APR 10 2000

Glaxo Wellcome
Attention: James Murray
Director Regulatory Affairs
Five Moore Drive
Research Triangle Park, NC 27709

Dear Mr. Murray:

Please refer to your supplemental new drug applications dated January 28, 1993 (S-009), June 19, 1997 (S-014), September 30, 1997 (S-015), August 27, 1998 (S-016), November 2, 1998 (S-017), March 10, 1999 (S-018), April 12, 1999 (S-019), July 7, 1999 (S-020), and September 30, 1999 (S-021), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Wellbutrin (bupropion hydrochloride) 75 mg and 100 mg Tablets.

We acknowledge receipt of your correspondence dated January 24, and received January 28, 2000, requesting that S-009 be withdrawn.

These supplemental new drug applications provide for the following revisions to product labeling:

18-644/S-009
The supplement provides for the results of a Phase 4 commitment regarding the steady state pharmacokinetics and disposition of bupropion and its metabolites. We note that the results of this study have already been incorporated into labeling under supplements SLR-016/018/020, and therefore, you have requested that this supplement be withdrawn.

Therefore, in accordance with 21 CFR 314.65, this supplemental application is withdrawn as of the date of our receipt of your notification, January 28, 2000.

18-644/S-014
This supplement provides for revisions to the **CONTRAINDICATIONS, WARNINGS**, and **PRECAUTIONS** sections to make the labeling more consistent with the Zyban labeling.

18-644/S-015
The supplement provides for the addition of a pregnancy registry paragraph in the **PRECAUTIONS-Pregnancy** section of labeling.

18-644/S-016
This supplement provides for the addition of geriatric data under the **CLINICAL PHARMACOLOGY** and **PRECAUTIONS** sections of labeling to comply with a Federal Register notice dated August 27, 1997, requiring that sponsors of psychotropic drugs add geriatric data to product labeling

18-644/S-017
The supplement provides for the following labeling revisions:

1. An addition to the **CONTRAINDICATIONS** section to state that Wellbutrin is contraindicated in patients who are allergic to bupropion or any of the other ingredients that make up the final dosage form.

2. A statement in the **PRECAUTIONS-Laboratory Tests** section to state that there are no specific laboratory tests recommended..

3. A revision in the **PRECAUTIONS-Pregnancy** section to update the pregnancy registry telephone number.

4. An addition to the **PRECAUTIONS-Pediatric Use** section to reflect that bupropion has been used in clinical trials in the pediatric population however there is insufficient data to assess the safety in pediatrics.

18-644/S-018
The supplement provides for the following labeling revisions:

1. An addition to the **PRECAUTIONS-Allergic Reactions** section to state allergic reactions experienced with bupropion use.

2. The addition of a new subsection under the **PRECAUTIONS** section entitled **Drugs Metabolized by Cytochrome P450IID6 (CYP2D6)** as well as an update to the **Clinical Pharmacology-Metabolism** and **PREAUTIONS-Drug Interactions** sections to update labeling regarding this metabolic pathway.

18-644/S-019
The supplement provides for the complete revision of the **OVERDOSAGE** section to comply with an Agency letter dated December 1, 1998.

18-644/S-020
This supplement provides for a revision to the **CLINICAL PHARMACOLOGY-Metabolism** and the **PRECAUTIONS-Geriatric Use** sections of labeling to add the results of a phannacokinetic study in the geriatric population.

18-644/S-021
This supplemental application provides for the following revisions:

1. The addition in the **PRECAUTIONS-Allergic Reactions** section to include the terms “serum sickness”.

2. The addition of a section under the **PRECAUTIONS** section entitled **Cardiovascular Effects** to note that hypertension has been associated with bupropion treatment.

3. The addition of a new subsection entitled **Body(General)** under the **ADVERSE REACTIONS-Other Events** section.

4. The addition of the term "hypertension" under the **ADVERSE REACTIONS-Other Events-Cardiovascular** section.

We have completed the review of these supplemental applications (NDA 18-644/S-014/S-015/S016/S-017/S-018/S-019/S-020/S-021)and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted September 20, 1999 (Label Code RL-749), which incorporates all of the revisions listed above. Accordingly, these supplemental applications are approved effective on the date of this letter.

Labeling changes of the kind which you have proposed are permitted by section 314.70(c) of the regulations to be instituted prior to approval of the supplement. It is understood that the changes, described in the above NDA supplements, have been made.

We additionally note that your Phase 4 commitment, enumerated in Agency letters dated December 31, 1984 and December 30, 1985, to explore the steady state pharinacokinetics and disposition of bupropion and its metabolites has been fulfilled.

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

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

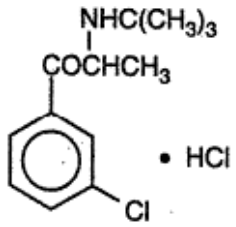
If you have any questions, call Paul David, R.Ph, Regulatory Management Officer, at (301) 594-5530.

Sincerely,

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

WELLBUTRIN® **PRODUCT INFORMATION**
(bupropion hydrochloride)
Tablets

DESCRIPTION: WELLBUTRIN (bupropion hydrochloride), an antidepressant of the aminoketone class, is chemically unrelated to tricyclic, tetracyclic, 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 empirical formula is $C_{13}H_{18}ClNO \bullet HCl$. 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 is supplied for oral administration as 75-mg (yellow-gold) and 100-mg (red) film-coated tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients: 75-mg tablet — D&C Yellow No. 10 Lake, FD&C Yellow No. 6 Lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, polyethylene glycol, talc, and titanium dioxide; .100-mg tablet — FD&C Red No. 40 Lake, FD&C Yellow No. 6 Lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, polyethylene glycol, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY:
Pharmacodynamics and Pharmacological Actions: The neurochemical mechanism of the antidepressant effect of bupropion is not known. Bupropion does not inhibit monoamine oxidase. Compared to classical tricyclic antidepressants, it is a weak blocker of the neuronal uptake of serotonin and norepinephrine; it also inhibits the neuronal re-uptake of dopamine to some extent.

Bupropion produces dose-related central nervous system (CNS) stimulant effects in animals, as evidenced by increased locomotor activity, increased rates of responding in various schedule-controlled operant behavior tasks, and, at high doses, induction of mild stereotyped behavior.

Bupropion causes convulsions in rodents and dogs at doses approximately tenfold the dose recommended as the human antidepressant dose.

Absorption, Distribution, Pharmacokinetics, Metabolism, and Elimination: ***Oral Bioavailability and Single-Dose Pharmacokinetics:*** In humans, following oral administration of WELLBUTRIN, peak plasma bupropion concentrations are usually achieved within 2 hours, followed by a biphasic decline. The average half-life of the second (postdistributional) phase is approximately 14 hours, with a range of 8 to 24 hours. Six hours after a single dose, plasma bupropion concentrations are approximately 30% of peak concentrations. Plasma bupropion concentrations are dose-proportional following single doses of 100 to 250 mg; however, it is not known if the proportionality between dose and plasma level is maintained in chronic use.

The absolute bioavailability of WELLBUTRIN Tablets in humans has not been determined because an intravenous formulation for human use is not available.

However, it appears likely that only a small proportion of any orally administered dose reaches the systemic circulation intact. For example, the absolute bioavailability of bupropion in animals (rats and dogs) ranges from 5% to 20%.

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

Several of the known metabolites of bupropion are pharmacologically active, but their potency and toxicity relative to bupropion have not been fully characterized. However, because of their longer elimination half-lives, the plasma concentrations of at least two of the known metabolites can be expected, especially in chronic use, to be very much higher than the plasma concentration of bupropion. This is of potential clinical importance because factors or conditions altering metabolic capacity (e.g., liver disease, congestive heart failure, age, concomitant medications, etc.) or elimination may be expected to influence the degree and extent of accumulation of these active metabolites.

Furthermore, bupropion has been shown to induce its own metabolism in three animal species (mice, rats, and dogs) following subchronic administration. If induction also occurs in humans, the relative contribution of bupropion and its metabolites to the clinical effects of WELLBUTRIN may be changed in chronic use. Plasma and urinary metabolites so far identified include biotransformation products formed via reduction of the carbonyl group and/or hydroxylation of the *tert*-butyl group of bupropion. Four basic metabolites have been identified.

They are the *erythro*- and *threo*-amino alcohols of bupropion, the *erythro*-amino diol of bupropion, and a morpholinol metabolite (formed from hydroxylation of the tert-butyl group of bupropion).

The morpholinol metabolite appears in the systemic circulation almost as rapidly as the parent drug following a single oral dose. Its peak level is three times the peak level of the parent drug; it has a half-life on the order of 24 hours; and its AUC 0 to 60 hours is about 15 times that of bupropion.

The *threo*-amino alcohol metabolite has a plasma concentration-time profile similar to that of the morpholinol metabolite. The *erythro*-amino alcohol and the *erythro*-amino diol metabolites generally cannot be detected in the systemic. circulation following a single oral dose of the parent drug. The morpholinol and the threo-amino alcohol metabolites have been found to be half as potent as bupropion in animal screening tests for antidepressant drugs.

In vitro findings suggest that cytochrome P450IIB6 (CYP2B6) is the principal isoenzyme involved in the formation of the morpholinol metabolite, while cytochrome P450 isoenzyrnes are not involved in the formation of the *threo*-amino alcohol metabolite.

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 P450IIB6 (CYP2D6), there is the potential for drug-drug interactions when bupropion is co-administered with drugs metabolized by this isoenzyme (see PRECAUTIONS: Drug Interactions).

During a chronic dosing study in 14 depressed patients with left ventricular dysfunction, it was found that there was substantial interpatient variability (twofold to fivefold) in the trough steady-state concentrations of bupropion and the morpholinol and *threo*-amino alcohol metabolites. In addition, the steady-state plasma concentrations of these metabolites were 10 to 100 times the steady-state concentrations of the parent drug.

The effect of other disease. states and altered organ function on the metabolism and/or elimination of bupropion has not been studied in detail. However, 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 conjugation in the liver prior to urinary excretion. The preliminary results of a comparative single-dose pharmacokinetic study in normal versus cirrhotic patients indicated that half-lives of the metabolites were prolonged by cirrhosis and that the metabolites accumulated to levels two to three times those in normals.

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).

In vitro tests show that bupropion is 80% or more bound to human albumin at plasma concentrations up to 800 umol/L (200 mcg/mL).

INDICATIONS AND USAGE: WELLBUTRIN is indicated for the treatment of depression. A physician considering WELLBUTRIN for the management of a patient's first episode of' depression should be aware that the drug may cause generalized seizures in a dose-dependent manner with an approximate incidence of 0.4% (4/1000). This incidence of seizures may exceed that of other marketed antidepressants by as much as fourfold. This relative risk is only an approximate estimate because no direct comparative studies have been conducted (see WARNINGS).

The efficacy of WELLBUTRIN has been established in three placebo-controlled trials, including two of approximately 3 weeks duration in depressed inpatients and one of approximately 6 weeks duration in depressed outpatients. The depressive disorder of the patients studied corresponds most closely to the Major Depression category of the APA Diagnostic and Statistical Manual Ill.

Major Depression implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least four of the following eight symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigability, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and suicidal ideation or attempts.

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

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

WELLBUTRIN 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 is also contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa because of a higher incidence of seizures noted in such patients treated with WELLBUTRIN.

The concurrent administration of WELLBUTRIN 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.

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

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

Seizures: Bupropion is associated with seizures in approximately 0.4% (4/1000) of patients treated at doses up to 450 mg/day. This incidence of seizures may exceed that of other marketed antidepressants by as much as fourfold. This relative risk is only an approximate estimate because no direct comparative studies have been conducted. The estimated seizure incidence for WELLBUTRIN increases almost tenfold between 450 and 600 mg/day, which is twice the usually required daily dose (300 mg) and one and one-third the maximum recommended daily dose (450 mg). Given the wide variability among individuals and their capacity to metabolize and eliminate drugs this disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing.

During the initial development, 25 among approximately 2400 patients treated with WELLBUTRIN experienced seizures. At the time of seizure, seven patients were receiving daily doses of 450 mg or below for an incidence of 0.33% (3/1000) within the recommended dose range. Twelve patients experienced seizures at 600 mg/day (2.3% incidence); six additional patients had seizures at daily doses between 600 and 900 mg (2.8% incidence).

A separate, prospective study was con ducted to determine the incidence of seizure during an 8-week treatment exposure in approximately 3200 additional patients who received daily doses of up to 450 mg. Patients were permitted to continue treatment beyond 8 weeks if clinically indicated. Eight seizures occurred during the initial 8-week treatment period and five seizures were reported in patients continuing treatment beyond 8 weeks, resulting in a total seizure incidence of 0.4%.

The risk of seizure appears to be strongly associated with dose. Sudden and large increments in dose may contribute to increased risk. While many seizures occurred early in the course of treatment, some seizures did occur after several weeks at fixed dose.

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

- **Patient factors: Predisposing factors that may increase the risk of seizure with bupropion use include history of head trauma or prior seizure, CNS tumor, and concomitant medications that lower**

seizure threshold.

- **Clinical situations: Circumstances associated with an increased seizure risk include, among others, excessive use of alcohol; abrupt withdrawal from alcohol or other sedatives; addiction to opiates, cocaine, or stimulants; use of over-the-counter stimulants and anorectics; and diabetes treated with oral hypoglycemics or insulin.**
- **Concomitant medications: Many medications (e.g., antipsychotics, antidepressants, theophylline, systemic steroids) and treatment regimens (e.g., abrupt discontinuation of benzodiazepines) are known to lower seizure threshold.**

Recommendations for Reducing the Risk of Seizure: **Retrospective analysis of clinical experience gained during the development of WELLBUTRIN suggests that the risk of seizure may be minimized if (1) the total daily dose of WELLBUTRIN does not exceed 450 mg, (2) the daily dose is administered three times daily, with each single dose *not to* exceed 150 mg to avoid high peak concentrations of bupropion and/or its metabolites, and (3) the rate of incrementation of dose is very gradual. Extreme caution should be used when WELLBUTRIN is (1) administered to patients with a history of seizure, cranial trauma, or other predisposition(s) toward seizure or (2) prescribed with other agents (e.g., antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) or treatment regimens (e.g., abrupt discontinuation of a benzodiazepine) that lower seizure threshold.**

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

PRECAUTIONS:

General: ***Agitation and Insomnia:*** A substantial proportion of patients treated with WELLBUTRIN experience some degree of increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment. In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs. In approximately 2% of patients, symptoms were sufficiently severe to require discontinuation of treatment with WELLBUTRIN.

Psychosis, Confusion, and Other Neuropsychiatric Phenomena: Patients treated with WELLBUTRIN have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many studies, it is impossible to provide

a precise estimate of the extent of risk imposed by treatment with WELLBUTRIN. In several cases, neuropsychiatric phenomena abated upon dose reduction and/or withdrawal of treatment.

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

Altered Appetite and Weight: A weight loss of greater than 5 lbs occurred in 28% of patients receiving WELLBUTRIN. This incidence is approximately double that seen in comparable patients treated with tricyclics or placebo. Furthermore, while 34.5% of patients receiving tricyclic antidepressants gained weight, only 9.4% of patients treated with WELLBUTRIN did. Consequently, if weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight reducing potential of WELLBUTRIN should be considered.

Suicide: The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Accordingly, prescriptions for WELLBIJTRIN 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 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 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 UHF, resulting in discontinuation of treatment in two patients for exacerbation of baseline hypertension.

Renal or Hepatic Impairment Because bupropion hydrochloride and its metabolites are almost completely excreted through the kidney and metabolites are likely to undergo conjugation in the liver prior to urinary excretion, treatment of patients with renal or hepatic impairment should be initiated at reduced dosage as bupropion and its metabolites may accumulate in such patients beyond concentrations expected in patients without renal or hepatic impairment. The patient should be closely monitored for possible toxic effects of elevated blood and tissue levels of drug and metabolites.

Information for Patients: Patients should be made aware that WFLLBUTRIN contains the same active ingredient found in ZYBAN, used as an aid to smoking cessation, and that WELLBUTRIN 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:

Patients should be instructed to take WELLBUTRIN in equally divided doses three or four times a day to minimize the risk of seizure

Patients should be told that any CNS-active drug like WELLBUTRIN may impair their ability to perform tasks requiring judgment or motor and cognitive skills. Consequently, until they are reasonably certain that WELLBUTRIN does 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 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.

Laboratory Tests: There are no specific laboratory tests recommended.

Drug Interactions: In vitro studies indicate that bupropion is primarily metabolized to the morpholinol metabolite by the cytochrome P450IIB6 (CYP2B6) isoenzyme. Therefore, the potential exists for a drug interaction between WELLBUTRIN and drugs that affect the CYP2B6 isoenzyme (e.g., orphenadrine and cyclophosphamide). The *threo*-amino alcohol metabolite of bupropion does not appear to be produced by the cytochrome P450IID6 (CYP2D6) isoenzymes. Few systematic data have been collected on the metabolism of WELLBUTRIN following concomitant administration with other drugs or, alternatively, the effect of concomitant administration of WELLBUTRIN on the metabolism of other drugs.

However, animal data suggest that WELLBUTRIN may be an inducer of drug metabolizing enzymes. This may be of potential clinical importance because the blood levels of coadministered drugs may be altered.

Alternatively, because bupropion is extensively metabolized, the coadministration of other drugs may affect its clinical activity. In particular, care should be exercised when administering drugs known to affect hepatic drug-metabolizing enzyme systems (e.g., carbamazepine, cimetidine, phenobarbital, phenytoin).

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 its morpholinol metabolite are inhibitors of the 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 CYP2O6, 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 WELLBUTRIN and L-dopa. Administration of WELLBUTRIN to patients receiving L-dopa concurrently should be undertaken with caution, using small initial doses and small gradual dose increases.

Drugs that Lower Seizure Threshold: Concurrent administration of WELLBUTRIN 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 small 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. 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; 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 borderline positive response (two to three times control mutation rate) in some strains in the Ames bacterial mutagenicity test, and a high oral dose (300 mg/kg, but not 100 or 200 mg/kg) produced a low incidence of chromosomal aberrations in rats. The relevance of these results in estimating the risk of human exposure to therapeutic doses is unknown.

A fertility study was performed in rats; no evidence of impairment of fertility was encountered at oral doses up to 300 mg/kg per day.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category B. Reproduction studies have been performed in rabbits and rats at doses up to 15 to 45 times the human daily dose and have revealed no definitive evidence of impaired fertility or harm to the fetus due to bupropion. (In rabbits, a slightly increased incidence of fetal abnormalities was seen in two studies, but there was no increase in any specific abnormality.) 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, Glaxo Wellcome Inc. 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 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, 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 in pediatric patients under 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 hydrochloride and its metabolites are almost completely excreted through the kidney and metabolites are likely to undergo conjugation in the liver prior to urinary excretion. The risk of toxic reaction to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see Use in Patients with Systemic Illness).

ADVERSE REACTIONS: (see also WARNINGS and PRECAUTIONS) Adverse events commonly encountered in patients treated with WELLBUTRIN are agitation, dry mouth, insomnia, headache/migraine, nausea/vomiting, constipation, and tremor.

Adverse events were sufficiently troublesome to cause discontinuation of treatment with WELLBUTRIN in approximately 10% of the

2400 patients and volunteers who participated in clinical trials during the product's initial development. The more common events causing discontinuation include neuropsychiatric disturbances (3.0%), primarily agitation and abnormalities in mental status; gastrointestinal disturbances (2.1%), primarily nausea and vomiting; neurological disturbances (1.7%), primarily seizures, headaches, and sleep disturbances; and dermatologic problems (1.4%), primarily rashes. It is important to note, however, that many of these events occurred at doses that exceed the recommended daily dose.

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. Consequently, the table below is presented solely to indicate the relative frequency of adverse events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of WELLBUTRIN under relatively similar of daily dosage (300 to 600 mg), setting, and duration (3 to 4 weeks). 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 must differ from those which 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 ref lect the relative severity and/or clinical importance of the events. A better perspective on the serious adverse events associated with the use of WELLBUTRIN is provided in WARNINGS and PRECAUTIONS.

Treatment Emergent Adverse Experience Incidence
in Placebo-Controlled Clinical Trials*
(Percent of Patients Reporting)

Adverse Experience	WELLBUTRIN Patients (n = 323)	Placebo Patients (n = 185)
Cardiovascular	5.3	4.3
Cardiac arrhythmias	22.3	16.2
Dizziness	4.3	1.6
Hypertension	2.5	2.2
Hypotension	3.7	2.2
Palpitations	1.2	0.5
Syncope	10.8	8.6
Tachycardia		
Dermatologic	2.2	0.0
Pruritus	8.0	6.5
Rash		

Treatment Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials* (Percent of Patients Reporting) *(cont'd)*

Adverse Experience	WELLBUTRIN Patients (n=323)	Placebo Patients (n=185)
Gastrointestinal		
Anorexia	18.3	18.4
Appetite increase	3.7	2.2
Constipation	26.0	17.3
Diarrhea	6.8	8.6
Dyspepsia	3.1	2.2
Nausea/vomiting	22.9	18.9
Weight gain	13.6	22.7
Weight loss	23.2	232
Genitourinary	3.4	3.1
Impotence	4.7	1.1
Menstrual complaints	2.5	2.2
Urinary frequency	1.9	2.2
Urinary retention		
Musculoskeletal Arthritis	3.1	2.7
Neurological Akathisia	1.5	1.1
Akinesia/bradykinesia cutaneous	8.0	8.6
temperature disturbance	1.9	1.6
Dry mouth		
Excessive sweating	27.6	18.4
Headache/migraine	22.3	14.6
Impaired sleep quality	25.7	22.2
Increased salivary flow	4.0	1.6
Insomnia	3.4	3.8
Muscle spasms	18.6	15.7
Pseudoparkinsonism	1.9	3.2
Sedation	1.5	1.6
Sensory disturbance	19.8	19.5
Tremor	4.0	3.2
	21.1	7.6
Neuropsychiatric	31.9	22.2
Agitation	3.1	1.1
Anxiety	8.4	4.9
confusion	3.1	1.6
Decreased libido	1.2	1.1
Delusions	3.1	3.8
Disturbed concentration	1.2	0.5
Euphoria	5.6	3.8
Hostility		
Nonspecific Fatigue	5.0	8.6
Fever/chills	1.2	0.5
Respiratory Upper respiratory	5.0	11.4
complaints		
Special Senses	5.3	3.2
Auditory disturbance	14.6	10.3
Blurred vision	3.1	1.1
Gustatory disturbance		

*Events reported by at least 1% of patients receiving WELLBUTRIN are included.

Other Events Observed During the Development of WELLBUTRIN:
The conditions and duration of exposure to WELLBUTRIN varied greatly, and a substantial proportion of the experience was gained in open and uncontrolled clinical settings. During this experience, numerous adverse events were reported; however, without appropriate controls, it is impossible to determine with certainty which events were or were not caused by WELLBUTRIN. The following enumeration is organized by organ system and describes events in terms of their relative frequency of reporting in the data base. Events of major clinical importance are also described in WARNINGS and PRECAUTIONS.

The following definitions of frequency are used: 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.

Cardiovascular: Frequent was edema; infrequent were chest pain, electrocardiogram (ECG) abnormalities (premature beats and nonspecific ST-T changes), and shortness of breath/dyspnea; rare were flushing, pallor, phlebitis, and myocardial infarction.

Dermatologic: Frequent were nonspecific rashes; infrequent were alopecia and dry skin; rare were change in hair color, hirsutism, and acne.

Endocrine: Infrequent was gynecomastia; rare were glycosuria and hormone level change.

Gastrointestinal: Infrequent were dysphagia, thirst disturbance, and liver damage/jaundice; rare were rectal complaints, colitis, gastrointestinal bleeding, intestinal perforation, and stomach ulcer.

Genitourinary: Frequent was nocturia; infrequent were vaginal irritation, testicular swelling, urinary tract infection, painful erection, and retarded ejaculation; rare were dysuria, enuresis, urinary incontinence, menopause, ovarian disorder, pelvic infection, cystitis, dyspareunia, and painful ejaculation.

Hematologic/Oncologic: Rare were lymphadenopathy, anemia, and pancytopenia.

Musculoskeletal: Rare was musculoskeletal chest pain.

Neurological: (see WARNINGS) Frequent were ataxia/incoordination, seizure, myoclonus, dyskinesia, and dystonia; infrequent were mydriasis, vertigo, and dysarthria; rare were electroencephalogram (EEG) abnormality, abnormal neurological exam, impaired attention, sciatica, and aphasia.

Neuropsychiatric: (see PRECAUTIONS) Frequent were mania/hypomania, increased libido, hallucinations, decrease in sexual function, and depression; infrequent were memory impairment, depersonalization, psychosis, dysphoria, mood instability, paranoia, formal thought disorder, and frigidity; rare was suicidal ideation.

Oral Complaints: Frequent was stomatitis; infrequent were tooth-ache, bruxism, gum irritation, and oral edema; rare was glossitis.

Respiratory Infrequent were bronchitis and shortness of breath! dyspnea; rare were epistaxis, rate or rhythm disorder, pneumonia, and pulmonary embolism.

Special Senses: Infrequent was visual disturbance; rare was diplopia.

Nonspecific*:*Frequent were flu-like symptoms; infrequent was non-specific pain; rare were body odor, surgically related pain, infection, medication reaction, and overdose.

Postintroduction Reports: Voluntary reports of adverse events temporally associated with bupropion that have been received since market Introduction and which may have no causal relationship with the drug include the following:

Body (General): arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness (see PRECAUTIONS).

Cardiovascular: hypertension (in some cases severe, see PRE-CAUTIONS), orthostatic hypotension, third degree heart block

Endocrine: syndrome of inappropriate antidiuretic hormone secretion, hyperglycemia, hypoglycemia

Gastrointestinal: esophagitis, hepatitis, liver damage ***Hemic and Lymphatic:*** ecchymosis, leukocytosis, leukopenia, thrombocytopenia

Musculosketetal: arthralgia, myalgia, muscle rigidity/fever/rhab-domyolysis, muscle weakness

Nervous: coma, delirium, dream abnormalities, paresthesia, unmasking of tarclive dyskinesia

Skin and Appendages: Stevens-Johnson syndrome, angioedema, exfoliative dermatitis, urticaria

Special Senses: tinnitus

DRUG ABUSE AND DEPENDENCE:

Humans: Controlled clinical studies 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 WELLBUTRIN 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 predict the abuse potential of drugs reliably. 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, which could not be tested because of the risk of seizure, might be modestly attractive to those who abuse stimulant drugs.
Animals: Studies in rodents have shown that bupropion exhibits some pharmacologic actions common to psychostimulants, including increases in locomotor activity and the production of a mild stereotyped behavior and increases in rates of responding in several schedule-controlled behavior paradigms. Drug discrimination studies in rats showed stimulus generalization between bupropion and amphetamine and other psychostimulants. Rhesus monkeys have been shown to self-administer bupropion intravenously.

OVERDOSAGE:

Human Overdose Experience: There has been extensive clinical experience with overdosage of WELLBUTRIN Tablets. 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 WELLBUTRIN and 300 mg of tranylcypromine experienced a grand mal seizure and recovered without further sequelae.

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

Although most patients recovered without sequelae, deaths associated with overdoses of WELLBUTRIN Tablets alone have been reported rarely in patients ingesting massive doses of WELLBUTRIN Tablets. 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, 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 ovordosage, 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 in a manner most likely to minimize the risk of seizure (see WARNINGS). Increases in dose should not exceed 100 mg/day in a 3-day period. 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.

No single dose of WELLBUTRIN should exceed 150 mg. WELLBUTRIN should be administered three times daily, preferably with at least 6 hours between successive doses.

Usual Dosage for Adults: The usual adult dose is 300 mg/day, given three times daily. Dosing should begin at 200 mg/day, given as 100 mg twice daily. Based on clinical response, this dose may be increased to 300 mg/day, given as 100 mg three times daily, no sooner than 3 days after beginning therapy (see table below).

Dosing Regimen

Treatment Day	Total Daily dose	Tablet Strength	Number of Tablets		
			Morning	Midday	Evening
1	300mg	100mg	1	1	1
4	200mg	100mg	1	0	1

Increasing the Dosage Above 300 mg/Day: As with other antidepressants, the full antidepressant effect of WELLBUTRIN may not be evident until 4 weeks of treatment or longer. An increase in dosage, up to a maximum of 450 mg/day, given in divided doses of not more than 150 mg each, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day. Dosing above 300 mg/day may be accomplished using the 75 or 100 mg tablets. The 100-mg tablet must be administered four times daily with at least 4 hours between successive doses, in order not to exceed the limit of 150 mg in a single dose. WELLBUTRIN should be discontinued in patients who do not demonstrate an adequate response after an appropriate period of treatment at 450 mg/day.
Maintenance: The lowest dose that maintains remission is recommended. Although it is not known how long the patient should remain on WELLBUTRIN, it is generally recognized that acute episodes of depression require several months or longer of antidepressant drug treatment.

HOW SUPPLIED: WELLBIJTRIN Tablets, 75 mg of bupropion hydrochloride, are yellow-gold. round, biconvex tablets printed with "WELLBUTRIN 75" in bottles of 100 (NDC 0173-0177-55).

WELLBUTRIN Tablets, 100 mg of bupropion hydrochloride, are red, round, biconvex tablets printed with "WELLBUTRIN 100" in bottles of 100 (NDC 0173-0178-55).

Store at 15 to 25C (59 to 77F). Protect from light and moisture.

GlaxoWellcome

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