CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-358/S-027

Name:	Wellbutrin SR Sustained-Release Tablets
Generic Name:	bupropion hydrochloride
Sponsor:	GlaxoSmithKline
Approval Date:	06/14/02

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-358/S-027

GlaxoWellcome Inc.
Attn: Leo Lucisano, R. Ph.
Five Moore Drive
Research Triangle Park, NC 27709

Dear Mr. Lucisano:

Please refer to your supplemental new drug application dated February 15, 2002, received February 19, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Wellbutrin SR® (bupropion hydrochloride) Tablets.

We also acknowledge receipt of your submission dated April 1, 2002.

This supplemental application provides for the use of a new 200 mg strength Wellbutrin SR tablet as an additional dosage strength. It includes the results of a bioequivalence study comparing the new 200 mg tablet to the currently marketed 100 mg tablet. In addition, the supplement includes proposed labeling (package insert, patient package insert, and container labeling) relevant to the new 200 mg strength.

We have completed our review of this supplemental application and it is approved, subject to the following comments:

Chemistry, Manufacturing, and Controls

We are approving this supplement with an 18 month expiration date for the drug product.

We also note the following approved dissolution specification for the 200 mg tablet:

Apparatus:	USP Apparatus II (Paddle) at 50 RPM	
Medium:	900 mL of water at 37±0.5°C	
Specifications:	at 1 hour:	25 – 45% of labeled strength released
	at 4 hours:	60 – 85% of labeled strength released
	at 8 hours:	NLT 80% of labeled strength released

Request for Submission of Final Printed Labeling (FPL)

We are approving this supplement based upon your submitted proposed labeling (package insert with Patient Package Insert). A clean copy of this labeling is provided as an attachment to this letter. The final printed labeling (FPL) must be identical to the enclosed labeling text and to the immediate container and carton labels as submitted on February 15, 2002.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded, and thus an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDA.* Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, but no more than 30 days after it is printed. Individually mount ten of the paper copies on heavy-weight paper or similar material. For administrative purposes, please designate these submissions "FPL for approved supplemental NDA 20-358/S-027". Approval of this labeling submission by FDA is not required before the labeling is used.

Communicating Important Information About this Drug Product

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

You are reminded that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you should have any questions, please contact Doris J. Bates, Ph.D., Regulatory Project Manager, at 301.594.5536.

Sincerely yours,

[see electronic signature page]

Russell Katz, MD
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment: electronic copy of agreed upon labeling test (package insert and PPI)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
6/14/02 09:29:55 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

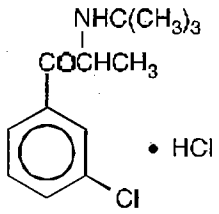
NDA 20-358/S-027

FINAL PRINTED LABELING

WELLBUTRIN SR®
(bupropion hydrochloride)
Sustained-Release Tablets

"Information for the Patient" enclosed.

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 designated as (±)-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), 150-mg (purple), and 200-mg (light pink), 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, polysorbate 80, and titanium dioxide and is printed with edible black ink. In addition, the 100-mg tablet contains FD&C Blue No. 1 Lake, the 150-mg tablet contains FD&C Blue No. 2 Lake and FD&C Red No. 40 Lake, and the 200-mg tablet contains FD&C Red No. 40 Lake.

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: Bupropion is a racemic mixture. The pharmacologic activity and pharmacokinetics of the individual enantiomers have not been studied.

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 84% bound to human plasma proteins at concentrations up to 200 mcg/mL. The extent of protein binding of the hydroxybupropion metabolite is similar to that for bupropion, whereas the extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion.

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.

Bupropion is extensively metabolized in humans. Three metabolites have been shown to be active: hydroxybupropion, which is formed via hydroxylation of the *tert*-butyl group of bupropion, and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, which are formed via reduction of the carbonyl group. In vitro findings suggest that cytochrome P450IIB6 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion, while cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion. Oxidation of the bupropion side chain results in the formation of a glycine conjugate of meta-chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency and toxicity of the metabolites relative to bupropion have not been fully characterized. Nevertheless, they may be clinically important because their plasma concentrations are higher than those of bupropion.

Because bupropion is extensively metabolized, there is the potential for drug-drug interactions, particularly with those agents that are metabolized by the cytochrome P450IIB6 (CYP2B6) isoenzyme. Although bupropion is not metabolized by cytochrome P450IID6 (CYP2D6), there is the potential for drug-drug interactions when bupropion is co-administered with drugs metabolized by this isoenzyme (see PRECAUTIONS: Drug Interactions).

Following a single dose in humans, peak plasma concentrations of hydroxybupropion occur approximately 6 hours after administration of WELLBUTRIN SR Tablets. Peak plasma concentrations of hydroxybupropion are approximately 10 times the peak level of the parent drug at steady state. The elimination half-life of hydroxybupropion 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 erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the hydroxybupropion 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, respectively.

In a study comparing chronic dosing with WELLBUTRIN SR Tablets 150 mg twice daily to the immediate-release formulation of bupropion at 100 mg three times daily, 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, given twice daily, and the immediate-release formulation of bupropion, given three times daily, are essentially bioequivalent for both bupropion and the three quantitatively important metabolites.

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 [CHF], 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 effect of hepatic impairment on the pharmacokinetics of bupropion was characterized in two single-dose studies, one in patients with alcoholic liver disease and one in patients with mild to severe cirrhosis. The first study showed that the half-life of hydroxybupropion was significantly longer in 8 patients with alcoholic liver disease than in 8 healthy volunteers (32±14 hours versus 21±5 hours, respectively). Although not statistically significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be greater (by 53% to 57%) in patients with alcoholic liver disease. The differences in half-life for bupropion and the other metabolites in the two patient groups were minimal.

The second study showed that there were no statistically significant differences in the pharmacokinetics of bupropion and its active metabolites in 9 patients with mild to moderate hepatic cirrhosis compared to 8 healthy volunteers. There was, however, more variability observed in some of the pharmacokinetic parameters for bupropion (AUC, C_{max}, and T_{max}) and its active metabolites ($t_{½}$) in patients with mild to moderate hepatic cirrhosis. In addition, in patients with severe hepatic cirrhosis, the bupropion C_{max} and AUC were substantially increased (mean difference: by approximately 70% and 3-fold, respectively) and more variable when compared to values in healthy volunteers; the mean bupropion half-life was also longer (by approximately 40%). For the metabolites, the mean C_{max} was lower (by approximately 30% to 70%), the mean AUC tended to be higher (by approximately 30% to 50%), the median T_{max} was later (by approximately 20 hours), and the mean half-lives were longer (by approximately 2- to 4-fold) in patients with severe hepatic cirrhosis than in healthy volunteers (see WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

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 CHF or an enlarged heart on x-ray),

no apparent effect on the pharmacokinetics of bupropion or its metabolites, compared to healthy normal volunteers, was revealed.

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 daily 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: Geriatric Use).

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.

Smokers: The effects of cigarette smoking on the pharmacokinetics of bupropion were studied in 34 healthy male and female volunteers; 17 were chronic cigarette smokers and 17 were nonsmokers. Following oral administration of a single 150-mg dose of bupropion, there was no statistically significant difference in C_{max}, half-life, t_{max}, AUC, or clearance of bupropion or its active metabolites between smokers and nonsmokers.

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 three times daily 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 twice daily was shown to be bioequivalent to 100 mg

three times daily of the immediate-release formulation of bupropion, with regard to both rate and extent of absorption, for parent drug and metabolites.

In a longer-term study, outpatients meeting DSM-IV criteria for major depressive disorder, recurrent type, who had responded during an 8-week open trial on WELLBUTRIN SR (150 mg twice daily) were randomized to continuation of their same WELLBUTRIN SR dose or placebo, for up to 44 weeks of observation for relapse. Response during the open phase was defined as CGI Improvement score of 1 (very much improved) or 2 (much improved) for each of the final three weeks. Relapse during the double-blind phase was defined as the investigator's judgement that drug treatment was needed for worsening depressive symptoms. Patients receiving continued WELLBUTRIN SR treatment experienced significantly lower relapse rates over the subsequent 44 weeks compared to those receiving placebo.

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

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.

The efficacy of WELLBUTRIN SR in maintaining an antidepressant response for up to 44 weeks following 8 weeks of acute treatment was demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use WELLBUTRIN SR 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 patients treated for bulimia 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. The risk of seizures is also related to patient factors, clinical situations, and concomitant medications, which must be considered in selection of patients for therapy with WELLBUTRIN SR. WELLBUTRIN SR should be discontinued and not restarted in patients who experience a seizure while on treatment.

- **Dose: At doses of WELLBUTRIN SR up to a dose of 300 mg/day, the incidence of seizure is approximately 0.1% (1/1000) and increases to approximately 0.4% (4/1000) at the maximum recommended dose of 400 mg/day.**

  Data for the immediate-release formulation of bupropion revealed a seizure incidence of approximately 0.4% (i.e., 13 of 3200 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 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 dose and one and one-half the maximum recommended daily dose (400 mg) of WELLBUTRIN SR Tablets. 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 3100 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 with regard to 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.

- **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, the presence of severe hepatic cirrhosis, 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 twice daily, 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.

Hepatic Impairment: WELLBUTRIN SR should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients a reduced frequency and/or dose is required, as peak bupropion levels are substantially increased and accumulation is likely to occur in such patients to a greater extent than usual. The dose should not exceed 100 mg every day or 150 mg every other day in these patients (see CLINICAL PHARMACOLOGY, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

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: Depressed 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/anaphylactic 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. A patient should stop taking WELLBUTRIN SR and consult a doctor if experiencing allergic or anaphylactoid/anaphylactic reactions (e.g., skin rash, pruritus, hives, chest pain, edema, and shortness of breath) during treatment.

Arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity have been reported in association with bupropion. These symptoms may resemble serum sickness.

Cardiovascular Effects: In clinical practice, hypertension, in some cases severe, requiring acute treatment, has been reported in patients receiving bupropion alone and in combination with nicotine replacement therapy. These events have been observed in both patients with and without evidence of preexisting hypertension.

Data from a comparative study of the sustained-release formulation of bupropion (ZYBAN® Sustained-Release Tablets), nicotine transdermal system (NTS), the combination of sustained-release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher incidence of treatment-emergent hypertension in patients treated with the combination of sustained-release bupropion and NTS. In this study, 6.1% of patients treated with the combination of sustained-release bupropion and NTS had treatment-emergent hypertension compared to 2.5%, 1.6%, and 3.1% of patients treated with sustained-release bupropion, NTS, and placebo, respectively. The majority of these patients had evidence of preexisting hypertension. Three patients (1.2%) treated with the combination of ZYBAN and NTS and one patient (0.4%) treated with NTS had study medication discontinued due to hypertension compared to none of the patients treated with ZYBAN or placebo. Monitoring of blood pressure is recommended in patients who receive the combination of bupropion and nicotine replacement.

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 depressed 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 treatment in two patients for exacerbation of baseline hypertension.

Hepatic Impairment: WELLBUTRIN SR should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients, a reduced frequency and/or dose is required. WELLBUTRIN SR should be used with caution in patients with hepatic impairment (including mild to moderate hepatic cirrhosis) and reduced frequency and/or dose should be considered in patients with mild to moderate hepatic cirrhosis.

All patients with hepatic impairment should be closely monitored for possible adverse effects that could indicate high drug and metabolite levels (see CLINICAL PHARMACOLOGY, WARNINGS, and DOSAGE AND ADMINISTRATION).

Renal Impairment: No studies have been conducted in patients with renal impairment. Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and excreted by the kidneys. WELLBUTRIN SR should be used with caution in patients with renal impairment and a reduced frequency and/or dose should be considered as bupropion and its metabolites may accumulate in such patients to a greater extent than usual. The patient should be closely monitored for possible adverse effects that could indicate high drug or metabolite levels

Information for Patients: See the tear-off leaflet at the end of this labeling for Information for the Patient.

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 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 WELLBUTRIN SR should be discontinued and not restarted if they experience a seizure while on treatment.

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: Few systemic data have been collected on the metabolism of WELLBUTRIN SR following concomitant administration with other drugs or, alternatively, the effect of concomitant administration of WELLBUTRIN SR on the metabolism of other drugs.

Because bupropion is extensively metabolized, the coadministration of other drugs may affect its clinical activity. In vitro studies indicate that bupropion is primarily metabolized to hydroxybupropion by the CYP2B6 isoenzyme. Therefore, the potential exists for a drug interaction between WELLBUTRIN SR and drugs that affect the CYP2B6 isoenzyme (e.g., orphenadrine and cyclophosphamide). The threohydrobupropion metabolite of bupropion does not appear to be produced by the cytochrome P450 isoenzymes. The effects of concomitant administration of cimetidine on the pharmacokinetics of bupropion and its active metabolites were studied in 24 healthy young male volunteers. Following oral administration of two 150-mg WELLBUTRIN SR Tablets with and without 800 mg of cimetidine, the pharmacokinetics of bupropion and hydroxybupropion were unaffected. However, there were 16% and 32% increases in the AUC and C_{max}, respectively, of the combined moieties of threohydrobupropion and erythrohydrobupropion.

While not systematically studied, certain drugs may induce the metabolism of bupropion (e.g., carbamazepine, phenobarbital, phenytoin).

Animal data indicated that bupropion may be an inducer of drug-metabolizing enzymes in humans. In one study, following chronic administration of bupropion, 100 mg three times daily to eight healthy male volunteers for 14 days, there was no evidence of induction of its own metabolism. Nevertheless, there may be the potential for clinically important alterations of blood levels of coadministered drugs.

Drugs Metabolized By Cytochrome P450IID6 (CYP2D6): Many drugs, including most antidepressants (SSRIs, many tricyclics), beta-blockers, antiarrhythmics, and antipsychotics are metabolized by the CYP2D6 isoenzyme. Although bupropion is not metabolized by this isoenzyme, bupropion and hydroxybupropion are inhibitors of CYP2D6 isoenzyme in vitro. In a study of 15 male subjects (ages 19 to 35 years) who were extensive metabolizers of the CYP2D6 isoenzyme, daily doses of bupropion given as 150 mg twice daily followed by a single dose of 50 mg desipramine increased the C_{max}, AUC, and $t_{1/2}$ of desipramine by an average of approximately two-, five-, and two-fold, respectively. The effect was present for at least 7 days after the last dose of bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6 has not been formally studied.

Therefore, co-administration of bupropion with drugs that are metabolized by CYP2D6 isoenzyme including certain antidepressants (e.g., nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine), beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone, flecainide), should be approached with caution and should be initiated at the lower end of the dose range of the concomitant medication. If bupropion is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need to decrease the dose of the original medication should be considered, particularly for those concomitant medications with a narrow therapeutic index.

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

Levodopa: 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.

Drugs That Lower Seizure Threshold: 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.

Nicotine Transdermal System: (see PRECAUTIONS: Cardiovascular Effects).

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/m^2 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/m^2 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.

To monitor fetal outcomes of pregnant women exposed to WELLBUTRIN SR, GlaxoSmithKline. maintains a Bupropion Pregnancy Registry. Health care providers are encouraged to register patients by calling (800) 336-2176.

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. The immediate-release formulation of bupropion was studied in 104 pediatric patients (age range, 6 to 16) in clinical trials of the drug for other indications. Although generally well tolerated, the limited exposure is insufficient to assess the safety of bupropion in pediatric patients.

Geriatric Use: Of the approximately 6000 patients who participated in clinical trials with bupropion sustained-release tablets (depression and smoking cessation studies), 275 were 65 and over and 47 were 75 and over. In addition, several hundred patients 65 and over participated in clinical trials using the immediate-release formulation of bupropion (depression studies). No overall differences in safety 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 is extensively metabolized in the liver to active metabolites, which are further metabolized and excreted by the kidneys. 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 PRECAUTIONS: Renal Impairment and DOSAGE AND ADMINISTRATION).

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.

516 **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%
Central nervous system 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 and postmarketing experience 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 = 1013), or patients who experienced an adverse event requiring discontinuation of treatment in an open-label surveillance study with WELLBUTRIN SR Tablets (n = 3100). 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 1/1000 patients, while rare events are those occurring in less than 1/1000 patients.

Adverse events for which frequencies are not provided occurred in clinical trials or postmarketing experience with 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. Also observed were arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness (see PRECAUTIONS).

Cardiovascular: Infrequent were postural hypotension, stroke, tachycardia, and vasodilation. Rare was syncope. Also observed were complete atrioventricular block, extrasystoles, hypotension, hypertension (in some cases severe, see PRECAUTIONS), 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 were hyperglycemia, hypoglycemia, and syndrome of inappropriate antidiuretic hormone.

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

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 and muscle weakness.

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 alopecia, 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 Inventories (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 and primates have shown that bupropion exhibits some pharmacologic actions common to psychostimulants. In rodents, it has been shown to increase locomotor activity, elicit a mild stereotyped behavioral response, and increase rates of responding in several schedule-controlled behavior paradigms. In primate models to assess the positive reinforcing effects of psychoactive drugs, bupropion was self-administered intravenously. In rats, bupropion produced amphetamine-like and cocaine-like discriminative stimulus effects in drug discrimination paradigms used to characterize the subjective effects of psychoactive drugs.

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 3000 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 3600 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 4200 mg and recovered without significant sequelae. Another patient who ingested 9000 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.

Overdosage Management: Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. EEG monitoring is also recommended for the first 48 hours post-ingestion. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients.

Activated charcoal should be administered. There is no experience with the use of forced diuresis, dialysis, hemoperfusion, or exchange transfusion in the management of bupropion overdoses. No specific antidotes for bupropion are known.

Due to the dose-related risk of seizures with WELLBUTRIN SR, hospitalization following suspected overdose should be considered. Based on studies in animals, it is recommended that seizures be treated with intravenous benzodiazepine administration and other supportive measures, as appropriate.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

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. WELLBUTRIN SR should be swallowed whole and not crushed, divided, or chewed.

Initial Treatment: The usual adult target dose for WELLBUTRIN SR Tablets is 300 mg/day, given as 150 mg twice daily. 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 twice daily, 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 twice daily, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day.

Maintenance Treatment: It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacological therapy beyond response to the acute episode. In a study in which patients with major depressive disorder, recurrent type, who had responded during 8 weeks of acute treatment with WELLBUTRIN SR were assigned randomly to placebo or to the same dose of WELLBUTRIN SR (150 mg twice daily) during 44 weeks of maintenance treatment as they had received during the acute stabilization phase, longer-term efficacy was demonstrated (see CLINICAL TRIALS under CLINICAL PHARMACOLOGY). Based on these limited data, it is unknown whether or not the dose of WELLBUTRIN SR needed

for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

Dosage Adjustment for Patients with Impaired Hepatic Function: WELLBUTRIN SR should be used with extreme caution in patients with severe hepatic cirrhosis. The dose should not exceed 100 mg every day or 150 mg every other day in these patients. WELLBUTRIN SR should be used with caution in patients with hepatic impairment (including mild to moderate hepatic cirrhosis) and a reduced frequency and/or dose should be considered in patients with mild to moderate hepatic cirrhosis (see CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS).

Dosage Adjustment for Patients with Impaired Renal Function: WELLBUTRIN SR should be used with caution in patients with renal impairment and a reduced frequency and/or dose should be considered (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

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) tablets.

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) tablets.

WELLBUTRIN SR Sustained-Release Tablets, 200 mg of bupropion hydrochloride, are light pink, round, biconvex, film-coated tablets printed with "WELLBUTRIN SR 200" in bottles of 60 (NDC 0173-0722-00) tablets.

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

Distributed by:
GlaxoSmithKline, Research Triangle Park, NC 27709

Manufactured by:
GlaxoSmithKline
Research Triangle Park, NC 27709
or
Catalytica Pharmaceuticals, Inc.
Greenville, NC 27834

(Date of Issue) RL-

PHARMACIST--DETACH HERE AND GIVE LEAFLET TO PATIENT.

Information for the Patient

WELLBUTRIN SR® (bupropion hydrochloride) Sustained-Release Tablets

Please read this information before you start taking WELLBUTRIN SR. Also read this leaflet each time you renew your prescription, in case anything has changed. This information is not intended to take the place of discussions between you and your doctor. You and your doctor should discuss WELLBUTRIN SR as it relates to the treatment of your depression. Do not let anyone else use your WELLBUTRIN SR.

IMPORTANT WARNING:

At a dose of up to 300 mg each day, there is a chance that approximately 1 out of every 1000 people taking bupropion hydrochloride, the active ingredient in WELLBUTRIN SR, will have a seizure. At a dose of 400 mg each day, there is a chance that approximately 4 out of every 1000 people will have a seizure. The chance of this happening increases if you:

- have or have had a seizure disorder (for example, epilepsy);
- have or have had an eating disorder (for example, bulimia or anorexia nervosa);
- take more than the recommended amount of WELLBUTRIN SR; or
- take other medicines with the same active ingredient that is in WELLBUTRIN SR, such as ZYBAN® (bupropion hydrochloride) Sustained-Release Tablets (used to help people quit smoking).

You can reduce the chance of experiencing a seizure by following your doctor's directions on how to take WELLBUTRIN SR. If you experience a seizure while taking WELLBUTRIN SR, stop taking the tablets immediately, contact your doctor, and do not restart WELLBUTRIN SR. In addition, tell your doctor if you have or have had other medical conditions. You should also discuss with your doctor whether WELLBUTRIN SR is right for you.

1. What is WELLBUTRIN SR?

WELLBUTRIN SR is a prescription medicine used to treat depression.

2. Who should not take WELLBUTRIN SR?

You should not take WELLBUTRIN SR if you:

- have or have had a seizure disorder (for example, epilepsy);
- are already taking ZYBAN or any other medicines that contain bupropion hydrochloride;
- have or have had an eating disorder (for example, bulimia or anorexia nervosa);
- are currently taking or have recently taken a monoamine oxidase inhibitor (MAOI); or
- are allergic to bupropion.

3. Are there special concerns for women?

WELLBUTRIN SR is not recommended for women who are pregnant or breast-feeding. Women should notify their doctor if they become pregnant or intend to become pregnant while taking WELLBUTRIN SR.

4. Are there any concerns for patients with liver or kidney problems?

If you have liver or kidney problems, tell your doctor before taking WELLBUTRIN SR. Depending on the severity of your condition, your doctor may need to adjust your dosage.

5. How should I take WELLBUTRIN SR?

- You should take WELLBUTRIN SR as directed by your doctor. The usual recommended dosing is to begin treatment with WELLBUTRIN SR by taking one 150-mg tablet in the morning. As early as day 4 of treatment, your doctor may increase your dose to one 150-mg tablet in the morning and one 150-mg tablet in the early evening (for a total of 300 mg each day).

  If your depression does not improve after several weeks, your doctor may increase the dose of WELLBUTRIN SR to a total of 400 mg each day (taken as 200 mg in the morning and 200 mg in the early evening). Doses should be taken at least 8 hours apart.
- **Never take an "extra" dose of WELLBUTRIN SR Tablets for any reason, even if you miss a dose.** If you forget to take a dose, do not take an extra tablet to "catch up" for the dose you forgot. Wait and take your next tablet at the regular time. Do not take more tablets than your doctor prescribed. This is important so you do not increase your chance of having a seizure.
- It is important to swallow WELLBUTRIN SR Tablets whole. Do not chew, divide, or crush tablets.

6. How long should I take WELLBUTRIN SR?

Only you and your doctor can determine how long you should take WELLBUTRIN SR. You and your doctor should discuss your signs and symptoms of depression regularly to determine how long you should take WELLBUTRIN SR. Do not stop taking your medicine or decrease the amount of medicine you are taking without talking to your doctor first.

7. What are possible side effects of WELLBUTRIN SR?

Like all medicines, WELLBUTRIN SR may cause side effects. Do not rely on this summary alone for information about side effects. Your doctor can discuss with you a more complete list of side effects that may be relevant to you.

- Hypertension (high blood pressure), in some cases severe, has been reported in patients taking WELLBUTRIN SR alone and in combination with nicotine replacement therapy (for example, a nicotine patch) used to help patients stop smoking. Tell your doctor if you are using or plan

to use nicotine replacement therapy because your doctor will probably want to check your blood pressure regularly to make sure that it stays within acceptable levels.

- The most common side effects of WELLBUTRIN SR in clinical studies were:
  At 300 mg/day: Loss of appetite, dry mouth, skin rash, sweating, ringing in the ears, and shakiness.
  At 400 mg/day: Abdominal (stomach) pain, agitation, anxiety, dizziness, dry mouth, difficulty sleeping, muscle pain, nausea, rapid heart beat, sore throat, sweating, ringing in the ears, and urinating more often.
- The side effects of WELLBUTRIN SR are generally mild and often disappear after a few weeks. If you have nausea, you may want to take your medicine with food. If you have difficulty sleeping, avoid taking your medicine too close to bedtime.
- The most common side effects that caused people to stop taking WELLBUTRIN SR during clinical studies were skin rash, nausea, agitation, and migraine (a severe type of headache).
- Stop taking WELLBUTRIN SR and contact your doctor or health care professional if you have signs of an allergic reaction such as a skin rash, or difficulty in breathing. It is not possible to predict whether a mild rash will develop into a more serious reaction. Therefore, if you experience a skin rash, hives, fever, swollen lymph glands, painful sores in the mouth or around the eyes, or swelling of lips or tongue, tell a doctor immediately, since these symptoms may be the first signs of a serious reaction. Discuss any other troublesome side effects with your doctor.
- Use caution before driving a car or operating complex, hazardous machinery until you know if WELLBUTRIN SR affects your ability to perform these tasks.

8. Will taking WELLBUTRIN SR change my body weight?

In clinical studies with WELLBUTRIN SR, some people lost weight and other people gained weight.

For people who lost weight, 14 out of 100 people taking 300 mg/day of WELLBUTRIN SR lost more than 5 lbs, 19 out of 100 people taking 400 mg/day lost more than 5 lbs, and 6 out of 100 people taking placebo (a sugar pill) lost more than 5 lbs.

For people who gained weight, 3 out of 100 people taking 300 mg/day of WELLBUTRIN SR gained more than 5 lbs, 2 out of 100 people taking 400 mg/day gained more than 5 lbs, and 4 out of 100 people taking placebo (a sugar pill) gained more than 5 lbs.

Since weight change (loss or gain) also can be a symptom of depression, you should discuss with your doctor whether WELLBUTRIN SR is right for you.

9. Should I drink alcohol while I am taking WELLBUTRIN SR?

It is best to not drink alcohol at all or to drink very little while taking WELLBUTRIN SR. If you usually drink a lot of alcohol, or if you drink a lot of alcohol and suddenly stop, you may increase your chance of having a seizure. Therefore, it is important to discuss your use of alcohol with your doctor before you begin taking WELLBUTRIN SR.

10. Will WELLBUTRIN SR affect other medicines I am taking?

WELLBUTRIN SR may affect other medicines you're taking. It is important not to take medicines that may increase the chance for you to have a seizure. Therefore, you should make sure that your doctor knows about all medicines—prescription and over-the-counter—you are taking or plan to take.

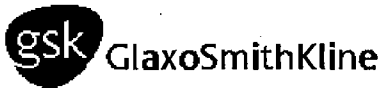
11. Do WELLBUTRIN SR Tablets have a characteristic odor?

WELLBUTRIN SR Tablets may have a characteristic odor. If present, this odor is normal.

12. How should I store WELLBUTRIN SR?

- Store WELLBUTRIN SR at room temperature, out of direct sunlight.
- Keep WELLBUTRIN SR in a tightly closed container.
- Keep WELLBUTRIN SR out of the reach of children.

This summary provides important information about WELLBUTRIN SR. This summary cannot replace the more detailed information that you need from your doctor. If you have any questions or concerns about either WELLBUTRIN SR or depression, talk to your doctor or other health care professional.



Distributed by:
GlaxoSmithKline, Research Triangle Park, NC 27709

Manufactured by:
GlaxoSmithKline
Research Triangle Park, NC 27709
or
Catalytica Pharmaceuticals, Inc.
Greenville, NC 27834

(Date of Issue) RL-

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-358/S-027

MEDICAL REVIEW(S)

REVIEW AND EVALUATION OF CLINICAL DATA

NDA:	20-358
Sponsor:	GlaxoSmithKline Inc.
Drug:	Wellbutrin SR® (bupropion sustained release)
Indication:	Treatment of Depression
Dates of Submission:	February 15, 2002
Materials Reviewed:	SNDA SCM-027

Background
Bupropion HCl sustained release (BSR) is approved for the treatment of depression and smoking cessation (marketed as Zyban®). There are two tablet strengths currently available for BSR 100-mg and 150-mg. The sponsor proposes a 200-mg tablet and provides chemistry and pharmacokinetic data in support of its approval. This review covers the clinical aspects of study AK110022. This is a PK study with no efficacy data. This brief review will focus on the clinical experience with the new tablet.

Study AK 110022
Objective
The objective of the study was to determine if BSR 200-mg tablet was bioequivalent with two 100-mg currently marketed tablets.

Subjects
36 healthy volunteer men and women aged 18-50 years were enrolled in the study. 35 subjects completed both treatment periods. One subject withdrew early and only completed one treatment period. 36 subjects were included in the safety analysis population and 35 subjects were included in the pharmacokinetic analysis population.

Design
This was a single-dose, two-way crossover study. Subjects received a single 200mg dose (two currently marketed Wellbutrin® 100mg SR tablets or a single Wellbutrin® SR 200mg tablet) of Wellbutrin® during each of the two treatment periods. Dosing during each of the treatment periods was separated by a minimum of 14 days. Study drug was administered to subjects following an overnight fast of at least 10 hours. Pharmacokinetic blood samples were collected through 168 hours (one week) post-dose during each treatment period. Follow-up evaluations were completed at the time of collection of the last blood sample during the last treatment period.

Assessments
There were no efficacy assessments performed. The primary variables of the study were PK parameters. The sponsor recorded adverse events and vital signs. Clinical laboratory values were drawn only for screening purposes but not recorded or analyzed in the study.

Results
There were no deaths, serious adverse events, or dropouts due to adverse events in the study. There were no treatment related clinically relevant changes in vital signs. The adverse events reported in the study were expected and mild to moderate in severity. No new or unexpected adverse events were identified.

Conclusions/Recommendations
There are no clinical safety concerns with the new 200-mg formulation. If the 200-mg tablet is judged to be bioequivalent to the 2 currently marketed 100-mg tablets and it meets CMC requirements then I recommend that the formulation be approved from a clinical perspective.

Paul J. Andreason, M.D.
Medical Review Officer, DNDP

cc: NDA 20-358
HFD-120
HFD-120/ P Andreason
D Bates
R Katz
T Laughren

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/s/

Paul Andreason
5/16/02 01:36:08 PM
MEDICAL OFFICER

Thomas Laughren
5/16/02 02:20:20 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-358/S-027

CHEMISTRY REVIEW(S)

CHEMIST REVIEW
OF SUPPLEMENT

1. ORGANIZATION:	HFD-120
2. NDA:	20-358
3. SUPPLEMENT NUMBERS/DATES:	SCM-027
letter date:	February 15, 2002
stamp date:	February 16, 2002
4. AMENDMENTS/REPORTS/DATES:	
5. RECEIVED BY CHEMIST:	February 20, 2002
6. APPLICANT NAME & ADDRESS	GlaxoSmithKline, PO Box 13398, Five Moore Drive, Research Triangle Park, North Carolina 27709
7. NAME OF DRUG:	Wellbutrin SR
8. NONPROPRIETARY NAME:	Bupropion Hydrochloride Sustained-Release Tablets
9. CHEMICAL NAME/STRUCTURE:	
10. DOSAGE FORM(S):	Tablets
11. POTENCY:	100 mg, 150 mg (already approved) 200 mg (subject of this supplement)
12. PHARMACOLOGICAL CATEGORY:	Antidepressant
13. HOW DISPENSED:	X (R_X) _____ (OTC)
14. RECORDS & REPORTS CURRENT:	_____ Yes _____ No
15. RELATED IND/NDA/DMF:	N/A

16. **SUPPLEMENT PROVIDES FOR**: This Prior Approval Supplement seeks approval of a 200 mg strength of WELLBUTRIN SR (bupropion hydrochloride) Sustained-Release Tablets. The 200 mg strength is intended to provide greater convenience to patients currently on a dosing regimen of 2 X 100 mg tablets twice a day.

17. COMMENTS: Wellbutrin SR Tablets are currently marketed in 100 mg and 150 mg strengths. Both of the currently approved drug product strengths have the same qualitative composition with a tablet matrix containing [ ] [ ] that controls the release of bupropion hydrochloride drug substance. The 200 mg strength tablet consists of [ ] [ ] and film coated with a light pink colorant [ ] [ ]

18. **CONCLUSIONS AND RECOMMENDATIONS**: This supplement may be approved.

19. REVIEWER NAME	SIGNATURE	DATE COMPLETED
Christy S. John, Ph.D.		
Acting Team Leader: Hasmukh Patel, Ph.D.		

CC:

NDA 20-358Division Files
HFD-120/CJohn
HFD-120/HPatel
HFD-120/DBates

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confidential commercial

information from

Chemistry Review

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/s/

Christy John
6/6/02 04:29:17 PM
CHEMIST

Hasmukh Patel
6/6/02 04:49:06 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-358/S-027

CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Submission Dates: 2/15/02

sNDA:	20-358
Name of Drug:	Wellbutrin (Bupropion Hydrochloride) SR Tablets, 200 mg
Indication of Drug:	Antidepressant
Sponsor:	Glaxo Wellcome
Type of Submission:	Prior Approval CMC, Labeling, BE Supplement
Reviewer:	Hong Zhao, Ph.D.

Introduction

Wellbutrin (Bupropion Hydrochloride) is an aminoketone antidepressant, chemically unrelated to serotonin reuptake inhibitors, tricyclic, tetracyclic or other known antidepressants. Wellbutrin is currently available in 75 mg and 100 mg immediate release tablets, requiring dosing three times daily, as well as 100 mg and 150 mg sustained release tablets, requiring twice daily dosing. Initiation of Wellbutrin SR treatment frequently begins at 150 mg/day with increases, as tolerated, to the 300 mg/day target dose. For some patients, it may be necessary to increase the dose to 200 mg twice daily to achieve clinical improvement.

This is a supplemental NDA for a new strength, 200 mg Wellbutrin SR (bupropion hydrochloride) Sustained-Release Tablet. The 200 mg strength tablet will provide greater convenience to patients currently on a dosing of 2x100 mg tablets twice a day, a dose which is within the currently approved dose range for Wellbutrin SR. Both of the currently approved Wellbutrin SR 100 mg and 150 mg tablets have the same qualitative composition with a tablet matrix containing [ ] that controls release of the bupropion hydrochloride drug substance. The new 200 mg strength tablet consists of the [ ] and film coated with a light pink colorant [ ] [ ] A bioequivalence study was conducted along with the in vitro dissolution testing to support the approval of the 200 mg new strength.

Bioequivalence Study Review

Study Design

This was a randomized, single-dose, two-way crossover study to evaluate the single dose bioequivalence of a new Wellbutrin SR 200 mg Tablet formulation versus the currently marketed Wellbutrin SR 2x100 mg Tablet formulation in thirty-six male and female healthy volunteers under fasted conditions. There were 14 days between two treatments. Study design is described in Table 1:

Table 1. Bioequivalence Study Design

Formulation	Batch No.	Dose	N (M/F)
200 mg New Strength	1ZM1622	1x200mg	36 (24/12)
Currently-marketed, 100 mg	1ZP0892	2x100 mg	36 (24/12)

Blood samples were collected up to 168 hours (predose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 32, 48, 72, 96, 120, and 168 hours post each dose) for concentration determination of bupropion and its active metabolites - hydroxybupropion, and the composite total of threohydrobupropion and erythrohydrobupropion (threo/ erythrohydrobupropion). The following pharmacokinetic parameters were obtained for bupropion: C_{max} and $AUC_{0-\infty}$, AUC_{0-t} and partial AUC (the AUC from time zero to the median t_{max} value for the reference formulation), and C_{max}, $AUC_{0-\infty}$, AUC_{0-t} and partial AUC for hydroxybupropion and the composite of threo/erythrohydrobupropion. Other PK parameters include t_{lag}, t_{max}, λ (elimination rate constant of the terminal phase) and AUC_{0-12h} and the ratios of $AUC_{0-12h}/AUC_{0-\infty}$ and $AUC_{0-t}/AUC_{0-\infty}$ were also estimated. Bioequivalence criterion (90% CI) were used to evaluate the data.

The race distribution among 36 subjects enrolled in this study is as follows: 19 Caucasians, 13 Blacks, 1 Asian, and 3 others. Mean age was 31.1 (19-48) years. One subject finished only 2x100 mg treatment and withdrew from the study due to treatment unrelated reasons.

Analytical Method

The analytical method used was an HPLC/MS/MS method which measured the concentrations of bupropion, hydroxybupropion, and threo/erythrohydrobupropion. In this assay, the isomeric aminoalcohol metabolites, threohydroxybupropion and erythrohydrobupropion are quantitated as the total of two compounds since this assay cannot differentiate between them because they have the same molecular weight. Measuring the combination of these two analytes instead of the individual components is considered reasonable because the pharmacologic activity of threohydroxybupropion and erythrohydrobupropion are similar in animals and the ratio of plasma concentrations of these metabolites appears to be similar at steady-state in humans. Results from quality control standards during the analyses of samples from Study AK110022 are presented in Table 2:

Table 2. Assay Performance

	Bupropion	Hydroxybupropion	Threo/Erythrohydrobupropion
Accuracy %Bias	≤±5.24	≤±2.42	≤±5.73
Precision %CV	≤11.6	≤6.69	≤10.2
Calibration Range	0.25-200 ng/ml	1.0-1000 ng/ml	0.25-200 ng/ml

Pharmacokinetic Results

Pharmacokinetic comparison of the 200 mg new strength Wellbutrin SR Tablets (Test) to the currently-marketed Wellbutrin SR 100 mg Tablets (Reference) under fasting conditions is shown below:

Table 3. Values of Pharmacokinetic Parameters (Arithmetic Means with %CV))

	Bupropion	Hydroxybupropion	Threo/erythrohydroxybupropion
C_{max} (ng/ml)			
Test (%CV)	158.1 (26%)	218.5 (56%)	132.2 (32%)
Reference (%CV)	144.9 (32%)	185.0 (53%)	126.2 (31%)
Ratio (90% CI)	**1.11 (1.04, 1.18)**	**1.19 (1.07, 1.32)**	**1.05 (1.00, 1.10)**

	Bupropion	Hydroxybupropion	Threo/erythrohydroxybupropion
AUC_∞ (ng.hr/ml)			
Test (%CV)	1645 (28%)	8521 (65%)	6398 (32%)
Reference (%CV)	1587 (33%)	7765 (69)	6401 (31%)
Ratio (90% CI)	**1.05 (1.00, 1.11)**	**1.12 (1.03, 1.22)**	**1.00 (0.96, 1.05)**
AUC_{last} (ng.hr/ml)			
Test (%CV)	1624 (28%)	8388 (65%)	5837 (31%)
Reference (%CV)	1566 (33%)	7640 (70%)	5710 (29)
Ratio (90% CI)	**1.05 (1.00, 1.11)**	**1.12 (1.03, 1.23)**	**1.02 (0.98, 1.06)**

Table 4. Values of Other Pharmacokinetic Parameters

	Bupropion	Hydroxybupropion	Threo/erythr hydroxybupropion
T_{max} (hr)			
Test	3.0 (1.0-5.0)	6.0 (3.0-32.0)	6.0 (3.0-8.0)
Reference	3.0 (1.0-5.0)	6.0 (3.0-16.0)	6.0 (3.0-12.0)
$t_{1/2}$ (hr)			
Test	25.2±6.9	24.8±5.9	48.1±14.5
Reference	24.7±6.2	24.5±6.5	53.0±19.0

Values reported for T_{max} are the median and range; for $t_{1/2}$ are mean±SD.

Conclusion

- Based on the results of the parent compound, it can be concluded that the new strength (200 mg) Wellbutrin SR Tablet is bioequivalent to currently marketed Wellbutrin 2x100 mg Tablets following single dose administration under fasted conditions.

- The newly formulated Wellbutrin SR 200 mg Tablets are well tolerated following a single dose administration.

Review of Dissolution Data

Dissolution Method and Specifications

Method used for dissolution tests is the NDA approved method as described below:

Apparatus:	USP Apparatus II (paddle) at 50 rpm
Medium:	900 mL of water at 37±0.5°C
Specifications:	in 1 hour, 25%-45% labeled strength released
	in 4 hours, 60%-85% labeled strength released
	in 8 hours, NLT 80% labeled strength released

Dissolution Results

Table 4. Mean Dissolution Data and Ranges for Biobatches

Time	1 hr	2 hrs	4 hrs	6 hrs	8 hrs
			(%) released		
T (1ZM1622)	30 (28-32)	44 (41-47)	64 (59-68)	78 (73-83)	89 (83-94)
R (1ZP0892)	31 (30-32)	45 (45-47)	67 (66-70)	82 (81-84)	91 (89-93)

T=New strength Wellbutrin SR 200mg Tablets, R=Currently marketed Wellbutrin SR 100mg Tablets.

Conclusion

- Dissolution data from all batches tested meet the approved specifications for Wellbutrin SR Tablets.

Recommendation

The results of bioequivalence study and dissolution tests support the approval of the proposed new strength Wellbutrin SR 200 mg Tablets.

Please convey this Recommendation to Clinical Review Team and Chemistry Review Team.

Hong Zhao, Ph.D._____

RD/FT Initialed by Raman Baweja, Ph.D._____

cc: sNDA: 20-358 (Wellbutrin SR Tablets), HFD-120, HFD-860 (Zhao, Baweja, Mehta), Central Documents Room (CDR-Biopharm)

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/s/

Hong Zhao
5/20/02 02:53:24 PM
BIOPHARMACEUTICS

Raman Baweja
5/20/02 03:55:36 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-358/S-027

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-358/S-027

Glaxo Wellcome Inc.
Attention: Leo Lucisano, R.Ph.
Five Moore Drive
Research Triangle Park, NC 27709

Dear Mr. Lucisano:

We acknowledge receipt of your July 15, 2002 submission containing final printed labeling in response to our June 14, 2002 letter approving your supplemental new drug application for Wellbutrin SR (bupropion hydrochloride) Tablets.

We have reviewed the labeling that you submitted in accordance with our June 14, 2002 letter and we find it acceptable.

If you have any questions, call Ms. Melaine Shin R.Ph., Regulatory Management Officer, at 301-594-5793.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation ODE I
Center for Drug Evaluation and Research

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/s/

Russell Katz
6/23/03 08:08:49 AM

Division of Neuropharmacological Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: **NDA 20-358/S-027**

Name of Drug: Wellbutrin SR® (bupropion hydrochloride) Sustained-Release Tablets

Applicant: GlaxoSmithKline

Material Reviewed:

- **NDA 20-358/S-027 (FA) : July 15, 2002**
- **NDA 20-358/S-027 AP letter based on submitted labeling text: June 14, 2002**

Background and Summary:

NDA 20-358/S-027 was approved on June 14, 2002 and the sponsor submitted the FPL on July 15, 2002.

Review and Conclusion:

I compared the submitted FPL to the labeling attached to the approval letter of June 14, 2002 and found them to be identical. Therefore, I recommend that we issue an acknowledge and retain letter.

Melaine Shin, R.Ph.
Regulatory Management Officer

Robbin Nighswander, R.Ph.
Supervisory Regulatory Health Project Manager

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/s/

Melaine Shin
1/3/03 02:05:51 PM
CSO

Robbin Nighswander
1/24/03 05:39:20 PM
CSO

Memo to the File
NDA 20-358 / SCM-027: Container and Carton Labeling Information
Wellbutrin SR (bupropion hydrochloride) 200 mg Tablets
June 10, 2002

This memorandum documents the following points:

- The initial submission of this supplement included mockups for bottle and blister labeling as well as the sample carton and sample display holder

- The Review Chemist has assessed the bottle and blister labels and found them acceptable for approval.

- The sample carton and display holder have been reviewed against the proposed package insert by the RPM. Neither piece includes any language of a promotional nature. Both pieces include appropriate reference to the sample status (non-retail distribution), trademark, nonproprietary name, Rx-only status, Zyban contraindication, storage conditions, and NDC number for the product. The storage conditions and NDC number for the sample cartonscorrespond to the storage conditions and NDC number listed in the package insert.

- The sample carton and display package are therefore acceptable for approval from a regulatory standpoint.

- The presence of this memo in the file indicates that these conclusions have been reviewed and agreed to by the CMC review team.

Doris J. Bates, Ph.D., Regulatory Project Manager
For P. Andreason, M.D., and T. Laughren, M.D.

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/s/

Doris Bates
6/12/02 03:46:20 PM
CSO

This memo has been reviewed and accepted by the CMC Team Leader, Dr. Thomas Oliver, and the Deputy Director of DNDC-1, Dr. Hasmukh Patel. Dr. Bates, the author, is a Ph.D. Chemist and former Review Chemist for FDA.

Memo to the File
NDA 20-358 / SCM-027: Financial Disclosure Information
Wellbutrin SR (bupropion hydrochloride) 200 mg Tablets
June 10, 2002

This memorandum documents the assessment of financial disclosure information for this supplement by the clinical reviewer and regulatory project manager.

This supplement included financial disclosure information germane to a single clinical study, Study AK 110022. The study was an open-label, randomized, single-dose, two-way crossover study comparing one x 200 mg to 2 x 100 mg Wellbutrin SR tablets.

There was one primary investigator for this biostudy, Thomas DeBerardinis, M.D. This investigator is not a GSK employee. Ten sub-investigators who are all employed by GSK also worked on the study in question. Financial disclosure information was provided and evaluated for Dr. DeBerardinis only.

Under the terms of the Rule, information provided to GSK and thence to FDA indicates that this individual was not directly compensated by the firm for the study in such a way that the compensation was affected by study results.

Further, it is stated that this investigator had no proprietary interest in the study drug, nor was any other compensation provided by the firm which would exceed the $25,000.00 threshold for 'significant payments of other sorts' per the Rule. This investigator also had no significant equity interest ($50,000 or more) in GSK.

Form FDA 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) was provided by the applicant.

This information, as provided, satisfies the requirements of the Financial Disclosure Rule, and there is no apparent financial conflict of interest that could have biased the covered study. The Clinical Team Leader has been informed of these facts.

Doris J. Bates, Ph.D., Regulatory Project Manager
For P. Andreason, M.D., and T. Laughren, M.D.

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/s/

Doris Bates
6/10/02 03:19:51 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-358/S-027

PRIOR APPROVAL SUPPLEMENT

GlaxoSmith Kline
Attention: James E. Murray
PO Box 13398
5 Moore Drive
Research Triangle Park, NC 27709

Dear Dr. Murray:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Wellbutrin SR
NDA Number: 20-358
Supplement number: SCM-027
Date of supplement: February 15, 2002
Date of receipt: February 19, 2002 (hard copy submission)

This supplement provides for a new 200 mg dosage strength of Wellbutrin SR tablets, intended for use by patients who are currently taking two 100 mg tablets BID under an approved dosing regimen.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 20, 2002,in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:
U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room, Room 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room, Room 4008
1451 Rockville Pike
Rockville, Maryland 20857

If you have any question, please call Doris J. Bates, Ph.D., Regulatory Project Manager, at (301)-594-5536.

Sincerely yours,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Doris Bates
2/21/02 05:18:59 PM

February 15, 2002

GlaxoSmithKline

GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709
Tel. 919 483 2100
www.gsk.com

Leah Andrews, Consumer Safety Officer
Office of Regulatory Affairs
Food and Drug Administration
Atlanta District Office
60 8th Street, NE
Atlanta, GA 30309

Re: NDA 20-358; WELLBUTRIN SR® (bupropion hydrochloride) Sustained-Release Tablets
Prior Approval Supplement: Qualification of 200 mg Strength

Dear Ms. Andrews:

In accordance with 21 CFR 314.50(l)(3), I am providing a Field Copy of the Chemistry, Manufacturing and Controls section of a Prior Approval Supplement that provides for qualification of a 200 mg strength of WELLBUTRIN SR® (bupropion hydrochloride) Sustained-Release Tablets.

I certify that the Field Copy is a true copy of the supplemental application submitted to the Division of Neuropharmacological Drug Products.

If you have any questions about this supplement, please contact Leo Lucisano at (919) 483-5848.

Sincerely,

Leo J Lucisano

Leo J. Lucisano, R.Ph.
Regional Director
CMC Regulatory Affairs