

CENTER FOR DRUG EVALUATION AND RESEARCH

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

CHEMISTRY REVIEW(S)



NDA 20-982

Paxil CR™ (paroxetine HCl) Tablets

GlaxoSmithKline

Gurpreet Gill-Sangha, Ph.D.

***DIVISION OF NEUROPHARMACOLOGICAL DRUG
PRODUCTS***

Review of Chemistry, Manufacturing, and Controls



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Chemistry Review Data Sheet

1. NDA 20-982
2. REVIEW #: 2
3. REVIEW DATE: 6-Feb-2002
4. REVIEWER: Gurpreet Gill-Sangha, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Chemistry Review #1

Document Date

16-Apr-1999

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

N(AZ)

N(BB)

Document Date

18-Dec-2001

9-Jan-2002

7. NAME & ADDRESS OF APPLICANT:

Name: GlaxoSmithKline

Address: One Franklin Plaza, PO Box 7929, Philadelphia, PA 19101

Representative: Susan Weill, Associate Director, US Regulatory Affairs

Telephone: (610) 917-6223

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Paxil Controlled Release
- b) Non-Proprietary Name (USAN): Paroxetine HCl
- c) Code Name/# (ONDC only): BRL-029060
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3



- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) 1
10. PHARMACOL. CATEGORY: Treatment of Panic Disorder
11. DOSAGE FORM: Controlled Release Tablets
12. STRENGTH/POTENCY: 12.5, 25 and 37.5 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note28]:

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

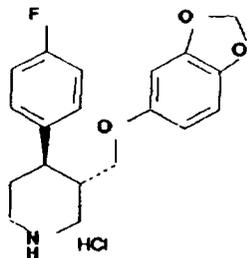
CA Name: (-)-trans-4R-(4'-fluorophenyl)-3S-[(3', 4'-methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate

USAN Name: Paroxetine HCl

Chemical Formula: $C_{19}H_{20}FNO_3 \cdot HCl \cdot 1.1/2H_2O$

Molecular Weight: 374.9 (329.4 as free base)

Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: None

CHEMISTRY REVIEW

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Chemistry Review #1	N20-982	Recommended for Approval for CMC on 16-Apr-1999 by Dr. Rik Lostritto
NDA	N20-936	Supporting Approved NDA

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	5-Feb-2002	Melissa Garcia from FDA Compliance
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Refer to N20-936		
OPDRA			
EA	Refer to N20-936		
Microbiology			



The Chemistry Review for NDA 20-982

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

N20-982 is recommended for approval from the chemistry standpoint based on the information submitted in the original NDA (reference to approved NDA 20-936 for all CMC information, subject of chemistry review #1 for N20-982) and the 3-Jan-2002 amendment (proposed package insert, subject of this review). Chemistry review #1 for N20-982 by Dr. Rik Lostritto had recommended approval of NDA from the CMC standpoint on 16-Apr-1999. However, an approvable letter was sent to the applicant because of other deficiencies. The 18-Dec-2001 amendment contained applicant's response to those deficiencies and proposed labeling. The DESCRIPTION and HOW SUPPLIED sections for the proposed labeling were reviewed and found acceptable.

The applicant GSK sent amendment N(BB) on 9-Jan-2002 reporting the current dissolution specifications for Paxil CR that were approved by FDA in 12-Dec-2000 approval letter for N20-936/SCM005 (supplement NDA for the 37.5 mg strength). The same specifications for 12.5 and 25 mg strengths were approved in 17-Aug-2000 FDA letter for N20-936/SCM002 and are therefore acceptable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Paxil CR is supplied as an enteric film-coated, controlled release round tablet as 12.5 mg (yellow), 25 mg (pink) and 37.5 mg (blue). Paxil CR was originally approved in N20-936 for treatment of depression on 16-Feb-1999. N20-982 for Paxil CR was submitted on 22-Apr-1998 for the indication of treatment of panic disorder. The drug product, Paxil CR, is a controlled release antidepressant and antipanic agent. The active ingredient is paroxetine HCl and it is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-trans-4R-(4'-fluorophenyl)-3S-[(3', 4'-methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate. Paroxetine HCl is an odorless, off-white



Executive Summary Section

powder having a melting point of 120° to 138 °C and a solubility of 5.4 mg/mL in water.

B. Description of How the Drug Product is Intended to be Used

The drug product is intended to be used orally.

C. Basis for Approvability or Not-Approval Recommendation

N20-982 is recommended for approval from CMC standpoint. Chemistry review #1 on 16-Apr-1999 recommended approval of N20-982 from CMC standpoint and this review found the proposed package insert sections for DESCRIPTION and HOW SUPPLIED sections acceptable for Paxil CR.

III. Administrative

A. Reviewer's Signature

Gurpreet Gill-Sangha

B. Endorsement Block

ChemistName/Date: Gurpreet Gill-Sangha/4-Feb-2002

ChemistryTeamLeaderName/Date: Hasmukh Patel

ProjectManagerName/Date: Melaine Shin

C. CC Block

**APPEARS THIS WAY
ON ORIGINAL**



Chemistry Assessment

II. DRUG PRODUCT

Reference is made to the approved N20-936 for information on chemistry, manufacturing and controls of the drug substance and drug product. The information submitted to N20-982 was found to be acceptable by Dr. Rik Lostritto on 16-Apr-1999 from CMC standpoint. N20-982 is identical to N20-936 in all respects of drug substance, drug product and container closure except the indication of panic disorder. N20-936 was for treatment of depression and N20-982 included treatment of panic disorder by Paxil CR. The 18-Dec-2001 amendment contained the response to the FDA approvable letter dated 3-Jan-2000 including the proposed package insert.

5. Regulatory Specifications And Methods For Drug Product

a. Sampling Procedures

No changes.

b. Regulatory Specifications And Methods

The current approved dissolution specifications for Paxil CR as per the 12-Dec-2000 approval letter for N20-936/SCM005 are as follows:

Apparatus:	USP II (paddle) at 150 rpm	
Dissolution Media:	Step 1: <u> </u>	
	Step 2: <u> </u>	
Specifications:	Step 1 <u> </u>	
	Step 2 <u> </u>	
	1 Hour – NMT <u> </u>	
	2 Hours – Between <u> </u>	dissolved
	4 Hours – Between <u> </u>	dissolved
	6 Hours – NLT <u> </u>	

VI. LABELING

The following is proposed draft label for the DESCRIPTION and HOW SUPPLIED sections provided by GSK with their double-underlined additions or strikethrough deletions:



Chemistry Assessment Section

[Note: FDA Response dated January 3, 2000 for NDA 20-982 was used as the basis for this version. Please note that as per FDA approval dated December 14, 2001 of Paxil tablets for PTSD, NDA 20-031/S-029, the general terms "depression" and "depressed" were replaced with the more specific reference to "major depressive disorder". Additions and deletions are indicated by double-underlined or strikethrough font, respectively.]

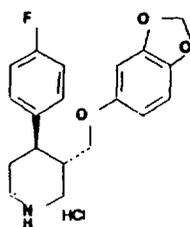
Px:LxCr

PAXIL CR™

brand of
(paroxetine hydrochloride)
Controlled-Release Tablets

DESCRIPTION

Paxil CR (paroxetine hydrochloride) is an orally administered antidepressant with a chemical structure unrelated to other selective serotonin reuptake inhibitors or to tricyclic, tetracyclic or other available antidepressant or antipanic agents. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-*trans*-4*R*-(4'-fluorophenyl)-3*S*-[(3',4'-methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate and has the empirical formula of $C_{19}H_{20}FNO_3 \cdot HCl \cdot 1/2H_2O$. The molecular weight is 374.8 (329.4 as free base). The structural formula is:



paroxetine hydrochloride

Paroxetine hydrochloride is an odorless, off-white powder, having a melting point range of 120° to 138°C and a solubility of 5.4 mg/mL in water.

[Note: The below revisions reflect a revised tablet description which was submitted as Supplement No. 2 to NDA 20-936 for the



Chemistry Assessment Section

12.5 and 25 mg tablet and approved by FDA on August 17, 2000. The new 37.5 mg tablet was submitted August 4, 2000 as Supplement No. 5 to NDA 20-936 and was approved by FDA on December 6, 2000.]

Each enteric, film-coated, controlled-release tablet contains paroxetine hydrochloride equivalent to paroxetine as follows: 12.5 mg-yellow, 25 mg-pink, 37.5 mg-blue. One layer of the tablet consists of a degradable barrier layer and the other contains the active material in a hydrophilic matrix.

Inactive ingredients consist of hydroxypropyl methylcellulose, polyvinylpyrrolidone, lactose monohydrate, magnesium stearate, colloidal silicon dioxide, glyceryl behenate, methacrylic acid copolymer type C, sodium lauryl sulfate, polysorbate 80, talc, triethyl citrate, and one or more of the following colorants: yellow ferric oxide, red ferric oxide, D&C Red No. 30, D&C Yellow No. 6, D&C Yellow No. 10, FD&C Blue No. 2.

HOW SUPPLIED

[Note: The below revisions reflect a revised tablet description which was submitted as Supplement No. 2 to NDA 20-936 for the 12.5 and 25 mg tablet and approved by FDA on August 17, 2000. The new 37.5 mg tablet was submitted August 4, 2000 as Supplement No. 5 to NDA 20-936 and was approved by FDA on December 6, 2000. Change from to "engraved" incorporated as per FDA letter dated December 12, 2001.]

Paxil CR is supplied as an enteric film-coated, controlled-release, round tablet, as follows:

12.5 mg , yellow tablets. engraved with Paxil CR and 12.5 NDC 0029-3206-13 Bottles of 30

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

/s/

Gurpreet Gill-Sangha
2/6/02 12:09:02 PM
CHEMIST

Hasmukh Patel
2/6/02 12:28:27 PM
CHEMIST

**APPEARS THIS WAY
ON ORIGINAL**

Shin, Melaine M

From: Susan.Weill@sbphrd.com
Sent: Wednesday, January 09, 2002 10:43 AM
To: SHINM@CDER.FDA.GOV
Subject: Paxil CR Dissolution Specifications

Hi Melaine-

Thanks for your phonemail this morning. Below, please find the dissolution specifications. A formal submission to NDA 20-982 will follow. Thanks for your help with this.

NDA 20-982

Reference is made to the January 3, 2000 approvable letter for Panic Disorder (NDA 20-982) and GlaxoSmithKline's response to this approvable letter submitted to FDA on December 18, 2001. Reference is also made to a January 2, 2002 phonemail message from Ms. Melaine Shin, requesting confirmation from GSK on the recommended dissolution specifications cited in the January 3, 2000 approvable letter.

The current dissolution specifications for Paxil CR were confirmed and approved by FDA in the December 12, 2000 approval letter to NDA 20-936/S-005 (the sNDA for the 37.5 mg strength). The same specifications for the 12.5mg and 25mg strength were approved in a August 17, 2000 letter from FDA (NDA 20-936/S-002). There are a few differences in the specifications from the January 2000 approvable letter for Panic Disorder and those currently agreed with FDA. The current specifications are outlined below and the differences from the January 3, 2000 approvable letter are underlined:

Apparatus: USP II (paddle) at 150 rpm
Dissolution Media Step 1: 0.1 N HCl (750mL) for 2 hours ⁽⁶⁰⁾
 Step 2: pH 7.5 tris buffer (1000mL) containing 50 mmol Tris
Specifications Step 1 (In HCl): 2 Hours - NMT
 Step 2 (In 0.05 M Tris Buffer at pH 7.5):
 1 Hour - NMT
 2 Hours - Between dissolved
 4 Hours - between dissolved
 6 Hours - NLT dissolved "

Also, in reference to the manufacturing site, the Cidra site was approved to manufacture Paxil CR in NDA 20-936/S-002 (approved August 17, 2000).

I hope that this addresses the dissolution specifications. Please do not hesitate to contact me at (610) 917-6223 should you have any questions.

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

2/12/02



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

12-6-00.

NDA 20-936/S-005

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 August 4, received August 9, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets.

We acknowledge receipt of your submission dated November 21, 2000.

This supplemental new drug application provides for a new 37.5 mg tablet strength with colored aqueous film coating to be manufactured at your SB, Cidra, Puerto Rico establishment facility.

We have completed the review of this supplemental application 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 labeling text. Accordingly, this supplemental application is approved effective on the date of this letter.

Additionally, we note your agreement, submitted in an amendment dated November 21, 2000, to adopt the same dissolution method and specification for the 37.5 mg tablet strength as that which was previously approved, in an Agency letter dated August 17, 2000, for the 12.5 mg and 25 mg tablet strengths. Therefore, the approved dissolution method and specifications for release and stability testing of the 37.5 mg tablet will be as follows:

- Apparatus: USP II (paddle) at 150 rpm
- Dissolution Media: _____
- Specifications: _____
- 1 hour - NMT — dissolved
- 2 hours - between — dissolved
- 4 hours - between — dissolved
- 6 hours - NLT — dissolved

We remind you that all appropriately updated documentation should be provided in the next annual report to this drug product.

Additionally, we acknowledge your commitment, submitted August 4, 2000, to place the first three commercial batches of the 37.5 mg tablets on stability in addition to your regular stability program for this drug product.

The final printed labeling (FPL) must be identical to the submitted draft labeling dated August 4, 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-005." 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

/s/

Russell Katz
12/6/00 07:59:09 AM

**APPEARS THIS WAY
ON ORIGINAL**

Number of Pages
Redacted 97 + 5 = 102



Draft Labeling
(not releasable)

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

JAN 27 1999

NDA 20-936

	<u>letterdate</u>	<u>stampdate</u>	<u>rec'd by chemist</u>	<u>completed</u>
INITIAL SUBMISSION:	19-DEC-97	19-DEC-97	30-DEC-97	27-APR-98
AMENDMENTS:	19-NOV-98	20-NOV-98	23-NOV-98	20-JAN-99
	18-DEC-98	21-DEC-98	28-DEC-98	20-JAN-99

CHEMIST REVIEW: # 2 SPONSOR: SMITHKLINE BEECHAM
PHARMACUETICALS

REVIEW CHEMIST: M.Zarifa, Ph.D ADDRESS: 1250 South Collegeville Road
P.O.Box 5089
Collegeville, PA 19426-0989

PRODUCT NAME:

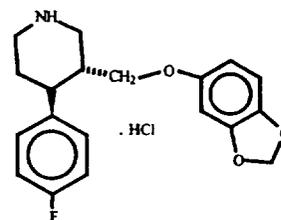
Proprietary: Paxil®
USAN [1997]: Paroxetine Hydrochloride
Code Name: BRL-029060

DOSAGE FORM/ROUTE OF ADMINISTRATION: 12.5, 25 mg CR Tablets/Oral

PHARMACOL.CATEGORY/PRINCIPAL INDICATION: Depression

STRUCTURAL FORMULA & CHEMICAL NAME:

(-)-(3S,4R)-4-(p-Fluorophenyl)-3-[(3,4-methylene-
dioxymethyl)piperidine hydrochloride hemihydrate



C₁₉H₂₀NO₃F . HCl . ½ H₂O Mol. Wt. 374.8 (329.4 free base)

REMARKS: In response to the CMC deficiency letter dated August 12, 1998, SKB provides description and validation data for the newly developed stability-indicating degradation method and the chiral method for the drug product. SKB submits an amended method validation package in triplicate. The new package includes the new degradation and chiral methods with their respective validation reports. The list of drug product specifications is amended to include chiral limits/test. The sponsor updates the stability data up to the 18-month time point. SEE CHEM. REVIEW NOTES.

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 20-936 to be APPROVED. Site Inspections are complete and Office of Compliance recommendation is satisfactory (see CMC Review 1). SKB's dissolution limits in the pH 7.5 buffer include a limit NLT _____ in 6 hours using USP apparatus II at 150 rpm. The Biopharmaceutical Division agreed on this specification for the 12.5 mg and 25 mg strengths. The sponsor will not market the _____ strengths. The available stability data at the present time support an expiry date not to exceed 18 months for the 12.5 mg and 25 mg tablets.

cc: ORIG: NDA
HFD-120/Div. File
HFD-120/PDavid

HFD-810/CHolberg
HFD-120/REB [unclear] RSeever
HFD-120/MGuzewska/MZarifa

INIT: RS/

Mona Zarifa, Ph.D., Chemist

filename: N020936.001

RELATED DOCUMENTS:

_____ Paxil (tablets), NDA 20-885 Paxil (capsules, under review)

SUPPORTING DOCUMENTS:

_____ NDA 20-031 (Paxil IR tablets)
_____ NDA 20-710 (Paxil suspension)

CONSULTS:

EER sent on Feb. 5, 1998. Inspection completed. See CMC Review 1.

Method Validation Request sent on January 21, 1999 and pending.

**APPEARS THIS WAY
ON ORIGINAL**

THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE

9 pages
—

DA-7
JUN 3 1998

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA 20-936

INITIAL SUBMISSION: letterdate 19-DEC-97 stampdate 19-DEC-97 rec'd by chemist 30-DEC-97 completed 27-APR-98

CHEMIST REVIEW: # 1 SPONSOR: SMITHKLINE BEECHAM PHARMACUETICALS

REVIEW CHEMIST: M.Zarifa, Ph.D ADDRESS: 1250 South Collegeville Road P.O.Box 5089 Collegeville, PA 19426-0989

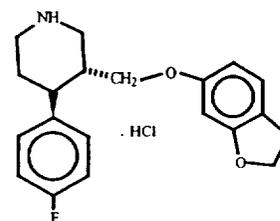
PRODUCT NAME:
Proprietary: Paxil®
USAN [1997]: Paroxetine Hydrochloride
Code Name: BRL-029060

DOSAGE FORM/ROUTE OF ADMINISTRATION: 12.5, 25, 37.5, and 50 mg CR Tablets/Oral

PHARMACOL.CATEGORY/PRINCIPAL INDICATION: Depression

STRUCTURAL FORMULA & CHEMICAL NAME:

(-)-(3S,4R)-4-(p-Fluorophenyl)-3-[(3,4methene-dioxphenoxy)methyl]piperidine hydrochloride hemihydrate

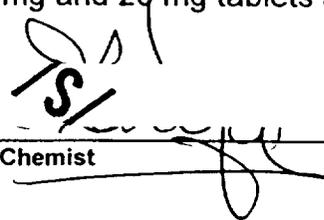


C₁₉H₂₀NO₃F. HCl . ½ H₂O Mol. Wt. 374.8 (329.4 free base)

REMARKS: SKB refers to approved NDA 20-031 (Tablets) and NDA 20-710 (Oral Suspension) for CMC on the drug substance. CMC information on the drug product is adequate but incomplete. SKB has not provided description or validation data for the newly developed stability-indicating method and the submitted method validation package is incomplete. The list of drug product specifications makes reference to the development test methods and does not correspond to the test methods described in the NDA. SEE CHEM. REVIEW NOTES.

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 20-936 to be APPROVABLE contingent upon receipt of missing CMC information and adequate responses to the CMC deficiencies. SKB's dissolution limits in the pH 7.5 buffer include a limit _____ in 6 hours using USP apparatus II at 150 rpm. This is an unusual speed and it is expected that the Biopharmaceutical Division will recommend reducing the speed to NMT 100 rpm and extend the dissolution sampling time (per Rae Yuan on June 3, 1998). The available stability data at the present time only support an expiry date not to exceed 12 months for the 12.5 mg and 25 mg tablets and 9 months for the _____ tablets.

cc: ORIG: NDA
HFD-120/Div. File
HFD-120/PDavid
HFD-810/CHoiberg
HFD-120/RLostritto/RSeever
HFD-120/MGuzewska/MZarifa
INIT: RSI RNS 6/3/98


Mona Zarifa, Ph.D., Chemist

**APPEARS THIS WAY
ON ORIGINAL**

NDA 20-936

PAXIL® CR Tablets

SMITHKLINE BEECHAM

3

RELATED DOCUMENTS:

, NDA 20-885 Paxil (capsules, under

review)

SUPPORTING DOCUMENTS:

NDA 20-031 (Paxil IR tablets)
NDA 20-710 (Paxil suspension)

CONSULTS:

EER sent out Feb. 5, 1998

**APPEARS THIS WAY
ON ORIGINAL**

THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE

10 pages

Ghin

APR 20 1999

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-982 **CHEM. REVIEW #** 1 **REVIEW DATE:** 04/16/99

SUBMISSION TYPE **DOCUMENT DATE** **CDER DATE** **ASSIGNED DATE**

ORIGINAL 04/22/98 04/22/98

NAME & ADDRESS OF APPLICANT: SmithKline Beecham Pharmaceuticals
 1250 Collegeville Road
 P.O. Box 5089
 Collegeville, PA 19426-0989

DRUG PRODUCT NAME

Proprietary: Paxil CR (paroxetine HCl) Controlled-Release Tablets
THIS IS AN APPROVED, MARKETED DRUG PRODUCT
(see NDA 20936, CR#2 dated 01/27/99)
Nonproprietary/USAN: Paroxetine HCl
Code Name/#: BRL-029060
Chem.Type/Ther.Class: 3S

PHARMACOL. CATEGORY/INDICATION: treatment of panic disorder

DOSAGE FORM: MR tablet

STRENGTHS: 12.5 and 25 mg

ROUTE OF ADMINISTRATION: Oral

DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

See USP Dictionary of USAN and International Drug Names, 1996, page 526 for structure of paroxetine base, $C_{19}H_{20}FN_3O_3$ which has a MW of 329.4. The hydrochloride salt is a hemihydrate in the to-be-marketed drug product, $C_{19}H_{20}FN_3O_3 \cdot HCl \cdot \frac{1}{2}H_2O$ which has a MW of 374.9.

SUPPORTING DOCUMENTS:

The drug substance, drug product and container closure of this NDA are exactly the same as that for an approved drug product; NDA 20936 for Paxil CR. NDA 20982 (subject of this review) is an efficacy supplement with no changes in drug substance (V1.3, pages 3-4), drug product (V1.3, page 5), container closure (V1.3, page 5) or labeling (V1.1, pages 30-31 "DESCRIPTION", pages 55-56 "HOW SUPPLIED" and storage statement, "Store at controlled room temperature between 20° and 25°C (68° and 77° F) [see USP]."

CONSULTS:

EER: Acceptable. Report attached in Appendix.

REMARKS/COMMENTS:

This is an efficacy supplement (new indication) for an approved drug product (Paxil CR). there are no changes in drug substance, drug product, container closure or to DESCRIPTION, HOW SUPPLIED and storage statements of the labeling in the proposed NDA (20982) to the approved NDA (20936). CR#2 for NDA 20936 is attached to this review for reference along with the EER report for NDA 20982.

Although this review is complete as of the date indicated below, an approvable letter was sent to the applicant on 3/10/99 (see attached e-mail dated 4/15/99). The Chemistry Reviewer and Team Leader indicated below were not aware of that letter. However, this review indicates that the application may be approved once the other conditions cited in the 3/10/99 approvable letter are fulfilled.

CONCLUSIONS & RECOMMENDATIONS: From a Chemistry perspective, this NDA may be approved.

/s/

~~_____~~
Rik Lostritto, Ph.D. Review Chemist

/s/

~~_____~~
Robert Seevers, Ph.D. Chemistry Team Leader

R/D Init by: _____

filename: C:n20982.r01

cc:

Org. NDA 20-960
HFD-120/Division File
HFD-120/RLostritto
HFD-120/RSeevers
HFD-120/MShin

APPENDIX TO NDA 20982 CR#1

**APPEARS THIS WAY
ON ORIGINAL**

Ghin

APR 20 1999

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-982 **CHEM. REVIEW #** 1 **REVIEW DATE:** 04/16/99

SUBMISSION TYPE **DOCUMENT DATE** **CDER DATE** **ASSIGNED DATE**

ORIGINAL 04/22/98 04/22/98

NAME & ADDRESS OF APPLICANT: SmithKline Beecham Pharmaceuticals
1250 Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-0989

DRUG PRODUCT NAME

Proprietary: Paxil CR (paroxetine HCl) Controlled-Release Tablets
THIS IS AN APPROVED, MARKETED DRUG PRODUCT
(see NDA 20936, CR#2 dated 01/27/99)
Nonproprietary/USAN: Paroxetine HCl
Code Name/#: BRL-029060
Chem.Type/Ther.Class: 3S

PHARMACOL. CATEGORY/INDICATION: treatment of panic disorder

DOSAGE FORM: _____

STRENGTHS: 12.5 and 25 mg ' _____

ROUTE OF ADMINISTRATION: Oral

DISPENSED: X Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

See USP Dictionary of USAN and International Drug Names, 1996, page 526 for structure of paroxetine base, $C_{19}H_{20}FNO_3$ which has a MW of 329.4. The hydrochloride salt is a hemihydrate in the to-be-marketed drug product, $C_{19}H_{20}FNO_3 \cdot HCl \cdot \frac{1}{2}H_2O$ which has a MW of 374.9.

SUPPORTING DOCUMENTS:

The drug substance, drug product and container closure of this NDA are exactly the same as that for an approved drug product; NDA 20936 for Paxil CR. NDA 20982 (subject of this review) is an efficacy supplement with no changes in drug substance (V1.3, pages 3-4), drug product (V1.3, page 5), container closure (V1.3, page 5) or labeling (V1.1, pages 30-31 "DESCRIPTION", pages 55-56 "HOW SUPPLIED" and storage statement, "Store at controlled room temperature between 20° and 25°C (68° and 77° F) [see USP]."

CONSULTS:

EER: Acceptable. Report attached in Appendix.

REMARKS/COMMENTS:

This is an efficacy supplement (new indication) for an approved drug product (Paxil CR). there are no changes in drug substance, drug product, container closure or to DESCRIPTION, HOW SUPPLIED and storage statements of the labeling in the proposed NDA (20982) to the approved NDA (20936). CR#2 for NDA 20936 is attached to this review for reference along with the EER report for NDA 20982.

Although this review is complete as of the date indicated below, an approvable letter was sent to the applicant on 3/10/99 (see attached e-mail dated 4/15/99). The Chemistry Reviewer and Team Leader indicated below were not aware of that letter. However, this review indicates that the application may be approved once the other conditions cited in the 3/10/99 approvable letter are fulfilled.

CONCLUSIONS & RECOMMENDATIONS: From a Chemistry perspective, this NDA may be approved.

/S/

~~_____~~
Rik Lostritto, Ph.D. Review Chemist

/S/

~~_____~~
Robert Seevers, Ph.D. Chemistry Team Leader

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APPENDIX TO NDA 20982 CR#1

Ghin

APR 20 1999

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-982 **CHEM. REVIEW #** 1 **REVIEW DATE:** 04/16/99

SUBMISSION TYPE **DOCUMENT DATE** **CDER DATE** **ASSIGNED DATE**

ORIGINAL 04/22/98 04/22/98

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 1250 Collegeville Road
 P.O. Box 5089
 Collegeville, PA 19426-0989

DRUG PRODUCT NAME

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DOSAGE FORM: _____

STRENGTHS: 12.5 and 25 mg _____

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SUPPORTING DOCUMENTS:

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CONSULTS:

EER: Acceptable. Report attached in Appendix.

REMARKS/COMMENTS:

This is an efficacy supplement (new indication) for an approved drug product (Paxil CR). there are no changes in drug substance, drug product, container closure or to DESCRIPTION, HOW SUPPLIED and storage statements of the labeling in the proposed NDA (20982) to the approved NDA (20936). CR#2 for NDA 20936 is attached to this review for reference along with the EER report for NDA 20982.

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CONCLUSIONS & RECOMMENDATIONS: From a Chemistry perspective, this NDA may be approved.

/S/

Rik Lostritto, Ph.D. Review Chemist

/S/

Robert Seevers, Ph.D. Chemistry Team Leader

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