CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 20358/S001/S003

Trade Name: WELLBUTRIN SR (SUSTAINED RELEASE) TABLETS

Generic Name: BUPROPION HYDROCHLORIDE

Sponsor: GLAXO WELLCOME, INC

Approval Date: 12/16/97

Indication(s): TREATMENT OF DEPRESSION
**APPLICATION:** 20358/S001/S003

## CONTENTS

<table>
<thead>
<tr>
<th>Item</th>
<th>Included</th>
<th>Pending Completion</th>
<th>Not Prepared</th>
<th>Not Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval Letter</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tentative Approval Letter</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Approvable Letter</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Final Printed Labeling</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical Review(s)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Chemistry Review(s)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>EA/FONSI</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pharmacology Review(s)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Statistical Review(s)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Microbiology Review(s)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Clinical Pharmacology</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Biopharmaceutics Review(s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioequivalence Review(s)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Administrative Document(s)/Correspondence</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
Dear Mr. Murray:

Please refer to your supplemental New Drug Applications dated June 19, 1997 (S-001), and September 30, 1997 (S-003) for Wellbutrin SR (bupropion Hydrochloride) Sustained Release tablets.

We have completed our review of your supplemental applications, and they are approved.

The supplemental applications referenced above provide for revised labeling with changes to the following sections:

**Supplement 001**

1. A revision to the Clinical Pharmacology - Hepatic section to include results of a hepatic study.

2. Revisions to the Contraindications, Warnings, and Precautions (Information for Patients) sections to indicate that Zyban, a marketed drug for smoking cessation, contains the same active ingredient found in Wellbutrin, and that concomitant use is contraindicated.

3. The deletion of the following phrase under the Warnings section, "Although scattered abnormalities in liver function tests were detected in patients participating in clinical trials, there is no clinical evidence that bupropion acts as a hepatoxin in humans."

4. The addition of a new subsection entitled Allergic Reactions under the Precautions section.

5. An update to the Adverse Reactions section to include events noted in smoking cessation trials and other adverse events seen in postmarketing experience.
Supplement 003

A revision to the Precautions - Pregnancy section to inform health care providers that Glaxo Wellcome maintains a Bupropion Pregnancy Registry.

Labeling changes of the kind listed above are permitted under section 21 CFR 314.70(c)(2) of the regulations to be made prior to approval of the supplement. We note that these changes have been effected.

Should you have any questions concerning this NDA, please contact Mr. Paul David, 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
cc:
NDA ORIG 20-358
HFD-120/DIV File
HFD-120/PLEber/TLaughren/PAndreason
HFD-120/PDavid
HFD-2
HFD-92
HFD-100
HFD-40 (LStockbridge)
HFD-638
HFD-730
District Office
11/24/97pd
DOC #: WELLBUT\SR\S-01-03.LTR
SUPPLEMENTAL APPLICATIONS APPROVED

APPEARS THIS WAY ON ORIGINAL
DESCRIPTION

WELLBUTRIN SR (bupropion hydrochloride), an antidepressant of the aminothiazole class, is chemically unrelated to tricyclic, tetracyclic, selective serotonin reuptake inhibitors or other known antidepressant agents. Its structure closely resembles that of desethylbupropion, it is related to phenylethylamines. It is (S)-(-)-3-chlorophenyl-2-(3,4-dihydroxyphenyl)-1-propionic acid hydrochloride. The molecular weight is 276.2. The molecular formula is C_{16}H_{15}ClNO_3.HCl. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water. It has a bitter taste and produces the sensation of local analgesia on the oral mucosa. The structural formula is:

\[
\text{H}_2\text{N} \quad \text{C} = \text{O} \quad \text{OH} \quad \text{C} = \text{O} \quad \text{Cl} \quad \text{NH}_2
\]

WELLBUTRIN SR Tablets are supplied for oral administration as 100-mg (blue) and 150-mg (purple) film-coated, sustained-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients: carnauba wax, ferric oxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol and titanium dioxide (opaque blue) and pink and coated with white (opaque black). In addition, the 100-mg tablets contain FD&C Blue No. 1 and polyethylene glycol 300. The 150-mg tablets contain FD&C Blue No. 2 Lake, FD&C Red No. 40, and FD&C Yellow No. 6.

CLINICAL PHARMACOLOGY

Pharmacodynamics: Bupropion is a relatively weak inhibitor of the cationic uptake sites of monoamine neurotransmitters, dopamine, and does not inhibit monamine oxidase. While the mechanism of action of bupropion, as with other antidepressants, is unknown, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms.

Pharmacokinetics: Following oral administration of WELLBUTRIN SR Tablets to healthy volunteers, plasma concentrations of bupropion are achieved within 2 hours. Food does not affect the AUC of bupropion by 1% and 17%, respectively, indicating that there is no clinically significant food effect.

In vitro tests show that bupropion is 80% or more bound to human albumin at plasma concentrations up to 2000 ng/ml. Bioavailability of bupropion is not significantly altered by concomitant ingestion of food.

The mean elimination half-life (t1/2) of bupropion after chronic dosing is 25 (10 to 50) hours, and steady-state plasma concentrations of bupropion are reached within 8 days.

Plasma and urinary metabolites so far identified include bioactivation products formed via reduction of the conjugation of the parent drug bupropion, the demethylation of bupropion, and a metabolite formed from bupropion and a second unknown metabolite. These metabolites of bupropion are pharmacokinetically active, but their relative contribution to the overall pharmacological activity of bupropion have not been fully characterized. They may be of clinical importance because the plasma concentrations of the metabolites are higher than those of bupropion.

Following a single dose in humans, peak plasma concentrations of the metabolite N-oxide occur approximately 4 hours after peak concentration of bupropion with the peak level of the parent drug 4-5 hours after steady state with WELLBUTRIN SR Tablets. The elimination half-life of the metabolite N-oxide is approximately 20 (15 to 30) hours, and its AUC at steady state is about 17 times that of the parent drug.

The times to peak concentrations for the entero- and water-soluble plasma metabolites are similar to that of the parent

N-oxide. Moreover, their elimination half-lives are 4-5 hours, 10 to 15 hours, and 20 to 40 hours, respectively, and steady-state AUC's are 5 to 7 times that of bupropion.

The arydlactone metabolite generally cannot be detected in plasma samples at the concentrations following a single oral dose of the parent drug.

A study comparing chronic dosing with WELLBUTRIN SR Tablets 150 mg b.i.d. to the immediate-release formulation of bupropion at 150 mg b.i.d., peak plasma concentrations and AUC's for all 3 of the detectable bupropion metabolites, thus, at steady state, WELLBUTRIN SR Tablets, and the immediate-release formulation of bupropion are essentially equivalent for both bupropion and the three quantitatively important metabolites.

INDICATIONS AND USAGE

WELLBUTRIN SR (bupropion hydrochloride) is indicated for the treatment of depression. A physician considering WELLBUTRIN SR Tablets for the management of a patient known or suspected to be suffering from untreated or inadequately treated depression should be aware that the drug may cause generalized seizures in a dose-dependent manner with an approximately incidence of 0.4% (4/1000) at the upper end of the recommended dose range, i.e., 400 mg/day, and 0.25% (2/1000) if a bupropion dose of 300 mg/day. Bupropion's toxicity index at the 400-mg/day level may exceed that of other marketed antidepressants and doses of WELLBUTRIN SR Tablets up to 300 mg/day by as much as twofold. This relative risk is only an approximate estimate because no direct comparative studies have been conducted.

The efficacy of bupropion in the treatment of depression was established in 2 well-controlled trials of depressed

patients and in 1 well-controlled trial of depressed

patients.
cystic fibrosis in patients with adolescent and adult cystic fibrosis (CF) treated with orlistat, a gastrointestinal lipase inhibitor.

The study aimed to evaluate the long-term safety and efficacy of orlistat treatment in patients with adolescent and adult cystic fibrosis. The primary endpoint was the change in body mass index (BMI) from baseline to week 52. Secondary endpoints included changes in weight, body composition, and quality of life measures.

The study was a randomized, double-blind, placebo-controlled trial conducted at 12 centers in the United States. Patients were randomized to receive either orlistat (60 mg twice daily) or placebo for 52 weeks. The trial enrolled 134 patients, aged 18 years or older, with cystic fibrosis who had been on a stable regimen of CF care for at least 1 year.

Results of the study showed a significant reduction in BMI, body weight, and waist circumference in the orlistat group compared to the placebo group. Additionally, there were improvements in body composition, with a decrease in percentage body fat and an increase in lean body mass. Quality of life measures also improved, with a decrease in respiratory symptoms and an increase in physical activity.

The study concluded that orlistat treatment for 52 weeks was safe and effective in reducing body weight and improving quality of life in patients with cystic fibrosis. These findings support the potential use of orlistat as an adjunctive therapy in the management of weight in patients with cystic fibrosis.
**WELLBUTRIN SR® (bupropion hydrochloride)**
Sustained-Release Tablets

**prolonged lesions of the liver at doses of 100 to 300 mg/day**

<table>
<thead>
<tr>
<th>Common Adverse Effects</th>
<th>WELLBUTRIN SR® 300 mg/dose (n = 116)</th>
<th>WELLBUTRIN SR® 400 mg/dose (n = 116)</th>
<th>Placebo (n = 116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>26%</td>
<td>25%</td>
<td>15%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8%</td>
<td>12%</td>
<td>1%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2%</td>
<td>7%</td>
<td>0%</td>
</tr>
<tr>
<td>Apprehension</td>
<td>2%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>3%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Fever</td>
<td>0%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Nausea</td>
<td>1%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>3%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Integumentary disorders</td>
<td>1%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Urinary tract abnormalities</td>
<td>1%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Skin disorders</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Neurovascular disorders</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Seizures</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Other unspecified</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated With WELLBUTRIN SR Tablets:**

<table>
<thead>
<tr>
<th>Common Adverse Effects</th>
<th>WELLBUTRIN SR® 300 mg/dose (n = 116)</th>
<th>WELLBUTRIN SR® 400 mg/dose (n = 116)</th>
<th>Placebo (n = 116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Infection</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Incidence Based on the Number of Female Patients:**

- Hypothyroidism
- Menstrual abnormalities
- Amenorrhea

**Drug Abuse and Dependence: Controlled Class:**
Bupropion is a controlled substance (CSA Schedule II).

**Special Sponsors**
Intravenous administration of bupropion should be conducted by medical personnel familiar with its toxicology and the management of overdose.

**Multigeneration**
In patients with hyperthyroidism, intravenous administration of bupropion should be conducted by medical personnel familiar with its toxicology and the management of overdose.

**Drug Abuse and Dependence:** Controlled Class
Bupropion is a controlled substance (CSA Schedule II).

**Special Sponsors**
Intravenous administration of bupropion should be conducted by medical personnel familiar with its toxicology and the management of overdose.

**Multigeneration**
In patients with hyperthyroidism, intravenous administration of bupropion should be conducted by medical personnel familiar with its toxicology and the management of overdose.
I. Background
Wellbutrin SR is the sustained release formulation of bupropion HCl which was approved in 1996. Zyban, another trade name for bupropion sustained release (BSR) has received approvable status from HFD-170 as an aid to smoking cessation, and final labeling is in draft form. This submission represents labeling changes to Wellbutrin SR labeling reflecting the release of Zyban and the addition of adverse events to the post-marketing events section.

II. Data Reviewed
Draft changes to Wellbutrin SR product labeling.

III. Conclusions and Recommendations
Suggested labeling changes to Wellbutrin sustained release formulation are accurate and consistent with proposed Zyban and Wellbutrin IR labeling. I recommend that the labeling changes recommended by the sponsor be adopted as they stand.

APPEARS THIS WAY ON ORIGINAL

Paul J. Andreason, M.D.

cc: NDA# 20-358
HFD-120
HFD-120/PAndreason
TLaughren
PDavid

Page 1  NDA 20-358
CHEMIST'S REVIEW OF SUPPLEMENT

7. APPLICANT NAME AND ADDRESS: GLAXOWELLCOME INC.
5 Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

8. NAME OF DRUG: WELLBUTRIN® SR
9. NONPROPRIETARY NAME: bupropion hydrochloride
10. CHEMICAL NAME / STRUCTURE: (±)-1-(3-chlorophenyl)-2-[(1,1-dimethyl-
ethyl)amino]-1-propanone hydrochloride

11. DOSAGE FORM(S): Extended Release Tablets
50 mg, 100 mg and 150 mg
12. POTENCY(ES): Depression
13. PHARMACOLOGICAL CATEGORY: XX (Rx) (OTC)
XX (YES) (NO)
14. HOW-DISPENSED: NDA 18-644, Wellbutrin Tablets (immediate release)
NDA 20-711, Zyban™ (bupropion hydrochloride)
Sustained Release Tablets for smoking cessation

17. SUPPLEMENT PROVIDES FOR:
Revision of the package insert and immediate container labels to add a warning against concurrent use of Wellbutrin and Zyban products. The supplement was submitted as "Changes Being Effectuated."

18. COMMENTS:
In addition to several warning statements in the package insert, the warning statement, "Do not use in combination with ZYBAN™, or any other medicines that contain bupropion hydrochloride.", was added to bottle labels. The sponsor has changed the placement of the trademark symbol, i.e., from "Wellbutrin" SR to "Wellbutrin SR®."

19. CONCLUSIONS AND RECOMMENDATIONS:
Supplement is approvable for Chemistry.

20. REVIEWER NAME
Martha R. Heimann, Ph.D.

SIGNATURE

DATE COMPLETED
7/22/97 July 22, 1997
APPLICATION NUMBER: 20358/S001/S003

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE
CSO LABELING REVIEW

Date of Review: November 24, 1997

NDA NUMBER: 20-358 (Tablets)
Submission Date: Original Application Approved October 4, 1996
Acknowledging and Retain FPL Letter dated 1-31-97 (label Code #RL-368)
SLR-001 dated 6-19-97
SLR-003 dated 9-30-97

Sponsor: Glaxo Wellcome

Product Name: Trade Name: Wellbutrin SR; Generic Name: bupropion HCl; Dosage Form: tablets

Product Indication: Antidepressant

Materials Reviewed:

1. Agency letter dated October 4, 1996, approving the original NDA. This letter had, as an attachment, the draft labeling which the firm was requested to use verbatim for FPL. Firm submitted the final printed labeling dated November 20, 1996, and an ack/retain letter issued 1-31-97.

2. Medical officer's reviews of SLR-001/003.

S-001 (Dated June 19, 1997)
Label Code: RL-436
Changes Being Effect: Yes
Reviewed by Chemist (container labels): Yes, acceptable

This amendment provides for the following revisions:

1. A revision to the Clinical Pharmacology - Hepatic section to include results of a hepatic study.

2. Revisions to the Contraindications, Warnings, and Precautions (Information for Patients) sections to indicate that Zyban, a marketed drug for smoking cessation, contains the same active ingredient found in Wellbutrin, and that concomitant use is contraindicated.

3. The deletion of the following phrase under the Warnings section, "Although scattered abnormalities in liver function tests were detected in patients participating in clinical trials, there is no clinical evidence that bupropion acts as a hepatotoxic in humans," since "liver failure" has been added to the Adverse Reactions section.

4. The addition of a new subsection entitled Allergic Reactions under the Precautions section.

5. An update to the Adverse Reactions section to include events noted in smoking cessation trials and other adverse events seen in postmarketing experience.

S-003 (Dated September 30, 1997)
Label Code: RL-455
Changes Being Effect: Yes
Reviewed by Medical Officer: Yes, acceptable

A revision to the Precautions - Pregnancy section to inform health care providers that Glaxo Wellcome maintains a Bupropion Pregnancy Registry.
CONCLUSIONS & RECOMMENDATIONS:

1. These supplemental applications only incorporate the revisions noted above.

2. I recommend that an approval letter issue for these applications.

/S/
Paul A. David, R.Ph.
Project Manager

/S/
John Purvis
Project Management Supervisor

ORIG NDA 20-358
HFD-120/DIV FILE/PDavid
WELLBUT/NDA'S-01-03.SLR
LABELING REVIEW
Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

Attention: James E. Murray

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Wellbutrin-SR Tablets

NDA Number: 20-358

Supplement Number: S-003

Date of Supplement: September 30, 1997

Date of Receipt: October 1, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the
Act on November 30, 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacologic Drug Products
Attention: Document Control Room
5600 Fishers Lane, HFD-120
Rockville, MD 20857

Sincerely yours,

(For) John Purvis
Chief, Project Management Staff
Division of Neuropharmacologic Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
September 30, 1997

Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
HFD-120, Woodmont II, Room 4037
1451 Rockville Pike
Rockville, MD 20852

Re: NDA 20-358; WELLBUTRIN SR® (bupropion hydrochloride) Sustained-Release Tablets
NDA 18-644; WELLBUTRIN® (bupropion hydrochloride) Tablets
Special Supplement: Changes Being Effected

Dear Dr. Leber:

Under the provisions of 21 CFR 314.70(c)(2)(i), we are revising our labeling for WELLBUTRIN® Tablets and WELLBUTRIN SR® Sustained-Release Tablets to add or strengthen a contraindication, warning, precaution, or adverse reaction. The following paragraph is being added to the PRECAUTIONS: Pregnancy section:

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

Twelve copies of the Final Printed Labeling for WELLBUTRIN Tablets and WELLBUTRIN SR Sustained-Release Tablets are provided, along with electronic versions on diskette in PDF and Word 6.0 formats. The changes are planned to be implemented at the next printing of the package inserts.

Please contact me at (919) 483-5119 for any inquiries regarding this submission.

Sincerely,

James E. Murray
Director
Regulatory Affairs

Glaxo Wellcome Research and Development
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Telephone
919 248 2100

A Division of
Glaxo Wellcome Inc.
Date: JUN 24 1997
NDA No.: 20-358

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

Attention: James E. Murray

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Wellbutrin SR Tablets
NDA Number: 20-358
Supplement Number: S-001
Date of Supplement: June 19, 1997
Date of Receipt: June 20, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the
Act on August 19, 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacologic Drug Products
Attention: Document Control Room
5600 Fishers Lane, HFD-120
Rockville, MD 20857

Sincerely yours,

/\C/
(For) John Purvis
Chief, Project Management Staff
Division of Neuropharmacologic Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
June 19, 1997

Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
HFD-120, Woodmont II, Room 4037
1451 Rockville Pike
Rockville, MD 20857

Re:
NDA 20-358; WELLBUTRIN® SR (bupropion hydrochloride) Sustained-Release Tablets
Special Supplement: Changes Being Effected

Dear Dr. Leber:

Reference is made
NDA 20-358 for WELLBUTRIN SR Tablets. Reference is also made to NDA 20-711 for ZYBAN™ (bupropion hydrochloride) Sustained Release Tablets approved May 14, 1997 as an aid to smoking cessation treatment. ZYBAN, WELLBUTRIN and WELLBUTRIN SR all contain the same active ingredient, bupropion hydrochloride.

As provided for in 21 CFR 314.70 (c)(2)(i), we are revising our labeling for both applications to add or strengthen a contraindication, warning, precaution, or adverse reaction. The “changes being effected” revisions to labeling are consistent with the recently approved Zyban labeling.

REvised PACKAGE INSERT

Glaxo Wellcome Inc.
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Telephone
919 248 7100
Please contact me at 919-483-5119 for any matters regarding this application. Thank you.

Sincerely,

James E. Murray
Director
Regulatory Affairs

cc: Mr. Paul David, HFD-120, 5 desk copies