CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-711

CHEMISTRY REVIEW(S)

Division of Anesthetic, Critical care and Addiction Drug Products

HFD-170

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-711

REVIEW # 2 **DATE REVIEWED:** 11.29.96 (GOAL DATE 5.20.97)

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT	10.16.96	10.17.96 (Partial response to information request fax dated 9th Sept 1996 from CSO, Ms. Bonnie McNeal)	
AMENDMENT	11.20.95 (COMMUNICATION FROM NANCY SAGER THAT EA & FONSI IS REQUIRED EVEN IF THE EA IS IDENTICAL TO THAT IN ANOTHER APPROVED EA)		
AMENDMENT	11.25.95 (QUITAB, PROPOSED TRADE NAME COMMUNICATION TO DAN BORING, CHAIR NLRC)		

NAME & ADDRESS OF APPLICANT:

Glaxo Wellcome Inc, 5 Moore Drive, Research Triangle, NC 27709, Mr. Eric Benson, Product Director RA, tel 919-483-3627.

DRUG PRODUCT NAME

Proprietary: Tradename was not submitted.
Established: Bupropion HCl SR Tablets
Code Name/#: CAS# 31677-93-7; BW 323U
Chem.Type/Ther.Class: 3S

PHARMACOL. CATEGORY: For use as an aid to smoking cessation.

DOSAGE FORM: Round biconvex film coated tablets with `Tradename 50 or Tradename 100 or Tradename 150' in bottles of 60 (NDC 0173-0000-00). Stored at CRT (US Pat No Re.33994).

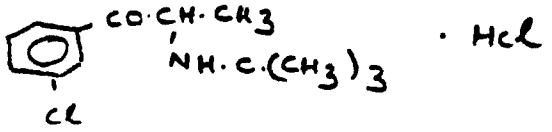
STRENGTHS: 50 mg white, 100 mg blue and 150 mg purple.

ROUTE OF ADMINISTRATION: Oral, 300 mg/day, 150 mg b.i.d.

DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

(+/-)-1-(3-chlorophenyl)-2(1,1-dimethylethyl)amino)-1-propanone hydrochloride. Mol. wt. 276.2. n-Octanol/water (pH 7.4) = 35.



SUPPORTING DOCUMENTS:

(1) IND

(2) NDA 20-358 for Bupropion HCl SR Tablets for antidepressant indication (WELLBUTRIN SR).

(3) NDA 18-644 for Bupropion HCl Tablets for antidepressant indication.
(4) US Pat no Re 33,994 for pharmaceutical delivery system cited on container label.
(5) US Patents 3,819,706 and 3,885,046 for meta chloro substituted butylamino propiophenones, cited in IND

CONSULTS:

REMARKS:

Q.1: Test results for related substances for 50 mg SR lot 3R2705, 150 mg SR lot 2Y2776, 150 mg SR lot 4P2748, 150 mg SR lot 5M2780.

R.1: Impurities in clinical test lots were submitted in a table form.

Comment: Adequate. Impurities in clinical test materials were in compliance with acceptance levels for impurities reported in NDA 20-358, chem rev 3 dated 2.15.96 by Dr. Parisek, HFD-120.

Q.2: FOI copy of EA, revised sales forecast with the inclusion of smoking cessation indication, and revised EIC and MEEC.

R.2: Separate FOI copy of EA was not submitted but suggested reconstruction of this document by inclusion and exclusion of specified pages in NDAs 20-711 and 20-538.

EIC for the aquatic compartment is 0.00088 ppm (no change).

Comment: I have decided to assemble myself the FOI copy of EA for lack of co-operation from the applicant.

Q.3: Dissolution in simulated gastric fluids since it was a claim cited in US Patent Re 33994.

R.3: Requested dissolution data in simulated gastric fluids is not available at Glaxo. This data was generated by Burroughs Wellcome in 1970s.

Comment: This is not `DEFICIENCY' but only `INFORMATION REQUEST' item. I have decided not to pursue this matter because dissolution test and specifications were approved for NDA 20-358.

Q.4: Tradename.

R.4: QUITAB.

Comment: QUITAB TRADE NAME request was forwarded on 11.25.96 to Dr. Dan Boring, Chair NLRC by Ms. Bonnie McNeal.

Q.5 US Patents 5541231 and 5427798 for the Bupropion formulation and

composition.

R.5 Two US patents were submitted.

Comment: Adequate response. US Pat 5541231 is for cysteine and glycine as stabilizers for Bupropion to maintain at least 80% potency after one year. US Pat 5427798 is for SR tablet compositions described in NDA 20-711. Bupropion plasma concentration in ng/ml versus time profiles for 50, 100 and 150 mg SR tablets were given in US Pat. Goal for SR tablets development seems to be to reduce the seizure rate compared to IR tablets.

Q.6: Stability of Bupropion, GA 10y: 814822 (1985).

R.6: Stability of Bupropion and its major metabolites in human plasma, Therapeutic Monitoring, vol 7, no 4, 1985, was submitted.

Comment: Adequate response. This article documents instability of Bupropion in plasma, half life of 11 hours at 37 C.

Q.7: Whether or not additional manufacturing and testing sites will be added o met the projected annual demand for the smoking cessation indication million tablets).

R.7: None.

Comment: Assumed no additional sites will be added. EER request was forwarded to Director of Atlanta District on 11.22.96. Profile class codes were CCS and TTR. EER initiated on 10.29.96 has two manufacturing sites, namely, Kent-England and Greenville-North Carolina-USA.

CONCLUSIONS AND RECOMMENDATIONS:

18 month expiry date was recommended for the drug product packaged as 60s in bottles for NDA 20-711. This recommendation was based on the memo from Dr. Robert Temple dated 3.11.96 for NDA 20-358.

FOI copy of EA, EA review and FONSI will be assembled for Ms. Nancy Sager within a few weeks.

cc:
Orig. NDA 20711
HFD-170/Division File
HFD-170/PMaturu,AD'Sa
HFD-170/BMcNeal

P. Maturu

P.Maturu, PhD, Primary Review Chemist

A.D'Sa, PhD, Acting Chemistry Team Leader

filename: N20711R3.96
ADEQUATE

Telecon dated 12/2/96:
Glaxo was asked about patent # 33994, and why it was included in package insert for NDA 20-711 but not in NDA 20-258. Explanation is awaited.

12/2/96

Division of Anesthetic, Critical care and Addiction Drug Products
HFD-170
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-711

REVIEW # 1 **DATE REVIEWED:** 7.25.96 (GOAL DATE 5.20.97)

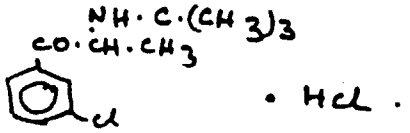
SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUBMISSION	5-17-96	5-20-96	6-4-96

NAME & ADDRESS OF APPLICANT:
Glaxo Wellcome Inc, 5 Moore Drive, Research Triangle, NC 27709, Mr. Eric Benson, Product Director RA, tel 919-483-3627.

DRUG PRODUCT NAME
Proprietary: Tradename was not submitted.
Established: Bupropion HCl SR Tablets
Code Name/#: CAS# 31677-93-7; BW 323U
Chem.Type/Ther.Class: 3S

PHARMACOL. CATEGORY: For use as an aid to smoking cessation.
DOSAGE FORM: Film coated round biconvex tablets packaged in bottles as 60s and stored at CRT (US Pat No Re.33994).
STRENGTHS: 50 mg white, 100 mg blue and 150 mg purple.
ROUTE OF ADMINISTRATION: Oral, 300 mg/day, 150 mg b.i.d.
DISPENSED: __X__ **Rx** _____ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:
(+/-)-1-(3-chlorophenyl)-2(1,1-dimethylethyl)amino)-1-propanone hydrochloride. Mol. wt. 276.2. n-Octanol/water (pH 7.4) = 35.



SUPPORTING DOCUMENTS:
(1) IND

(2) NDA 20-358 for Bupropion HCl SR Tablets for antidepressant indication (WELLBUTRIN SR).
(3) NDA 18-644 for Bupropion HCl Tablets for antidepressant indication.
(4) US Pat no Re 33,994 for pharmaceutical delivery system cited on container label.
(5) US Patents 3,819,706 and 3,885,046 for meta chloro substituted butylamino propiophenones, cited in IND

CONSULTS:
EA consult may be needed. Sales forecast was not revised with the inclusion of smoking cessation indication.

REMARKS:

- NDA 20711 did not contain any CMC information. CMC information for the drug substance, drug product, environmental assessment (EA), were cross referenced to NDA 18654 (drug substance) and NDA 20358 (drug product and EA). CMC information in these NDAs were reviewed and concluded as ADEQUATE by C.Parisek and F.Zinsitz (HFD-120).

- To make my assessment, I compared NDA 20711/IND standards for the smoking cessation indication study materials with NDA 20358 standards for antidepressant indication, and found them INADEQUATE. For example, the clinical materials used to study smoking cessation indication were not tested for related substances. See enclosed COA for 50 mg SR lot 3R2705, 150 mg SR lot 2Y2776, 150 mg SR lot 4P2748, 150 mg SR lot 5M2780, and NDA 20538 drug product standards. FOI copy of EA was not submitted with revised sales forecast with the inclusion of smoking cessation indication sales figures, and revised EIC and MEEC. Dissolution in simulated gastric fluids was not performed when it was a requirement cited in US Patent Re 33994 for SR drug product cited on the container label. Tradename was not submitted for smoking cessation indication, and Wellbutrin trade name was used for antidepressant indication.

CONCLUSIONS & RECOMMENDATIONS:

CMC standards for smoking cessation study materials are INADEQUATE when compared to NDA 20358 drug standards for antidepressant indication.

Please provide the following CMC information.

(1) Test results for related substances for 50 mg SR lot 3R2705, 150 mg SR lot 2Y2776, 150 mg SR lot 4P2748, 150 mg SR lot 5M2780.
(2) FOI copy of EA, revised sales forecast with the inclusion of smoking cessation indication, and revised EIC and MEEC.
(3) Dissolution in simulated gastric fluids when it was a requirement cited in US Patent Re 33994 for SR drug product.
(4) Tradename.

cc:
Orig. NDA 20711
HFD-170/Division File
HFD-170/PMaturu,AD'Sa
HFD-170/BMcNeal

filename: N20711.967
INFORMATION REQUEST

P. Maturu / 7.26.96
P.Maturu, PhD, Primary Review Chemist

9/4/96
A.D'Sa, PhD, Acting Chemistry Team Leader