER REQUEST

COMMENTS/SPECIAL INSTRUCTIONS(ATTACH ADDITIONAL SHEETS IF NECESSARY)

Ray,

Please find attached a 2 volume chemistry manufacturing and controls supplemental application providing for a change to manufacture Paxil CR at Cidra, PR as well as providing for a change in the regulatory dissolution methods. The reviewing chemist is Dr. Rik Lostritto.

Please note that the primary UF goal date is 8-19-00, and the secondary UF goal date is 10-19-00. ←

I have also attached, for your convenience, relevant meeting minutes, letters, and T-Cons dated 7-2-99, 7-6-99, 7-28-99, 9-14-99, and 3-20-00, regarding our discussions with SB on these changes.

Should you have any questions, please contact the Project Manager, Mr. Paul David, at 594-5530.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (CHECK ONE) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER R. Baweja 5/2/2000	SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-936/S-002

APR 26 2000

SmithKline Beecham Pharmaceuticals
1250 S. Collegevile, Road
P.O. Box5089
Collegeville, PA 19426

Attention: Deborah E. Zuber
Assistant Director North American Regulatory Affairs

Dear Ms. Zuber:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Paxil CR Tablets

NDA Number: 20-936

Supplement Number: 002

Date of Supplement: 17-Apr-00

Date of Receipt: 19-Apr-00

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on 18-Jun-2000 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Attention: Document Control Room 4008
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

4/26/00

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 20-936/002
HFD-120/Div. Files
HFD-120/CSO/David

filename:

SUPPLEMENT ACKNOWLEDGEMENT

SmithKline Beecham
Pharmaceuticals

NDA SUPPLEMENT

ORIGINAL

NDA NO. 20-936 REF NO. SCM-002
NDA SUPPL FOR Manufacturing Change

April 17, 2000

NDA 20-936
Paxil® (paroxetine hydrochloride, hemihydrate) CR Tablets

Russell Katz, M.D., Director
Division of Neuropharmacological
Drug Products (HFN-120, Room 10B-45)
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
APR 19 2000
RECEIVED HFD-120

RE: Prior Approval Supplement: Chemistry Manufacturing and Controls

Dear Dr. Katz:

Reference is made to the approved New Drug Application NDA 20-936 for Paxil® Controlled Release Tablets, 12.5 mg and 25 mg strengths and to the Supplement S-001 approved on July 2, 1999. This prior approval supplement provides for additional manufacturing and controls data for the Paxil® CR Tablets manufactured at the SmithKline Beecham Cidra, Puerto Rico facility.

This submission provides chemistry manufacturing and controls data to support the following proposed manufacturing changes for product approved at the SB Cidra, Puerto Rico facility.

1. The original commercial image (two-tone bilayered enteric coated tablets) 12.5 mg and 25 mg strengths manufactured at the Cidra PR facility was approved on July 2, 1999 in Supplment S-001. The additional CMC data for the proposed new commercial image tablet (colored (b) (4) film coated enteric coated tablets) contained in that submission (b) (4) (b) (4) (b) (4) it was agreed with FDA that additional qualification batches of the original commercial image manufactured at the Cidra PR facility could be color film coated to

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

supplement the original submission. These additional Cidra qualification batches were manufactured in March 1999 and had been stored in the SB, Cidra warehouse for (b)(4) months prior to application of the additional colored film coating in July 1999. This submission contains the following data:

- Certificates of analysis of the original commercial image tablets manufactured in March 1999.
- Batch analysis on the original commercial image tablets after storage for (b)( ) months in the SB Cidra warehouse (including dissolution profile data).
- Batch analysis on the new commercial image (single colored tablets) tablets produced by application of an additional colored film coat at the Cidra PR facility (including dissolution profile data). SUPAC–MR comparative dissolution profiles (USP Stage II i.e., 12 tablet) versus the (b)(4) month old original commercial image tablet batches.
- SUPAC–MR comparative dissolution Stage II (12 tablet) profiles in four different media and calculation of the f2 similarity factor.
- Executed batch records for the batches that were colored (b) (4) film coated at the Cidra, PR, facility.
- A stability commitment to place the first commercial batch of each strength of new commercial image on stability and the data provided in annual reports.

In addition, administrative typographical errors have been corrected in S-001 Sections 4.A.2.1 through 4.A.2.5. No technical information on these pages have changed. The corrections include misspelled words and column header formats.

Copies of Sections 4.A.2.1 through 4.A.2.7 have been included for ease of review.

(b) (4)

Based on these data SmithKline Beecham is requesting approval of the additional colored (b) (4) film coating for Paxil® CR manufactured at Cidra, PR.

2. Supplement S-001 contained a revision to the dissolution specification approved with the initial NDA. FDA informed SmithKline Beecham in a

teleconference on July 28, 1999 that the specification revision had not been approved along with the Cidra manufacture of the original commercial image tablets. This supplement provides the justification and the data to support the revision to the dissolution specification. The dissolution data generated on the additional colored (b) (4) film coated tablet batches were compared to both, the FDA approved dissolution specification and the proposed dissolution specification. The comparative data is located in the tabbed section entitled "Proposed Dissolution Specification". The data show a high frequency of having to progress to USP Stage II and III testing. The currently approved SB Cidra 12.5 mg and 25 mg tablets (original commercial image) also show a high frequency of USP Stage II and III testing. Statistical evaluation of the in-vitro dissolution data from SB Crawley and Cidra 12.5 mg and 25 mg tablet batches used in Bioequivalence studies are supportive of wider dissolution limits. This, allied with frequency of progression to USP Stage II and III testing, supports the proposal to revise the current approved dissolution specification.

3. This submission also provides for the approval of a revision to the approved drug product dissolution method. The revised method had been included in Supplement S-001 as commercial method (b) (4) and (b) (4) (b) (4) This dissolution method has been solely used to generate all the SUPAC-MR dissolution data and initial release data contained in this submission. It was also used to generate all the dissolution data at release and on stability in the approved Supplement S-001.

   In the FDA approvable letter of October 9, 1998, the Division of Pharmaceutical Evaluation I (Office of Clinical Pharmacology and Biopharmaceutics) requested that SB agree to the following dissolution method:

   Apparatus: USP II (paddles) 150 rpm
   Dissolution media:
   Step 1: 0.1 M HCl (750 mL) for 2 hours
   Step 2: pH 7.5 Tris Buffer containing (b) (4) mmol Tris, (b) (4) fo (b) (4) hours

   In SB's response of December 18, 1998, SB stated the dissolution method was acceptable, with the provision that the ionic strength of the method be reduced. This is achieved by elimination of (b) (4) and the use of 50 mmol Tris, rather than the (b) (4) mmol Tris utilized in the original method.

SB encountered analytical problems with the original methodology (that ultimately approved by FDA) which resulted in artefactually fast release which was attributable to the high ionic strength of the method causing (b) (4) of the (b) (4) matrix. This had been discussed in the originally submitted NDA 20-936 and SB had given a commitment to re-develop and cross-validate a new lower ionic strength method (Cidra (b) (4) (b) (4) These data were provided in a response, however the FDA approved the NDA with the older method. Due to the issues with the method, the revised methodology (which provides an equivalent release rate to the old method, but prevents the artefactually fast release) is now routinely utilized within SB for release and stability testing. These methods, Cidra metho (b) (4) were used in developing data for S-001 and for this supplement. Method validation and cross-validation are provided in Appendix 3 under dissolution methods within this supplement. They were also previously provided in Supplement S-001. These are identified as:

97PTHW_0014/1 [Original Validation] - "Validation of Dissolution Methodology (b) (4) for Paroxetine (b) (4) 'Geomatrix'® Controlled Release Tablets"

97PTHW_0014/1 [Cross-Validation Summary] - "Supplementary Cross Validation of Dissolution Methodology (b) (4) for Paroxetine (b) (4) Geomatrix'® Controlled Release Tablets"

97PTHW_0014/4 [Updated Validation] – "Validation of Dissolution Methodology (b) (4) for Paroxetine (b) (4) Geomatrix'® Controlled Release Tablets"

Subsequently, SB has received an FDA letter dated October 18, 1999 (copy provided in Appendix 10) requesting that SB further investigate the dissolution method. The FDA laboratories encountered a problem with the second stage of the dissolution method. The FDA testing laboratory used the original methodology approved by FDA (b) (4) (b) (4) Both version 2 and version 5 of this method used two point readings. Both method versions were validated to detect interference. SB does acknowledge the inadequacies of version 2 with regard to artefactually fast release and this prompted development and validation of the existing method(version 5).

4. The FDA approval letter of July 2, 1999 also contained a comment #3. This is restated below:

"We note that the existing commercial image tablets start out with an initial hardness (b) (4) (b) (4)

We recommend that you address these discrepancies more thoroughly in future submission concerning the new commercial image."

The response to this question is provided in Appendix 7 of this supplement.

Revisions to the labeling "Description" and "How Supplied" Sections will be provided as final draft labeling upon approval. Since this product has not been commercialized to date, final labeling has not been issued. Draft labeling for Paxil® CR Tablets, 12.5 and 25 mg, was provided in S-001, Volume 2.1.001, Item 2: Labeling.

If you should have questions or comments concerning this Supplement, please do not hesitate to call me at (610) 917-6884 or fax at (610) 917-4704.

Sincerely,

Deborah E. Zuber

Deborah E. Zuber, R.Ph.
Assistant Director
North American Regulatory Affairs