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APPLICATION NUMBER:

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

APPROVAL LETTER

NDA 20-711/S-002
NDA 20-711/S-004

Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park,
North Carolina 27709

Attention: Eric B. Benson
Product Director, Regulatory Affairs

Dear Mr. Benson:

Please refer to your supplemental New Drug Applications dated October 7, 1997 (S-002) and August 27, 1998 (S-004), received October 9, 1998 (S-002) and August 28, 1998 (S-004), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyban (bupropion hydrochloride) Sustained-Release Tablets, 100mg and 150mg.

We also acknowledge receipt of your submission dated September 17, 1998 (S-004).

We note that these supplements were submitted as a 'Special Supplement - Changes Being Effected' under 21 CFR 314.70(c).

S-002:

This supplemental New Drug Application provides for revised labeling under the provisions of 21 CFR 314.70(c)(2)(i), 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 supplemental New Drug Application 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.

Your submissions stated October 7, 1997 and August 27, 1998 as the implementation dates for the changes, respectively.

We have completed the review of these supplemental applications, including the submitted draft labeling 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 draft labeling in the submissions dated February 24, 1999 with the revisions listed below. Accordingly, the supplemental applications are approved effective on the date of this letter. The revisions are as follows:

CLINICAL PHARMACOLOGY:

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 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.** (see PRECAUTIONS: ~~Use in the Elderly~~ Geriatric Use).

PRECAUTIONS:

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 Registry. 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 ~~5,600~~ 6000 patients who participated in clinical trials with bupropion sustained-release tablets (depression and smoking cessation studies), ~~303~~ 275 were ~~60~~ 65 and over and 47 were 75 and over ~~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.~~ 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 or 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.** (see CLINICAL PHARMACOLOGY).

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 it may be useful to monitor renal function (see Use in Patients with Systemic Illness).

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

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 supplement NDA 20-711/S-004." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials 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 materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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

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, contact Indira Kumar, Consumer Safety Officer, at (301) 827-7410.

Sincerely,

Cynthia G. McCormick, M.D.
Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure