CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 18644/S010/S012/S013

Trade Name: WELLBUTRIN TABLETS

Generic Name: BUPROPION HYDROCHLORIDE

Sponsor: GLAXO WELLCOME, INC

Approval Date: 11/27/95 AND 10/31/96

Indication(s): TREATMENT OF DEPRESSION

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 18644/S010/S012/S013

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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Approvable Letter				X
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Medical Review(s)				X
Chemistry Review(s)	X			
EA/FONSI				X
Pharmacology Review(s)	X			
Statistical Review(s)				X
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)				X
Bioequivalence Review(s)				X
Administrative Document(s)/ Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 18644/S010/S012/S013

APPROVAL LETTER

NDA 18-644/S-013

OCT 31 1996

Glaxo Wellcome Inc.
Attn: Beverly G. Lewis
Five Moore Drive
Research Triangle Par, NC 27709

Dear Ms. Lewis:

Please refer to your supplemental new drug application of April 30, 1996 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Wellbutrin (bupropion hydrochloride) Tablets.

The supplemental application provides for replacement of the
Assay methods, and revised specifications, for the new drug substance bupropion hydrochloride. The supplement was submitted as "Special Supplement - Changes Being Effected", with an implementation date on or about June 11, 1996.

We have completed our review of this supplemental new drug application and it is approved.

We remind you that methods validation of the Related Substance and Assay methods has not been completed by our laboratories. At the present time it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

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

If you have any questions concerning this NDA, please contact Mr. Paul David, Regulatory Management Officer, at (301)-594-2850.

Sincerely yours,

/S/

Stanley W. Blum, Ph.D.
Chemistry Team Leader, DNDC I
Division of Neuropharmacological Drug Products (HFD-120)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: Original NDA 18-644/S-013
Div. File HFD-120/
/CParisek/
/CSO/PDavid/
/BRosloff/GFitzgerald/
HFR-SE100/ATL-DO/
HFD-80/
N:\BLUM\18644013.LET

/S/ 10/31/96

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NDA 18-644/S-010/S-012

NOV 27 1995

Burroughs-Wellcome Company
Attention: Michael J. Dalton, Pharm.D.
Head, Department of Pharmaceutical Products
Drug Regulatory Affairs
3030 Cornwallis Road
Research Triangle Park, North Carolina 27709

Dear Dr. Dalton:

Please refer to your supplemental New Drug Applications dated March 5, 1993 (S-010), and June 15, 1994 (S-012), submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Wellbutrin[R] (bupropion hydrochloride) immediate release tablets.

We acknowledge receipt of your annual reports dated May 13, 1992 (Y-006), April 2, 1993 (Y-007), August 22, 1994 (Y-008), and August 14, 1995 (Y-009).

We have completed our review of your supplemental applications, and they are Approved, effective as of the date of this letter.

The supplemental applications referenced above provide for revised labeling with changes as listed below:

S-010

Under **ADVERSE REACTIONS:**

1. The addition of a new subsection entitled Endocrine and the addition of the term "Stevens-Johnson Syndrome" to the Skin and Appendages subsection.

2. Renaming the subsection entitled **Other Events Observed During the Development of Wellbutrin** to **Postintroduction Reports.**

S-012

This supplement provides for the distribution of a generic form of Wellbutrin.

Additionally, we note that your annual reports, referenced above, provided for the following revisions:

1. Under **ADVERSE REACTIONS, Postintroduction Reports** subsection, the addition of "third degree heart block" under the Cardiovascular subsection.

2. Under **DESCRIPTION,** the revision of the inactive ingredients (due to reformulation to aqueous film-coating).

3. Under **HOW SUPPLIED** section, the revision of the storage statement.

Labeling changes of the kind which you have proposed are permitted by section 314.70© of the regulations to be made prior to approval of the supplement. It is understood that the above changes have been made.

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

Should you have any questions concerning this NDA, please contact Mr. Paul David, Consumer Safety Officer, at (301) 443-3504.

Sincerely yours,

/S/

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

cc:
ORIG NDA/18-644
HFD-120/DIV FILE /S/ 11-20-95
HFD-120/PLeber
HFD-120/TLaughren/PAndreason/PDavid /S/ 11/16/95 /S/ 11/16/95
HFD-120/SBlum/CParisek C Parisek 11/16/95
HFD-100 /S/ 11/16/95
HFD-80
HFD-638
HFD-735
HFC-130/JAllen
11/02/95pd
DOC #WELLBUT/IR/S-10-12.LTR
SUPPLEMENTAL NDA APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18644/S010/S012/S013

FINAL PRINTED LABELING

NDA 18-644

FINAL PRINTED LABELING

Labeling: Final
NDA No: 18 644 Rec'd.
Reviewed by:

WELLBUTRIN® Tablets (bupropion hydrochloride)

Insert

WELLBUTRIN® Tablets
(BUPROPION HYDROCHLORIDE)

Wellcome

646033

NOV 27 1995

APPROVED

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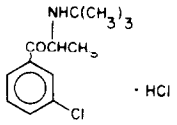
DESCRIPTION: Wellbutrin (bupropion hydrochloride),* an antidepressant of the aminoketone class, is chemically unrelated to tricyclic, tetracyclic, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is designated as 2-*tert*-butylamino-3'-chloropropiophenone hydrochloride. The molecular weight is 276.2. The empirical formula is $C_{13}H_{18}ClNO \cdot HCl$. Bupropion 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, light mineral oil, microcrystalline cellulose, talc and titanium dioxide; 100 mg tablet – FD&C Red No. 40 Lake, FD&C Yellow No. 6 Lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, light mineral oil, microcrystalline cellulose, 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 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 man, 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 (post-distributional) 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 man 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 [illegible] and dogs) ranges from 5-20

extent.

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The absolute bioavailability of Wellbutrin tablets in man 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 5-20%.

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 0-60 hrs 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.

During a chronic dosing study in 14 depressed patients with left ventricular dysfunction, it was found that there was substantial interpatient variability (two- 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 10-100 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 effect of age on plasma concentrations of bupropion and its metabolites has not been characterized.

In vitro tests show that bupropion is 80% or more bound to human albumin at plasma concentrations up to 800 micromolar (200 µg/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 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.

The efficacy of Wellbutrin has been established in three placebo-controlled trials, including two of approximately three weeks duration in depressed inpatients, and one of approximately six 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 III*.

Major Depression implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least two 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

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Depression category of the APA Diagnostic and Statistical Manual III.

Major Depression implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least two 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 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 it.

WARNINGS:

SEIZURES: Wellbutrin 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, 7 patients were receiving daily doses of 450 mg or below, for an incidence of 0.33% (3/1000) within the recommended dose range. Twelve (12) patients experienced seizures at 600 mg per day (2.3% incidence); 6 additional patients had seizures at daily doses between 600 and 900 mg (2.8% incidence).

A separate, prospective study was conducted 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 (8) seizures occurred during the initial 8-week treatment period and 5 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 and the presence of predisposing factors. A significant predisposing factor (e.g., history of head trauma or prior seizure, CNS tumor, concomitant medications that lower seizure threshold, etc.) was present in approximately one-half of the patients experiencing a seizure. 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.

***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 t.i.d., 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, 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. Although scattered abnormalities in liver function tests were detected in patients participating in clinical trials, there is no clinical evidence that bupropion acts as a hepatotoxin in humans.

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 Wellbutrin treatment.

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 pounds occurred in 28% of Wellbutrin patients. This incidence is

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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 pounds occurred in 28% of Wellbutrin patients. 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 Wellbutrin should be written for the smallest number of tablets consistent with good patient management.

Use in Patients with Systemic Illness: 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. Wellbutrin was well tolerated in patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants.

Because bupropion HCl 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: 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 physician if they are [illegible] 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 physician if they become pregnant or intend to become pregnant during therapy.

Drug Interactions: No systematic data have been collected on the consequences of the concomitant administration of Wellbutrin and 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 co-administered drugs may be altered.

Alternatively, because bupropion is extensively metabolized, the co-administration 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).

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

Limited clinical data suggest a higher incidence of adverse experiences in patients receiving concurrent administration of 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.

Concurrent administration of Wellbutrin and agents which lower seizure threshold should be undertaken only with extreme caution (see WARNINGS). Low initial dosing and small gradual dose increases should be employed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg/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/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 (2-3 times control mutation rate) in some strains in the Ames bacterial mutagenicity test, and a high oral dose (300, 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/day.

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Pregnancy: ***Teratogenic Effects:*** Pregnancy Category B: Reproduction studies have been performed in rabbits and rats at doses up to 15-45 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.

Labor and Delivery: The effect of Wellbutrin on labor and delivery in humans is unknown.

Nursing Mothers: 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 individuals under 18 years old have not been established.

Use in the Elderly: Wellbutrin has not been systematically evaluated in older patients.

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 Wellbutrin treatment in approximately ten percent 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 conditions of daily dosage (300-600 mg), setting, and duration (3-4 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 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 is provided in the WARNINGS and PRECAUTIONS sections.

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		
Cardiac Arrhythmias	5.3	4.3
Dizziness	22.3	16.2
Hypertension	4.3	1.6
Hypotension	2.5	2.2
Palpitations	3.7	2.2
Syncope	1.2	0.5
Tachycardia	10.8	8.6
DERMATOLOGIC		
Pruritus	2.2	0.0
Rash	8.0	6.5
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	23.2
GENITOURINARY		
Impotence	3.4	3.1
Menstrual Complaints	4.7	1.1
Urinary Frequency	2.5	2.2
Urinary Retention	1.9	2.2
MUSCULOSKELETAL		
Arthritis	3.1	2.7
NEUROLOGICAL		
Akathisia	1.5	1.1
Akinesia/Bradykinesia	8.0	8.6
Cutaneous Temperature Disturbance	1.9	1.6
Dry Mouth	27.6	18.4
Excessive Sweating	22.3	14.6
Headache/Migraine	25.7	22.2
Impaired Sleep Quality	4.0	1.6
Increased Salivary Flow	3.4	3.8
Insomnia	18.6	15.7

Impotence	3.4	3.1
Menstrual Complaints	4.7	1.1
Urinary Frequency	2.5	2.2
Urinary Retention	1.9	2.2
MUSCULOSKELETAL		
Arthritis	3.1	2.7
NEUROLOGICAL		
Akathisia	1.5	1.1
Akinesia/Bradykinesia	8.0	8.6
Cutaneous Temperature Disturbance	1.9	1.6
Dry Mouth	27.6	18.4
Excessive Sweating	22.3	14.6
Headache/Migraine	25.7	22.2
Impaired Sleep Quality	4.0	1.6
Increased Salivary Flow	3.4	3.8
Insomnia	18.6	15.7
Muscle Spasms	1.9	3.2
Pseudoparkinsonism	1.5	1.6
Sedation	19.8	19.5
Sensory Disturbance	4.0	3.2
Tremor	21.1	7.6
NEUROPSYCHIATRIC		
Agitation	31.9	22.2
Anxiety	3.1	1.1
Confusion	8.4	4.9
Decreased Libido	3.1	1.6
Delusions	1.2	1.1
Disturbed Concentration	3.1	3.8
Euphoria	1.2	0.5
Hostility	5.6	3.8
NONSPECIFIC		
Fatigue	5.0	8.6
Fever/Chills	1.2	0.5
RESPIRATORY		
Upper Respiratory Complaints	5.0	11.4
SPECIAL SENSES		
Auditory Disturbance	5.3	3.2
Blurred Vision	14.6	10.3
Gustatory Disturbance	3.1	1.1

*Events reported by at least 1% of Wellbutrin patients 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 the WARNINGS and PRECAUTIONS sections of the labeling.

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, EKG 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, G.I. 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 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 toothache, 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 nonspecific pain; rare were body odor, surgically related pain, infection, medication reaction and overdose.

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

Cardiovascular: orthostatic hypotension, third degree heart block

Endocrine: syndrome of inappropriate antidiuretic hormone secretion

Gastrointestinal: esophagitis, hepatitis

Hemic and Lymphatic: ecchymosis, leukocytosis, leukopenia

Musculoskeletal: arthralgia, myalgia, muscle rigidity/fever/rhabdomyolysis

Nervous

Musculoskeletal: arthralgia, myalgia, muscle rigidity/fever/rhabdomyolysis

Nervous: coma, delirium, dream abnormalities, paresthesia, unmasking of tardive 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 Wellbutrin produced mild amphetamine-like activity as compared to placebo on the morphine-benzedrine subscale of the Addiction Research Center Index (ARCI) and a score intermediate between placebo and amphetamine on the Liking Scale of the ARCI. These scales measure general feelings of euphoria and drug desirability.

Findings in clinical trials, however, are not known to 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:

Lethal Doses in Animals: In rats, the acute oral LD_{50} values were 607 mg/kg (males) and 482 mg/kg (females). Respective values for mice were 544 mg/kg and 636 mg/kg. Signs of acute toxicity included labored breathing, salivation, arched back, ptosis, ataxia, and convulsions.

Human Overdose Experience: There has been limited clinical experience with overdosage of Wellbutrin. 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, Wellbutrin overdoses 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 alone included hallucinations, loss of consciousness, and tachycardia. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported when Wellbutrin was part of multiple drug overdoses.

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

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

If the patient is stuporous, comatose, or convulsing, airway intubation is recommended prior to undertaking gastric lavage. Although there is little clinical experience with lavage following an overdose of Wellbutrin, it is likely to be of benefit within the first 12 hours after ingestion since absorption of the drug may not yet be complete.

While diuresis, dialysis, or hemoperfusion are sometimes used to treat drug overdosage, there is no experience with their use in the management of Wellbutrin overdose. Because diffusion of Wellbutrin from tissue to plasma may be slow, dialysis may be of minimal benefit several hours after overdose.

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

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

DOSAGE AND ADMINISTRATION:

General Dosing Considerations: It is particularly important to administer Wellbutrin 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 t.i.d., preferably with at least 6 hours between successive doses.

Usual Dosage for Adults: The usual adult dose is 300 mg/day, given t.i.d. Dosing should begin at 200 mg/day, given as 100 mg b.i.d. Based on clinical response, this dose may be increased to 300 mg/day, given as 100 mg t.i.d., 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	200 mg	100 mg	1	0	1
4	300 mg	100 mg	1	1	1

EARS THIS WAY
ORIGINAL

be induced by syrup of ipecac. Activated charcoal also may be administered every 6 hours during the first 12 hours after ingestion. Baseline laboratory values should be obtained. Electrocardiogram and EEG monitoring also are recommended for the next 48 hours. Adequate fluid intake should be provided.

If the patient is stuporous, comatose, or convulsing, airway intubation is recommended prior to undertaking gastric lavage. Although there is little clinical experience with lavage following an overdose of Wellbutrin, it is likely to be of benefit within the first 12 hours after ingestion since absorption of the drug may not yet be complete.

While diuresis, dialysis, or hemoperfusion are sometimes used to treat drug overdosage, there is no experience with their use in the management of Wellbutrin overdose. Because diffusion of Wellbutrin from tissue to plasma may be slow, dialysis may be of minimal benefit several hours after overdose.

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

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

DOSAGE AND ADMINISTRATION:

General Dosing Considerations: It is particularly important to administer Wellbutrin 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 t.i.d., preferably with at least 6 hours between successive doses.

Usual Dosage for Adults: The usual adult dose is 300 mg/day, given t.i.d. Dosing should begin at 200 mg/day, given as 100 mg b.i.d. Based on clinical response, this dose may be increased to 300 mg/day, given as 100 mg t.i.d., 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	200 mg	100 mg	1	0	1
4	300 mg	100 mg	1	1	1

Increasing the Dosage Above 300 mg/Day: As with other ... depressants, 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 q.i.d. 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.

Elderly Patients: In general, older patients are known to metabolize drugs more slowly and to be more sensitive to the anticholinergic, sedative, and cardiovascular side effects of antidepressant drugs. Clinical trials enrolled several hundred patients 60 years of age and older. The experience with these patients and younger ones was similar.

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: Wellbutrin (bupropion hydrochloride) Tablets are supplied as 75 mg (yellow-gold) round, biconvex tablets printed "WELLBUTRIN" and "75," bottles of 100 (NDC 0081-0177-55); and 100 mg (red) round, biconvex tablets printed "WELLBUTRIN" and "100," bottles of 100 (NDC 0081-0178-55).

Store at 15° to 25°C (59° to 77°F).

*U.S. Patent No. 381[illegible]
U.S. Patent No. 3885046 (Use Patent)

Burroughs Wellcome Co.
Research Triangle Park, NC 27709
Printed in U.S.A. October 1992 646033

INDICATIONS AND USAGE: Wellbutrin is indicated for the treat...

(200 µg/mL)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18644/S010/S012/S013

CHEMISTRY REVIEW(S)

OCT 30 1996

CHEMISTS REVIEW OF SUPPLEMENT

1. ORGANIZATION: HFD-120

2. NDA NUMBER: **18-644**

4. SUPPLEMENT NUMBERS/DATES: **SCS-013**

LETTERDATE 30-APR-96

STAMPDATE 01-MAY-96

5. AMENDMENTS/REPORTS/DATES:

LETTERDATE -

STAMPDATE - **REV. COMP.**

6. REC'D BY CHM: 07-MAY-96 18-OCT-96

7. APPLICANT NAME AND ADDRESS: GLAXO WELLCOME INC.
Five Moore Drive
Research Triangle Park, NC 27709

8.-NAME OF DRUG: **WELLBUTRIN®**

9. NONPROPRIETARY NAME: Bupropion hydrochloride

10. CHEMICAL NAME/STRUCTURE: (±)-2-(*tert*-butylamino)-3'-chloropropiophenone, hydrochloride

11. DOSAGE FORM(S): TABLETS

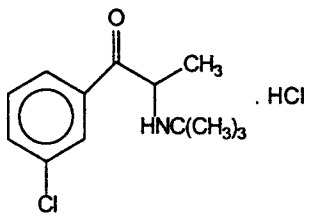
12. POTENCY(IES): 50mg, 75mg, 100mg

13. PHARM. CATEGORY: Antidepressant

14. HOW DISPENSED: XXX (Rx) ___

15. RECORDS AND REPORTSCURRENT: XXX (YES) ___

16. RELATED IND/NDA/DMF(S): -



WELLBUTRIN (bupropion hydrochloride)

17. SUPPLEMENT PROVIDES FOR: revised analytical controls for the drug substance bupropion hydrochloride.

Submitted as "SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED," effective about June 11, 1996.

18. COMMENTS:

19. CONCLUSIONS AND RECOMMENDATIONS:

20. REVIEWER NAME *SIGNATURE* *DATE COMPLETED*

Charles B. Parisek, Ph.D. /S/ 18-OCT-96

Copies:
ORIG; NDA 18-644
HFD-120/CParisek/CSO-PDavid/

INIT: SWB/ /S/ 10/29/96

filename: n018644.013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18644/S010/S012/S013

PHARMACOLOGY REVIEW(S)

36.1

NDA 18-644 (Wellbutrin)

Memo on Submission of 8/20/96 (14 day rat study)

APPEARS THIS WAY
ON ORIGINAL

This submission consists of a 14 day tox. study in SD rats with drug spiked with 0.5% of each of 4 newly detected impurities. It is stated that revised analytical methodology allowed for adequate separation and quantitation of these impurities and that they "are believed to have always been present in the drug substance". The findings in the study were generally compatible with previous rat studies, with the exception of a finding of enhanced acinar development in mammary gland in all F groups; this persisted through a 14 day recovery period. It is difficult to attribute this effect to the impurities since there were no groups given un-spiked drug for comparison; at any rate this may be a moot point since the impurities may have always been present as noted above. Rather, the purpose of witing this memo is to document in the file the appearance of an apparently previously unreported effect of the drug on rat mammary gland.

Attached is the sponsor's summary of this study, as well as the page from the summary table of histpathological findings at terminal sacrifice showing the mammary gland results.

/S/

Barry Rosloff

5/29/97

APPEARS THIS WAY
ON ORIGINAL

cc: Rosloff, Fitzgerald

NDA 18-644 submission of 8/20/96 and division file

APPEARS THIS WAY
ON ORIGINAL

A 14–Day Oral Toxicity Study in Hsd: Sprague Dawley®SD® Rats Given 323U66 HCl (Containing Impurities)

SUMMARY

SUMMARY MATERIALS AND METHODS	
No. Animals/Sex/Dose Group	15 Groups 1 and 4 10 Groups 2 and 3
Dose Groups (mg/kg/day HCl)	0, 75, 150, 300
Compound Preparation	323U66UCX HCl (WELLBUTRIN®) with a level of 0.5% w/w for each impurity identified (relative to 323U66 HCl)
Impurity Identification	(b)(4)
Dose Schedule	Once daily for 14–15 consecutive days. Five rats/sex groups 1 and 4 were held for a 14 day postdose recovery period.
Dose Volume (mL/kg)	10 (Oral by gavage)
Concentrations (mg/mL)	7.5, 15, 30
Vehicle	Sterile Water
Observations	Clinical signs, body weights, food consumption, hematology, clinical chemistry, urinalysis, ophthalmology, organ weights, gross pathology, and histopathology.

RESULTS

Parameter Evaluation	323U66 HCl (mg/kg/day)			
	0	75	150	300
Deaths	0/30	0/20	0/20	3/30
Clinical Signs Increased Activity	No	Yes	Yes	Yes
Chewing Cage Wire	No	Yes	Yes	Yes
Hematology, Clinical Chemistry, Urinalysis, Ophthalmology	—	No	No	No
Body Weights	—	No	No	No
Food Consumption (decrease)	—	No	No	Yes (females)
Organ Weights Liver (increase)	—	No	Yes	Yes
Kidney (increase)	—	No	No	Yes (males)
Gross Pathology	—	No	No	No
Histopathology Liver Hypertrophy	—	No	Yes	Yes

Parameter Evaluation	323U66 HCl (mg/kg/day)			
	0	75	150	300
Mammary Gland Enhanced Acinar Development (females)	—	Yes	Yes	Yes
Kidney Nephropathy/Hyaline Droplet	—	No	No	Yes (males)

CONCLUSION

The administration of 75, 150 or 300 mg/kg/day of 323U66 HCl, spiked with impurities, 175U66 HCl, 4U65 HCl, 996U80 HCl and 377U86 HCl at a level of 0.5% w/w each (relative to 323U66 HCl) produced effects consistent with those noted in previous toxicity studies (TTEP/70/0009, TTEP/92/0011, and TTEP/93/0061). Therefore, the impurities, did not introduce any unacceptable toxicity.

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A 14-Day Oral Toxicity Study in Hsd:Sprague Dawley SD Rats Given 323U66HCl (Containing Impurities), Terminal Necropsy

FINDINGS	TREATMENT	INCIDENCE OF LESIONS (NUMERIC) MALES 0 mg/kg/day	75 mg/kg/day	150 mg/kg/day	300 mg/kg/day	FEMALES 0 mg/kg/day	75 mg/kg/day	150 mg/kg/day	300 mg/kg/day
Colon:									
No abnormality detected									
Caecum:									
No abnormality detected									
Ileum:									
No abnormality detected									
Skin:									
No abnormality detected									
Mammary glands:									
No abnormality detected									
Ductal development									
slight									
moderate									
Alveolar development									
very slight									
slight									
moderate									
Salivary gland:									
No abnormality detected									

Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified

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55
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18644/S010/S012/S013

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

GlaxoWellcome

ORIGINAL
NDA SUPPLEMENT

NDA NO. 18-644 REF. NO. SCS-043

NDA SUPPL FOR Control 1

April 30, 1996

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

Re: NDA 18-644; WELLBUTRIN® (bupropion hydrochloride) Tablets
Special Supplement: Changes Being Effected: CMC/Nonclinical Pharmacology and Toxicology

Dear Dr. Leber:

We submit herewith a Special Supplement - Changes Being Effected, providing for revised analytical controls for the drug substance bupropion hydrochloride, used in the manufacture of WELLBUTRIN® (bupropion hydrochloride) Tablets.

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

Telephone
919 248 2100

In accord with 21 CFR 314.70(c)(1), the changes provided herein increase assurance that the product will have the quality and purity which it is represented to possess.

Should you require any additional information regarding the toxicology study provided herein, please contact Mr. Eric Benson at (919) 483-3627. Should you have any questions regarding the chemistry, manufacturing, and controls, please feel free to contact me at (919) 483-5030.

Sincerely,

Beverly G. Lewis

Beverly G. Lewis
Manager, CMC Submissions
Regulatory Affairs & Compliance

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

GlaxoWellcome

ORIGINAL

NDA SUPPL AMEND

SCS-013

(BP)

August 20, 1996

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

Re: NDA 18-644; WELLBUTRIN® (bupropion hydrochloride) Tablets
Information Amendment: Pharmacology and Toxicology

Dear Dr. Leber:

Reference is made to the April 30, 1996 Special Supplement - Changes Being Effected, that provided for revised analytical controls for the drug substance bupropion hydrochloride used in the manufacture of WELLBUTRIN® (bupropion hydrochloride) Tablets. The revised methodology allowed for adequate separation and quantitation of newly detected impurities that are believed to have always been present in the drug substance. The supplement also included a draft, unaudited report of a 14-day toxicology study in which these impurities were evaluated.

At this time, we are submitting the final report of the aformentioned toxicology study entitled: **"A 14-Day Oral Toxicity Study in Hsd:Sprague Dawley®SD® Rats given 323U66 HCl (Containing Impurities)"**. The conclusion of this final report remains the same as that in the draft report, i.e. the impurities did not introduce any unacceptable toxicity.

If there are any questions or comments regarding this submission, please contact Eric Benson, Product Director, Regulatory Affairs, at (919) 483-3627.

Sincerely,

James E. Murray

James E. Murray
Director
Regulatory Affairs

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

Telephone
919 248 2100

CSO LABELING REVIEW
NDA 18-644

OCT 31 1995

Date of Review: October 31, 1995

Applicant Name and Address: Burroughs-Wellcome Company
Attention: Michael J. Dalton, Pharm.D.
Head, Department of Pharmaceutical Products
Drug Regulatory Affairs
3030 Cornwallis Road
Research Triangle Park, North Carolina 27709

Product Name:
Trade Name: Wellbutrin
Generic Name: Bupropion hydrochloride
Dosage Form: tablets

Product Classification: Aminoketone
Product Indication: antidepressant

S-008 Approved August 31, 1992

S-010 Dated 3-5-93
S-012 Dated 6-15-94

Materials Reviewed:

1. Last approved FPL, 18-644/S-008 (Agency approval letter dated August 31, 1992).

2. Reviews for the above supplements.

3. Annual reports.

EVALUATION

S-009 (submitted January 28, 1993, and amended on March 11. 1993 and February 23, 1995)

Label Code:	N/A
Reviewed by Medical officer:	Yes - Acceptable
Reviewed by Pharmacologist:	Yes - Requires revisions (See 20-358 Wellbutrin SR Pharmacology Review)
Reviewed by Biopharmaceutics:	No
Changes Being Effected:	No

Since all of the reviews are not completed, this supplemental application will not be acted upon.

S-010 (submitted March 5, 1993)
Label Code: 646033
Reviewed by Medical officer Yes - Acceptable
Changes Being Effected: YES

Under **ADVERSE REACTIONS:**

1. The addition of a new subsection entitled Endocrine and the addition of the term "Stevens-Johnson Syndrome" to the Skin and Appendages subsection.

2. Renaming the subsection entitled from **Other Events Observed During the Development of Wellbutrin** to **Postintroduction Reports**.

S-012 (submitted June 15, 1994)
Label Code: 433414
Reviewed by Medical officer Yes - Acceptable
Changes Being Effected: YES

This supplement provides for the distribution of a generic form of Wellbutrin. The labeling is identical to the approved Wellbutrin except for the additions noted in S-010 and the annual reports, and the deletions to the Wellbutrin proprietary name.

ANNUAL REPORTS

Y-005 (Annual report dated 6-5-91)
Reported changes made as a result of the approval of Supplements 004 and 008.

Y-006 (Annual report dated 5-13-92)
No major revisions

APPEARS THIS WAY
ON ORIGINAL

Y-007 (Annual Report dated 4-2-93)
Revision under **ADVERSE REACTIONS** section to change the subsection entitled Observed During Clinical Practice to Postintroduction Reports. First paragraph of this section has also been revised. In addition "third degree heart block" has been added to the Cardiovascular subsection.

Y-008 (Annual Report dated 8-22-94)
No major revisions

APPEARS THIS WAY
ON ORIGINAL

Y-009 Annual report dated 8-14-95: Under **DESCRIPTION,** provides for statement to revise inactive ingredients (due to reformulation to aqueous film-coating) and a revised storage statement under the **HOW SUPPLIED** section.

CONCLUSIONS & RECOMMENDATIONS:

1. The supplements noted above only provide for the changes listed in this review. The generic labeling of Wellbutrin (SLR-012) distributed by Welgen

is identical to the approved Wellbutrin labeling except for any mentions of the innovator product.

2. An approval letter should issue for the SLR-010 and SLR-012.

/S/

Paul A. David, R.Ph.
Regulatory Management Officer

APPEARS THIS WAY
ON ORIGINAL

/S/

John Purvis
Supervisory CSO

ATTACHMENTS
A. Last approved labeling (S-008)
B. Generic Bupropio labaling (S-012), Label Code 433414
C. Most recent Wellbutrin labeling (Y-009), Label Code 646042

cc:
ORIG NDA 18-644
HFD-120/ DIV FILE
HFD-120/PDavid
10/31/95pd
C:\WELLBUT\IR\S-10-12.SLR

APPEARS THIS WAY
ON ORIGINAL

PRIN SUPPLEMENT

ORIGINAL

Wellcome

Burroughs Wellcome Co.

3030 Cornwallis Road
P.O. Box 12700
Research Triangle Park, N.C. 27709-2700

cables & telegrams
Tadord Raleigh, N.C.
TWX 5109270915
tel. 919-248-3000

"Special Supplement – Changes Being Effected"

NDA NO. 18-644 REF. NO. SLR012

NDA SUPPL FOR 7P2

June 15, 1994

Paul D. Leber, M.D., Director
Division of Neuropharmacological
Drug Products, HFD–120
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA 18–644
WELLBUTRIN® (bupropion hydrochloride) Tablets

APPEARS THIS WAY ON ORIGINAL

Dear Dr. Leber:

In accordance with 21 CFR 314.70 (c)(1), we submit herewith a "Special Supplement – Changes Being Effected" for WELLBUTRIN Tablets, 75 mg and 100 mg

TRZO/94/0765

Wellcome

We are providing herewith twelve copies of final printed labeling.

We certify that a Field Copy of this supplement has been provided to our local FDA District Office.

Should you require additional information, please do not hesitate to call Ms. Susan Skinner (919) 707–2326.

Sincerely,

Anne F. McKay
Director
Drug Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

TRZO/94/0765

Archival Copy

ORIGINAL

NDA SUPPLEMENT

Wellcome

Burroughs Wellcome Co.

3030 Cornwallis Road
Research Triangle Park, N.C. 27709

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SPECIAL SUPPLEMENT-CHANGES BEING EFFECTED

March 5, 1993

NDA NO. 18-644 REF. NO. SLR 010

NDA SUPPL FOR PI

Paul Leber, M.D. Director
Division of Neuropharmacological Drug Products, HFD-120
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 18-644
WELLBUTRIN® Tablets
(bupropion hydrochloride)

Dear Dr. Leber:

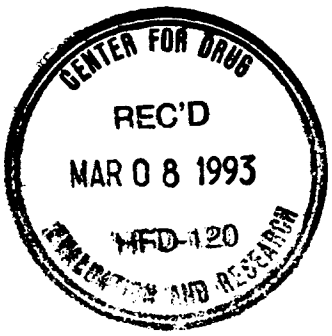
We are submitting herewith 12 copies of a final printed package insert for WELLBUTRIN® Tablets which is being revised in accordance with 21 CFR 314.70(c)(2)(i). The revised insert will first be used in packaging on or about April 20, 1993.

The package insert has been revised under ADVERSE REACTIONS to add an *Endocrine* section, and to add Stevens-Johnson syndrome to the *Skin and Appendages* section. These revisions are based on voluntary reports of adverse reactions received by Burroughs Wellcome Co. from August 1989 through December 1991 (Wellbutrin 461, 9/28/90; Wellbutrin 506, 1/31/91; Wellbutrin 822, 7/03/91; Wellbutrin 940, 2/05/92; Wellbutrin 351, 8/17/90; Wellbutrin 824, 7/29/91 [Follow-up 12/4/91]; Wellbutrin 1007, 2/05/92 [Follow-up 2/27/92]).

An annotated package insert showing the revisions is attached as TAB 1.

If you have any questions regarding the above changes, please contact Ross Raymond, at (919) 248-8736.

Sincerely,



Michael J. Dalton, Pharm. D.
Head, Pharmaceutical Products
Drug Regulatory Affairs

MJD/ldr
TRZO/93/0280
Attachment