CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-936/S006
20-031/S032
20-710/S010
20-885/S003

Trade Name: Paxil CR
Paxil Tablets
Paxil Capsules
Paxil Oral Suspension

Generic Name: (paroxetine hydrochloride)

Sponsor: SmithKline Beecham Pharmaceuticals

Approval Date: April 30, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-936/S006
20-031/S032
20-710/S010
20-885/S003

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	X
Labeling	
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	
Chemistry Review(s)	X
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Other Reviews	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-936/S006
20-031/S032
20-710/S010
20-885/S003

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-031/SCM032, 20-710/SCM-010, 20-885/SCM003, 20-936/SCM006

SmithKline Beecham Pharmaceuticals
Attention: Deborah E. Zuber
Assistant Director, US Regulatory Affairs
1250 South Collegeville Road, PO Box 4089
Collegeville, PA 19426-0989

Dear Ms. Zuber:

Please refer to your supplemental new drug application dated November 6, 2000 received November 7, 2000 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paxil® Tablets, Paxil® Capsules, Paxil® CR Tablets, Paxil® Oral Suspension.

We acknowledge receipt of your submission dated November 6, 2000. These "Changes Being Effected" Supplemental New Drug Applications provide for updated CMC information in DMF 15039 covering (b) (4) of Paroxetine HCl using approved (b) (4) County Cork, Ireland.

We have completed the review of these supplemental applications and they are approved with the following comment.

You have provided release data on values of "Other Single Impurity" for the (b) (4) batches manufactured using approved (b) (4) Cork, Ireland (b) (4) However, the "Other Single Impurity" has shown values greater than (b) (4)% on stability. We recommend that you change the specification of "Other Single Impurity" to an appropriate value such (b) (4)% or submit a Prior Approval supplement for an acceptable improved regulatory method for determining the "Highest Other Single Impurity" at NMT (b) (4)%.

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,

{See appended electronic signature page}

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

cc:
Archival NDA 20-031/20-710/20-885/20-936
HFD-120/Div. Files
HFD-120/GGill-Sangha
HFD-120/RSeevers
HFD-120/PDavid
HFD-095/DDMS-IMT
HFD-810/DNDC Division Director
DISTRICT OFFICE

Drafted by: ggs/April 26, 2001
filename: C:/data/My Documents/data gill/Supplement NDA/20-031-710-885-93/
AP-32-10-6-3LTR.doc

APPROVAL (AP)

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

/s/

Robert H. Seevers
4/30/01 12:14:24 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-936/S006

20-031/S032

20-710/S010

20-885/S003

OTHER ACTION LETTER(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-031/SCM032
NDA 20-885/SCM003
NDA 20-936/SCM006
NDA 20-710/SCM010

INFORMATION REQUEST LETTER

SmithKline Beecham Pharmaceuticals
Attention: Deborah E. Zuber, R.Ph.
Assistant Director, NA Regulatory Affairs
1250 South Collegeville Road, P.O. Box 4089
Collegeville, PA 19426-0989

Dear Ms. Zuber:

Please refer to your supplemental new drug applications dated November 6, 2000 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paxil® Tablets, Paxil® Capsules, Paxil® CR Tablets, Paxil® Oral Suspension.

We also refer to your submissions dated December 29, 2000.

We are reviewing the Chemistry section of your submissions and have the following comments and information requests. We need your prompt written response to continue our evaluation of your supplemental application.

1. Your amendment dated December 29, 2000 requests approval for modified manufacturing route of paroxetine HCl at (b) (4) 15039. The amendment (pages 13-14, 17-18) states that the following data are provided to support the changes proposed:
   - (b) (4)
   - Batch analysis data on (b) (4) and comparative batch analysis between current approved drug substance and alternate modified route of manufacture
   - Stability data for batches manufactured via (b) (4) (b) (4) under ICH conditions for DMF's 15039 (b) (4) includes:
     - (b) month stability data for (b) batches for DMF 15039,
     - (4) (4) (b) (4)
   - Relevant raw material specifications and analytical methods including intermediate specifications, analytical methods and method validation for (b) (4)

   However, these data have not been provided either in the supplement, the amendment dated December 29, 2000 or the respective DMF's. This supplement cannot be approved until these data are submitted and reviewed. Please provide the data to support the changes proposed for use of (b) (4) method at (b) (4) for manufacture of drug substance, paroxetine HCl, as soon as possible.

2. DMF' (b) (4) 15039 are both for the manufacturing of paroxetine HCl (b) (4) (b) (4) As per DMF 15039 cover letter, only DMF 15039 will be referenced in the future Paxil® submissions. However, the proposed changes in your amendment dated December 29, 2000 will result in manufacturing (b) (4) SB County Cork, Irelanc (b) (4) (b) (4) for both DMF' (b) (4) 15039. As a consequence, both DMF's will (b) (4)

3. The modified route of manufacture (b) (4) requires use of (b) (4) (b) (4) You have not provided data to establish absence of any new impurities generated materials including (b) (4) Please propose, monitor and report in-process controls and analytical methods for possible new impurities and include all impurities greater thai (b) (4) % in the drug substance specifications.

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

Sincerely,

{See appended electronic signature page}

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

/s/

Robert H. Seevers
2/8/01 01:26:06 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-936/S006

20-031/S032

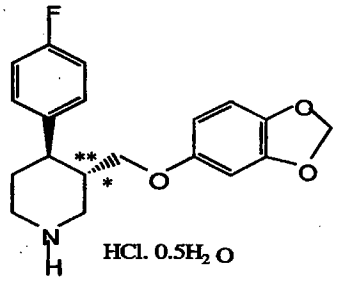
20-710/S010

20-885/S003

CHEMISTRY REVIEW(S)

CHEMIST REVIEW
OF **SUPPLEMENTS**

1. ORGANIZATION:	HFD-120
2. NDA:	**20-031, 20-885 20-936, 20-710**
3. SUPPLEMENT NUMBERS/ DATES:	**SCM032, SCM003, SCM006, SCM010 respectively**
letter date:	November 6, 2000
stamp date:	November 7, 2000
4. AMENDMENTS/REPORTS/DATES:	
5. RECEIVED BY CHEMIST:	December 4, 2000
6. APPLICANT NAME & ADDRESS	Smithkline Beecham Pharmaceuticals 1250 S. Collegeville Road, PO Box 5089, PA 19426-0989
7. NAME OF DRUG:	Paxil®
8. NONPROPRIETARY NAME:	Paroxetine hydrochloride
9. CHEMICAL NAME/STRUCTURE:	(-)trans-4R-(4'-fluorophenyl)-3S-[3',4'-methylenedioxyphenoxymethyl]-piperidine hydrochloride hemihydrate



10. DOSAGE FORM(S):	N20-031 – Paxil® Tablets N20-885 – Paxil® CR Tablets N20-936 – Paxil® CR Tablets N20-710 – Paxil® Oral Suspension
11. POTENCY:	N20-031 – Paxil® Tablets (10, 20, 30, 40 mg) N20-885 – Paxil® Capsules (10, 20, 30, 40 mg) N20-936 – Paxil® CR Tablets (12.5 and 25 mg) N20-710 – Paxil® Oral Suspension (10 mg/5 mL)
12. PHARMACOLOGICAL CATEGORY:	Depression, Obsessive Compulsive Disorder, and Panic Disorder
13. HOW DISPENSED:	X (R_X) _____ (OTC)
14. RECORDS & REPORTS CURRENT:	X Yes _____ No
15. RELATED IND/NDA/DMF:	DMF 15039

SUPPLEMENT PROVIDES FOR:
Minor changes in DMF 15039 covering scale-up of production (b) (4) paroxetine hydrochloride hemihydrate from (b) (4) County Cork, Ireland.

COMMENTS:
The changes are minor for increased production using approved (b) (4) as the manufacturing method. However, the sponsor has not responded to a pending agency's comment on drug substance specifications. See review notes and DMF's 15039 (b) (4) deficiency letter dated 3/19/01 for details.

CONCLUSIONS & RECOMMENDATIONS:
N20-031/SCM032, N20-710/SCM010, N20-885/SCM003, N20-936/SCM006 are recommended **APPROVABLE** contingent on the response and evaluation of the DMF 15039 deficiency letter. A DMF deficiency letter dated March 19, 2001 was sent to SKB. This is CR #1 and another review will be done followed by SKB response to DMF deficiency letter. Please see attached review notes.

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 20-031/SCM032
NDA 20-885/SCM003
NDA 20-936/SCM006
NDA 20-710/SCM010
HFD-120/Division File
HFD-120/GGill-Sangha
HFD-120/PDavid
HFD-120/RSeevers
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✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry-20-936
S 006

/s/

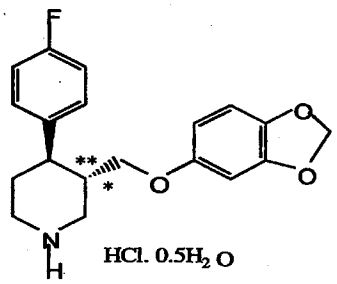
Gurpreet Gill-Sangha
3/22/01 12:56:24 PM
CHEMIST

This is the review #1 for all 4 CBE supplements

Robert H. Seevers
3/22/01 01:02:51 PM
CHEMIST

CHEMIST REVIEW
OF **SUPPLEMENTS**

1. ORGANIZATION: HFD-120
2. NDA: **20-031, 20-885**
20-936, 20-710
3. SUPPLEMENT NUMBERS/ DATES: **SCM034, SCM004,**
SCM007, SCM011 respectively
letter date: December 29, 2000
stamp date: January 3, 2001
4. AMENDMENTS/REPORTS/DATES:
5. RECEIVED BY CHEMIST: January 7, 2001
6. APPLICANT NAME & ADDRESS: Smithkline Beecham Pharmaceuticals
1250 S. Collegeville Road, PO Box 5089, PA 19426-0989
7. NAME OF DRUG: Paxil®
8. NONPROPRIETARY NAME: Paroxetine hydrochloride
9. CHEMICAL NAME/STRUCTURE: (-)trans-4R-(4'-fluorophenyl)-3S-[3',4'-methylenedioxyphenoxymethyl]-piperidine hydrochloride h



10. DOSAGE FORM(S): N20-031 – Paxil® Tablets
N20-885 – Paxil® Capsules
N20-936 – Paxil® CR Tablets
N20-710 – Paxil® Oral Suspension

11. POTENCY: N20-031 – Paxil® Tablets (10, 20, 30, 40 mg)
N20-885 – Paxil® Capsules (10, 20, 30, 40 mg)
N20-936 – Paxil® CR Tablets (12.5 and 25 mg)
N20-710 – Paxil® Oral Suspension (10 mg/5 mL)

12. PHARMACOLOGICAL CATEGORY: Depression, Obsessive Compulsive Disorder, and Panic Disorder
13. HOW DISPENSED: X (Rx) ____ (OTC)
14. RECORDS & REPORTS CURRENT: X Yes ____ No
15. RELATED IND/NDA/DMF: DMF 15039 (b) (4)

SUPPLEMENT PROVIDES FOR:
Prior Approval supplements for use of an alternate modified route of manufacture (b) (4) of paroxetine HCl using (b) (4) The changes in manufacture will affect two DMF's for paroxetine HCl (b) (4) DMF # 15039.

COMMENTS:
These PA supplements were initially accidentally filed as an amendment to another Paxil supplement. This was corrected on March 1, 2001. An IR letter was sent to SKB (GSK) on February 8, 2001 for information

regarding these PA supplements. However, the IR letter and response refer to the earlier supplements N20-031/SCM032, N20-885/SCM003, N20-936/SCM006 and N20-710/SCM010. The response to IR sent on February 15, 2001 for N20-031/SCM032, N20-885/SCM003, N20-936/SCM006 and N20-710/SCM010 is evaluated in this review.

CONCLUSIONS & RECOMMENDATIONS:
N20-031/SCM034, N20-710/SCM011, N20-885/SCM004, N20-936/SCM007 are recommended **APPROVABLE** contingent on the response and evaluation of the deficiencies. Please see attached review notes and deficiency letter for DMF's (b) (4) 15039 dated March 19, 2001 for details.

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 20-031/SCM034
NDA 20-885/SCM004
NDA 20-936/SCM007
NDA 20-710/SCM011
HFD-120/Division File
HFD-120/GGill-Sangha
HFD-120/PDavid
HFD-120/RSeevers
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✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry-20-936
5008

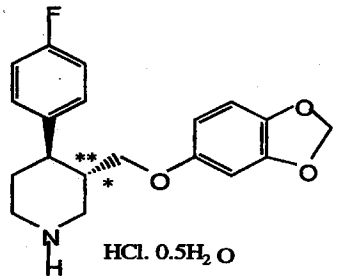
/s/

Gurpreet Gill-Sangha
3/22/01 12:50:01 PM
CHEMIST

This is review #1 for all 4 PA supplements with the response to IR letter

Robert H. Seevers
3/22/01 01:00:48 PM
CHEMIST

CHEMIST REVIEW OF **SUPPLEMENTS**	1. ORGANIZATION: HFD-120
	2. NDA: **20-031, 20-885 20-936, 20-710**
	3. SUPPLEMENT NUMBERS/ DATES: **SCM032, SCM003, SCM006, SCM010 respectively**
	letter date: November 6, 2000
	stamp date: November 7, 2000
	4. AMENDMENTS/REPORTS/DATES: Response to DMF 15039 deficiency letter
	5. RECEIVED BY CHEMIST: December 4, 2000
6. APPLICANT NAME & ADDRESS	Smithkline Beecham Pharmaceuticals 1250 S. Collegeville Road, PO Box 5089, PA 19426-0989
7. NAME OF DRUG:	Paxil®
8. NONPROPRIETARY NAME:	Paroxetine hydrochloride
9. CHEMICAL NAME/STRUCTURE:	(-)trans-4R-(4'-fluorophenyl)-3S-[3',4'-methylenedioxyphenoxymethyl]-piperidine hydrochloride hemihydrate



10. DOSAGE FORM(S):	N20-031 – Paxil® Tablets N20-885 – Paxil® Capsules N20-936 – Paxil® CR Tablets N20-710 – Paxil® Oral Suspension
11. POTENCY:	N20-031 – Paxil® Tablets (10, 20, 30, 40 mg) N20-885 – Paxil® Capsules (10, 20, 30, 40 mg) N20-936 – Paxil® CR Tablets (12.5 and 25 mg) N20-710 – Paxil® Oral Suspension (10 mg/5 mL)
12. PHARMACOLOGICAL CATEGORY:	Depression, Obsessive Compulsive Disorder, and Panic Disorder
13. HOW DISPENSED:	X (Rx) (OTC)
14. RECORDS & REPORTS CURRENT:	X Yes No
15. RELATED IND/NDA/DMF:	DMF 15039

SUPPLEMENT PROVIDES FOR:
Minor changes in DMF 15039 covering scale-up of production (b) (4) of paroxetine hydrochloride hemihydrate from (b) (4) County Cork, Ireland.

COMMENTS:
The responses to the two questions related to these supplements from deficiency letter for DMF 15039 dated 3/22/01 are evaluated in CR#2 of DMF 15039. Please see attached CR#2 for DMF 15039 for details.

CONCLUSIONS & RECOMMENDATIONS:
N20-031/SCM032, N20-710/SCM010, N20-885/SCM003, N20-936/SCM006 are to be recommended **APPROVED** with noted comment about an appropriate specification limit or improve the regulatory method for the highest other single impurity as NMT (b) (4) %. See draft letter and attached DMF 15039 CR#2 for details.

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 20-031/SCM032
NDA 20-885/SCM003
NDA 20-936/SCM006
NDA 20-710/SCM010
HFD-120/Division File
HFD-120/GGill-Sangha
HFD-120/PDavid
HFD-120/RSeevers
File: C:/data/My Documents/data gill/supplement NDA/20-031-710-936-885/rev2-32-10-6-3.doc

DRAFT LETTER:

You have provided release data on values of "Other Single Impurity" for the (b) (4) batches manufactured using approved (b) (4) Cork, Ireland (b) (4) However, the "Other Single Impurity" has shown values greater than (b) (4)% on stability. We recommend that you change the specification of "Other Single Impurity" to an appropriate value such as (b) (4)% or submit a Prior Approval supplement for an acceptable improved regulatory method for determining the "Highest Other Single Impurity" at NMT (b) (4)%.

18 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
5006