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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 20358/S001/S003

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 20358/S001/S003

APPROVAL LETTER

NDA 20-358/S-001/S-003

APPEARS THIS WAY
ON ORIGINAL

DEC 16 1997

Glaxo Wellcome Inc.
Attention: James E. Murray
Director, Regulatory Affairs
Five Moore Drive
Research Triangle Park, North Carolina 27709

APPEARS THIS WAY
ON ORIGINAL

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:

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Supplement 001

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

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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.

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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.

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

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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/ 12/4/97

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-120PDavid
HF-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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20358/S001/S003

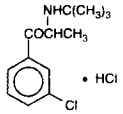
FINAL PRINTED LABELING

PRODUCT INFORMATION

WELLBUTRIN SR®
(bupropion hydrochloride)
Sustained-Release Tablets

WELLBUTRIN SR® (bupropion hydrochloride)
Sustained-Release Tablets

DESCRIPTION: WELLBUTRIN SR (bupropion hydrochloride), an antidepressant of the aminoketone class, is chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitor, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.2. The molecular formula is $C_{13}H_{18}ClNO \cdot HCl$. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa. The structural formula is:



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, cysteine hydrochloride, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide and is printed with edible black ink. In addition, the 100-mg tablet contains FD&C Blue No. 1 Lake and polysorbate 80, and the 150-mg tablet contains FD&C Blue No. 2 Lake, FD&C Red No. 40 Lake, and polysorbate 80.

CLINICAL PHARMACOLOGY:

Pharmacodynamics: Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine, serotonin, and dopamine, and does not inhibit monoamine 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, peak plasma concentrations of bupropion are achieved within 3 hours. Food increased C_{max} and AUC of bupropion by 11% 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 200 µg/mL. Plasma protein binding of the major metabolites of bupropion has not been studied.

Following oral administration of 200 mg of ^{14}C-bupropion in humans, 87% and 10% of the radioactive dose were recovered in the urine and feces, respectively. The fraction of the oral dose of bupropion excreted unchanged was only 0.5%, a finding consistent with the extensive metabolism of bupropion.

The mean elimination half-life (±SD) of bupropion after chronic dosing is 21 (±9) hours, and steady-state plasma concentrations of bupropion are reached within 8 days.

Plasma and urinary metabolites so far identified include biotransformation products formed via reduction of the carbonyl group and/or hydroxylation of the *tert*-butyl group of bupropion. Four basic metabolites have been identified. They are the *erythro*- and *threo*-amino alcohols of bupropion, the *erythro*-amino diol of bupropion, and a morpholinol metabolite (formed from hydroxylation of the *tert*-butyl group of bupropion). These metabolites of bupropion are pharmacologically active, but their potency and toxicity relative to 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 morpholinol metabolite occur approximately 6 hours after administration of WELLBUTRIN SR Tablets. Peak plasma concentrations of the morpholinol metabolite are approximately 10 times the peak level of the parent drug at steady state with WELLBUTRIN SR Tablets. The elimination half-life of the morpholinol metabolite is approximately 20 (±5) hours, and its AUC at steady state is about 17 times that of bupropion.

The times to peak concentrations for the *erythro*- and *threo*-amino alcohol metabolites are similar to that of the morpholinol metabolite. However, their elimination half-lives are longer, 33 (±10) and 37 (±13) hours, respectively, and steady-state AUCs are 1.5 and 7 times that of bupropion.

The *erythro*-amino diol metabolite generally cannot be detected in the systemic circulation following a single oral dose of the parent drug.

In a study comparing chronic dosing with WELLBUTRIN SR Tablets 150 mg b.i.d. to the immediate-release formulation of bupropion at 100 mg t.i.d., peak plasma concentrations of bupropion at steady state for WELLBUTRIN SR Tablets were approximately 85% of those achieved with the immediate-release formulation. There was equivalence for bupropion AUCs, as well as equivalence for both peak plasma concentration and AUCs for all three of the detectable bupropion metabolites. Thus, at steady state, WELLBUTRIN SR Tablets and the immediate-release formulation of bupropion are essentially bioequivalent for both bupropion and the three quantitatively important metabolites.

WELLBUTRIN SR® (bupropion hydrochloride)
Sustained-Release Tablets

Bupropion and its metabolites exhibit linear kinetics following chronic administration of 300 to 450 mg/day.

Population Subgroups: Factors or conditions altering metabolic capacity (e.g., liver disease, congestive heart failure, age, concomitant medications, etc.) or elimination may be expected to influence the degree and extent of accumulation of the active metabolites of bupropion. The elimination of the major metabolites of bupropion may be affected by reduced renal or hepatic function because they are moderately polar compounds and are likely to undergo further metabolism or conjugation in the liver prior to urinary excretion.

Hepatic: The disposition of bupropion following a single 200-mg oral dose was compared in eight healthy volunteers and eight weight- and age-matched volunteers with alcoholic liver disease. The half-life of the morpholinol metabolite was significantly prolonged in subjects with alcoholic liver disease (32 hours [±41%] versus 21 hours [±23%]). The differences in half-life for bupropion and the other metabolites in the two patient groups were minimal.

Renal : The effect of renal disease on the pharmacokinetics of bupropion has not been studied. The elimination of the major metabolites of bupropion may be affected by reduced renal function.

Left Ventricular Dysfunction: During a chronic dosing study with bupropion in 14 depressed patients with left ventricular dysfunction (history of congestive heart failure or an enlarged heart on x-ray), there was substantial interpatient variability (twofold to fivefold) in the trough steady-state concentrations of bupropion and the morpholinol and *threo*-amino alcohol metabolites. This variability was in the same range of the variability observed in healthy volunteers (threefold to eightfold). In addition, the steady-state plasma concentrations of these metabolites were 10 to 100 times the steady-state concentrations of the parent drug.

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 efficacy studies involving patients dosed in a range of 300 to 750 mg/day, on a t.i.d. schedule, revealed no relationship between age (18 to 83 years) and plasma concentration of bupropion. These data suggest there is no prominent effect of age on bupropion concentration (see PRECAUTIONS: Use in the Elderly).

Gender: A single-dose study involving 12 healthy male and 12 healthy female volunteers revealed no sex-related differences in the pharmacokinetic parameters of bupropion.

Clinical Trials: The efficacy of the immediate-release formulation of bupropion as a treatment for depression was established in two 4-week, placebo-controlled trials in adult inpatients with depression and in one 6-week, placebo-controlled trial in adult outpatients with depression. In the first study, patients were titrated in a bupropion dose range of 300 to 600 mg/day on a t.i.d. schedule; 78% of patients received maximum doses of 450 mg/day or less. This trial demonstrated the effectiveness of the immediate-release formulation of bupropion on the Hamilton Depression Rating Scale (HDRS) total score, the depressed mood item (item 1) from that scale, and the Clinical Global Impressions (CGI) severity score. A second study included two fixed doses of the immediate-release formulation of bupropion (300 and 450 mg/day) and placebo. This trial demonstrated the effectiveness of the immediate-release formulation of bupropion, but only at the 450-mg/day dose; the results were positive for the HDRS total score and the CGI severity score, but not for HDRS item 1. In the third study, outpatients received 300 mg/day of the immediate-release formulation of bupropion. This study demonstrated the effectiveness of the immediate-release formulation of bupropion on the HDRS total score, HDRS item 1, the Montgomery-Asberg Depression Rating Scale, the CGI severity score, and the CGI improvement score.

Although there are not as yet independent trials demonstrating the antidepressant effectiveness of the sustained-release formulation of bupropion, studies have demonstrated the bioequivalence of the immediate-release and sustained-release forms of bupropion under steady-state conditions, i.e., bupropion sustained-release 150 mg b.i.d. was shown to be bioequivalent to 100 mg t.i.d. of the immediate-release formulation of bupropion, with regard to both rate and extent of absorption, for parent drug and metabolites.

INDICATIONS AND USAGE: WELLBUTRIN SR is indicated for the treatment of depression.

A physician considering WELLBUTRIN SR Tablets for the management of a patient's first episode of depression should be aware that the drug may cause generalized seizures in a dose-dependent manner with an approximate incidence of 0.4% (4/1,000) at the upper end of the recommended dose range, i.e., 400 mg/day, and an incidence of 0.1% (1/1,000) at a bupropion dose of 300 mg/day. Bupropion's seizure incidence at the 400-mg/day dose may exceed that of other marketed antidepressants and doses of WELLBUTRIN SR Tablets up to 300 mg/day by as much as fourfold. This relative risk is only an approximate estimate because no direct comparative studies have been conducted (see WARNINGS).

The efficacy of bupropion in the treatment of depression was established in two 4-week controlled trials of depressed inpatients and in one 6-week controlled trial of depressed

outpatients whose diagnoses corresponded most closely to the Major Depression category of the APA Diagnostic and Statistical Manual (DSM) (see CLINICAL PHARMACOLOGY).

A major depressive episode (DSM-IV) implies the presence of 1) depressed mood or 2) loss of interest or pleasure; in addition, at least five of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

Effectiveness of bupropion in long-term use (more than 6 weeks) has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use WELLBUTRIN SR Tablets for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS: WELLBUTRIN SR is contraindicated in patients with a seizure disorder.

WELLBUTRIN SR is contraindicated in patients treated with ZYBAN™ (bupropion hydrochloride) Sustained-Release Tablets, or any other medications that contain bupropion because the incidence of seizure is dose dependent.

WELLBUTRIN SR is contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa because of a higher incidence of seizures noted in such patients treated with the immediate-release formulation of bupropion.

The concurrent administration of WELLBUTRIN SR Tablets and a monoamine oxidase (MAO) inhibitor is contraindicated. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with WELLBUTRIN SR Tablets.

WELLBUTRIN SR is contraindicated in patients who have shown an allergic response to bupropion or the other ingredients that make up WELLBUTRIN SR Tablets.

WARNINGS: Patients should be made aware that WELLBUTRIN SR contains the same active ingredient found in ZYBAN, used as an aid to smoking cessation treatment, and that WELLBUTRIN SR should not be used in combination with ZYBAN, or any other medications that contain bupropion. Seizures: Bupropion is associated with a dose-related risk of seizures. At doses of WELLBUTRIN SR up to a dose of 300 mg/day, the incidence of seizures is approximately 0.1% (1/1,000) but increases to approximately 0.4% (4/1,000) at the maximum recommended dose of 400 mg/day. The risk of seizure also appears to be strongly associated with the presence of predisposing factors.

Data for the immediate-release bupropion revealed a seizure incidence of approximately 0.4% (i.e., 13 of 3,200 patients followed prospectively) in patients treated at doses in a range of 300 to 450 mg/day. The 450-mg/day upper limit of this dose range is close to the currently recommended maximum dose of 400 mg/day for WELLBUTRIN SR Tablets. This seizure incidence (0.4%) may exceed that of other marketed antidepressants and doses of WELLBUTRIN SR Tablets up to 300 mg/day by as much as fourfold. This relative risk is only an approximate estimate because no direct comparative studies have been conducted.

Additional data accumulated for the immediate-release formulation of bupropion suggested that the estimated seizure incidence increases almost tenfold between 450 and 600 mg/day, which is twice the usual adult target dose and one and one-half the maximum recommended daily dose (400 mg) of WELLBUTRIN SR Tablets. Given the wide variability among individuals and their capacity to metabolize and eliminate drugs, this disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing.

Data for WELLBUTRIN SR Tablets revealed a seizure incidence of approximately 0.1% (i.e., 3 of 3,100 patients followed prospectively) in patients treated at doses in a range of 100 to 300 mg/day. It is not possible to know if the lower seizure incidence observed in this study involving the sustained-release formulation of bupropion resulted from the different formulation or the lower dose used. However, as noted above, the immediate-release and sustained-release formulations are bioequivalent regarding both rate and extent of absorption during steady state, the most pertinent condition to estimating seizure incidence since most observed seizures occur under steady-state conditions.

The risk of seizure is also related to patient factors, clinical situations, and concomitant medications, which must be considered in selection of patients for therapy with WELLBUTRIN SR.

- **Patient factors: Predisposing factors that may increase the risk of seizure with bupropion use include history of head trauma or prior seizure, central nervous system (CNS) tumor, and concomitant medications that lower seizure threshold.**
- **Clinical situations: Circumstances associated with an increased seizure risk include, among others, excessive use of alcohol; abrupt withdrawal from alcohol or other sedatives; addiction to opiates, cocaine, or stimulants; use of over-the-counter stimulants and anorectics; and diabetes treated with oral hypoglycemics or insulin.**
- **Concomitant medications: Many medications (e.g., antipsychotics, antidepressants, theophylline, systemic steroids) and treatment regimens (e.g., abrupt discontinuation of benzodiazepines) are known to lower seizure threshold.**

Recommendations for Reducing the Risk of Seizure: **Retrospective analysis of clinical experience gained during the development of bupropion suggests that the risk of seizure may be minimized if**

- **the total daily dose of WELLBUTRIN SR Tablets does *not* exceed 400 mg,**
- **the daily dose is administered b.. d., and**
- **the rate of incrementation of dose is gradual.**
- **No single dose should exceed 200 mg to avoid high peak concentrations of bupropion and/or its metabolites.**
- **WELLBUTRIN SR should be administered with extreme caution to patients with a history of seizure, cranial trauma, or other predisposition(s) toward seizure, or patients treated with other agents (e.g., antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) or treatment regimens (e.g., abrupt discontinuation of a benzodiazepine) that lower seizure threshold.**

Potential for Hepatotoxicity: In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted.

PRECAUTIONS:

General: ***Agitation and Insomnia:*** Patients in placebo-controlled trials with WELLBUTRIN SR Tablets experienced agitation, anxiety, and insomnia as shown in Table 1.

Table 1
Incidence of Agitation, Anxiety, and Insomnia in Placebo-Controlled Trials

Adverse Event Term	WELLBUTRIN SR® 300 mg/day (n = 376)	WELLBUTRIN SR 400 mg/day (n = 114)	Placebo (n = 385)
Agitation	3%	9%	2%
Anxiety	5%	6%	3%
Insomnia	11%	16%	6%

In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs.

Symptoms were sufficiently severe to require discontinuation of treatment in 1% and 2.6% of patients treated with 300 and 400 mg/day, respectively, of WELLBUTRIN SR Tablets and 0.8% of patients treated with placebo.

Psychosis, Confusion, and Other Neuropsychiatric Phenomena: Patients treated with an immediate-release formulation of bupropion or with WELLBUTRIN SR Tablets have been reported to show a variety of neuropsychiatric signs and symptoms, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment.

Activation of Psychosis and/or Mania: Antidepressants can precipitate manic episodes in bipolar disorder patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. WELLBUTRIN SR is expected to pose similar risks.

Altered Appetite and Weight: In placebo-controlled studies, patients experienced weight gain or weight loss as shown in Table 2.

Table 2
Incidence of Weight Gain and Weight Loss in Placebo-Controlled Trials

Weight Change	WELLBUTRIN SR® 300 mg/day (n = 339)	WELLBUTRIN SR 400 mg/day (n = 112)	Placebo (n = 347)
Gained >5 lbs	3%	2%	4%
Lost >5 lbs	14%	19%	6%

In studies conducted with the immediate-release formulation of bupropion, 35% of patients receiving tricyclic antidepressants gained weight, compared to 9% of patients treated with the immediate-release formulation of bupropion. If weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight-reducing potential of WELLBUTRIN SR Tablets should be considered.

Suicide: The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Accordingly, prescriptions for WELLBUTRIN SR Tablets should be written for the smallest number of tablets consistent with good patient management.

Allergic Reactions: Anaphylactoid reactions characterized by symptoms such as pruritus, urticaria, angioedema, and dyspnea requiring medical treatment have been reported in clinical trials with bupropion. In addition, there have been rare spontaneous postmarketing reports of erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated with bupropion.

Use in Patients With Systemic Illness: There is no clinical experience establishing the safety of WELLBUTRIN SR Tablets in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups. Bupropion was well tolerated in patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants, and was also generally well tolerated in a group of 36 depressed inpatients with stable congestive heart failure (CHF). However, bupropion was associated with a rise in supine blood pressure in the study of patients with CHF, resulting in discontinuation of two patients for exacerbation of baseline hypertension.

Because 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, treatment of patients with renal or hepatic impairment should be initiated at reduced dosage as bupropion and its metabolites may accumulate in such patients to a greater extent than usual. The patient should be closely monitored for possible toxic effects of elevated blood and tissue levels of drug and metabolites.

Information for Patients: Patients should be made aware that WELLBUTRIN SR contains the same active ingredient found in ZYBAN, used as an aid to smoking cessation, and that WELLBUTRIN SR should not be used in combination with ZYBAN or any other medications that contain bupropion hydrochloride.

Physicians are advised to discuss the following issues with patients:

As dose is increased during initial titration to doses above 150 mg/day, patients should be instructed to take WELLBUTRIN SR Tablets in two divided doses, preferably with at least 8 hours between successive doses, to minimize the risk of seizures.

Patients should be told that any CNS-active drug like WELLBUTRIN SR Tablets may impair their ability to perform tasks requiring judgment or motor and cognitive skills. Consequently, until they are reasonably certain that WELLBUTRIN SR Tablets do not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery.

Patients should be told that the use and cessation of use of alcohol may alter the seizure threshold, and, therefore, that the consumption of alcohol should be minimized, and, if possible, avoided completely.

Patients should be advised to inform their physicians if they are taking or plan to take any prescription or over-the-counter drugs. Concern is warranted because WELLBUTRIN SR Tablets and other drugs may affect each other's metabolism.

Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to swallow WELLBUTRIN SR Tablets whole so that the release rate is not altered. Do not chew, divide, or crush tablets.

Laboratory Tests: There are no specific laboratory tests recommended.

Drug Interactions: Although no systematic data have been collected on the consequences of the concomitant administration of WELLBUTRIN SR Tablets and other drugs, animal data suggest that bupropion may be an inducer of drug-metabolizing enzymes. This may be of potential clinical importance because the blood levels of coadministered drugs may be altered.

Alternatively, because bupropion is extensively metabolized, the coadministration of other drugs may affect its clinical activity. In particular, certain drugs may induce the metabolism of bupropion (e.g., *carbamazepine, phenobarbital, phenytoin*), while *other drugs* may inhibit the metabolism of bupropion (e.g., cimetidine).

In vitro studies indicate that bupropion is primarily metabolized to the morpholinol metabolite by the cytochrome $P_{450}IIB_6$ isoenzyme. Therefore, the potential exists for a drug interaction between WELLBUTRIN SR and drugs that affect the cytochrome $P_{450}IIB_6$ metabolism (e.g., orphenadrine and cyclophosphamide). The *threo*-amino alcohol metabolite of bupropion does not appear to be produced by the cytochrome P_{450} system.

Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine (see CONTRAINDICATIONS).

Limited clinical data suggest a higher incidence of adverse experiences in patients receiving concurrent administration of bupropion and levodopa. Administration of WELLBUTRIN SR Tablets to patients receiving levodopa concurrently should be undertaken with caution, using small initial doses and gradual dose increases.

Concurrent administration of WELLBUTRIN SR Tablets and agents (e.g., antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) or treatment regimens (e.g., abrupt discontinuation of benzodiazepines) that lower seizure threshold should be undertaken only with extreme caution (see WARNINGS). Low initial dosing and gradual dose increases should be employed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg per day, respectively. These doses are approximately seven and two times the maximum recommended human dose (MRHD), respectively, on a mg/m^2 basis. In the rat study there was an increase in nodular

proliferative lesions of the liver at doses of 100 to 300 mg/kg per day (approximately two to seven times the MRHD on a mg/m² basis); lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

Bupropion produced a positive response (two to three times control mutation rate) in two of five strains in the Ames bacterial mutagenicity test and an increase in chromosomal aberrations in one of three in vivo rat bone marrow cytogenetic studies.

A fertility study in rats at doses up to 300 mg/kg revealed no evidence of impaired fertility.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Teratology studies have been performed at doses up to 450 mg/kg in rats, and at doses up to 150 mg/kg in rabbits (approximately 7 to 11 and 7 times the MRHD, respectively, on a mg/m² basis), and have revealed no evidence of 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.

Labor and Delivery: The effect of WELLBUTRIN SR Tablets on labor and delivery in humans is unknown.

Nursing Mothers: Like many other drugs, bupropion and its metabolites are secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from WELLBUTRIN SR Tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and effectiveness of WELLBUTRIN SR Tablets in pediatric patients below 18 years old have not been established.

Use in the Elderly: In general, older patients are known to metabolize drugs more slowly and to be more sensitive to the anticholinergic, sedative, and cardiovascular side effects of antidepressant drugs. A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects (see CLINICAL PHARMACOLOGY). Of the approximately 4,100 patients who participated in clinical trials with WELLBUTRIN SR Tablets, 204 were 60 to 69 years old and 68 were 70 years of age or older. The experience with patients 60 years of age or older was similar to that in younger patients.

ADVERSE REACTIONS: (See also WARNINGS and PRECAUTIONS)

The information included under the Incidence in Controlled Trials subsection of ADVERSE REACTIONS is based primarily on data from controlled clinical trials with WELLBUTRIN SR Tablets. Information on additional adverse events associated with the sustained-release formulation of bupropion in smoking cessation trials, as well as the immediate-release formulation of bupropion, is included in a separate section (see Other Events Observed During the Clinical Development and Postmarketing Experience of Bupropion).

Incidence in Controlled Trials With WELLBUTRIN SR: ***Adverse Events Associated With Discontinuation of Treatment Among Patients Treated With WELLBUTRIN SR Tablets:*** In placebo-controlled clinical trials, 9% and 11% of patients treated with 300 and 400 mg/day, respectively, of WELLBUTRIN SR Tablets and 4% of patients treated with placebo discontinued treatment due to adverse events. The specific adverse events in these trials that led to discontinuation in at least 1% of patients treated with either 300 or 400 mg/day of WELLBUTRIN SR Tablets and at a rate at least twice the placebo rate are listed in Table 3.

Table 3
Treatment Discontinuations Due to Adverse Events in Placebo-Controlled Trials

Adverse Event Term	WELLBUTRIN SR® 300 mg/day (n = 376)	WELLBUTRIN SR 400 mg/day (n = 114)	Placebo (n = 385)
Rash	2.4%	0.9%	0.0%
Nausea	0.8%	1.8%	0.3%
Agitation	0.3%	1.8%	0.3%
Migraine	0.0%	1.8%	0.3%

Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated With WELLBUTRIN SR Tablets: Table 4 enumerates treatment-emergent adverse events that occurred among patients treated with 300 and 400 mg/day of WELLBUTRIN SR Tablets and with placebo in placebo-controlled trials. Events that occurred in either the 300- or 400-mg/day group at an incidence of 1% or more and were more frequent than in the placebo group are included. Reported adverse events were classified using a COSTART-based Dictionary.

Accurate estimates of the incidence of adverse events associated with the use of any drug are difficult to obtain. Estimates are influenced by drug dose, detection technique, setting, physician judgments, etc. The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. These incidence figures also cannot be compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions.

Finally, it is important to emphasize that the tabulation does not reflect the relative severity and/or clinical importance of the events. A better perspective on the serious adverse events associated with the use of WELLBUTRIN SR Tablets is provided in the WARNINGS and PRECAUTIONS sections.

Table 4
Treatment-Emergent Adverse Events in Placebo-Controlled Trials*

Body System/ Adverse Event	WELLBUTRIN SR® 300 mg/day (n = 376)	WELLBUTRIN SR 400 mg/day (n = 114)	Placebo (n = 385)
Body (General)			
Headache	26%	25%	23%
Infection	8%	9%	6%
Abdominal pain	3%	9%	2%
Asthenia	2%	4%	2%
Chest pain	3%	4%	1%
Pain	2%	3%	2%
Fever	1%	2%	—
Cardiovascular			
Palpitation	2%	6%	2%
Flushing	1%	4%	—
Migraine	1%	4%	1%
Hot flashes	1%	3%	1%
Digestive			
Dry mouth	17%	24%	7%
Nausea	13%	18%	8%
Constipation	10%	5%	7%
Diarrhea	5%	7%	6%
Anorexia	5%	3%	2%
Vomiting	4%	2%	2%
Dysphagia	0%	2%	0%
Musculoskeletal			
Myalgia	2%	6%	3%
Arthralgia	1%	4%	1%
Arthritis	0%	2%	0%
Twitch	1%	2%	—
Nervous system			
Insomnia	11%	16%	6%
Dizziness	7%	11%	5%
Agitation	3%	9%	2%
Anxiety	5%	6%	3%
Tremor	6%	3%	1%
Nervousness	5%	3%	3%
Somnolence	2%	3%	2%
Irritability	3%	2%	2%
Memory decreased	—	3%	1%
Paresthesia	1%	2%	1%
CNS stimulation	2%	1%	1%
Respiratory			
Pharyngitis	3%	11%	2%
Sinusitis	3%	1%	2%
Increased cough	1%	2%	1%
Skin			
Sweating	6%	5%	2%
Rash	5%	4%	1%
Pruritus	2%	4%	2%
Urticaria	2%	1%	0%
Special senses			
Tinnitus	6%	6%	2%
Taste perversion	2%	4%	—
Amblyopia	3%	2%	2%
Urogenital			
Urinary frequency	2%	5%	2%
Urinary urgency	—	2%	0%
Vaginal hemorrhage†	0%	2%	—
Urinary tract infection	1%	0%	—

*Adverse events that occurred in at least 1% of patients treated with either 300 or 400 mg/day of WELLBUTRIN SR Tablets, but equally or more frequently in the placebo group, were: abnormal dreams, accidental injury, acne, appetite increased, back pain, bronchitis, dysmenorrhea, dyspepsia, flatulence, flu syndrome, hypertension, neck pain, respiratory disorder, rhinitis, and tooth disorder.

†Incidence based on the number of female patients.

—Hyphen denotes adverse events occurring in greater than 0 but less than 0.5% of patients.

Incidence of Commonly Observed Adverse Events in Controlled Clinical Trials: Adverse events from Table 4 occurring in at least 5% of patients treated with WELLBUTRIN SR Tablets and at a rate at least twice the placebo rate are listed below for the 300- and 400-mg/day dose groups.

WELLBUTRIN SR 300 mg/day: Anorexia, dry mouth, rash, sweating, tinnitus, and tremor.

WELLBUTRIN SR 400 mg/day: Abdominal pain, agitation, anxiety, dizziness, dry mouth, insomnia, myalgia, nausea, palpitation, pharyngitis, sweating, tinnitus, and urinary frequency.

Other Events Observed During the Clinical Development and Postmarketing Experience of Bupropion: In addition to the adverse events noted above, the following events have been reported in clinical trials with the sustained-release formulation of bupropion in depressed patients and in nondepressed smokers, as well as in clinical trials and postmarketing clinical experience with the immediate-release formulation of bupropion.

Adverse events for which frequencies are provided below occurred in clinical trials with the sustained-release formulation of bupropion. The frequencies represent the proportion of patients who experienced a treatment-emergent adverse event on at least one occasion in placebo-controlled studies for depression (n = 987) or smoking cessation (n = 1,013), or patients who experienced an adverse event requiring discontinuation of treatment in an open-label surveillance study with WELLBUTRIN SR Tablets (n = 3,100). All treatment-emergent adverse events are included except those listed in Tables 1 through 4, those events listed in other safety-related sections, those adverse events subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, those events not reasonably associated with the use of the drug, and those events that were not serious and occurred in fewer than two patients. Events of major clinical importance are described in the WARNINGS and PRECAUTIONS sections of the labeling.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions of frequency: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1,000 patients, while rare events are those occurring in less than 1/1,000 patients.

Adverse events for which frequencies are not provided occurred in clinical trials or postmarketing experience with the immediate-release formulation of bupropion. Only those adverse events not previously listed for sustained-release bupropion are included. The extent to which these events may be associated with WELLBUTRIN SR is unknown.

Body (General): Infrequent were chills, facial edema, musculoskeletal chest pain, and photosensitivity. Rare was malaise.

Cardiovascular: Infrequent were postural hypotension, stroke, tachycardia, and vasodilation. Rare was syncope. Also observed were complete AV block, extrasystoles, hypotension, myocardial infarction, phlebitis, and pulmonary embolism.

Digestive: Infrequent were abnormal liver function, bruxism, gastric reflux, gingivitis, glossitis, increased salivation, jaundice, mouth ulcers, stomatitis, and thirst. Rare was edema of tongue. Also observed were colitis, esophagitis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, intestinal perforation, liver damage, pancreatitis, and stomach ulcer.

Endocrine: Also observed was syndrome of inappropriate antidiuretic hormone.

Hemic and Lymphatic: Infrequent was ecchymosis. Also observed were anemia, leukocytosis, leukopenia, lymphadenopathy, and pancytopenia.

Metabolic and Nutritional: Infrequent were edema and peripheral edema. Also observed was glycosuria.

Musculoskeletal: Infrequent were leg cramps. Also observed were muscle rigidity/fever/rhabdomyolysis.

Nervous System: Infrequent were abnormal coordination, decreased libido, depersonalization, dysphoria, emotional lability, hostility, hyperkinesia, hypertonia, hypesthesia, suicidal ideation, and vertigo. Rare were amnesia, ataxia, derealization, and hypomania. Also observed were abnormal electroencephalogram (EEG), akinesia, aphasia, coma, delirium, dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome, hypokinesia, increased libido, manic reaction, neuralgia, neuropathy, paranoid reaction, and unmasking tardive dyskinesia.

Respiratory: Rare was bronchospasm. Also observed was pneumonia.

Skin: Rare was maculopapular rash. Also observed were angioedema, exfoliative dermatitis, and hirsutism.

Special Senses: Infrequent were accommodation abnormality and dry eye. Also observed were deafness, diplopia, and mydriasis.

Urogenital: Infrequent were impotence, polyuria, and prostate disorder. Also observed were abnormal ejaculation, cystitis, dyspareunia, dysuria, gynecomastia, menopause, painful erection, salpingitis, urinary incontinence, urinary retention, and vaginitis.

DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: Bupropion is not a controlled substance.

Humans: Controlled clinical studies of bupropion conducted in normal volunteers, in subjects with a history of multiple drug abuse, and in depressed patients showed some increase in motor activity and agitation/excitement.

In a population of individuals experienced with drugs of abuse, a single dose of 400 mg of bupropion produced mild amphetamine-like activity as compared to placebo on the morphine-Benzedrine subscale of the Addiction Research Center Index (ARCI), and a score intermediate between placebo and amphetamine on the Liking Scale of the ARCI. These scales

measure general feelings of euphoria and drug desirability.

Findings in clinical trials, however, are not known to reliably predict the abuse potential of drugs. Nonetheless, evidence from single-dose studies does suggest that the recommended daily dosage of bupropion when administered in divided doses is not likely to be especially reinforcing to amphetamine or stimulant abusers. However, higher doses that could not be tested because of the risk of seizure might be modestly attractive to those who abuse stimulant drugs.

Animals: Studies in rodents have shown that bupropion exhibits some pharmacologic actions common to psychostimulants, including increases in locomotor activity and the production of a mild stereotyped behavior and increases in rates of responding in several schedule-controlled behavior paradigms. Drug discrimination studies in rats showed stimulus generalization between bupropion and amphetamine and other psychostimulants. Rhesus monkeys have been shown to self-administer bupropion intravenously.

OVERDOSAGE:

Human Overdose Experience: There has been very limited experience with overdosage of WELLBUTRIN SR Tablets; three cases were reported during clinical trials. One patient ingested 3,000 mg of WELLBUTRIN SR Tablets and vomited quickly after the overdose; the patient experienced blurred vision and lightheadedness. A second patient ingested a "handful" of WELLBUTRIN SR Tablets and experienced confusion, lethargy, nausea, jitteriness, and seizure. A third patient ingested 3,600 mg of WELLBUTRIN SR Tablets and a bottle of wine; the patient experienced nausea, visual hallucinations, and "grogginess". None of the patients experienced further sequelae.

There has been extensive experience with overdosage of the immediate-release formulation of bupropion. Thirteen overdoses occurred during clinical trials. Twelve patients ingested 850 to 4,200 mg and recovered without significant sequelae. Another patient who ingested 9,000 mg of the immediate-release formulation of bupropion and 300 mg of tranylcypromine experienced a grand mal seizure and recovered without further sequelae.

Since introduction, overdoses of up to 17,500 mg of the immediate-release formulation of bupropion have been reported. Seizure was reported in approximately one third of all cases. Other serious reactions reported with overdoses of the immediate-release formulation of bupropion alone included hallucinations, loss of consciousness, and sinus tachycardia. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported when the immediate-release formulation of bupropion was part of multiple drug overdoses.

Although most patients recovered without sequelae, deaths associated with overdoses of the immediate-release formulation of bupropion alone have been reported rarely in patients ingesting massive doses of the drug. Multiple uncontrolled seizures, bradycardia, cardiac failure, and cardiac arrest prior to death were reported in these patients.

Management of Overdose: Following suspected overdose, hospitalization is advised. If the patient is conscious, vomiting should be induced by syrup of ipecac. Activated charcoal also may be administered every 6 hours during the first 12 hours after ingestion. Baseline laboratory values should be obtained. Electrocardiogram and EEG monitoring also are recommended for the next 48 hours. Adequate fluid intake should be provided.

If the patient is stuporous, comatose, or convulsing, airway intubation is recommended prior to undertaking gastric lavage. Although there is little clinical experience with lavage following an overdose of the immediate-release formulation of bupropion and none with WELLBUTRIN SR Tablets, it is likely to be of benefit within the first 12 hours after ingestion since absorption of the drug may not yet be complete.

Although diuresis, dialysis, or hemoperfusion are sometimes used to treat drug overdosage, there is no experience with their use in the management of overdoses of WELLBUTRIN SR Tablets. Because diffusion of bupropion and its metabolites from tissue to plasma may be slow, dialysis may be of minimal benefit.

Based on studies in animals, it is recommended that seizures be treated with an intravenous benzodiazepine preparation and other supportive measures, as appropriate.

Further information about the treatment of overdoses may be available from a poison control center.

DOSAGE AND ADMINISTRATION:

General Dosing Considerations: It is particularly important to administer WELLBUTRIN SR Tablets in a manner most likely to minimize the risk of seizure (see WARNINGS). Gradual escalation in dosage is also important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these effects may be managed by temporary reduction of dose or the short-term administration of an intermediate to long-acting sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment. Insomnia may also be minimized by avoiding bedtime doses. If distressing, untoward effects supervene, dose escalation should be stopped.

Initial Treatment: The usual adult target dose for WELLBUTRIN SR Tablets is 300 mg/day, given as 150 mg b.i.d. Dosing with WELLBUTRIN SR Tablets should begin at 150 mg/day given as a single daily dose in the morning. If the 150-mg initial dose is adequately tolerated, an increase to the 300-mg/day target dose, given as 150 mg b.i.d., may be made as early as day 4 of dosing. There should be an interval of at least 8 hours between successive doses.

Increasing the Dosage Above 300 mg/day: As with other antidepressants, the full antidepressant effect of WELLBUTRIN SR Tablets may not be evident until 4 weeks of treatment or longer. An increase in dosage to the maximum of 400 mg/day, given as 200 mg b.i.d., may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day.

Maintenance: The lowest dose that maintains remission is recommended. Although it is not known how long the patient should remain on WELLBUTRIN SR Tablets, it is generally recognized that acute episodes of depression require several months or longer of antidepressant drug treatment.

HOW SUPPLIED: WELLBUTRIN SR Sustained-Release Tablets, 100 mg of bupropion hydrochloride, are blue, round, biconvex, film-coated tablets printed with "WELLBUTRIN SR 100" in bottles of 60 (NDC 0173-0947-55).

WELLBUTRIN SR Sustained-Release Tablets, 150 mg of bupropion hydrochloride, are purple, round, biconvex, film-coated tablets printed with "WELLBUTRIN SR 150" in bottles of 60 (NDC 0173-0135-55).

Store at controlled Room Temperature, 20°-25°C (68°-77°F) [see USP]. Dispense in a tight, light-resistant container as defined in the USP.

GlaxoWellcome
Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

U.S. Patent Nos. 5,358,970; 5,427,798; and Re. 33,994

June 1997 RL-436

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20358/S001/S003

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data
NDA #20-358

JUL 17 1997

Sponsor:	GlaxoWellcome
Drug:	Wellbutrin (bupropion)
Material Submitted:	Draft labeling changes
Correspondence Date:	June 19, 1997
Date Received:	June 20, 1997

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.

/S/ 7/16/97

Paul J. Andreason, M.D.

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

7-17-97
/S/

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20358/S001/S003

CHEMISTRY REVIEW(S)

AUG 15 1997

CHEMIST'S REVIEW OF SUPPLEMENT

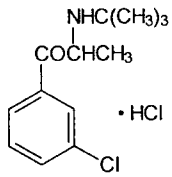
1. ORGANIZATION:	HFD-120
2. NDA NUMBER:	20-358
4. SUPPLEMENT NUMBERS:	SLR-001
LETTER DATE	19-JUN-97
STAMP DATE	20-JUN-97
5. AMENDMENTS/REPORTS:	
LETTER DATE	*N/A*
STAMP DATE	*N/A*
6. RECEIVED BY CHEMIST:	23-JUN-97

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-dimethylethyl)amino]-1-propanone hydrochloride



11. DOSAGE FORM(S): Extended Release Tablets

12. POTENCY(IES): 50 mg, 100 mg and 150 mg

13. PHARMACOLOGICAL CATEGORY: Depression

14. HOW DISPENSED: XX (Rx) ___ (OTC)

15. RECORDS / REPORTS CURRENT: XX (YES) ___ (NO)

16. RELATED IND / NDA / DMF(S): 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 Effected."

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	SIGNATURE	DATE COMPLETED
Martha R. Heimann, Ph.D.	/S/	7/22/97 July 22, 1997

cc: Orig.; NDA 18-644
HFD-120/Div. File
HFD-120/PDavid
HFD-120/MHeimann/22-JUL-97
INIT: SWB/ 8.15.97

Filename: S20358.001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20358/S001/S003

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

NOV 24 1997

CSO LABELING REVIEW

Date of Review: November 24, 1997

NDA NUMBER: 20-358 (Tablets)
Submission Date: Original Application Approved October 4, 1996
Acknowledge 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 Effected: Yes
Reviewed by Medical Officer: Yes, acceptable
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 hepatoxin 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 Effected: 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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date OCT 10 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-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,

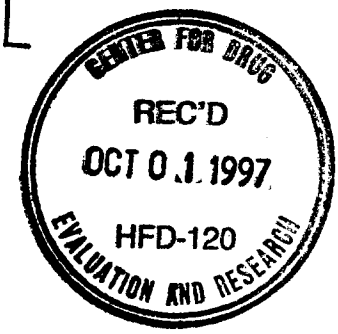
/S/

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

ARCHIVAL COPY

ORIGINAL

GlaxoWellcome



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

NDA NO. 20-358 REF. NO. SLR-003
NDA SUPPL FOR Labeling

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,

APPEARS THIS WAY
ON ORIGINAL

/S/

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.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date JUN 24 1997

NDA No. 20-358

Glaxo Wellcom 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: Wellburtrin 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,

/S/

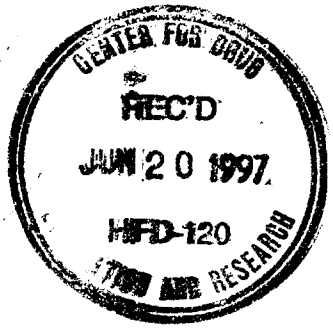
(For) John Purvis
Chief, Project Management Staff
Division of Neuropharmacologic Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

★ U.S. GPO: 1995-404-897/20714

GlaxoWellcome

ORIGINAL

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

APPEARS THIS WAY ON ORIGINAL

NDA NO. 20-358 REF. NO. SAR 037

NDA SUBMITTED FOR Labeling

Re:

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

APPEARS THIS WAY ON ORIGINAL

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.

APPEARS THIS WAY ON ORIGINAL

REVISED PACKAGE INSERT

Glaxo Wellcome Inc.

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Telephone
919 248 2100

2 Page(s) Redacted

DRAFT LABELING

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