# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20-711 / S-002**
**20-711 / S-004**

# ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

**Division of Anesthetic, Critical Care, and Addiction Drug Products**

**CONSUMER SAFETY OFFICER REVIEW**

**Application Numbers**: NDA 20-711/S-002
NDA 20-711/S-004

**Name of Drug**: Zyban (bupropion hydrochloride) sustained-release, 100 mg and 150 mg Tablets

**Sponsor**: Glaxo Wellcome Inc.

**CSO**: Indira Kumar

**Material Reviewed**

S-002:
Revised Labeling to add or strengthen a contraindication, warning, precaution, or adverse reaction to the PRECAUTIONS: Pregnancy section, dated October 7, 1997, compared with the last approved label, dated May 17, 1997.

S-004:
Geriatric Labeling Supplement, dated August 27, 1998, compared with the last approved label, dated May 17, 1997.

**Submission Date(s)**: S-002: October 7, 1997.
S-004: August 27th, 1998 and September 17th, 1998.

**Receipt Date(s)**: S-002: October 8, 1997.
S-004: August 28th, 1998 and September 18th, 1999

**Background and Summary Description**:

S-002:

This supplement was submitted as a "Special Supplement: Changes Being Effected" under the provisions of 21 CFR 314.70(c)(2)(I), the sponsor revised their label for ZYBAN™ Sustained-Release Tablets to add or strengthen a contraindication, warning, precaution, or adverse reaction. The following paragraph was added to the PRECAUTIONS: Pregnancy section:

To monitor fetal outcomes of pregnant women exposed to ZYBAN, GlaxoWellcome Inc. maintains a Bupropion Pregnancy Register. Health care providers are encouraged to register patients by calling (800) 722-9292, ext. 39441.

S-004:

This supplement was submitted as a 'Special Supplement - Changes Being Effected' under 21 CFR 314.70(c) and provides for revised labeling under the provisions of 21 CFR 314.70(c)(2)(ii), to add or strengthen a contraindication, warning, precaution, or adverse reaction or (iii) to add or strengthen an instruction about dosing and administration, as permitted under the geriatric use final rule. The following changes have been proposed to the labeling:

1. Revision under CLINICAL PHARMACOLOGY: Pharmacokinetics: Age: Addition of previously approved wording appearing under PRECAUTIONS: Use in the Elderly concerning a single-dose pharmacokinetic study performed in young and elderly patients. This study, "The Disposition of Bupropion and Its Basic metabolites in Young and Elderly Healthy Volunteers" was submitted to NDA 18-644, WELLBUTRIN (bupropion hydrochloride) Tablets on October 15, 1992 and the package insert wording was approved under NDA 20-358, WELLBUTRIN SR (bupropion hydrochloride) Sustained-Release Tablets on October 4, 1996.

2. Revision under PRECAUTIONS: Use in the Elderly - This subsection wording has been revised to meet the new Geriatric Use rule.

**Status Report**

**Reviews Completed**: CSO Review – Indira Kumar – 2/23/99 (S-002 and S-004)
Medical Officer Review – A.W. Longmire, M.D. - 2/23/99 (S-004)

**Review Concurrence:**

Medical: A.W. Longmire, M.D. _____
C. Winchell, M.D./Team Leader _____
Division Director: Cynthia G. McCormick, M.D. _____

**CSO Review**

Please note that the sponsor's proposed revisions are indicated by strikeovers and underlined text. The agency's proposed revisions are bolded.

**BOX WARNING**: Not applicable

**DESCRIPTION**: No Changes noted.

**CLINICAL PHARMACOLOGY**: Under the **Age** Subsection (S-004)

*Age:* The effects of age on the pharmacokinetics of bupropion and its metabolites have not been fully characterized, but an exploration of steady-state bupropion concentrations from several depression efficacy studies involving patients dosed in a range of 300 to 750 mg/day, on a three times a day schedule, revealed no relationship between age (18 to 83 years) and plasma concentration of bupropion. A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in the elderly subjects was similar to that of younger subjects. These data suggest there is no prominent effect of age on bupropion concentration; **however, another pharmacokinetic study, single and multiple dose, has suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites (Medical Reviewer's Addition).** (see PRECAUTIONS: ~~Use in the Elderly~~ Geriatric Use). (S-004)

**CLINICAL TRIALS:** No changes noted.

**INDICATIONS AND USAGE**: No changes noted.

**CONTRAINDICATIONS:** No changes noted.

**WARNINGS**: No changes noted.

**PRECAUTIONS**: Changes to Pregnancy (S-002) and Geriatric Use categories (S-004).

S-002:

**Pregnancy**: ***Teratogenic Effects: Pregnancy Category B:*** Teratology studies have been performed at doses up to 450 mg/kg in rats (approximately 14 times the MRHD on a $mg/m^2$ basis), and at doses up to 150 mg/kg in rabbits (approximately 10 times the MRHD on a $mg/m^2$ basis). There is no evidence of impaired fertility or harm to the fetus due to bupropion. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before pharmacological approaches are used.

To monitor fetal outcomes of pregnant women exposed to ZYBAN, Glaxo Wellcome Inc. maintains a Bupropion Pregnancy Register. Health care providers are encouraged to register patients by calling (800) 722-9292, ext. 39441.

S-004:

~~Use in the Elderly~~ **Geriatric Use:** ~~In general, older patients are known to metabolize drugs more slowly and to be more sensitive to the side effects of drugs~~. Of the approximately 6000 patients who participate in clinical trials with bupropion sustained-release tablets (depression and smoking cessation studies), 275 were 65 and over and 47 were 75 and over. In addition, several hundred patients 65 and over participated in clinical trials using the immediate-release formulation of bupropion (depression studies). No overall differences in safety and effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects; **however, another pharmacokinetic study, single and multiple dose, has suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites (Medical Reviewer Additions)** (see CLINICAL PHARMACOLOGY).
~~Of the approximately 5600 patients who participated in clinical trials with bupropion sustained-release tablets (depression and smoking cessation studies), 303 were 60 to 69 years old and 88 were 70 years of age or older. The experience with patients 60 years of age or older was similar to that in younger patients.~~

Bupropion hydrochloride and its metabolites are almost completely excreted through the kidney and metabolites are likely to undergo conjugation in the liver prior to urinary excretion. The risk of toxic reaction to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and may be useful to monitor renal function (see Use in Patients with Systemic Illness).

**ADVERSE REACTIONS**: No changes noted.

**DRUG ABUSE AND DEPENDENCE**: No changes noted.

**OVERDOSAGE**: No changes noted.

**DOSAGE AND ADMINISTRATION**: No changes noted.

**HOW SUPPLIED**: ~~100mg~~ (deleted)

cc:
Archival NDA 20-711
HFD-170/Div. Files
HFD-170/I.Kumar
HFD-170/C. P. Moody
HFD-170/C. G. McCormick
HFD-170/C. Winchell/A.W. Longmire/C. Li
HFD-120/D. Bates/P. Andreason
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-103/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-21/ACS (with labeling) - for drug discussed at advisory committee meeting.
HFD-95/DDMS (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: IK/February 23, 1999/12:35pm/2:00pm
Initialed by:
Final:
Filename: 20711 Zyban S-002 S004 CSO Review 2-23-99

APPROVAL (AP)

Consumer Safety Officer

Supervisory Comment/Concurrence

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-711/ S-001, S-003, S-004, S-012

Glaxo Wellcome Inc.
Five Moore Drive
PO Box 13398
Research Triangle Park, NC 27709

Attention: Eric Benson
Director, Regulatory Affairs, Psychiatry

Dear Mr. Benson:

We acknowledge the receipt of your February 28, 2001, submission containing final printed labeling in response to our February 7, 2001, letter approving your supplemental new drug application (S-012) for Zyban (bupropion hydrochloride) Sustained-Release Tablets.

We also refer to your submissions dated July 7, and October 1, 1999, containing final printed labeling (FPL) for supplements S-001, S-003, and S-004 which were approved on February 24, and September 10, 1999. We note that these submissions have been superseded by supplement S-012 which was approved on February 7, 2001. Therefore, these submissions will not be reviewed, but they will be retained in our files.

We have reviewed the labeling (package insert) that you submitted in accordance with our February 7, 2001, letter and we find it acceptable.

If you have any questions, call Judit Milstein, Regulatory Project Manager, at (301) 827-7440.

Sincerely,

*{See appended electronic signature page}*

Cathie Schumaker, R.Ph.
Chief, Project Management Staff
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/s/
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Cathie Schumaker
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