APPLICATION NUMBER: 020936

CHEMISTRY REVIEW(S)
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS  

INITIAL SUBMISSION:  

AMENDMENTS:  
20-JAN-99  20-JAN-99

CHEMIST REVIEW:  
# 2  SPONSOR: SMITHKLINE BEECHAM PHARMACEUTICALS

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
dioxyphenoxy)methyl]piperidine hydrochloride hemihydrate

C_{19}H_{20}NO_{3}F·HCl·\frac{1}{2} H_2O  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.

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 20-936 to be APPROVED. Site Inspections are complete and Office of Compliance recommendation is satisfactory.

SKB's dissolution limits in the pH 7.5 buffer include a limit dissolved in 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 37.5 mg and 50 mg 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.

/S/
Mona Zarifa, Ph.D., Chemist

cc: ORIG: NDA  
HFD-120/Div. File  
HFD-120/Col  
HFD-810/CHolberg  
HFD-120/RLostritto/RSeever  
HFD-120/MGuzewski/MZarifa
INIT: RS/
filename: N020936.001
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA 20-936

INITIAL SUBMISSION: letterdate stampdate rec'd by chemist completed

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:

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

\[ C_{19}H_{25}NO_{3}F \text{. HCl} \cdot \frac{1}{2} \text{H}_2\text{O} \quad \text{Mol. Wt. 374.8 (329.4 free base)} \]

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.

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 dissolved in 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 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 data not to exceed 12 months for the 12.5 mg and 25 mg tablets and 9 months for the 37.5 mg and 50 mg tablets.

cc: ORIG: NDA
HFD-120/Div. File
HFD-120/PDavid
HFD-810/CHoiberg
HFD-120/RLosstritto/RSeever
HFD-120/MGuzewska/MZarifa

INIT: RS/ S/ C15/98

filename: N020936.000