CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 20885

Trade Name: PAXIL CAPSULES

Generic Name: PAROXETINE HYDROCHLORIDE

Sponsor: SMITHKLINE BEECHAM PHARMACEUTICALS

Approval Date: 10/9/98

Indication(s): DEPRESSION, OCD, PANIC DISORDER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 20885

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				X
Approvable Letter				X
Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI				X
Pharmacology Review(s)				X
Statistical Review(s)				X
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)				X
Administrative Document(s)/ Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 20885

APPROVAL LETTER

NDA 20-885

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 pending New Drug Application dated December 22, and received December 24, 1997, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paxil (paroxetine hydrochloride) 10 mg, 20 mg, 30 mg, and 40 mg Capsules.

We acknowledge receipt of your submissions dated January 9, February 16, March 31, May 4, May 6, September 16, and September 28, 1998. The user fee goal for this application is December 24, 1998.

This new drug application provides for a new formulation of Paxil (paroxetine HCL) in a capsule dosage form.

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 your proposed draft labeling dated December 22, 1997. Accordingly, the application is approved effective on the date of this letter.

CLINICAL

The final printed labeling (FPL) must be identical to the last approved Paxil (paroxetine HCL) tablet labeling [PX:L12] except for the following revisions.

1. All references to the tablet and oral suspension may be removed in the **Description**, **Pharmacology**, **Indications**, **Dosage and Administration**, and **How Supplied** sections since you have requested that this FPL solely reflect the capsule formulation.

2. A new paragraph may be added in the **Description** and **How Supplied** sections to describe the capsule formulation. This should be identical to your draft labeling submitted on December 22, 1997.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)

(b)(4)(CC)----------
-------- ---------- ----------

BIOPHARMACEUTICS

1. The bioequivalency study has adequately linked 10 and 40 mg Paxil capsules to the approved tablet formulation at the respective strengths.

2. The composition variation of (b)(4)(TS)---------- ----------and composition variation of(b)(4)(TS)-------- ----------xists for the filler material (b)(4)(CC)---------- the two middle strengths have demonstrated the same ----------st and the highest strengths of Paxil capsule. Therefore, the two middle strengths capsules can be granted a waiver of bio-studies.

3. The dissolution data for individual capsules at(b)(4)(CC)--are not available. The submitted dissolution data shows that capsules at all stre----------dissolved (b)(4)(CC)---------- Therefore, the following method for dissolution and specificatio-- ---------- the 10 mg, 20 mg, 30 mg, and 40 mg capsule strengths:

   USP Apparatus I (Basket) 60 rpm
   900 mL Simulated Gastric Fluid (SGF) without enzymes at 37°C
   Sampling time: 15 minutes
   Specifications: NLT (b)

Please submit 20 copies of the FPL as soon as it is available, in no case 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 20-885." Approval of this submission by FDA is not required before the labeling is used.

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

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.

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

Sincerely yours,

/S/

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

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20885

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data
NDA # 20,885

Sponsor:	SmithKline Beecham Pharmaceuticals
Drug:	PAXIL (paroxetine HCl)
Dosage Form:	Capsules
Indications:	Depression, OCD, Panic Disorder
Correspondence Date:	December 22, 1997
Date Received:	December 24, 1997
PDUFA Date:	December 24, 1998

I. Background

Paxil (paroxetine hydrochloride) is a selective-serotonin reuptake inhibitor which is currently approved in the U.S. in tablet and liquid forms for the treatment of depression, obsessive-compulsive disorder, and panic disorder. This NDA is intended to support a capsule formulation of Paxil in strengths of 10mg, 20mg, 30mg, and 40mg. The rationale, intended use, and potential clinical benefits of the capsules are identical to the currently marketed formulations.

This product has never been marketed in any foreign country and, to date, no marketing applications have been reviewed by any foreign regulatory body.

In support of this application, the sponsor has provided the report of a bioequivalence study (Study 533) as well as supportive Chemistry, Manufacturing, and Controls information. No clinical studies of safety or efficacy have been conducted with the capsule formulation.

Study 533 compared the single dose PK parameters of the capsule versus the marketed tablet and was conducted in two parts: Part I compared the capsule with the tablet at the highest strength (40mg) and Part II compared the capsule with the tablet at the lowest strength (10mg, given as two units or 20mg).[1] On face, bioequivalence between the capsule and

[1]The 10mg strength was given as two capsules or tablets (20mg) because paroxetine levels seen after a 10mg dose were too low to be accurately measured.

marketed tablet, with respect to Cmax and AUC(0→∞), appears to be confirmed at these strengths. The sponsor claims that, based on similarities in both formulation and dissolution profiles, bioequivalence for the intermediate strengths (20 and 30mg) can be inferred. The pharmacokinetic data from this study will be reviewed in detail by the biopharmaceutics reviewer and will not be further addressed in this review.

Also not addressed in this review is information in the Chemistry, Manufacturing, and Controls section, which will be examined by the chemistry reviewer.

This review will focus on the safety data from study 533.

II. Study 533

A. Study Investigators/Sites

The principal investigator was Dr. Rita Hust. The study was conducted at the Clinical Pharmacology Unit, FOCUS Clinical Drug Development GmbH, Neuss, Germany.

B. Study Design

This trial was conducted in two parts, each with an open-label, randomized, two-period crossover design. Subjects participated in only one part of the study. Part I comprised two periods in which 40mg capsules and 40mg marketed tablets were given in random order as single doses. Similarly, during the two Part II periods, 2×10mg capsules and 2×10mg marketed tablets were given in random order as single doses. A period ≥10 days separated the two dose administrations within each part of the study. Dosing was done in a fasted state. Subjects reported to the research unit on dosing days and remained until at least 24 hours post-dose; the remaining assessments were done on an outpatient basis.

C. Study Population

All study subjects were healthy adult volunteers. In Part I, 50 subjects (26 male and 24 female) in the age range were dosed. In Part II, 50 subjects were planned but only 48 subjects (34 male and 14 female) in the age range received treatment.

The number of subjects receiving each treatment is as follows:

Treatment	N
Paroxetine 40mg capsule	48
Paxil 40mg tablet	48
Paroxetine 2×10mg capsules	48
Paxil 2×10mg tablets	47

In all, six subjects prematurely terminated participation. Four dropped out during Part I for the following reasons: protocol deviation, unsuitability due to collapsing veins, and adverse experiences (2 subjects). Two dropped out of Part II, both for protocol deviations.

D. Safety Assessments

Adverse experiences were elicited pre-study, pre-dose, and 12, 24, 48, 72, 96, and 120 hours post-dose, as well as at a post-study follow-up visit 7-14 days after study completion.

Measurements of pulse and blood pressure and a 12-lead ECG were done pre-study and at the follow-up examination.

Likewise, routine laboratory testing was done pre-study and at the follow-up examination.[2] For females, pregnancy testing was performed pre-study, pre-dose, and at follow-up.

E. Safety Findings

There were no deaths or other serious adverse events[3] during this study.

Two subjects withdrew due to adverse experiences:

- Subject 121 was a 23 year old female who experienced diarrhea 1.5 hours after taking the 40mg capsule, with 6 additional episodes over the next 2.5 hours. She also had nausea about 3 hours post-dose and, over the next 5 hours, had 25 episodes of vomiting. Vomiting was treated with metoclopramide and she was withdrawn.

- Subject 132 was a 55 year old male who experienced diarrhea about 1.75 hours after receiving the 40mg tablet and, beginning about 3.5 hours post-dose, 5 episodes of vomiting over the next 19 hours.

Criteria for vital sign, ECG, and laboratory values of potential clinical concern are provided in the study report on pages 39, 40, and 41, respectively.

---

[2]Laboratory assessments included clinical chemistry (CPK, ALT, AST, GGT, alkaline phosphatase, LDH, BUN, creatinine, albumin, total bilirubin, potassium, sodium, and glucose), hematology (hematocrit, hemoglobin, RBC, MCV, MCH, MCHC, WBC with differential, , platelets), and urinalysis (pH, glucose, protein, ketones, bilirubin, urobilinogen, nitrite, blood, WBC, and specific gravity).

[3]Serious as defined in 21 CFR 312.32(a)..

Two subjects met criteria for abnormal systolic BP (one increased and one decreased) at the post-study follow-up visit. The last dose administered in both subjects was as the marketed tablet.

Also, four subjects had abnormally low glucose values and two had low hematocrits at the post-study follow-up. The last dose administered to all six was the marketed tablet.

No subjects had an ECG value of potential clinical concern.

The proportions of subjects with specific treatment emergent adverse events were comparable between the capsule and tablet groups at both dose levels. Only three adverse events observed in this study are not included in current Paxil labeling:

- vomiting, mostly with the 40mg dose formulations: four subjects had vomiting only after a 40mg capsule dose and another three only after a 40mg tablet dose.
- tenesmus, experienced by one subject after a 40mg capsule dose.
- unintended pregnancy: subject 203 became pregnant during the study; as of the sixth month of gestation, the course is uncomplicated.

III. Discussion and Conclusions

There are few remarkable safety findings from this study. It is somewhat surprising that vomiting had not been reported during any premarketing studies with paroxetine. Nonetheless, the results of this study do not suggest that the risk of vomiting after the capsule is substantially greater than after the tablet formulation.

The observations of vital sign and laboratory abnormalities noted above are difficult to interpret given that these parameters were evaluated only pre-study and at follow-up several days after the last study dose. If one assumes that these abnormalities are directly related to blood level of drug, then attribution to either formulation is considered unlikely in view of the elimination half-life of paroxetine (about 24 hours). The theoretical possibility exists that paroxetine exerted a pharmacodynamic effect characterized by hysteresis vis-a-vis blood concentration, in which case a drug relationship cannot be ruled out. An overarching consideration is the probable bioequivalence between the capsule and marketed tablet and the extensive safety experience with paroxetine to date which has not suggested adverse effects on blood pressure, blood glucose, or RBC counts. In this context, the possibility that these findings

represent a unique toxicity of the capsule formulation is deemed very remote.

It should be noted that this study evaluated the safety of the capsule formulation under somewhat limited conditions relative to typical clinical use, which will include many more patients, patients with concurrent medical conditions, patients taking concomitant medications, and patients receiving higher paroxetine doses and for much longer durations of treatment.

However, study 533 provided no evidence of any unique safety problems with the capsule formulation and, assuming that the chemistry reviewer finds the product excipients to be reasonably safe, there are no reasons to expect any unique problems.

From a clinical safety standpoint, I have no objection to approval of this NDA. Also, there is no indication for substantive modification of Paxil labeling with respect to clinical safety and efficacy.

/S/

Gregory M. Dubitsky, M.D.
January 21, 1998

cc: NDA# 20,885
HFD-120
HFD-120/GDubitsky
TLaughren
PDavid

2-6-98

I agree that there are no concerns regarding the safety of the Paxil capsules which by this stage that would alter their approvability or impact on the Paxil labeli

/S/

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20885

CHEMISTRY REVIEW(S)

JUN 2 1998

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS **NDA 20-885**

	letterdate	stampdate	rec'd by chemist	completed
INITIAL SUBMISSION:	22-DEC-97	24-DEC-97	07-JAN-98	27-MAR-98
	16-FEB-98	19-FEB-98	20-FEB-98	01-JUN-98
	04-MAY-98	11-MAY-98	24-MAY-98	01-JUN-98
	19-MAY-98		29-MAY-98	01-JUN-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

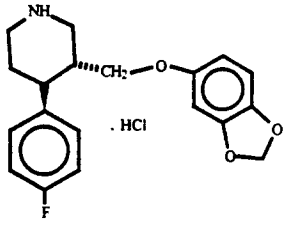
PRODUCT NAME:

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

DOSAGE FORM/ROUTE OF ADMINISTRATION: 10, 20, 30, 40 mg Capsules/Oral

PHARMACOL.CATEGORY/PRINCIPAL INDICATION: Depression

STRUCTURAL FORMULA & CHEMICAL NAME:



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

$C_{19}H_{20}NO_3F$. HCl . ½ H_2O **Mol. Wt.** 374.8 (329.4 free base)

REMARKS: SKB refers to approved NDA 20-031 (Tablets) for CMC on the drug substance. SKB claims categorical exclusion from an environmental assessment in the amendment dated February 16, 1998. The amendments dated May 4 and May 19, 1998 provides the completed methods validation packages

The CMC portion on the drug product is now adequate with a few remaining deficiencies. The available stability data presently support a 9-month expiry date.

CONCLUSIONS & RECOMMENDATIONS: Sites have been inspected and found adequate (see Office of Compliance's recommendation in the attached EER). Recommend NDA 20-885 to be APPROVED contingent upon satisfactory response to CMC deficiencies.

/S/

Mona Zarifa, Ph.D., Chemist

cc: ORIG: NDA
HFD-120/Div. File
HFD-[redacted]
HFD-810/CHolberg
HFD-120/RSeevers/MGuzewska/MZarifa
INIT: RS **filename: N020885.000**

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS **NDA 20-885**

	letterdate	stampdate	rec'd by chemist	completed
INITIAL SUBMISSION:	22-DEC-97	24-DEC-97	07-JAN-98	27-MAR-98
	28-SEP-98	01-OCT-98	02-OCT-98	05-OCT-98

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

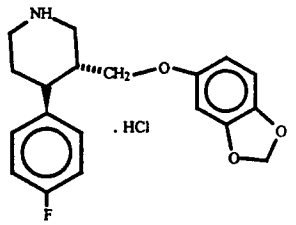
PRODUCT NAME:

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

DOSAGE FORM/ROUTE OF ADMINISTRATION: 10, 20, 30, 40 mg Capsules/Oral

PHARMACOL.CATEGORY/PRINCIPAL INDICATION: Depression

STRUCTURAL FORMULA & CHEMICAL NAME:



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

$C_{19}H_{20}NO_3F$. HCl . ½ H_2O **Mol. Wt.** 374.8 (329.4 free base)

REMARKS: This amendment provides an update of the stability studies on the drug product.

CONCLUSIONS & RECOMMENDATIONS: Sites have been inspected and found adequate (see Office of Compliance's recommendation in the attached EER). Recommend NDA 20-885 to be APPROVED.

The expiry date at this time cannot exceed 18 months based on the available actual stability data.

/S/

Mona Zarifa, Ph.D., Chemist

cc: ORIG: NDA
HFD-120/Div. File
HFD-120/PDavid
HFD-810/CHolberg
HFD-120/RSeevers/MZarifa
INIT: RS /S/ 01/99 **filename: N020885.001**

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20885

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

RECEIVED SEP 30 1998
SEP 30 1998

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-885
Paxil® (Paroxetine hydrochloride)
(10, 20, 30 and 40 mg Capsule)

Type of submission: original NDA
Submission Date: Dec, 22, 1997

Sponsor: Smithkline Beecham

INDICATION: antidepressant agent

REVIEWER: Rae Yuan, Ph.D.

Paroxetine is currently available in tablet formulation at 10, 20, 30 and 40 mg. In this submission, the sponsor seeks approval for capsule formulation at all four strengths. A single pharmacokinetic study is submitted to demonstrate the bioequivalence between capsule and tablet formulations at 10 mg and 40 mg.

The sponsor has conducted an open, randomized, two-period, single dose crossover BE study (see **Attachment I** for the details of the study), which was conducted in 2 parts. In part I, 50 subjects received single dose of one 40 mg capsule and one 40 mg tablet, administered separately under fasting condition. Forty six subjects completed the study (two subjects were withdrawn due to adverse experiences, one due to unsuitable vein and one due to a protocol deviation) . In part II, 48 healthy subjects received single dose of two 10 mg capsules and two 10 mg tablets under fasting condition, and 47 completed the study (one was withdrawn due to protocol deviation). No subject participated in more than one part of the study. Because of the experience of large within-subject variation with the paroxetine tablet (30%), the sample size of this study (at least n=40) was decided as such to ensure adequate statistical power to demonstrate the equivalency of the 2 formulations. Each part of the study includes 10 day washout period to separate the two dosing events. For the 10 mg dose, the sponsor used two dose units instead of one, because paroxetine plasma concentrations after a single 10 mg dose would have fallen below the detection limit. The plasma sampling time and washout period appear to be adequate to determine the pharmacokinetic parameters. The study results demonstrate that 90% confidence interval for Cmax and AUC are and respectively, for 10 mg formulation; and and respectively, for 40 mg formulation. Although there was a larger than expected within subject variation (at 40 mg (~44.2% and 45.5% for Cmax and AUC, respectively found in the study, vs. 30% as expected), the sample size was still

adequate to demonstrate the bioequivalency. For 10 mg strength, the within subject variation for Cmax and AUC were 28.1% and 25%, respectively. There was no sequence (carry-over) or period effect. There were also no significant difference in Tmax and t1/2 between the tablet formulation and capsule formulation for either strength.

The above statistical analysis was carried out by the sponsor on all the subjects who have completed the study. During the review process, we received inspection report stating that there were high incidences of vomiting and diarrhea during this bioequivalence study. Considering the possibility that vomiting or diarrhea could affect the pharmacokinetics of drug, the clinical division requested the sponsor to re-analyze the bioequivalence data excluding the subjects who experienced these incidences. The results are as follow:

At 40 mg, 5 subjects experienced vomiting and 68% experienced diarrhea. Excluding the 5 subjects with vomiting incidence, the sponsor demonstrated that AUC comparison was still within 90% confidence interval , but Cmax fell by a small margin Among the excluded 5 subjects, only one (in tablet formulation group) vomited around the tablet dissolving time (in vitro dissolution time is 15 min). Excluding only this subject, both AUC and Cmax met 90% confidence interval criteria. The proportion of subjects with diarrhea was similar for both formulations (48% for capsule and 52% for tablet) and all incidences were considered mild to moderate (<10% throughout). Thus, the sponsor proposed that the overall impact of diarrhea was neutral. At low dose (2x 10 mg), only one subject had vomiting and 20% of the subjects had diarrhea. Since diarrhea subjects are equally distributed among the two formulations, the impact of diarrhea on PK analysis of the two formulation should not be significant. The reviewer had compared the PK parameters from the subjects with or without diarrhea, no clear trend could be found.

The composition of the proposed capsule formulation at 4 dosage strengths are not proportional (see **Attachment II**).

. According to SUPAC guidance on Immediate Release Solid Oral Dosage Forms,

with that for the 10 mg capsule demonstrates

Applying SUPAC guidance, the proposed waiver of bioequivalence study for the middle strengths of capsule can be accepted.

The dissolution method and specification for capsule formulation at all strengths are proposed based on those for the tablet formulation. The comparison of the two dissolution methods are as follows:

Dissolution for Tablets	Dissolution for Capsules
USP Apparatus II (paddle)	Apparatus I (Basket)
Stirring Speed: 60 RPM	the same as for the tablets
Medium: 900 mL Simulated Gastric Fluid (SGF) without enzymes at 37C	the same as for the tablets
Sampling time:	
Sepcifications:	

(see the **Attachment III** for individual dissolution data)

Comments to be sent to the sponsor:

1. The bioequivalency study has adequately linked 10 and 40 mg Paxil capsules to the approved tablet formulation at the respective strengths.
2. The composition variation , and composition variation of filler materia[1] the two middle strengths have demonstrated the same and the highest strengths of Paxil capsule. Therefore, the two middle strengths capsules can be granted a waiver of bio-studies.
3. The dissolution data for individual capsules at 30 min are not available. The submitted dissolution data shows that capsules at all , dissolved at , the following method for dissolution and specification for capsules:

USP Apparatus I (Basket) 60 rpm
900 mL Simulated Gastric Fluid (SGF) without enzymes at 37C
Sampling time:
Sepcifications:

Recommendations:

The proposed Paxil capsule formulation at all strengths are acceptable to OCPB, provided that the sponsor adopts the dissolution specification proposed by the agency. Please convey Comments 1-3 to the sponsor

Rae Yuan, Ph.D. /S/

Team Leader: Chandra Sahajwalla /S/ 9/30/98

Date of Signature: 9/30/98

Office of Clinical Pharmacology and Biopharmaceutics/Division I

CC list: HFD-120; CSO; HFD-860 (Yuan, Sahajwalla, Mehta); CDR (Barbara Murphy)

APPEARS THIS WAY
ON ORIGINAL

Attachment I

BRL-29060

Study 533

Report Synopsis

Title

A study to demonstrate bioequivalence between the paroxetine capsule and the Paxil tablet formulations at the highest and the lowest dosage strengths..

Investigator(s) and Center(s)

Publications

None as of June 1997

Study Dates

This study was conducted from 28 January 1997 to 13 March 1997.

Objective(s)

The primary objective of this single dose, two-period crossover study was to demonstrate bioequivalence between the proposed capsule formulation of paroxetine and the currently-marketed Paxil tablet formulation at doses of 40 mg (using 40 mg capsules and tablets) and 20 mg (using 2 x 10 mg capsules and tablets).

Study Design

The study was conducted to an open, randomised, two-period crossover study design in each of the two study parts. Each subject received both formulations of one strength randomly on two occasions with a period of at least 10 days between the two doses within each part. Subjects did not participate in more than one part.

Study Population

In Part I, fifty healthy male (26) and female (24) subjects (to ensure 40 completers) were dosed with 40 mg Paxil tablets and 40 mg paroxetine capsules. In Part II, another 48 healthy male (34) and female (14) subjects were dosed with 20 mg Paxil tablets (2 x 10 mg) and 20 mg paroxetine capsules (2 x 10 mg).

Treatment and Administration

Subjects received randomly, on two separate days, a single Paxil tablet (40 mg) and a 40 mg paroxetine capsule (Part I) or a single dose of 20 mg Paxil tablets (2 x 10 mg) and 20 mg paroxetine capsules (2 x 10 mg) (Part II). A period of at least 10 days separated the two doses within each part. Subjects were dosed in the fasted state. Throughout this report, the currently-marketed Paxil tablet and the proposed paroxetine capsule formulations are referred to as 'tablet' and 'capsule', respectively.

BRL-29060 paroxetine 40 mg capsules (batch no.: .M96352), Paxil 40 mg tablets (batch no.: U96344) (Part I), 10 mg paroxetine capsules (batch no.: M96378) and 10 mg Paxil tablets (batch no.: U97014) (Part II) for oral administration were supplied by SmithKline Beecham Pharmaceuticals as open-label bulk supplies.

Evaluation Criteria

Safety Parameters

Clinical safety was evaluated by measurement of clinical chemistry, haematology and urinalysis parameters prestudy and at follow-up. Semi-supine blood pressure and pulse rate and a 12-lead ECG were recorded pre- and poststudy. Adverse experiences (AEs) were elicited by direct questioning of each subject using a non-leading prompt predose and 12, 24, 48, 72, 96 and 120 hours after dosing and at follow-up.

Pharmacokinetic Parameters

On each dosing occasion, blood samples (approx. 5 mL) were collected into tubes predose, and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, 24, 32, 48, 72, 96 and 120 hours after dosing. Paroxetine plasma concentrations were quantitated using a method based on followed by . The paroxetine plasma concentration versus time data were subjected to non-compartmental pharmacokinetic analysis to obtain Cmax, Tmax, AUC(0-inf) and T½.

Statistical Methods

Data from Part I (40 mg) and Part II (2 x 10 mg) were analysed separately. Following log-transformation (to the base e), the primary endpoints AUC(0-inf) and Cmax were analysed separately by ANOVA, fitting terms for sequence, subject (within sequence), period and regimen. Point estimates and 90% confidence intervals were

10.18 Summary statistics of paroxetine pharmacokinetic parameters in healthy subjects after single oral administration of the proposed paroxetine capsule formulation (40 mg) and the currently marketed Paxil tablet formulation (40 mg) [Part I]

Parameter	Regimen	n	Arithm. Mean	S.D.	Min.	Median	Max.
Cmax (ng/mL)	capsule	46	24.316	19.584		19.398	
	tablet	46	24.238	17.570		18.873	
Tmax (h)	capsule	46	6.74	1.83		6.00	
	tablet	46	6.30	1.88		6.00	
AUC (ng.h/mL)	capsule	46	763.8	1093.7		263.1	
	tablet	46	689.8	893.7		316.7	
Half Life (h)	capsule	46	18.16	11.32		13.77	
	tablet	46	18.08	10.27		15.20	

Parameter	Regimen	n	Geometric Mean	CVbetw. (%)
Cmax (ng/mL)	capsule	46	17.328	112.26
	tablet	46	18.050	105.79
AUC (ng.h/mL)	capsule	46	342.2	207.66
	tablet	46	343.8	186.84

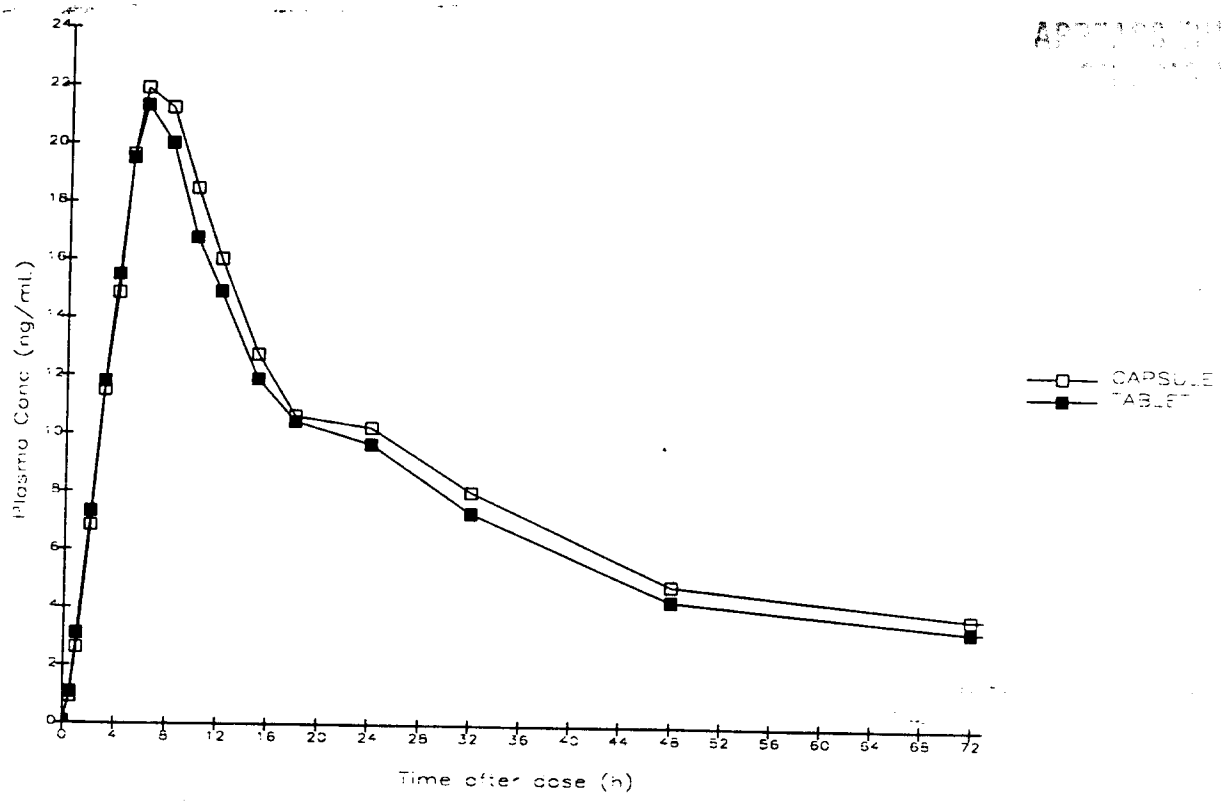
KEY:
capsule = single dose of a 40 mg paroxetine capsule
tablet = single dose of a 40 mg Paxil tablet

1 PAGE(S) REDACTED

CONTAINED TRADE SECRETS and/or CONFIDENTIAL/ COMMERCIAL INFORMATION

11.1. Mean plasma concentrations of paroxetine in 46 healthy subjects after single oral administration of the proposed paroxetine capsule formulation (40 mg) and the currently marketed Paxil tablet formulation (40 mg) [Part I]

Data plotted to 72 hours only



10.19 Summary statistics of paroxetine pharmacokinetic parameters in healthy subjects after single oral administration of the proposed paroxetine capsule formulation (2 x 10 mg) and the currently marketed Paxil tablet formulation (2 x 10 mg) [Part II]

Parameter	Regimen	n	Arithm. Mean	S.D.	Min.	Median	Max.
Cmax (ng/mL)	capsule	47	4.690	3.807		3.397	
	tablet	47	5.073	3.964		3.636	
Tmax (h)	capsule	47	5.60	1.42		6.00	
	tablet	47	5.30	1.61		5.00	
AUC (ng.h/mL)	capsule	47	100.81	149.14		51.98	7
	tablet	47	103.37	134.93		54.43	5
Half Life (h)	capsule	47	13.61	6.73		12.64	
	tablet	47	13.96	7.12		11.60	

Parameter	Regimen	n	Geometric Mean	CVbetw. (%)
Cmax (ng/mL)	capsule	47	3.279	111.79
	tablet	47	3.637	104.87
AUC (ng.h/mL)	capsule	47	51.01	168.92
	tablet	47	54.36	169.98

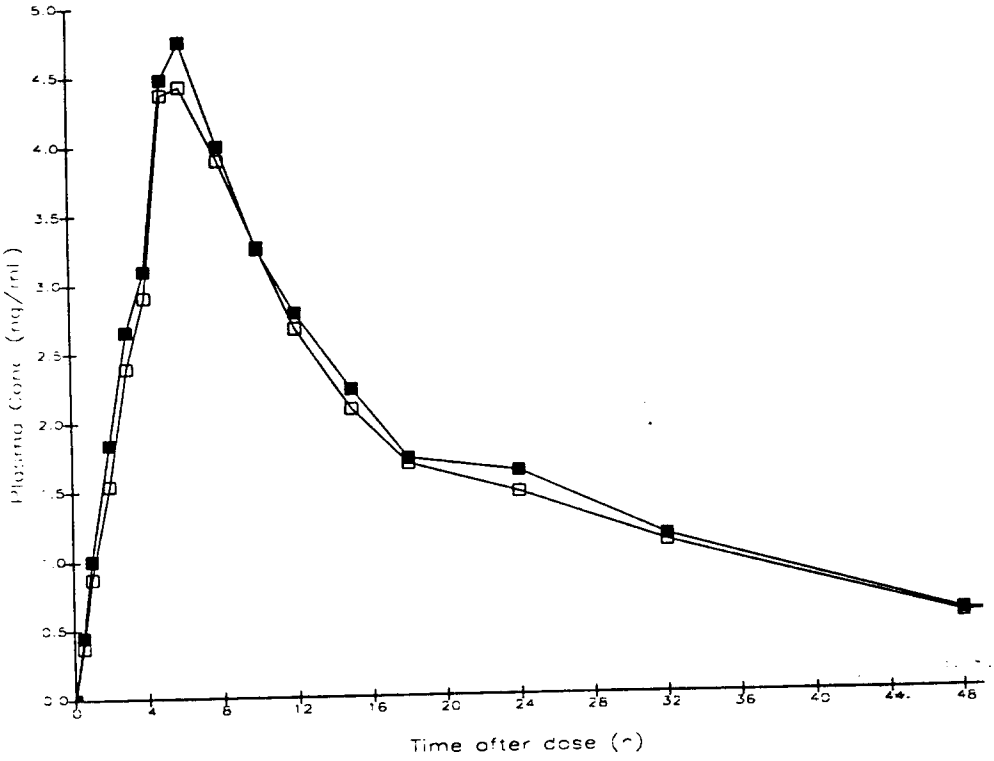
KEY:
capsule = single dose of 20 mg paroxetine capsules (2 x 10 mg)
tablet = single dose of 20 mg Paxil tablets (2 x 10 mg)

1 PAGES REDACTED

CONTAINED TRADE SECRETS and/or CONFIDENTIAL/ COMMERCIAL INFORMATION

11.2. Mean plasma concentrations of paroxetine in 47 healthy subjects after single oral administration of the proposed paroxetine capsule formulation (2 x 10 mg) and the currently marketed Paxil tablet formulation (2 x 10 mg) [Part II]

Data plotted to 48 hours only



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ON ORIGINAL

re-analysis of the data Excluding vomiting subjects

Table 1: Subjects vomiting in Part I of study 29060/533 (40 mg)

Subject no.	Formulation	Time of onset (post-dose)	Severity (no. of episodes)
101	Capsule	2h 30m	moderate (3)
103	Capsule	4h 41m	mild (1)
113	Tablet	4h 36m	mild (4)
125	Capsule	7h 28m	moderate (6)
148	Tablet	0h 38m	mild (1)

Note: two other subjects vomited (121 and 132), but neither completed the study

Therefore, in addition to reanalyzing the AUC(0-inf) and Cmax data from Part I excluding all five subjects, the data have also been reanalyzed excluding subject 148 only. These results are summarized in Table 2, together with the original analysis (no exclusions) for comparison:

Table 2: Summary of statistical analyses of Part I data

Data-set	Parameter	PE*	90% CI	CVw(%)
Excluding all 5 subjects (101, 103, 113, 125, 148)	AUC(0-inf)	0.95	0.81, 1.12	45.3%
	Cmax	0.92	*0.79, 1.08*	44.8%
Excluding subject 148 only	AUC(0-inf)	0.97	0.84, 1.13	43.9%
	Cmax	0.94	0.81, 1.09	43.8%
Original analysis (all 46 completers)	AUC(0-inf)	1.00	0.85, 1.16	45.5%
	Cmax	0.96	0.83, 1.11	44.2%

*PE = point estimate (ratio of adjusted geometric means between formulations, capsule:tablet)
Full details of the reanalyses are provided in the Appendices, with data listings (sorted by ratio)

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CONTAINED TRADE SECRETS and/or CONFIDENTIAL/ COMMERCIAL INFORMATION

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20885

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

David

NDA 20-885

AUG 12 1998

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

Dear Mr. Kline:

Please refer to your New Drug Application for Paxil (paroxetine hydrochloride) Capsules.

We have completed our review of the chemistry and manufacturing section of your submission and, we have the following comments and information requests:

1. Please provide a representative batch composition of each strength in the text of the NDA. Presently, this information is to be found only in the proposed manufacturing orders and directions, which give the amounts of ingredients to make The text states that the batch size A clarification is requested.

2. The available stability results to date do not support an expiration date beyond 9 months. Note that the earlier data reported and generated using the previous assay version will not be acceptable for inclusion in statistical projections of the expiry date. Any proposal for an expiry date to exceed 9 months should be supported by actual stability data.

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

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

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

Sincerely yours,

/S/

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

cc:
NDA ORIG 20-885
HFD-120/DIV File
HFD-120/PLeber/TCaughren/GDubitsky
HFD-120/PDavid /S/ 8/5/98
HFD-120/MGuzewska/MZarifa/RSeevers/RLostritto /S/ 8/5/98
HFD-860/CSahajwalla/RYuan
HFD-810/DNDC Division Director
DISTRICT OFFICE

APPEARS THIS WAY ON ORIGINAL

08/05/98pd
DOC #PAXIL\CAPSULES\CMCDEF.LTR
INFORMATION REQUEST (IR)

David

NDA 20-885

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

JUL 31 1998

Dear Mr. Kline:

Please refer to your new drug application (NDA) for Paxil (paroxetine hydrochloride) 10 mg, 20 mg, 30 mg, and 40 mg Capsules.

Our Division of Scientific Investigations has completed their review of the clinical and analytical portions of your pivotal bioequivalence study, protocol #533, and they have the following requests and comments:

> The bioavailability data from subjects who vomited (subjects 101, 103, 113, 125, and 148) following dosing should be excluded from the bioequivalence determination in study Part I.

Please respond to these concerns, as well, in your response.

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

Sincerely yours.

/S/

7/27/98

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

cc:
NDA ORIG 20-885 /S/ 7-24-98
HFD-120/DIV File
HFD-120/PLeber/TLaughren/GDubitsky /S/ 7/24/98
HFD-120/PDavid /S/ 14/98
HFD-860/CSahajwalla/RYuan /S/ 98/S/ 21/98
HFD-345/MYau/CViswanathan
07/14/98pd
Doc # PAXIL/CAPSULES/DSI.LTR
INFORMATION REQUEST

MEMORANDUM

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

FROM: Food and Drug Administration
Center for Drug Evaluation & Research/ORM/ODEI
Division of Neuropharmacological Drug Products
HFD-120
Psychiatric Drug Products Group
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-936 (Paxil CR)
Request for Safety Analysis

DATE: February 9, 1998

We note that your NDA submission dated December 19, 1997, does address the possibility of drug-demographic interactions within the two key studies, 448 and 449 (see section 17 of the Integrated Summary of Safety). The subgroup analyses provided do not appear to entail a consideration of the placebo reporting rate within each subgroup; therefore, we also ask that this analysis be based on comparisons of relative risk and odds ratios between subgroups rather than simply the reporting rate for paroxetine-treated patients. More detailed instructions for the desired analysis are provided in the following paragraph.

Please perform an analysis of the effects of demographic variables (age, gender, and race) on the incidence of common and likely drug-related adverse events, i.e., those events occurring at a frequency $\geq$ 5% in the drug group and $\geq$ twice the placebo rate within the pool of studies 448 and 449. We ask that you use the following methodology; we have used gender as an example. For the identified adverse events, calculate the relative risks for males (RR_m) and females (RR_f) with reference to placebo and their respective 95% confidence intervals within this pool of studies. Then compute the ratios of the relative risks of females to males (RR_f/RR_m). Next, compute odds ratios for each subgroup and also a common odds ratio (using the Mantel-Haenszel method), along with 95% confidence intervals. Finally, test the homogeneity of the odds ratios between the subgroups for each selected adverse event using the Breslow-Day Chi-Square and provide the p-values. Please submit results as shown in the two tables in Attachment 1. Similar analyses should be carried out for age effects by comparing age

subgroups (e.g. <65 and ≥65 years old) and for race effects by comparing 2 race subgroups (e.g. Caucasian and non-Caucasian) for these same adverse events.

Your timely response to this request is much appreciated. Should any questions arise, please contact Dr. Dubitsky at (301)594-5543.

/S/

Gregory M. Dubitsky, M.D.
Medical Reviewer
Psychiatric Drug Products Group

/S/ 2-6-98

Thomas P. Laughren, M.D.
Group Leader
Psychiatric Drug Products Group

cc: HFD-120/GDubitsky
TLaughren
PDavid

Attachment: One (Two Tables)

ATTACHMENT 1

RELATIVE RISK AND CONFIDENCE INTERVALS FOR SELECTED STUDY EVENTS									
Adverse Event	MALES				FEMALES				RR = $RR_f \div RR_m$
	Paxil CR (n=) N (%)[1]	Placebo (n=) N (%)	RR_m[2]	95% C.I.	Paxil CR (n=) N (%)	Placebo (n=) N (%)	RR_f[3]	95% C.I.	

1 N = number of patients with the event and % = (N ÷ n) × 100%.
2 RR_m = relative risk for male patients (Paxil CR/placebo).
3 RR_f = relative risk for female patients (Paxil CR/placebo).

ODDS RATIOS BY GENDER FOR SELECTED ADVERSE EVENTS						
Adverse Event	Odds Ratios[1]		Common Odds Ratio[2]	95% C.I.	Breslow-Day[3]	
	Males	Females			$\chi^2(1)$	p-value

1 Odds ratios computed with reference to placebo patients.
2 Common Odds Ratios computed using the Mantel-Haenszel method.
3 Breslow-Day test for homogeneity of the odds ratios.

David

NDA 20-885

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

JAN 8 1998

Dear Mr. Kline:

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

Name of Drug Product: Paxil (paroxetine hydrochloride) 10 mg, 20 mg, 30 mg, and 40 mg Capsules

Therapeutic Classification: Standard

Date of Application: December 22, 1997

Date of Receipt: December 24, 1997

Our Reference Number: 20-885

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 22, 1998 in accordance with 21 CFR 314.101(a).

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

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

Sincerely yours,

/S/ 1/7/98

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

cc:
NDA ORIG 20-885 /S/ 1-7-98
HFD-120/DIV File
HFD-120/PLeber/TLaughren/GDubitsky
HFD-120/PDavid /S/
DISTRICT OFFICE
01/06/98pd
Doc # PAXIL/CAPSULES/ACK.LTR
ACKNOWLEDGMENT (AC)

TELEPHONE CONTACT MEMORANDUM

NDA/IND #:	**NDA 20-885**
DATE:	February 13, 1998
PRODUCT NAME:	Paxil Capsules
FIRM NAME:	SmithKline Beecham (SKB)
CONVERSATION WITH:	Debbie Zuber and Tom Hogan
TELEPHONE #:	(610)917-6884
FDA Contact:	Mona Zarifa

I called to discuss deficiencies in the NDA.

1. I pointed out that a chirality test is needed. They said they have a test established and they will send an amendment to address the deficiency.

2. I asked them about the assay method

they included a statement that method transfer has been done successfully.

/S/

Mona Zarifa, Review Chemist

INIT: MG/
CC: HFD-120 Div. File

Filename: 20885.Tel

TELEPHONE CONTACT MEMORANDUM

NDA/IND #:	**NDA 20-885**
DATE:	March 26, 1998
PRODUCT NAME:	Paxil Capsules
FIRM NAME:	SmithKline Beecham (SKB)
CONVERSATION WITH:	Tom Hogan
TELEPHONE #:	(610)917-6884
FDA Contact:	Mona Zarifa

I called to discuss deficiencies in the Method Validation package. The package in the application includes only one copy and does not contain sample assignments. Also, the package lacks clarification as to which assay method is used documentation is missing. Mr. Hogan said he will relay the message to Debbie Zuber and will ensure that SKB complete the package and send three copies.

/S/

Mona Zarifa, Review Chemist

INIT: MG/
CC: HFD-120 Div. File

Filename: 20885a.Tel

NDA 20-885

Paxil® (paroxetine hydrochloride) Capsules

ITEM 13/14 - PATENT INFORMATION

The following patent information is being submitted pursuant to 21 C.F.R. 314.53.

Patent No.	Expiry Date	Type of Patent	Patent owner
4 721 723	December 29, 2006 The patent expiration date shown above was calculated in accordance with the U.S. Patent and Trademark Office's Federal Register notice of March 27, 1995. SB believes, however, that the correct expiration date, as properly calculated in accordance with the law and in particular with Section 532 of the Uruguay Round Agreements Act, P.L. 103-564, is September 24, 2008. SB reserves the right to modify the patent data in the future. SB also reserves the right to assert this position against persons or parties who may seek to make, use, offer for sale, import, or sell the approved drug prior to September 24, 2008.	Drug	Beecham Group p.l.c. Brentford, England

EXCLUSIVITY SUMMARY for NDA # 20-885 SUPPL # _____

Trade Name Paxil Capsules Generic Name Paroxetine HCL 10 mg, 20 mg, 30 mg and 40 mg Capsules –
Applicant Name SmithKline Beecham HFD-120
Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA? YES /_X_/ NO /___/

b) Is it an effectiveness supplement? YES /___/ NO /_X_/

If yes, what type(SE1, SE2, etc.)? _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES /__/ NO /_X__/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The sponsor, SKB, does agree that this is strictly an in vivo biopharmaceutic equivalency study to compare the already marketed immediate release tablet formulation to this pending NDA capsule formulation.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /X___/ NO /__/

If yes, NDA # 20-031___ Drug Name Paxil (paroxetine HCL) Tablets

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

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

YES /___/ NO /___/

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

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

1. Single active ingredient product.

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

YES /___/ NO /___/

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

NDA # _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but

that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /X___/

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

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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

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

YES /___/ NO /___/

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

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

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

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

YES /___/ NO /___/

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

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain: _____

_____

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

YES /___/ NO /___/

If yes, explain: _____

_____

© If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #_____

Investigation #2, Study # _____

Investigation #3, Study # _____

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

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

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

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

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

APPEARS THIS WAY
ON ORIGINAL

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

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

Investigation #1__, Study #_____

Investigation #2__, Study #_____

Investigation #__, Study # _____

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

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

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

Investigation #1

IND #_____ YES /__/ NO /___/ Explain: _____

_____

_____

Investigation #2

IND #_____ YES /__/ NO /___/ Explain: _____

_____

_____

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

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

© Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

/S/ 10-5-98

Signature of preparer Date

Title: Project Manager

/S/ 10/9/98

Signature of Division Director Date

cc:
Archival NDA 20-885
HFD-120/Division File
HFD-120/PDavid
HFD-85/Mary Ann Holovac

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

NDA 20-885

Paxil® (paroxetine hydrochloride) Capsules

DEBARRMENT STATEMENT

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, SmithKline Beecham hereby certifies that, to the best of its knowledge and belief, we did not and will not use in any capacity, in connection with this application, the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act.