These records are from CDER's historical file of information previously disclosed under the Freedom of Information Act (FOIA) for this drug approval and are being posted as is. They have not been previously posted on Drugs@FDA because of the quality (e.g., readability) of some of the records. The documents were redacted before amendments to FOIA required that the volume of redacted information be identified and/or the FOIA exemption be cited. These are the best available copies.

MADE IN JAPAN

NDA 18-644

MADE IN JAPAN

AP /LTR

Extra copy

NDA 18-644

DEC 30 1985

Burroughs Wellcome Company
Attention: Donald A. Knight
3030 Cornwallis Road
Research Triangle Park, North Carolina 27709

Dear Mr. Knight:

Please refer to your new drug application dated December 28, 1981, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation Wellbutrin (bupropion hydrochloride) Tablets, NDA 18-644.

We also acknowledge receipt of your additional communications dated:

March 14, 1985
March 19, 1985
March 21, 1985
April 9, 1985
May 1, 1985
May 21, 1985
June 11, 1985
June 21, 1985
August 9, 1985
September 20, 1985
September 26, 1985
September 30, 1985
November 20, 1985
November 26, 1985

We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that bupropion is safe and effective for use as recommended in the revised labeling that was developed at our meeting on December 20, 1985. Accordingly, the application is approved, effective on the date of this letter, provided that the precise text of the labeling to be employed is that incorporated in the body of this letter.

Twelve copies of the final printed version of the revised labeling (including container and package labeling) must be submitted to FDA prior to marketing. Marketing of the drug before the changes specified above are made and submitted to FDA renders the product misbranded under 21 U.S.C. 352.

In addition to the submission of revised labeling, the approval of the application is conditioned upon your commitment, made earlier, to undertake the program of post-marketing studies enumerated in our December 31, 1984 approvable letter. Also, as agreed at our December 20, 1985 meeting, you will modify your plans for the post-marketing chronic, repeated dose, dose proportionality 'bio' study to evaluate not only bupropion but its major, active metabolites. As agreed December 30, 1985, by telephone conversation between Richard Kiernan and Dr. Stanley Blum, the Dissolution Specification will be: Q=80% at 45 minutes, using the paddle method (50 rpm) in 900 mL water at 37°C. Finally, you must also submit, within a reasonable interval, the laboratory test results and cross-tabulations requested earlier.

The approved labeling of Wellbutrin follows:

Final labeling:
December 20, 1985

WELLBUTRIN® Tablets (bupropion hydrochloride)

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 $C_{13}H_{18}ClNO.HCl$. 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 50 mg (white), 75 mg (yellow-gold), and 100 mg (red) film-coated tablets.

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 ten fold 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 (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 five-fold) 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 200 micromolar (200 ug/ml).

INDICATIONS AND USAGE:

WELLBUTRIN is indicated for the treatment of depression in patients who fail to respond adequately to or who cannot tolerate alternative antidepressant treatments. Wellbutrin is not recommended as an antidepressant of first choice for most patients because its use at doses approximately one and one third times greater than the usually required daily dose (450mg) is associated with a high risk of seizure (see Warnings).

The efficacy of WELLBUTRIN was demonstrated in placebo controlled clinical trials which enrolled principally hospitalized patients with diagnoses of depressive neurosis or manic-depressive (depressed type) disorder. The depressive illness of the patients studied most closely corresponds 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 fatiyability, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and suicidal ideation or attempts.

Evidence to demonstrate the sustained effectiveness of WELLBUTRIN after three weeks of use in placebo controlled investigations is not presently available.

CONTRAINDICATONS:

Because of its potential to induce seizures, Wellbutrin should not be used in patients with a convulsive disorder.

The concurrent administration of WELLBUTRIN and a monoamine oxicase (MAO) inhibitor is contraindicated; at least 14 days should elapse between discontinuation of a MAO inhibitor and initiation of treatment with WELLBUTRIN.

WELLBUTRIN is contraindicated in patients who have shown an allergic response to it.

WARNINGS:

Convulsions: (This title will appear in bold, emphasized capitals)

(The following two paragraphs will be printed in bold, dark type.)

Wellbutrin appears to possess a greater epileptogenic potential than other marketed antidepressants. While the estimated risk of seizure at doses of 450mg and below does not appear excessive in comparison to the risk reported for other antidepressant drug products, the estimated risk increases almost 10 fold between a dose of 450 and 600 mg a day. Given the wide variability among individuals in their capacity to metabolize and eliminate drugs, this disproportionate increase in seizure incidence with dose incrementation is a cause for concern.

During the period of premarketing evaluation, 25 among approximately 2400 patients treated with Wellbutrin experienced seizures. At the time of seizure, seven (7) patients were receiving daily doses of Wellbutrin at or below the lowest documented effective daily dose of 450mg. Twelve (12) patients experienced seizures at daily doses of 600mg; six (6) additional patients had seizures at daily doses between 600 and 900 mg. The risk of seizure appears to be strongly associated with dose and may be increased by predisposing factors (e.g. head trauma, CNS tumor, etc.) or a history of prior seizure. In addition, sudden and large increments in dose may contribute to an increased risk. While many seizures occurred early in the course of treatment, some seizures did occur after several weeks of use at fixed dose.

(end bold, dark type)

N.B. A new column will be added to the following table. The column, placed at the very left side of the table will identify the first two rows (less than 450mg and 450 mg as being "within the recommended dose" and the last two rows (600mg and 600 to 900mg) as being "above the recommended dose"

INCIDENCE OF SEIZURES IN PATIENTS RECEIVING WELLBUTRIN

WELLBUTRIN Dose mg/day	Total Seizure Incidence (%)	Seizure Incidence in Patients Without Seizure Predisposition (%)
less than 450	0.2%	0.0%
450	0.3%	0.2%
600	2.3%	1.3%
600-900	2.8%	1.9%

N.B. The next sentence will appear in bold, dark capitals:

Dosage and administration recommendations should be strictly followed to minimize the risk of seizure (see DOSAGE and ADMINISTRATION).

(end bold caps; resume bold, dark type.)

Extreme caution should be used when combining WELLBUTRIN with other agents which lower seizure threshold, or when administering WELLBUTRIN to patients with a history of seizure disorder or cranial trauma.

N. B. (End all emphasized type.)

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 an 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 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 tablet. 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. Conseqently, until they are reasonably certain that Wellbutrin does not aduversely 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 minimzed, and, if possible, avoided completely.

Patients should be advised to inform their physician 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 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 (2-3x 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.

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:

It is not known whether WELLBUTRIN is excreted in the milk of lactating women. Because many drugs are excreted in human milk, caution should be exercised when WELLBUTRIN is administered to women who are nursing.

Pediatric Use:

The safety and effectiveness of WELLBUTRIN in individuals under 18 years old has 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 the product's premarketing clinical trials. 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, primarily rashes (1.1%). 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 [illegible] 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 (300-600mg), 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 section.

N.P. NOTE TO THE FIRM: At this point insert, using the same tabular format as in our 12/18/85 draft labeling, the new incidence figures provided in your 12/20/85 table of Emergent or Exacerbated ADRs from studies 05, 08, 09, 14 and 25.

As agreed, all events occurring at an incidence below 1.0% among Wellbutrin treated subjects will be eliminated. These events, however will be added, if missing, to the narrative enumeration of ADRs in the section, titled "Other events observed during the premarketing evaluation of Wellbutrin." It will also be necessary to delete from the same narrative section any item now appearing in the 12/20 tabular enumeration that did not appear in the 12/18 FDA draft.

A copy of an edited version of the 12/20 table is attached.

TABLE IS INSERTED AT THIS POINT N.P. FOOTNOTE IS NOW REQUIRED INDICATING THAT TABULATION IS LIMITED TO EVENTS AT OR ABOVE 1 percent:

*Events reported by 1% of patients are included.

<u>Other events observed during the entire premarketing evaluation of Wellbutrin.</u>

During its premarketing assessment, Wellbutrin was evaluated in almost 2400 subjects. 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 at incidences below 1/1000.

N.B. NOTE THAT THE NEW DEFINITIONS EMPLOYED FOR THIS SECTION REQUIRE ITS REVISION TO REMOVE UNNECESSARY REFERENCES TO EVENTS THAT DID NOT OCCUR AT A "frequent" LEVEL OF INCIDENCE. Again, appropriate additions and deletions as required by the insertion of the 12/20 ADR tabulation should be made. The text below remains without these changes inserted; Burroughs-Wellcome staff will make these changes. Corrections in the text made at our 12/20 joint meeting, however, have been inserted in CAPITALS to draw attention to the change-- in FPL capitalization should not be used.

Cardiovascular: The most frequent were palpitations, edema and syncope; less frequent were chest pain, EKG abnormalities (PREMATURE BEATS AND NON-SPECIFIC ST-T changes), and shortness of breath/dyspnea; and rare were pallor and phlebitis.

Dermatologic: Pruritis, non-specific rashs were frequent; less frequent were alopecia and dry skin; change in hair color and hirsutism were rare.

Endocrine: No event occurred at an incidence of 1.0%; gynecomastia was a less frequent event; glycosuria and 'hormone level changes' were reported at a rare incidence level.

Gastrointestinal: No events occurred at a frequency exceeding one percent; less frequent events were dysphagia, thirst disturbance and liver damage/jaundice; rare events were rectal complaints, colitis, G.I. bleeding and intestinal perforation.

Genitourinary: Urinary frequency was reported at a level considered frequent; less frequent events were testicular swelling, urinary tract infection, painful erection and retarded ejaculation; rare events included dysuria, enuresis, urinary incontinence, menopause, ovarian disorder, pelvic infection, cystitis, dyspareunia and painful ejaculation.

Hematologic/Oncologic: Lymphadenopathy was reported rarely.

Neurological: (see Warnings) Frequent events were impaired sleep quality, ataxia/ incoordination, seizure, cutaneous temperature disturbance, myoclonus and dyskinesia; less frequent were mydriasis, vertigo and dysarthria; and rare events included EEG abnormality, abnormal neurological exam, impaired attention and sciatica.

Neuropsychiatric: (see Precautions) The most frequent events were disturbed concentration, increased libido, hallucinations, depression and delusions; less frequent were memory impairment, depersonalization, psychosis, dysphoria, mood instability, paranoia, formal thought disorder and frigidity; suicidal ideation was reported as a rare event.

Oral Complaints: Stomatitis occurred at a frequent incidence rate. Less frequent events were toothache, bruxism, gum irritation and oral edema; glossitis was reported rarely.

Respiratory: No events were reported at a frequency exceeding one percent. Less frequent events were bronchitis and shortness of breath/dyspnea; epistaxis and rate or rhythm disorder was reported rarely.

Special Senses: No events were reported at an incidence greater than one percent. Visual disturbances were reported less frequently and reports of diplopia were rare.

Nonspecific: Frequent events were fever/chills and flu-like symptoms; less frequent was nonspecific pain; body odor, surgically related pain, infection, medication reaction and overdose were reported rarely.

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.

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:

At doses that are one and one-third times the usually required dose (450mg/day), (See Warnings), the observed incidence of seizure increases by as much as ten fold. This predicts a relatively narrow therapeutic ratio for the safe use of bupropion, especially as there is considerable inter-individual variability in the capacity of patients to metabolize drugs.

Consequently, it is particularly important to administer bupropion in a manner that is most likely to minimize the risk of seizure. Retrospective analysis of clinical experience gained during its premarketing development suggests that the risk of seizure may be minimized if 1) the total daily dose of WELLBUTRIN does not exceed 450mg, 2) the daily dose is administered in divided doses to avoid high peak concentrations of bupropion and/or its metabolites, and 3) the rate of incrementation of dose is very gradual.

WELLBUTRIN should, therefore, be given t.i.d., preferably with intervals of at least 6 hours between successive doses. Besides its apparent value in lowering the risk of seizure, gradual dose escalation is important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these side effects may be managed by temporary reduction of dose or the transitory administration of a sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment.

The following suggested dosing regimen incorporates the principles described above.

Usual Adult Dosage:

A starting dose of 225 mg/day given as 75 mg t.i.d. is recommended. Based on clinical response this dose may be increased by 75 mg/day no sooner than every three days according to the following schedule up to a total maximum daily dose of 450 mg/day. Of course, if distressing untoward effects supervene, dose escalation should be stopped.

Dosing Schedule

Treatment Day	75 mg Tablets			Total Daily Dose
	Morning	Midday	Evening	
1	1	1	1	225 mg
4	2	1	1	300 mg
7	2	2	1	375 mg
10	2	2	2	450 mg

In patients who do not demonstrate an adequate response after an appropriate period of treatment at 450 mg/day, drug should be discontinued. While no systematic study of withdrawal has been conducted, it seems prudent to recommend gradual tapering of drug over a period of a week.

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. The maximum recommended maintenance dose is 450 mg/day. While it is generally recommended that a course of antidepressant drug treatment should continue for several months and many patients have been treated with WELLBUTRIN in long-term clinical trials of up to 2 years duration, there has been no systematic

placebo-controlled evaluation of the efficacy of WELLBUTRIN for a period beyond three to four weeks.

HOW SUPPLIED:

WELLBUTRIN (bupropion hydrochloride) tablets are supplied as follows:

50 mg (white) round biconvex tablets printed "WELLBUTRIN" and "50"
-bottles of 100 (NDC 0081-0176-55)

75 mg (yellow-gold) round biconvex tablets printed "WELLBUTRIN" and "75"
-bottles of 100 (NDC 0081-0177-55)

100 mg (red) round biconvex tablets printed "WELLBUTRIN" and "100"
-bottles of 100 (NDC 0081-0178-55)

Store at 15°-30°C (59°-86°F)

END OF TEXT

Twelve copies of the final printed version of the revised labeling must be submitted to the FDA prior to marketing (21 CFR 314.[illegible]).

Should additional information relating to the safety and effectiveness of these drug products become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

Please submit one market package of the drug when it is available.

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

Sincerely yours,

RT 12/30/85

Robert Temple, M.D.
Acting Director
Office of Drug Research and Review
Center for Drugs and Biologics

cc:
Orig. NDA 18-644
ATL-DO
HFN-100
HFN-120
HFN-120/Leber/revisions/
HFN-226/Hepp
HFN-713/Marticello/Stein
HFN-120/Zinsitz/Shultz
HFN-120/Rosloff/Contrera
HFN-120/Laughren/Lee
HFN-120/Vocci
HFN-120/TDeCicco/10/28/85/12/23/85
DOC 1053x

12/26/85

DMB for FZ, RCS 12/26/85
JMR 12/26/85 Mar 12/24/85
JC Sholtz 12-27-85

MADE IN JAPAN

AE / LTR

6 c 1

12/31/84

NDA 18-644

Burroughs Wellcome Company
Attention: Donald A. Knight
3030 Cornwallis Road
Research Triangle Park, North Carolina 27709

Gentlemen:

Please refer to your new drug application dated December 28, 1981 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation Wellbutrin (bupropion hydrochloride) Tablets, NDA 18-644.

We also refer to your additional communications dated:

June 10, 1982 (submitted to IND)
July 1, 1982
July 22, 1982
October 7, 1982
November 8, 1982
November 10, 1982
December 1, 1982
December 8, 1982
January 25, 1983
February 17, 1983
March 18, 1983
March 31, 1983
April 25, 1983
April 27, 1983
April 28, 1983
June 6, 1983
June 23, 1983
July 13, 1983
August 3, 1983
August 15, 1983
September 9, 1983
September 19, 1983
October 26, 1983
November 3, 1983
February 3, 1984
March 20, 1984
April 13, 1984
May 3, 1984
May 8, 1984
May 16, 1984
May 22, 1984
June 6, 1984
July 25, 1984
September 18, 1984
November 27, 1984

We have completed our review of this application as submitted with draft labeling.

The application is approvable provided that:

1) You agree to (a) perform the modifications of your analytical methods for the product described in the section entitled Analytical Methods; (b) reposition the Caution statement from the side panel of the 100 mg strength, 100 tablet container to the front; and (c) replace the proposed quality control in vitro dissolution test method (paddle) with the basket method which was used throughout the development of Wellbutrin (i.e., USP XX Apparatus 1, 100 rpm, 500 ml of 0.6% HCl 37°C.) The recommended dissolution specification for the basket method should be not less than 75 percent (Q) drug dissolved in 20 minutes.

2) You make a commitment to conduct additional clinical investigations, to be initiated within the first year of marketing, that will provide evidence to demonstrate that the antidepressant effect of Wellbutrin persists beyond three weeks. This information is essential if the labeling of Wellbutrin is to provide adequate directions for its use. Our reasoning about this matter is described in detail, including a suggestion for design of the study, in the section entitled Clinical Studies.

3) You make a commitment to conduct a clinical investigation to elucidate the relationship between bupropion's dose, the timing of the administration of this dose, the clinical response and the untoward event incidence. Understanding this relationship is especially important in view of the apparent high incidence of seizures to date, particularly among individuals receiving higher doses of bupropion.

4) You initiate a comprehensive post-marketing program to evaluate the potential of bupropion to cause seizures in actual medical use. As you are aware the power of controlled trials to detect rare events is limited; consequently, the important issue of epileptogenic risk should also be assessed using epidemiological-styled strategies. Acceptable approaches might include following prospectively cohorts of users (e.g., in the style of the Puget Sound Health Cooperative program) or retrospective analyses of third party data bases. An alternative to be explored is a large cohort involving randomized assignment of patients to bupropion and a standard drug followed forward under not especially close surveillance, but nonetheless, surveillance sufficient to detect seizures.

5) You conduct a long term, post-marketing, epidemiologically styled investigation, with yearly interim analyses, to determine the extent of abuse and diversion of buproprion in comparison to other antidepressant drug products.

6) You conduct the following biopharmaceutic investigations within 180 days of final approval of the application:

   a) A multiple-dose, dose proportionality study that covers the dosing recommended in the product's labeling.

   b) One or more investigations suitable for determining the pharmacokinetic parameters of bupropion in the elderly, that is, those over the age of 65.

7) You submit a comprehensive Safety Update covering all clinical experience with bupropion, regardless of the use investigated. This

update should provide an enumeration of all patients who suffered a mortal or morbid event and any who were forced to withdraw from treatment because of an adverse experience regardless of assumptions or judgments about the relationship of drug treatment to the observed or reported reaction.

8) You make substantive changes in the draft labeling regarding the description of the product's clinical and pharmacological effects, the claimed indication and the population for which its use should be considered, and the warnings and directions for its use. The labeling we would tentatively agree to accept, if all other conditions are met, is described in detail in the section entitled Labeling.

Analytical Methods

The results of our laboratory investigations show that with some relatively minor modifications the proposed methods will be suitable for regulatory and control purposes. Our comments and suggestions are the following:

a) IR Identification

Our initial curves of the New Drug Substance (NDS) and the reference standard, as KBr pellets, did not match in the regions around 100 and 700 cm^{-1}. When the bupropion KBr mixture was prepared by use of a "Wigglebug," the spectra were similar. We feel that the initial problem was due to a difference in particle size of the standard and NDS. Visual inspection of the two indicated a different appearance as well. A Wigglebug, or other similar mechanical vibrating ball mill, should be specified in the method as one means of preparation of the KBr mixture.

b) NDS Assay

As further evidence of a particle size problem, our initial attempt with the HPLC assay for the NDS yielded results which were below the NDA specifications. Use of a sonic bath corrected this problem. Aliquots were chromatographed every 5 minutes until reproducible areas were obtained. A total of 15 minutes in the bath was required.

c) Melting Range

The NDA specifications include the melting range; however, the certificates of analysis do not include the results of this procedure. The Atlanta District reported difficulties with the melting point determination; their results were low. We found the melting range for the standard to be 217-220° and for the NDS to be 215-218°. Determination by Differential Scanning Calorimetry (DSC) gave somewhat variable results,

generally at the high end of the allowed 215-226° range or above it. Since there are already two identification tests, IR and HPLC, and since both FDA laboratories obtained unsatisfactory results, it might be appropriate to eliminate this test. In further support of this deletion is the fact that testing for the related substances by TLC provides another built-in identification test.

d) We recommend inclusion of an upper limit in the specifications for the chloride assay.

e) We also recommend that specification limits on impurities be reduced to reflect those found in the drug substance used in clinical studies and reported in your March 18, 1983 amendment.

Clinical Studies

The application provides evidence that bupropion is effective when used for periods up to three weeks in inpatients. We are unable to determine, however, whether its antidepressant effect persists beyond three weeks, and we find the data on its efficacy in an outpatient setting equivocal. We are also concerned about the relative paucity of systematically obtained information on the relationship between the dose of bupropion administered, the incidence of adverse events and the therapeutic effect.

In regard to bupropion's efficacy in outpatients, the only placebo controlled study in this population, 09, provides inconclusive evidence. As you pointed out in your submission of September 18, 1984, in one analysis some measures in the -01 substudy are supportive of efficacy; however, the 09-02 substudy fails totally to confirm this finding.

In regard to the question of sustained efficacy, there is virtually no useful evidence. While some of the active standard drug controlled investigations evaluated patients for a period beyond three weeks, their outcome (i.e., standard drug superior to bupropion [#15], or a failure to detect a difference between bupropion and standard drug) does not provide convincing support for the sustained efficacy of bupropion. Active control studies may fail to detect a difference between treatments for reasons unrelated to drug effect. Only clinical investigations that demonstrate that an experimental drug is superior to a control treatment can provide unequivocal evidence that drug rather than spontaneous remission (or other factors) accounts for clinical improvement seen over the course of a study.

In some situations, admittedly, active control studies that fail to distinguish among treatments may provide useful information about efficacy. However, such situations are limited to those wherein the course of untreated patients is known with great certainty from historical evidence.

To be sure, general clinical experience suggests that patients recovered or recovering from a recent episode of depression are more likely to suffer a relapse if antidepressant treatment is withdrawn rather than maintained. However, a single, reliable estimate of relapse rate in untreated remitted

depressed patients, the sine qua non for the valid interpretation of antidepressant trials controlled only with an active drug, is simply not knowable.

Furthermore, even advocates of active control designs for the determination of drug efficacy admit that their use is questionable when their power to detect a difference is weak. Unfortunately, because of sample attrition (dropouts), statistical power to detect clincally substantial differences is especially poor in the later stages of the bupropion trials.

We acknowledge that similar questions might be raised about the sustained efficacy of currently marketed antidepressants. However, extensive clinical experience with the "older" antidepressants provides some measure of reassurance regarding their sustained efficacy. Unfortunately, that reassurance cannot be extrapolated readily to bupropion.

As you have indicated, bupropion is a novel drug, at least in regard to its mechanism of action which presumably differs from that of other antidepressants. Furthermore, bupropion shares some features in common with amphetamine or amphetamine-like drug substances, drugs which are known to produce only transient improvements in mood in some depressed subjects. Typically, tolerance occurs to the euphoriant effect of amphetamine, accounting for the general view that amphetamine and similar drugs cannot be considered true antidepressants. Therefore, we wish to be certain that the effects of bupropion do not rapidly dissipate with the passage of time.

Also, the only credible evidence supporting the efficacy of bupropion is derived from trials that are atypical by usual standards of antidepressant drug development. As noted above, they are of comparatively short duration, effectively three weeks, rather than the usual four to six weeks. Second, they were conducted in an inpatient setting which is not representative of the conditions under which the drug will be used most frequently, i.e., in an outpatient setting. As mentioned earlier, the only placebo controlled outpatient trial failed to demonstrate consistent support for the efficacy of bupropion.

Finally, the matter of the relationship between bupropion's dose and its adverse event profile and efficacy is especially important because bupropion's potential to cause seizures is apparently dose related. This is of particular concern because doses that cause seizures in a substantial proportion of the population (i.e., 800mg) are not far removed from the recommeded daily total dose of 750mg.

Consequently, we believe that additional clinical data on the proper use of bupropion is needed. The data should be obtained in controlled trials that can provide (1) evidence of bupropion's sustained efficacy, and (2) information about the relationship between the dose of bupropion administered, the extent of therapeutic response, and the incidence of adverse events.

We intend that information obtained in these studies will be used to revise and expand the information provided in labeling as directions for use.

It is essential that information bearing on these matters be collected in studies designed to demonstrate a difference between treatments. Thus, bupropion, administered at some dose within the range recommended in its labeling, may be compared with any number of control treatments, (e.g. placebo, a lower dose of bupropion, and/or a standard antidepressant) with the goal of showing its superiority to the control.

You are, of course, free to develop any specific designs that satisfy these requirements. The following "discontinuation" design study is offered as one possible approach to assess the duration of effectiveness question.

> Recently recovered depressed patients who were treated for their acute episode of depression with bupropion and are being "maintained" on bupropion during the early phase of their remission would be considered candidates for participation in the study. (As you are aware, recently "recovered" patients are usually maintained on antidepressant treatment for several months after their "recovery", that is, return to euthymia.) After one or two months of "euthymia" on bupropion, patients would be randomly assigned to 1) continued treatment with bupropion or 2) placebo. The sustained efficacy of bupropion would be demonstrated by a superior outcome of patients assigned to bupropion. Of course, the variable(s) used to assess outcome would need to be declared prior to the study and defined in operational terms (e.g. lower relapse rate, significant difference in clinical global depression score, etc.)
>
> We recognize that a procedure which provides for the withdrawal of treatment from recently recovered patients may be open to criticism or objection because of the belief, mentioned earlier, that continued treatment for six months or more reduces the risk for relapse. We are not aware of any persuasive body of evidence derived from adequately controlled experiments which directly addresses the question of how long antidepressant treatment should be continued. Not only can the case be made that such a study is ethically justified, but it can provide critically important information on the question of the need for extended drug treatment. Furthermore, the trial can be carried out with provision for subject rescue (i.e., reinstitution of treatment with known antidepressant). If this is done blindly, the difference in rates of rescue between the treatment groups can itself be used as an outcome assessment measure.

As you will recognize, other designs are possible, and we would welcome the opportunity to work with you to develop a specific experimental approach that would be mutually acceptable.

We are also prepared to discuss the details and to work cooperatively with your staff on the design of studies to further evaluate bupropion's potential to cause seizures or drug abuse problems and the biopharmaceutic study listed above.

Labeling

The draft labeling submitted is unsatisfactory as it is promotional in tone and contains claims and statements that either lack evidential support or are inadequately documented, and extensive revision is necessary. As noted earlier, labeling we would be prepared to accept follows. This labeling is intended to bring the form and tone of Wellbutrin's labeling into conformity with the labeling of other recently marketed antidepressant drug products.

The labeling follows the outline of 21 CFR 201.57. When text is provided by the agency, please use it without modification. In other sections, instructions or suggestions are provided. (The suggestions are indented and appear within brackets, [sic].) It is important, however, when providing new text, to supply appropriate documentation and annotations for any statement. The annotations will not appear in the final labeling, but are essential for our review.

The labeling should be printed and submitted in the format in which it will appear, but it will still be considered draft labeling. Therefore, the number of total copies printed should be limited, as further revision may be necessary.

Labeling text:

Wellbutrin^{R} Tablets (bupropion hydrochloride)

DESCRIPTION:

Wellbutrin^{R} (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 similar to those of fenfluramine and amphetamine. It is designated as 2-tert-butylamino-3'-chloropropiophenone hydrochloride. The molecular weight is 276.2. The empirical formula is $C_{13}H_{18}ClNO \cdot HCl$. Wellbutrin 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:

[insert chemical structure]

Bupropion is supplied for oral administration as 50 mg (white), 75 mg (yellow-gold), and 100 mg (red) film-coated tablets.

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, but it does inhibit the neuronal re-uptake of dopamine to some extent, and animal studies suggest that it may act through dopaminergic mechanisms.

[To Firm: Please use this section to describe, if known, the results of studies on the binding of bupropion to dopaminergic, serotoninergic, adrenergic, cholinergic and other CNS receptors.]

In animals, bupropion exerts dose-related CNS stimulant effects.

[To Firm: Please describe these CNS behavioral effects in greater detail.]

In animals, bupropion is epileptogenic at multiples of the human therapeutic dose (HTD).

[To Firm: In the next section, describe the epileptogenic action of bupropion observed in animal studies. In your description describe any differences between acute and chronic threshhold and the actual dose, in mg/kg, for each condition and species. You may compare these doses directly with the recommended maximum human dose.]

Absorption, Distribution, Pharmacokinetics, Metabolism and Elimination:

In man, following oral administration of Wellbutrin (bupropion), peak plasma concentrations are usually achieved within 2 hours, followed by a biphasic decline.

[To Firm: Please provide an indication of just what fraction of the oral dose is bioavailable; that is, how extensive is first pass or presystemic metabolism. Also, at this point, indicate which metabolites of bupropion have pharmacologic activity. It is important to provide ADME information on active metabolites, especially if they are likely, by virtue of either accumulation or intrinsic activity, to contribute to the beneficial or untoward effects of bupropion.]

The average half-life of the parent drug in its initial phase is 1-2 hours, and the half-life of the second phase is approximately 14 hours, with a range of eight to 24 hours in individual values. Plasma concentrations are dose-proportional following a single dose of 100 to 250 mg. Six hours after dosing, plasma levels are approximately 30% of peak levels. Considerable variation among individuals in serum "trough" concentration (i.e., C_{min}) has

been observed. In one study of patients 50 years and older, three of the 11 individuals demonstrated C_{min} values three to five times higher than those observed in the other eight patients who participated in the study.

Bupropion induces its own metabolism in three animal species.

> [To Firm: If you have any specific information about which enzyme system(s) is (are) induced, you may add it here. Please, however, do not characterize the extent of activation or induction with qualitative modifiers. Identify the metabolites and their routes of excretion. Discuss, in quantitative terms, how much and over what time course the parent compound accumulates. Provide, if available, similar data on all active metabolites. Provide, too, basic information on other parameters such as the volume of distribution, and describe the sites of principal metabolism -- gut, liver, kidney, etc. -- and the major routes of elimination. Describe how disease states or altered organ function may influence metabolism and/or elimination.]

In-vitro tests show that bupropion is 80% or more bound to human albumin at plasma concentrations up to 800 micromoles.

INDICATIONS AND USAGE:

Bupropion is indicated for the treatment of depression. However, because experience in clinical studies suggests that Wellbutrin (bupropion) may pose a greater risk of seizure than other antidepressant drug products (see Warnings), Wellbutrin should not generally be considered as the antidepressant of first choice for most depressed patients.

The efficacy of bupropion was demonstrated in clinical trials of three weeks duration which enrolled principally hospitalized patients with diagnoses of depressive neurosis and manic-depressive (depressed phase) disorder. The depressive illness of the hospitalized patients studied meets the Major Depressive Episode criteria of the APA Diagnostic and Statistical Manual III.

Major Depressive Episode 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.

The only placebo controlled trial of bupropion in depressed outpatients failed to provide unequivocal evidence of its efficacy.

Evidence to demonstrate the sustained effectiveness of bupropion after three weeks of use is not available from adequate and well controlled investigations, leaving unanswered the question of what constitutes the appropriate duration of treatment of patients who show a postive clinical response.

CONTRAINDICATIONS:

The concurrent administration of bupropion and a monoamine oxidase (MAO) inhibitor is contraindicated; at least 14 days should occur after discontinuation of an MAO inhibitor before beginning treatment with bupropion. Bupropion is contraindicated in patients who have shown an allergic response to it and in those taking medications which lower the seizure threshold.

WARNINGS:

[Note to Firm: The following statement should appear in bold type, within a box.]

Convulsions:

During the period of its clinical investigation, there were 20 reports of major motor seizures among approximately 2000 patients treated with bupropion at doses within and above the recommended dosing range. In 14 of 20 the dose at the time seizures occurred was 600mg per day or more, and in five subjects, the daily dose exceeded 11mg/kg (5mg/lb). Of particular importance, only one of these patients had a history of seizure disorder. Consequently, attention should be paid to the relative risks and benefits of bupropion in all patients, particularly at doses approaching the limits recommended (see DOSAGE AND ADMINISTRATION). Use of bupropion should be avoided in patients with a history of seizure disorder or cranial trauma.

[The box may close here.]

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 suggestive of impaired liver function were noted. Although scattered abnormalities in liver function tests were detected in patients participating in clinical trials, there is no direct evidence that bupropion acts as an hepatotoxin in humans. Nonetheless, the possibility of hepatotoxicity should be kept in mind, particularly in patients treated for protracted periods and those with preexisting impairment of hepatic function.

PRECAUTIONS:

General:

Suicidal patients:

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

Weight loss:

Bupropion appears to exert an anorexigenic effect. Weight gain of five or more pounds was only about one-third as likely among patients treated with bupropion as among patients receiving tricyclic antidepressants. Weight loss of five or more pounds was noted in about ten percent more bupropion patients than those on placebo in clinical trials. This effect should be considered when prescribing for patients who have lost weight in association with their depressive episode.

Agitation:

Many patients treated with bupropion, especially shortly after the initiation of treatment, experience increased restlessness, agitation, anxiety and insomnia. In controlled trials, these symptoms were often of sufficient magnitude to require treatment with sedative/hypnotic drugs and, in some instances, symptoms were sufficiently severe to require that affected patients be withdrawn from treatment with bupropion.

Use in patients with systemic illness:

There is no clinical experience establishing the safety of bupropion 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.

Because bupropion and its metabolites are almost completely excreted through the kidney, treatment of patients with renal impairment should be initiated at reduced dosage. 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 instructed to take bupropion on a t.i.d. basis and not as a single daily dose.

Patients should notify their physician if they become pregnant or intend to become pregnant during therapy.

Drug Interactions:

No information is available concerning the consequences of the concomitant administration of bupropion and other antidepressants. However, bupropion does induce hepatic enzyme systems, and this may influence the metabolism of other drugs. The effect of concurrent administration of other drugs on the metabolism and/or blood level of bupropion has not been studied. Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine (see CONTRAINDICATIONS).

Animal studies also suggest that bupropion potentiates the effects of L-dopa. Administration of bupropion to patients receiving L-dopa concurrently should be undertaken with caution, using small initial doses and small increments of bupropion.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

In a two year 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. In the bupropion studies, no increase in malignant tumors was seen in liver or other organs in either rats or mice.

Bupropion produced a borderline positive response 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.

Pregnancy:

Teratogenic Effects:

Pregnancy Category B. Reproduction studies have been performed in rabbits and rats at doses up to 30-60 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 bupropion on labor and delivery in humans is unknown.

Nursing Mothers:

It is not known whether bupropion is excreted in the milk of lactating women. Because many drugs are excreted in human milk, caution should be exercised when bupropion is administered to lactating women who are nursing.

Pediatric Use:

The safety and effectiveness of bupropion in individuals under 18 years old has not been established.

ADVERSE REACTIONS:

[To Firm: This section should consist of the following:

A. An introductory part which states in narrative style the more common reactions encountered with use of the drug, listing the effects which represent pharmacological extensions of drug action, i.e., what the physician and the patient may expect in routine use;

B. A table showing the incidence of adverse effects encountered during the controlled trials; and, finally,

C. A list of all adverse reactions, organized by body system or symptom class in the manner traditionally found in this section of the package insert.

In regard to the enumeration of events for item B, we request that the incidence rates for adverse reactions be based upon data obtained from controlled clinical trials that allow valid comparisons of incidence between treatments. We are especially interested in the incidence rates of events in all the controlled trials which included placebo, whether they were of two- or three-way design. Events enumerated for incidence calculations should include all events reported regardless of their significance or alleged cause. Incidence rates used should not be adjusted in any way (e.g., placebo incidence should not be subtracted from the drug incidence rate, adjustments for "baseline" should not be made, etc.). Incidence rates should be calculated separately for studies 06, 08-01, 14-01, and 15.

We define the treatment specific incidence for each event as the proportion of patients in the study experiencing, reporting, or being reported to experience the event while on treatment among the total randomized to the treatment and receiving at least one dose of the treatment.

Events occuring prior to treatment assignment should not be considered as adverse drug reactions unless the severity of the sign or symptom present at baseline worsened after treatment began. We make this point explicitly because your submission does not make clear how you constructed incidence figures. We suspect that you may have included phenomena in your tabulations of adverse events that occurred before patients were assigned to treatment. In our view, inclusion of events or phenomena present at baseline that subsequently abated, or remained unchanged merely adds background "noise" to the adverse reaction data base. For example, inclusion of depression, the basis for patient selection for treatment, as an adverse reaction is pointless. The inclusion and tabulation of less clearly defined phenomena, especially if most individuals experiencing the phenomena did so before they were assigned to treatment, causes even greater confusion. For example, your tabulation of adverse reactions includes the term "toxic confusion" and records that 15 to 20 percent of patients experienced this event. It is not clear to us what this means. Did patients entering the studies present with the clincal features of an organic brain syndrome or did they develop an organic delirium while on treatment? This distinction cannot be made when the adverse reaction tabulation contains baseline data.

In any event, while you have made it clear that you employed a systematic checklist to collect adverse event data, you have failed to explain how data obtained using this technique was combined with treatment emergent events that were reported spontaneously. Obviously, the two types of data are not easily combined. An event elicited using a checklist at baseline may not correspond qualitatively to a treatment emergent event that is actively brought to the investigator's attention, either by the patient or the staff.

Thus, we ask that the data on adverse reactions be retabulated to include only those events that were treatment emergent. We are most interested in the treatment emergent events that were spontaneously reported or observed. However, you may present the tabulations using both approaches, one with events reported spontaneously and the second with events elicited using the checklist. The latter should distinguish between patients whose symptoms or signs became more severe and those whose symptoms or signs arose de novo.

The problem of retrospective classification of untoward events using commonly understood terminology remains, and we ask that you follow a procedure we have successfully employed with other sponsors in the past.

> Because terminology for adverse events is often idiosyncratic, it will be necessary to construct a glossary so that related events may be enumerated under a single term. For example, motor restlessness, hyperactivity, wandering, and pacing may all be subsumed under the term agitation. Clustering of related events is intended to produce

a list of untoward events of reasonable length. After you have constructed such a glossary, we suggest that you provide us an opportunity to review it with you. Once we have agreed on the terms, the comparative incidence of each glossary term within each study for each treatment should be enumerated in tabular form. Generally, pooling across all studies is inappropriate because patients were studied at different doses, for various lengths of time, under variable conditions. It is advisable, however, to pool data from groups of studies planned and conducted according to common protocols. For example, the studies providing evidence of efficacy in this application may serve as the source of adverse reaction data for display in this section of the labeling.

Please use the text which follows exactly.]

There was no significant difference in the incidence of abnormalities in laboratory values in patients receiving either bupropion or placebo during the clinical trials except for elevations of blood glucose and LDH to abnormal levels, both of which occurred in approximately five percent of patients treated with bupropion.

DRUG ABUSE AND DEPENDENCE:

Studies in rodents have shown that bupropion exhibits some pharmacologic actions common to psychostimulants, including increases in locomotor activity and the production of stereotyped behavior and anorexia. Bupropion showed effects similar to amphetamine in several animal models of schedule-controlled behavior, and a drug discrimination study in rats showed stimulus generalization between bupropion and amphetamine and other psychostimulants. Monkeys were shown to self-administer bupropion intravenously. In contrast, 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 but provided no appreciable evidence of a psychostimulant effect. Tolerance to the antidepressant action of bupropion did not develop, and phenomena thought to constitute an amphetamine withdrawal syndrome were not seen during the post-treatment period. In a population of individuals experienced with drugs of abuse, a dose of 400 mg produced a modest elevation over placebo responses 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.

OVERDOSAGE:

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.

There has been very limited clinical experience with overdosage of bupropion. Three patients ingested 2000-3000 mg and recovered without incident.

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. 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 at present there is no clinical experience with lavage following an overdose of bupropion, it is likely to be of benefit within the first 12 hours post-dose 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 as to their effects in the management of Wellbutrin overdose. Because diffusion of bupropion 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:

Dosage should be initiated at a low level and increased gradually, noting the clinical response and any evidence of intolerance. Bupropion should be given on a t.i.d. basis, preferably with intervals of at least 6 hours between successive doses. Once and twice a day dosing has not been evaluated. It is likely that many patients will experience increased agitation and signs of motor restlessness and insomnia during the first several days of treatment. These untoward consequences may be managed by a more gradual escalation of dose or by the transitory administration of a sedative hypnotic. The latter adjunctive treatment need not be continued beyond the first week as tolerance to these activating effects of bupropion appears to develop in a few days.

[To Firm: Please develop the evidence and logic behind the dosage recommendations given in your draft labeling. We find no basis for your recommendation that mild to moderate depression be treated with lower doses of bupropion than severe depression. There may be little need to make such a distinction if dose escalation is titrated.

Because several of the patients who convulsed at 600 or 750 mg daily doses weighed less than 120 lb, we recommend that the upper limit of dose be stated "not to exceed 5 mg/lb (11 mg/kg)."

In any case, please provide a full explanation of the basis of your dosing recommendations.]

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. In clinical trials, older adults tolerated bupropion at the doses listed above. Usage of an initial dose of 300 mg/day is recommended, with adjustments according to effect.

Maintenance:

The lowest dose which maintains remission is recommended. This is likely to be within the range of 300-450 mg/day for most patients. While it is generally recommended that a course of antidepressant drug treatment should continue for several months, there has been no systematic evaluation of the efficacy of bupropion for a period beyond four weeks.

HOW SUPPLIED:

Wellbutrin (bupropion hydrochloride) tablets are supplied as follows:

50 mg (white) round biconvex tablets coded "WELLBUTRIN" and "50" - bottles of 100 (NDC 0081-0176-55)

75 mg (yellow-gold) round biconvex tablets coded "WELLBUTRIN" and "75" - bottles of 100 (NDC 0081-0177-55)

100 mg (red) round biconvex tablets coded "WELLBUTRIN" and "100" - bottles of 100 (NDC 0081-0178-55)

Store at 15°-30°C (59°-86°F).

End of Labeling Commentary

Our announced intention to approve your application is based upon your acceptance of the conditions enumerated in this letter. In particular, the development of satisfactory labeling and the submission of a fully documented and comprehensive Safety Update remain as major projects.

The Safety Update should contain any new data bearing on the safe use of Wellbutrin. Given the need for an extensive revision of the ADR section of the labeling, it would make sense to include the basis for ADR tabulations (e.g., glossary of terms, data eumeration, etc.) as part of the Safety Update.

If additional information relating to the safety or effectiveness of this drug becomes available before we receive the revised labeling, further revision of the labeling may be required.

We would appreciate your submitting copies of the introductory promotional material which is proposed for this product. Copies should be submitted with a cover letter to both the Division of Neuropharmacological Drug Products and the Division of Drug Advertising and Labeling. Please submit all proposed materials in draft or mock-up form, not final printed form. Also, please do not use Form FD-2253 for this submission; this form is for routine use, not proposed materials.

Please submit twelve copies of the printed labels and other labeling.

In addition, it is required that information and case reports of adverse reactions not previously submitted to your IND or NDA be provided.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Sincerely yours,

R Temple 12/31/84

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics

cc:
Orig. NDA 18-644
ATL-DO
HFN-100
HFN-120
HFN-120/Leber working copy October 23, 1984; revised 11/27/84
Hayes (revised 11/28/84)/Davis T A Hayes 11-29-84
Shultz/Zinsitz
Contrera/Rosloff
DeCicco
HFN-713/Stein
rd/mlm/10/17/84/10/23/84
ft/mlm/10/26/84
ft/mb/11/29/84
DOC 1513C

DOC 11/29/84
BNR 11/30/84

MADE IN JAPAN

SBA

Summary for Basis of Approval

NDA 18-644

Applicant:
Burroughs Wellcome Company
Research Triangle Park, NC 27709

Drug Generic Name:
bupropion hydrochloride

Brand Name:
Wellbutrin

I. Indications for Use:

WELLBUTRIN® is indicated for the treatment of depression in patients who fail to respond adequately to or who cannot tolerate alternative antidepressant treatments. Wellbutrin is not recommended as an antidepressant of first choice for most patients because its use at doses approximately one and one third times greater than the usually required daily dose (450 mg) is associated with a high risk of seizure (see Warnings).

The efficacy of WELLBUTRIN was demonstrated in placebo controlled clinical trials which enrolled principally hospitalized patients with diagnoses of depressive neurosis or manic-depressive (depressed type) disorder. The depressive illness of the patients studied most closely corresponds 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.

Evidence to demonstrate the sustained effectiveness of WELLBUTRIN after three weeks of use in placebo controlled investigations is not presently available.

II. Dosage form, route of administration and recommended dosage:

At doses that are one and one-third times the usually required dose (450 mg/day), (See Warnings), the observed incidence of seizure increases by as much as ten fold. This predicts a relatively narrow therapeutic ratio for the safe use of bupropion, especially as there is considerable inter-individual variability in the capacity of patients to metabolize drugs.

Consequently, it is particularly important to administer bupropion in a manner that is most likely to minimize the risk of seizure. Retrospective analysis of clinical experience gained during its premarketing development 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 in divided doses to avoid high peak concentrations of bupropion and/or its metabolites, and 3) the rate of incrementation of dose is very gradual.

WELLBUTRIN should therefore be given t.i.d., preferably with intervals of at least 6 hours between successive doses. Besides its apparent value in lowering the risk of seizure, gradual dose escalation is important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these side effects may be managed by temporary reduction of dose or the transitory administration of a sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment.

The following suggested dosing regimen incorporates the principles described above.

Usual Adult Dosage:

A starting dose of 225 mg/day given as 75 mg t.i.d. is recommended. Based on clinical response this dose may be increased by 75 mg/day no sooner than every three days according to the following schedule up to a total maximum daily dose of 450 mg/day. Of course, if distressing untoward effects supervene, dose escalation should be stopped.

Dosing Schedule

Treatment Day	75 mg Tablets			Total Daily Dose
	Morning	Midday	Evening	
1	1	1	1	225 mg
4	2	1	1	300 mg
7	2	2	1	375 mg
10	2	2	2	450 mg

In patients who do not demonstrate an adequate response after an appropriate period of treatment at 450 mg/day, drug should be discontinued.

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. The maximum recommended maintenance dose is 450 mg/day. While it is generally recommended that a course of antidepressant drug treatment should continue for several months and many patients have been treated with WELLBUTRIN in long-term clinical trials of up to 2 years duration, there has been no systematic placebo-controlled evaluation of the efficacy of WELLBUTRIN for a period beyond three to four weeks.

III. Chemistry:

A. Manufacturing and Controls: The description of the synthesis included in the application provides additional details not completely covered by the referenced U.S. Patent 3,819,706 which permits evaluation of the specifications and tests including those limits on impurities detected by the use of TLC and HPLC.

B. Stability Studies: Stability data has been included for all proposed marketed dosage strengths which support the recommended 18 month expiration dating for the drug product stored within the label stated limits.

C. Methods Validation: The analytical methods were validated by both the New York District and the Division of Drug Chemistry Laboratories and found satisfactory for regulatory purposes.

D. Labeling: The draft labels for 50 mg, 75 mg and 100 mg strengths include the required statements; however, those labels used for containers of 100's of the tablet strengths require repositioning of the Caution statement from the vertical side panel to the horizontal center panel.

E. Establishment Inspection: Evaluation of establishment inspection reports on January 18, 1983 by HFN-320 indicate the referenced fac ities are in conformance with CGMP's.

F. Environmental Impact Analysis Report: A statement on EIAR has been provided in accordance with 21 CFR, Part 25(g). This statement has been reviewed and found to be acceptable.

IV. Biopharmaceutics:

Using normal healthy volunteers, five full-scale bupropion HCl bioavailability/pharmacokinetic type studies were conducted along with several in-vitro dissolution studies.

1. In study No. 27, seven fasting male volunteers received 200 mg of an aqueous solution of ^{14}C-bupropion HCl orally. Blood, urine and fecal samples were collected for 96 hours.

   Study results indicated that over 96 hours, approximately 87% of the administered radiolabeled dose was excreted in urine, and approximately 10% was excreted in the feces. For those two routes of elimination, only a negligible amount of the parent drug, i.e., less than 1%, was recovered by each route. From the results of this study and from animal data, it appears that bupropion undergoes significant first-pass metabolism.

Nine metabolites were identified in urine; four were shown to have some pharmacologic activity in mice. For this study, the mean elimination (beta phase) half-lives were about 21 and 32 hours for bupropion and total plasma radioactivity, respectively.

2. In study No. 30, eighteen fasting male volunteers received single oral doses of 2 x 50 mg WELLBUTRIN tablets, and 100 mg and 250 mg of bupropion in an aqueous solution of bupropion HCl in a three period crossover study. Plasma samples were collected for 60 hours following administration. The 50 mg tablet lot tested was used in four clinical trials, including one that was positive; it was made on production-size equipment using the same procedures as those for the marketed drug.

   This study demonstrated that a single dose of two 50 mg tablets is equivalent in its absorption to the 100 mg aqueous solution, and that bupropion plasma concentrations are dose proportional following the 100 and 250 mg doses which are the lowest and highest (t.i.d.) doses recommended in the labeling.

3. Study No. 07A was a crossover bioequivalence study in which 16 fasting male volunteers received single doses of 4 x 50 mg capsules, 2 x 100 mg capsules, 4 x 50 mg tablets and 2 x 100 mg tablets. Plasma samples were collected for 24 hours following each dose. Calculated area under the plasma level vs. time curves (AUC) for this interval (0-24 hours) accounted for about 88% of AUC, calculated from time zero to time infinity.

   The tested batches of capsules were used in early clinical trials and it was necessary to compare them to the final marketed product. The batches of tablets in this study, however, were made by procedures different from those used for making the final marketed product. Although this study demonstrated that the different treatments are bioequivalent in absorption, other data are needed to conclude that capsules are equivalent to the marketed product (see study 07D).

4. Study No. 07B was a crossover in which 12 females and 12 males received 1 x 50 mg tablet, 1 x 100 mg tablet, and 2 x 100 mg tablets while fasting. Plasma samples were collected over 24 hours, and calculated AUC_{0-24} values accounted for about 88% of $AUC_{0-infinity}$ values. The tablet batches in this study were the same batches tested in Study No. 07A.

   This study demonstrated bupropion to be dose proportional over a dosing range of 50 to 200 mg.

5. Study No. 07D was an additional study period (fourth) added to Study No. 07B. Eleven male volunteers received 1 x 50 mg modified tablet and 11 female volunteers received 1 x 100 mg modified tablet. The modified tablets were from pilot batches that were made by the same procedures used for the final marketed tablets and were used in clinical trials.

This study demonstrated the 50 mg modified tablet to be similar in its extent of drug absorption to the 50 mg reference tablet. The 100 mg modified tablet, which had poorer in vitro dissolution, was shown to be marginally equivalent in its extent of drug absorption to the 100 mg reference tablet.

Using an in vitro dissolution test method (USP XX, Apparatus 1, 500 ml of 0.6% HCl, 100 rpm, 37°C) that tended to reflect in vivo drug absorption, three production size batches each of the 75 mg and 100 mg tablets, formulations proportionally similar in their active and inactive ingredients to the 50 mg tablet, were shown to have in vitro dissolution characteristics similar to the 50 mg tablet batch tested in Study No. 30.

Other general pharmacokinetic information from bio-studies included the following:

1. Bupropion plasma concentration-time data following single oral doses are described by a two-compartment open model with first-order absorption.

2. The half-life for the initial disposition phase (alpha phase) for the drug's bierponential decay curve is approximately 1-2 hours. The decay curve's second phase half-life (beta phase) is approximately 14 hours, with a range of about 8 to 24 hours.

3. Peak bupropion plasma concentrations occur within two hours following oral administration.

4. Bupropion is approximately 80% bound to human serum albumin.

As a condition of approval the Applicant is required to conduct as Phase IV studies 1) a multiple-dose dose proportionality study that covers the drug's recommended dosing range and 2) a multiple-dose study in geriatric patients.

The basis for requiring the Phase IV studies are the following:

1. The Applicant has conducted only single dose bioavailability/pharmacokinetic studies. From animal studies in the mouse, rat, and dog, bupropion has been shown to induce its own metabolism. For example, mouse whole body bupropion levels were reduced 58% following subchronic treatment for 10 days; dog plasma levels declined by 76% and 90% for two different dose levels following chronic treatment for 366 days).

2. Bupropion is extensively metabolized. Only a small fraction of the absorbed dose reaches the systemic circulation intact. Bupropion has at least two metabolites with significant pharmacologic activity. Because of their longer elimination half-lives, these metabolites, are likely to accumulate when bupropion is administered repeatedly.

For both reasons, well-controlled multiple dose bioavailability/pharmacokinetic studies are needed. In addition all bioavailability/pharmacokinetic studies have been carried out in normal healthy young volunteers. Although no differences in the drug's clinical behavior have yet been seen in different age groups, there should be a specific evaluation of metabolism and kinetics in the elderly who may have altered hepatic metabolism of drugs.

IV. Pharmacology:

A. Survey of Effects: Bupropion (BUP) is structurally similar to amphetamine, fenfluramine, diethylpropion, and other phenethylamine derivatives. Its pharmacological profile is that of a CNS stimulant with several similarities to amphetamine.

BUP was active in three types of tests predictive of antidepressant activity: prevention or reversal of tetrabenazine/reserpine effects in mouse, decreased immobility in the Porsolt behavioral despair test in rats, and potentiation of the behavioral effects of pargyline plus DOPA in mice.

BUP was shown to be a relatively weak blocker of the uptake of NE (norepinephrine) and 5-hydroxytryptamine (5-HT) into brain and peripheral nerve compared with classical tricyclics. It was somewhat more potent in blocking dopamine (DA) uptake, although the dose in rat (40 mg/kg i.p.) needed to produce serum levels high enough to cause 50% inhibition of DA (or NE) uptake into brain synaptosomes was 4x greater than the ED_{50}% in the Porsolt test. (The reverse holds true for imipramine regarding the potency ratio for "antidepressant effect" and NE uptake blockade.) The relationship between the blockade of DA (or NE) uptake and the "antidepressant" effect of BUP, therefore, is problematic. However, destruction of dopaminergic neurons with 6-hydroxydopamine + DMI blocked the effect of BUP in the Porsolt test in rats, suggesting that DA neurons are involved in some way. BUP did not inhibit MAO or elevate brain NE or DA at relatively high doses.

B. Comparison with Amphetamine and other CNS Stimulants: Many similarities between the pharmacological profiles of BUP and amphetamine (and other CNS stimulants) were noted, along with some differences, as follows:

1. BUP, amphetamine, and methylphenidate all produce dose-related antitetrabenazine effects and cause dose-related increases in locomotor activity in mice. However, the ratio of the i.p. ED_{50}% values for these two effects was approximately 1:2 for BUP, compared with 2:1 for amphetamine or methylphenidate. (In contrast, classical tricyclics cause decreased locomotor activity above "antidepressant" doses.)

2. Amphetamine and methylphenidate reversed tetrabenazine-induced sedation in mice whether given before or after the tetrabenazine; BUP was active only when given before.

3. Selective depletion of brain DA blocked the locomotor effects of both BUP and amphetamine; selective depletion of NE had no effect on either drug.

4. The locomotor effect of BUP and methylphenidate depends primarily on a storage (reserpine-sensitive) pool of catecholamines, whereas that of amphetamine depends primarily on newly synthesized (alpha-methyltyrosine sensitive) catecholamines.

5. BUP caused an increase in stereotyped behavior in rats; no direct comparison to amphetamine was made.

6. Several behavioral (operant) tests showed the profile of BUP to be more similar to amphetamine than to classical tricyclics.

7. BUP had an anorexic effect in mice. (Oral potency was at least 2x less than that of fenfluramine and diethylpropion; amphetamine was not tested.)

8. Drug discrimination studies in rats showed similarities between BUP and several CNS stimulants (e.g., amphetamine, methylphenidate, caffeine, cocaine) as well as the newer antidepressants viloxazine and nomifensine.

9. At high doses BUP caused hypothermia in mice, whereas amphetamine caused hyperthermia.

10. Grouping of mice caused an increase in the i.p. lethality of amphetamine but had no effect on that of BUP; BUP decreased the lethality of amphetamine in grouped mice.

C. Cardiac Effects: Cardiovascular studies showed rather large but generally transient decreases in cardiac output and right ventricular contractile force, and both increases and decreases in heart rate (HR) and blood pressure (BP), at i.v. doses of 1-20 mg/kg in anesthetized dogs and cats. (It is not clear if these results were corrected for vehicle effects). In conscious dogs, 20 mg/kg p.o. caused slight increases in HR and BP lasting at least 6 hrs.; in conscious rats 50 mg/kg caused a slight increase in HR lasting 3 hrs. Comparison drugs were not used in these studies so that the relative potency of BUP in causing these changes is not known. No effect on EKG (aside from increased HR) was seen in dogs at 10 mg/kg i.v. (2 mg/kg/min). In dogs, 5-10 mg/kg i.v. caused rather large increases in respiratory rate and smaller increases in minute volume. A relatively weak depressant effect on cardiac tissue in various in vitro preparations was noted which may have been due to the local anesthetic properties of BUP (equipotent with cocaine in guinea pig cornea); the potency of BUP was generally 5-15x less than that of imipramine and amitriptyline.

D. Receptor Agonist/Antagonist Effects: Several studies were performed to assess the anticholinergic effects of BUP, and such effects were generally weak or absent. Antagonist actions at other receptors (adrenergic, serotonergic, and histaminergic) were also generally weak or absent, although reference drugs which could have validated the systems and formed a basis for estimating the relative potency of

BUP were not used. Likewise, binding studies showed little or no interaction of BUP with a variety of receptors, but no reference drugs were used.

E. ADME/Pharmacokinetics: ADME/pharmacokinetic studies were performed in rat, mouse, and dog. After oral dosing, plasma levels of BUP peaked rapidly (within 1/4-1/2 hr.) and declined rapidly with a T 1/2 in the 1-4 hr. range. Over a dosage range of 10-100 mg/kg p.o. in rats, plasma levels increased with increasing dose but slightly less than proportionately at the highest dose. Studies comparing plasma AUC after i.v. and p.o. dosing showed a bioavailability of 8-21% in rats and 4% in dogs; however, excretion studies using labeled drug showed complete absorption in dogs and a high, if not complete, degree of absorption in rats after p.o. dosing. BUP was widely distributed in rat tissues; levels were highest in liver and lung after p.o. and i.p. dosing, respectively; lowest levels were in plasma. BUP was shown to be rapidly and extensively metabolized, in agreement with the low oral bioavailability of the drug. Plasma and tissue levels of metabolites were generally substantially higher than those of unchanged drug, except in the brain. Very little unchanged BUP was found in rat or dog urine; acidic metabolites were predominant; m-chlorohippuric and m-chlorobenzoic acids, and a conjugate of the former were identified, presumably arising from side chain oxidation. In human urine, in contrast, acidic and basic metabolites were present in nearly equal amounts. Plasma and tissue levels of metabolites declined much more slowly than those of unchanged drug; in one study the plasma T 1/2 for metabolites appeared to be about 12 hours, suggesting that whereas the parent drug is unlikely to accumulate with repeated dosing due to its short T 1/2, metabolites may. In one mouse study, however, 10 days dosing did not lead to an accumulation of metabolites; such a tendency may have been counteracted by an enzyme-induction effect, since levels of unchanged BUP were decreased.

The ability of BUP to induce liver microsomal metabolic enzymes was demonstrated in rat, mouse, and dog. In rat, pre-treatment with 15-50 mg/kg/day p.o. for 13 days decreased the rise of BUP in plasma seen after an acute dose of 50 mg/kg i.p., and 50 mg/kg/day p.o. for 4 days decreased the rise of BUP in tissues seen after an acute dose of 50 mg/kg i.p. In mouse, 50 mg/kg i.p. for 8 or 10 days decreased the rise in whole body level of BUP seen after an acute dose of 50 mg/kg. In dog, plasma levels after 1 year treatment at 40 or 80 mg/kg/day p.o. were significantly less than those seen on day 1.

Studies on pentobarbital sleep time in mice showed a decrease after 5-150 mg/kg/day p.o. for 10 days; the effect at HD was slightly less than the effect of phenobarbital pretreatment at 80 mg/kg/day; in rats a slight decrease was seen at high doses (100-150 mg/kg/day) only. It is possible that part or all of these effects on pentobarbital sleep time were due to CNS stimulation by BUP. Thus, although BUP appears to induce its own metabolism, its ability to induce the metabolism of other compounds has not been clearly demonstrated.

Excretion of BUP + metabolites was shown to be primarily via the kidney in rats (78%) and exclusively by this route in dogs.

Over concentration ranges that were stated to be "normally found in animals and during clinical studies in man," BUP was 75-85% bound to plasma proteins from mouse, rat, dog, and man. Binding was generally constant over the concentration ranges used, although it tended to fall off in man at the highest concentration (1000 micromolar).

There appear to be some sex differences in the disposition of BUP, at least in rats. Plasma and tissue levels of unchanged drug, plasma AUC, and oral bioavailability were several-fold greater in F; T 1/2 was greater in F in one rat study, but apparently not in another. There did not appear to be any important sex differences in metabolic pattern or excretion, although data on these points were limited. No sex differences in plasma levels in dogs were apparent, although only two dogs per sex were used. The acute toxicity of BUP in rats was slightly greater in F than M, but the reverse appeared to be true in the chronic rat toxicity studies.

F. Toxicology: The acute oral LD_{50} was 544 (M) and 636 (F) mg/kg in mouse, and 607 (M) and 482 (F) mg/kg in rat. Acute i.p. LD_{50} was 273 and 263 mg/kg in male mice and male rats, respectively. Prominent acute signs in the mouse included: ataxia, convulsions, prostration, ptosis, and compulsive gnawing by both routes, plus labored breathing, decreased respiration, and salivation after i.p. only. Signs in the rat included: ataxia, loss of righting reflex, labored breathing, prostration, salivation, ptosis, arched back, and compulsive gnawing by both routes.

Acute p. o. toxic interaction studies were performed in rats. Phenelzine (at highest no-effect and highest non-lethal doses) caused a marked decrease in the LD_{50} of BUP. (However, no pharmacodynamic interactions were seen in several tests at lower doses). Only a slight potentiation of the lethality of BUP was caused by treatment with ethanol at its highest non-lethal dose; this was seen in F only. Lethal potentiation was noted between BUP and amitriptyline (each given at 1/2 LD_{50}), in F only.

The following oral subacute/chronic toxicity/carcinogenicity studies were performed (daily dose in mg/kg in parentheses):

Rat	(Long Evans)	3 month (150, 300, 450)
Rat	(Charles River CD)	55 week (25, 50, 100)
Rat	(Charles River CD)	2 year (100, 200, 300)
Mouse	(Charles River CD-1)	21-22 month (50, 100, 150)
Dog	(Beagle)	3 month (15, 35, 75 to 150)
Dog	(Beagle)	1 year (40, 80, 150)

The principal findings are as follows:

1. Rat:

a. General: Increased mortality, associated with convulsions, was seen in the 2 year study at all doses (except LD M), and was marked at HD (300 mg/kg). No effect on mortality was seen in the 55 week study (HD = 100 mg/kg); in the 3 month study 2/20 died at 450 mg/kg. Observed signs included urinary incontinence/urine staining (all studies, all doses), dried blood around nose/mouth (55 wk and 2 yr studies, all doses), and convulsions (2 yr study, all doses). Slight decreases in bodyweight gain were seen in all M groups in the 2 yr study. Slight decreases in blood glucose were seen above 100-150 mg/kg.

b. Gross/Histopathology: The most prominent findings were:

(1) Liver: In the two-year study there was an increase in incidence of hyperplastic nodules and hepatocellular hypertrophy at all doses; hyperplasia was increased at LD and MD only. (In a consultant report many of the hyperplastic nodules were reclassified as "foci or areas of altered hepatocytes.") The incidence of these findings is underestimated in the drug groups in a dose-related fashion due to the increased mortality and the late appearance of the lesion. (Most hyperplastic nodules were found at the terminal sacrifice, and almost all were found after 90 weeks). There was no increase in the incidence of hepatocellular carcinoma; the observed incidence 0/147, 3/140, 1/141, and 1/123 in control, LD, MD, and HD, respectively is within the historical control range. Similar findings were not seen in the 55 week study (HD = 100); in the 3 month study a low incidence of hyperplasia and "prominent cellular organelles" was seen at all doses. Increased liver weights were seen in all studies at all doses except LD in the 3 month study. Grossly, in the 2 year study, slight increases in the incidence of masses/nodules/raised area (F only) and dark red/brown/hemorrhagic foci were seen at all doses at termination but not among deaths.

The significance of these proliferative lesions in the liver is not straight-forward. The sponsor suggests they may arise as either (1) a result of microsomal enzyme induction or (2) an adaptive response to hepatic injury. Regarding the former, BUP has been shown to induce its own metabolism (see above). Regarding the latter, no other indication of hepatic damage (including blood chemistry) was obtained in rats, although some indications of liver damage were obtained in dogs.

Nonetheless, there has been controversy concerning the possible role of hyperplastic nodules in the development of hepatocarcinomas in rodents. Several years ago some

pathologists suggested that such lesions should be considered "pre-neoplastic" or "neoplastic" because it was hypothesized that they could progress to malignant tumors (Squire and Levitt, Cancer Res. 35: 3214, 1975; Williams, Biochem. et Biophys. Acta 605: 167, 1980). These pathologists thus suggested replacing the term "hyperplastic nodule" with "neoplastic nodule". (It has also been suggested that "foci of cellular alteration" are also "pre-neoplastic" in the sense that they might progress to neoplastic nodules or even directly to malignant tumors.)

The subject was discussed at a symposium (Rodent Liver Nodules - Significance to Human Cancer Risk?, International Symposium of the Society of Toxicological Pathologists, May 10-12, 1982, Reston, Va.; proceedings published in Toxicologic Pathology, Volume 10, Number 2, 1982). Data was presented to challange the view that proliferative hepatic lesions are progenitors of hepatic malignancy. The outcome of several types of experimentally induced hepatic nodules, including those induced by drugs, was reviewed. In several cases, nodules and foci of cellular alteration regressed after cessation of treatment, documenting that proliferative lesions are not inherently malignant. The fact that proliferative lesions are not necessarily transplantable was considered to add additional support to conclusion that these lesions may be entirely benign. In any event, based on these and related observations, symposium participants reached an informal consensus th[at] the term "neoplastic nodule" was a misnomer and that su[ch] lesions do not necessarily progress irretrievably to malignancy. However, while these proliferative lesions may not be autonomous and do not necessarily progress to malignancy, it is possible that they might progress under the influence of continued drug administration or, alternatively, they may simply be "markers" for malignancy, i.e., if a drug produces such lesions it is an indication that the drug is also likely to produce malignancies. Again, based on an informal vote a majority of pathologists present at this symposium appeared to believe that the production of nodules or foci of cellular alteration in the liver by a chemical is not sufficient evidence to establish that chemical as a hepatocarcinogen. Although several potent hepatocarcinogens do produce nodules and foci of cellular alteration, there are several examples of drugs, dietary regimens, and surgical manipulations which produced nodules or foci but did not produce malignancies despite prolonged treatment. Thus, no generalization about the carcinogenicity of agents which cause nodules is possible.

Thus, bupropion's capacity to produce proliferative lesions raises questions that cannot be answered absolutely. It is reassuring, however, that despite continued administration of bupropion in a lifetime rat study, the proliferative

lesions did not progress to malignancy. In addition, the nodules were very late appearing (most seen at terminal sacrifice; almost all after 90 weeks), in contrast to the effects of established hepatocarcinogens. In summary, the evidence at this time does not support identification of BUP as a hepatocarcinogen.

(2) Hemosiderosis: In the 55 week rat study an increase in hemosiderosis (as determined either by H + E stain, iron stain, or presence of pigment-containing macrophages) was seen in spleen, kidney, lung, and liver. This was seen primarily at HD, but lung and liver were not examined at the lower doses. Likewise, in the two year study, evidence of increased hemosiderosis was seen in spleen, lung, and lymph nodes at MD and HD; these organs were not examined in LD animals. No other pathological findings were present to help explain the increased hemosiderosis. Hematology did not reveal any striking abnormalities. (2/20 HD in the 55 week study had low Hb, Hct, and RBC; no effect was seen in the two year study; slight decreases in Hb and Hct were seen in the 3 month study, but no hemosiderosis reported.)

(3) Kidney: Slight increases in the incidence of chronic nephritis were seen in the 55 week study (HD only) and in the MD and HD groups in the two-year study in which LD was not examined. (There were no consistent effects on lab tests indicative of renal function; in the 55 week study there were elevations of BUN in 3/40 rats at MD and HD.) Kidney weights were elevated in all studies at all doses.

c. Neoplasia: There were no drug-related increases.

2. Mouse:

a. General: In the 22 month study, mortality was increased in all M groups and HD F. There was no effect on weight gain. As in rats, convulsions were seen (MD and HD). Laboratory studies were not performed.

b. Gross/Histopathology: In the 22 month study most prominent postmortem findings were in the uterus, consisting of a dose-related increased incidence of extremely dilated blood vessels, with thrombus, in all F groups; this increase was seen both among mice which died and those which survived to termination, suggesting it is not associated with lethality. On gross examination, there was an increased incidence of uterine nodules/masses; according to the histopathologic report, these were extremely dilated veins with thrombosis. The antemortem urogenital staining noted was probably also related to these changes.

An increased (dose-related) incidence of acute metritis and/or pyometritis in the uterus was also seen in all drug groups, along with a slight increase in the incidence of uterine hemorrhage in all drug groups (not dose-related). Splenomegaly and hematopoiesis in spleen and liver were also seen in F; the pathology report considered these to be secondary to the uterine blood loss, although an independent analysis by the sponsor did not show a good correlation between the uterine and spleen/liver changes. Changes similar to those in uterus were not clearly seen in other organs, although a low frequency of hemorrhage and ulcer in stomach and small intestine was noted, primarily at HD. The incidence of thrombus in heart was increased in HD among deaths but not at termination, and the incidence of congestion and/or hemorrhage in lung was increased in HD M. An increased incidence of atrophic tubules in testes at HD was also seen in this study, although there was no effect on the incidence of aspermatogenesis.

c. Neoplasia: There was no drug-related effect on the incidence of neoplastic changes.

3. Dog:

a. General: No significant toxic effects were seen in the 90 day study (HD = 75 to 150), a slight increase in liver weight was seen with no associated pathology. In the one year study, the HD (150 mg/kg) produced 3/16 deaths; this dose also produced convulsions in one dog and body trembling in several others. Emesis and ptyalism were seen at both MD and HD. Bodyweight gain was decreased at HD. There was a dose-related elevation of serum alkaline phosphatase in all groups at all months measured, and the magnitude increased over time; no elevations were seen in recovery dogs. Elevations of SGOT and SGPT were also seen mainly at the higher doses, starting at three months but not clearly progressive over time. Some recovery dogs still had elevated SGPT after the recovery period, but of smaller magnitude. Slight increases in BSP retention were seen at MD and HD. Liver weights were increased in all groups (dose-related) at both six and 12 months but not at recovery.

b. Gross/Histopathology: In the 1 year study microscopic exam of liver showed several drug-related changes including finely granular "ground glass" cytoplasm (MD and HD, seen at 12 months but not at six months or after recovery period), dark brown pigment in hepatocytes and phagocytic cells (MD and HD, seen at 12 but not at six months, and seen at all doses after recovery period), slight coarse vacuolation of hepatocytes (seen in HD at 12 months and in LD and MD at six months and in the one MD which died; not seen after recovery period), and bile duct proliferation (very slight to slight, seen at MD and HD at 6 months and at HD at 12 months, also seen after recovery period in 2/4 LD and 2/3 HD and in 1/4 control but absent in three at MD). Kidney weight was elevated in all groups at 6 months; at 12 months an increased relative weight only was seen at MD and

HD. Histologically, the incidence and severity of brown pigment in tubular epithelium was increased in all groups at termination. The incidence of this finding among recovery dogs was similar across groups although severity was greater at MD and HD. No clear abnormalities of renal function were noted.

G. Mutagenicity: BUP was weakly positive in some Salmonella strains in the Ames Test. (TA 100, both with and without metabolic activation, and TA 1535, with activation only.) Greatest effects were 2-3 X control revertant count; positive controls caused 6-10 X increases. In a rat bone marrow chromosome study, an increase in aberrations was seen at 300 but not 100-200 mg/kg p.o., given for 5 days; the increase was 2-3 X control compared to 6-19 X for the positive control. In a study of binding to rat liver DNA after oral administration, it was found that the binding of BUP (+ metabolites) was much lower than that of known hepatocarcinogens; it was concluded that the effect is nonspecific.

H. Reproduction: A two generation reproduction and fertility study was performed in rats. Both M and F (of the F 0 generation only) were drug treated at dosages of 100, 200, and 300 mg/kg/day. Except for wobbly gait in one MD and one HD, no drug-related signs were observed. Bodyweight gain was slightly increased in all treated groups, but was not dose-related. There was no drug-related increase in mortality. No drug effects on M or F mating performance, on F fertility or reproductive parameters, or on pup (F 1 generation) survival and body weight were seen. There were no significant effects on mating or reproductive performance of the F 1 generation. Pup survival (F 2 generation) was not affected by treatment, although F 2 pups in all drug groups had slightly increased body weight.

Segment II reproduction studies were performed in rats and rabbits. In rats (dosages = 150, 300, and 450 mg/kg/day), signs including ataxia, urinary incontinence, and gnawing were seen primarily in HD dams. Mortality was increased at HD (24/53 = 45%). Bodyweights were transiently decreased in all drug groups after the first dose. There was a slight decrease in fetal weight and length in all drug groups, not dose-related. There were no drug-related effects on gross or visceral fetal abnormalities. A slightly increased incidence of reduced or absent ossification of some bones was seen at MD and HD and to a smaller extent at LD; this was reflected in a slight increase in total skeletal findings in all drug groups.

Two segment II reproduction studies were performed in rabbits, one within the sponsor's lab and the other by International Research and Development Corporation. Dosages were 25 (latter study only), 50, 100, and 150 mg/kg/day. Does displayed slight hypoactivity at 100 and 150 mg/kg, and convulsions, ataxia, tremors, and hyperpnea were seen in some does at 150; convulsions were also seen in one doe at 100 mg/kg. In one study, decreased doe food consumption on individual days was seen in all drug groups, but no overall effects on body weight were seen; however, the other study showed reduced weight gain at 100 and 150 mg/kg. There was no drug-related increase

in mortality in either study. Fetal weight was slightly reduced in all drug groups at 50 mg/kg and above, and these reductions were dose-related. Fetal length (reported in one study) was slightly reduced at 150 mg/kg. There was a trend toward an increase in gross, visceral, and skeletal abnormalities in fetuses of all drug groups, which was partly dose-related. The increase in gross and visceral abnormalities does not appear to be biologically significant in that no pattern of abnormalities was seen, i.e. there was no significant increase in any particular type of abnormality, and the overall percent of fetuses affected was relatively low. Regarding skeletal abnormalities, a significant increase in supernumerary ribs occurred in all drug groups which was dose-related in one study but not in another. In addition, one study showed an increase in reduced ossification of the palate (all drug groups, not dose-related), and the other study showed an increase in delayed ossification of the fifth phalanx of the forelimb at HD only as well as a low incidence of barbell-shaped thoracic centra in all drug groups. Reduced ossification (also seen in rat study) and supernumerary ribs are considered to be normal variations, and it is concluded that the above skeletal findings, as well as the findings of decreased fetal weight and length, were secondary consequences of maternal toxicity.

V. Clinical Evidence:

This section presents 1) a brief overview, 2) a description of the adequate and well-controlled clinical trials which provided evidence of efficacy, 3) a brief review of other adequate and well controlled controlled trials which failed to support the efficacy claim, and 4) two sections listing general and special safety considerations pertinent to this drug product.

A. General: The approval decision is based on clinical studies enrolling a total of approximately 2400 patients. The original NDA provided reports on clinical trials involving 1300 patients and volunteers. Prior to final approval, however, data and information from experience with an additional 1000 or so individuals was submitted and reviewed.

The agency relied solely upon the results of placebo controlled investigations to reach its conclusion that bupropion is an effective antidepressant. The amended application provided full reports on 5 investigations that employed placebo controls: numbers 06, 08, 09, 14 and 25. The agency also evaluated the results of all active control investigations. Only one of the latter, study 15, demonstrated consistent, statistically significant differences among treatments.

Among the placebo controlled trials, only 06 and 25 provide clear support for the antidepressant efficacy of bupropion under the conditions of use recommended in its approved labeling. Study 14 is a strongly positive study, but a substantial proportion of the individuals who participated in it were treated with bupropion at

doses exceeding the maximum recommended daily dose (450 mg/day). Study 08 was equivocal in its results, showing significant treatment by investigator interactions between its two major components (08-01 and 08-02).

B. Studies demonstrating or supporting efficacy for this indication:

Two placebo controlled inpatient studies of similar parallel design provide persuasive evidence of bupropion's efficacy as an antidepressant.

1. Study 06 (K. Brodie, W. Zung, L. Fabre, and D. Garver)

a. Design: The study was planned as a 28-day trial comparing titrated doses of bupropion with placebo. Because of its design, which allowed withdrawals at day 21, many patients failed to complete the full 28 days and 21 days is a more accurate description of the study's duration.

The inclusion criteria in this and other inpatient studies required that patients be non-psychotic and exhibit a depressed mood (characterized as sad, blue, low, despondent, hopeless, or gloomy) plus at least four of these symptoms:

anhedonia
poor appetite
sle 'ifficulty (insomnia or hypersomnia)
loss of energy, fatigue, lethargy
agitation
retardation
decrease in libido
loss of interest in work or usual activities
feelings of self-reproach or guilt
diminished ability to think or concentrate
thoughts of death and/or suicide attempts
feelings of helplessness and hopelessness
anxiety or tension
bodily complaints

Exclusion criteria for this and other studies were as follows:

actively suicidal ideation
schizophrenia
organic CNS disease
severe dementia
incapable of spontaneous conversation or behavior
seizure disorders
alcoholism
glaucoma
prostatic hypertrophy
abnormal laboratory or ECG values

women of childbearing potential who were not willing to sign an intent to avoid pregnancy form
lactating women, if breastfeeding

Patients were randomly assigned to either BUP or PBO. Drug was administered according to a titration schedule that allowed for individual dose adjustment. In the first week, patients received BUP in a dose of 300 to 400 mg (divided t.i.d.). From day 8 to the end of the study, the dosage could be increased to 600 mg/day. Psychoactive drugs were interdicted, except chloral hydrate for sleep.

Weekly assessments included the Hamilton Depression (HAM-D), Hamilton Anxiety (HAM-A), Self-Rating Depression (Zung-D), Self-Rating Anxiety Scale (Zung-A), Clinical Global Impressions (CGI), Dosage Records and Treatment Emergent Symptoms (DOTES) Scales and the Patient Termination Record. The protocol permitted replacement of any subject who dropped from the study before 21 days and interdicted use of psychoactive drugs.

b. Conduct and Execution: A total of 85 adult inpatients were enrolled. The principal diagnoses (DSM-II classification) were:

manic-depressive (depressed)	55%
depressive neurosis	35%
involutional melancholia	8%
manic-depressive (circular)	2%

Over the evaluable course of the study (days 1-21), the dose of BUP for the vast majority of patients was 450 mg or less. At day 7, all participants were on 450 mg or less. At day 14, 42 of 50 participants were receiving 450 mg or less. At day 21, 38/49 patients were receiving 450 mg or less. Ten patients (BUP x 7, PBO x 3) received hypnotic drugs at some time during the study, usually flurazepam. Dropouts occurred for:

ineffectiveness or deterioration	2 PBO
adverse reactions	1 BUP, 1 PBO
intercurrent illness	1 BUP
did not return or refused treatment	4 BUP
administrative or uncooperative	1 BUP, 2 PBO

The number of patients participating after day 21 was markedly reduced from the original number.

c. Results: Because a substantial number of patients dropped out before the day 28 ratings, analyses were performed on the combined data from all three sites using the day 21 ratings or the last observation carried forward (LOCF) for those who dropped out earlier. Four combined study analyses were performed by weighting centers equally as well as proportionally to sample size and by subtracting as well as not subtracting baseline scores. These analyses all provided consistent statistical evidence of effectiveness which is provided in the following table:

Protocol 06

LOCF (21) Analyses of Wellbutrin Minus Placebo
Change from Baseline Score for
All Patients Randomized
Investigators Weighted Proportionally to Sample Size

Scale	# of Patients	Wellb. Minus Pbo Change from Baseline	2-tail p-value
HAMD Total	81	3.82	.05
CGI-SI	81	.631	.04
Depr. Item* of HAMD	79**	NA*	.01

* Based on Blocked Wilcoxon Rank Sum test of LOCF(21) value blocked on baseline value

** Two observations fell into blocks with no other data.

2. Study 25: (Investigators: G. Chouinard, A. Haleris, O. Karabanow and M. Mandel/C.Welch).

a. Design: The study was planned as a four site, multicenter parallel comparison of two levels of bupropion (300 mg and 450 mg a day) with placebo. The original goal of the study was to evaluate the "efficacy and chronic dose tolerance of low doses of [bupropion] in ...hospitialized depressed patients." The study called for each site to contribute 30 patients, 10 assigned to each of the three treatment arms.

Inclusion and exclusion criteria were essentially identical to those employed in study 6 described above. Patients recruited were overtly depressed, non-psychotic, without evidence of severe dementia or a recent history of alcohol or substance abuse. The current depressive episode had to have been present at least 4 weeks and not longer than 2 years. A minimum total score of 18 on the 21 item version of the Hamilton Depression Scale and at least a moderate rating on the Global Severity Scale were required for admission.

Schizoaffective and schizophrenic patients were to be excluded. Patients could also be excluded for medical reasons if it was thought necessary by investigators or monitors.

Concomitant medications: Washout of active psychotropic medications was required before the start of active medication: one month for fluphenazine esters, two weeks for MAOIs and

phenothiazines, and one week for benzodiazepines. During the trial, the protocol disallowed the use of all psychotropic medications save chloral hydrate for sleep.

Rating instruments for assessment of outcome included the Hamilton Depression and Anxiety Scales, the patient rated Zung Depression and Anxiety Scales, Clinical Global Impressions, and the SCL 90. Laboratory tests and side effect assessment was carried out predrug and throughout the trial.

The protocol allowed replacement of patients who terminated prior to day 21.

b. Conduct and Execution:

One hundred and twenty eight patients were randomized to treatment. Eighteen patients did not have a rating obtained on drug treatment. Because of the protocol design which allowed withdrawals at day 21, many patients did not complete the full 28 days of the study. Indeed, 24/43 placebo, 22/45 bupropion 300 mg and 24/40 bupropion 450 mg patients did not complete the study. The causes of premature termination, however varied with treatment assignment. Among the 43 placebo patients, 16 discontinued because of deterioration or lack of efficacy. Among the 85 treated with bupropion only 14 terminated for similar reasons. In contrast, no placebo patient was terminated because of an adverse effect, but 4/45 bupropion 300 mg and 7/40 bupropion 450 mg patients were.

c. Analysis of Results:

The study was analysed by 1) an intent to treat analysis employing a last observation carried forward (LOCF) methodology and 2) an observed cases (i.e., those patients actually observed at a particular time) analysis. 109 patients were evaluated in the LOCF analysis; 19 patients who had been randomized to treatment were excluded due to the absence of efficacy assessments during double-blind treatment.

The results of the LOCF analysis at day 21 are generally more favorable than those obtained with the observed cases method. The differences between the results of the two analyses are related to the fact that both the timing of withdrawals and the scores of the patients at the time of their withdrawal differ as a function of treatment assignment. In particular, there are more dropouts before day 21 among placebo patients (6) than among bupropion 300 mg (4) and bupropion 450 mg (4). Furthermore, as the causes for dropout would predict (see above), the status of bupropion assigned patients at the time of their withdrawal was generally better those assigned to placebo. For dropouts on bupropion 300 mg, the average improvement in the Ham D total score was 16 points. For dropouts from the bupropion

450 mg group, the average improvement was 20 points. In contrast, the average improvement among placebo dropouts was only 6.5 points.

In summary, the missing data brought forward in the LOCF is generally more favorable to drug and less favorable to placebo. In contrast, the observed cases analysis is strongly biased against bupropion because prematurely terminating bupropion patients who were doing comparatively well and prematurely terminating placebo patients who were doing comparatively poorly were excluded from it.

In its assessment of study 25, the agency relied primarily upon the results of the LOCF analysis evaluated at day 21. Day 21 was selected because of the large number of dropouts that occurred in all groups following that study day. The results of the LOCF analysis are presented below for the HAM D total score.

Hamilton Depression Total Score: Study 25
LOCF data: Mean decrease from baseline

Day	Placebo	Bupropion 300mg	Bupropion 450mg	PBO vs. 300mg*	PBO vs. 450mg*
7	9.6	8.8	10.4	.64	.65
14	13.1	13.2	17.0	.95	.06
21	13.3	16.1	17.7	.21	.06

*(2-tail 'p' values)

By day 21 (LOCF analysis) patients assigned to 450 mg of bupropion improved to a statistically significant greater extent (or nearly so) than those on placebo on other standard measures of efficacy (i.e., Ham-D retardation factor (p=0.03), Clincal Global improvement rating (p=0.06) and Clinical Global Severity of Illness (p=0.014)). The LOCF analysis, however, failed to detect statistically significant differences between bupropion and placebo on the HAM-D depression item (i.e., at day 21, p=0.26 and p=0.87 respectively for the 300 mg and 450 mg groups). This failing may reflect the early timepoint employed for trial assessment. If the depression item reflects primarily verbal reports of patients, it is likely to lag behind other measures of improvement, much as improvement judged by self-report scales lags behind improvement judged by observer scales in depressed patients.

d. Conclusion:

Despite the relatively high drop-out rate, analysis of the drop-out pattern and use of scores at the time patients left the study show a clear improvement in the treated group on the Hamilton Total Score and the Clinical Global Items providing evidence of bupropion's antidepressant efficacy. The study does <u>not</u>, however, demonstrate the efficacy of a 300 mg dose.

The following study supports the efficacy of bupropion at doses between 450 and 600 mg. Because a substantial proportion of patient were treated at doses outside the recommended dose range, the study cannot be considered a persuasive source of evidence of efficacy for the drug's approval under the proposed labeling. However, given the wide variability in the capacity of individuals to metabolize drugs, and the variability of the pharmacodynamic response, the study does lend additional support to the conclusion that bupropion is effective as an antidepressant.

3. .Study 14 (J. Feighner and J. Cohn)

a. Design: This was a five week (four weeks of treatment, one week of follow-up) randomized comparison of titrated bupropion and placebo at two centers.

b. Conduct and Execution: There were 117 patients enrolled and 86 included in the efficacy analysis (60 BUP, mean age = 45.9 yr; 26 PBO, mean age = 48.2 yr; 50 M, 36 F). The sponsor's analyses excluded five patients (BUP x 2, PBO x 3) who received psychoactive concomitant medications for eight or more days for anxiety or agitation, 25 who were treated (BUP x 14, PBO x 11) for less than 14 days, and one who received less than the minimum dose of BUP for 27 days. Principal diagnoses were:

depressive neurosis	50%
manic depressive (depressed)	40%

Dosage of BUP was 300 mg for days 1-4, 400 mg for days 5-7, and 600 mg up to day 28. Mean dose at days 22-28 was about 470 mg (546 at center 02 vs 392 at center 01); 13 patients (BUP x 8, PBO x 5) received flurazepam or diphenhydramine concurrently for sleep. Patients who failed to complete the study included:

ineffective or deterioration	(22)	10 BUP, 12 PBO
adverse effects	(8)	6 BUP, 2 PBO
intercurrent illness	(4)	3 BUP, 1 PBO
did not return or refused treatment	(12)	7 BUP, 5 PBO
administrative reasons		1 BUP

Medication was discontinued in 16 BUP and five PBO patients for clinically significant adverse experiences. Adverse reactions to BUP included seizure (1), agitation/excitement (3), increased insomnia and anxiety (1), and total body rash (1).

c. Results: There were quantitative but no qualitative center by treatment interactions, with marked BUP/PBO differences at center 01 with 49 patients (34 BUP, 15 PBO), and minimal differences at center 02. Additional analyses, with techniques similar to those described above for study 06, disclosed the following two-tailed p-values:

Protocol 14

LOCF (21) Differences in Change from Baseline between Wellbutrin and Placebo Groups

All Patients Randomized
Investigators Weighted Proportionally to Sample Size

Scale	# of Patients	Differences for Change from Baseline Scores	2-tail p-value
HAMD Total	114	6.94	.01
CGI	114	.594	.01
Depr. Item* of HAMD	113**	NA*	.01

* Based on Blocked Wilcoxon Rank Sum test of LOCF(21) value blocked on baseline value.
** One Wellbrutrin observation fell into a block with no other data.

C. Studies of adequate design that failed to provide support for the indication:

1. Study 08 (A. Halaris and W. Fann)

a. Design: This was a five week (four weeks of treatment, one week of followup) study. Data from three centers following a single protocol were submitted. Inclusion criteria were identical to those for Study 06, above.

b. Conduct and Execution: Sixty-eight patients were enrolled and 59 were included in the analysis (34 with mean age of 42.8 yr on BUP, 25 with mean age of 40.8 yr on PBO; 40 M, 26 F, and two unlisted). Principal diagnoses were:

depressive neurosis	60%
manic-depressive (depressed)	30%
other diagnoses	10%

Dosage started at 300 mg/day and was increased to 750 mg/day by day 11 if lower doses were well-tolerated. Mean daily dose of BUP for weeks 2-4 was about 725 mg. Thirty patients received either chloral hydrate or flurazepam for sleep at some time during the study. In addition to measures listed above, this study employed the BPRS, and the POMS at center 01. Dropouts were attributed to:

ineffectiveness	1 BUP
adverse reactions	3 BUP
intercurrent illness	2 BUP

After inspections disclosed that one investigator had violated regulations pertaining to the conduct of clinical studies, the investigator was disqualified from handling investigational drugs, and results from all 16 patients at that site were excluded from subsequent consideration for efficacy.

c. Results: A strong qualitative treatment by center interaction was found; center 02 was essentially negative while the results at center 01 supported the efficacy of bupropion. Because it had been designed as a multicenter trial, the agency examined only the combined results of these two centers; a subset analysis of each subcenter was conducted but was not relied upon.

Because of the strong qualitative treatment by investigator interaction, no combined data analysis of Study 08 could be considered reliable.

2. Study 09 (L. Fabre and J. Mendels)

a. Design: This was an eight week study with one week of PBO washout, six weeks of treatment, and one week of followup comparing two dose ranges of BUP to PBO at two centers. The low dose (LD) group started at 150 mg and was increased to 400 mg/day at day 15; the high dose (HD) group received double these amounts. Inclusion and exclusion criteria were similar to those listed above. After approximately one-fourth of the patients were completed, the study was amended to delete the HD group because one patient had a seizure at 900 mg/day.

b. Conduct and Execution: A total of 160 outpatients were entered; 29 were removed during the initial PBO week, and 131 were admitted to the randomized treatment period. Mean daily doses ranged from 137 to 331 mg in the LD and from 287 to 687 mg in the HD group. Patients were excluded from the sponsor's efficacy analysis if they either failed to complete two weeks of randomized treatment or required unacceptably large doses of anxiolytic drugs; 97 were included on this basis; 66 F & 31 M, 40 LD, 42 PBO, and 15 HD. Principal diagnoses were:

manic depressive (depressed)	60%
depressive neurosis	35%

Dropouts were attributed to:	LD	HD	PBO	Total
did not return or refused treatment	9	4	6	19
did not meed study criteria	1			1
ineffectiveness/deterioration		1		1
adverse reactions	6	4	1	11
Totals	16	9	7	32

c. Results: With data combined across centers, neither dose range was significantly more effective than PBO at any period on the rating scales employed. Patients rated much or very much improved at termination included 62% on LD, 60% on HD, and 43% on PBO.

D. Active control studies bearing on the relative efficacy of bupropion:

Active control trials are generally poor sources of information about the efficacy of antidepressant drugs. In the typical case, the study results in a finding of no difference between the treatments compared. However, even if there is adequate statistical power, such a result cannot be accepted uncritically as evidence of drug effect. A finding of no difference may occur for many reasons other than that both drugs were effective; for example, neither drug may have worked in the population studied. Consequently, the finding that six of the seven active control studies submitted in the NDA failed to distinguish between bupropion and an active control was not considered evidence of bupropion's antidepressant efficacy.

However, when one active treatment betters another in an adequate and well controlled investigation, the difference can generally be attributed to a drug effect of the superior drug, unless the inferior drug had been used in a manner that actually made patients worse than they would have been had they received no drug at all. Of course, such a finding does not speak to the question of whether the poorer performing drug is effective, a point that should be born in mind when considering the results of study 15 described below. The study suggests that in some settings, bupropion may not be as effective as traditional antidepressant drugs.

1. Study 15 (R. Remick, A. Cooper, J. Mendels, A. Singh, M. Amin, and G. Chouinard)

a. Design: This was a 92 day comparison to amitriptyline (AMI), with an initial week of PBO washout, at six centers. After the first week, patients received either 300 mg BUP or 75 mg AMI for one week; BUP could then be increased to 450 mg and AMI dosage doubled.

b. Conduct and Execution: A total of 196 outpatients were enrolled, and 190 continued after the PBO week. Five patients randomized but treated for one day or less were excluded from efficacy analyses as well as two who had no evaluations after treatment was instituted. Prescription of concomitant drugs was more frequent in BUP patients; twenty such patients and six randomized to AMI were excluded at FDA request because they received antihistamines or psychoactive drugs concomitantly. After four weeks on active drugs, at least 70% of randomized

patients remained under treatment at all six centers; at center 02, 70% were retained through six weeks.

c. Results: For the combined centers, results favored AMI numerically on the Ham-D total score and change from baseline, Ham-D retardation factor, Ham-D depression item score and change from baseline, CGI Severity and change from baseline, and CGI Improvement. These differences achieved statistical significance for AMI over BUP on all except the retardation factor change item at most observation points in both weighted and unweighted analyses.

E. Limits on Evidence of Efficacy and Duration of Effect: On the basis of the evidence available it is not known whether bupropion maintains its therapeutic effect for more than three weeks. The number of patients remaining in placebo controlled trials after that point does not permit any conclusions for a longer duration. BUP failed to do better than the control treatment in both outpatient studies, in one compared to PBO and, in the other, to amitriptyline.

F. Safety Data from Clinical Studies: More than 2400 patients participated in clincal studies of bupropion during its premarketing testing and evaluation. The original NDA reported on data involving approximately 1300 individuals. In subsequent amendments, including the 'safety update,' the sponsor provided additional reports and summaries of experience with an additional thousand or so patients. The safety review focused primarily upon events that led to the discontinuation or death of patients. The safety review also considered the pattern and relative incidence of abnormalities in vital signs, laboratory and special tests, and reports of adverse events. Of particular importance for comparative and relative event incidence assessment are data submitted to the original NDA from four double-blind, PBO-controlled studies involving over 300 patients; two double-blind studies controlled with amitriptyline (AMI) in which over 100 patients received BUP, including about 25 who received the drug for up to three months. All information concerning more chronic experience with bupropion, however, is derived from open clinical trials.

1. Effects on Vital Signs and Physical Measurements:

a. Heart Rate: Doses of BUP up to 800 mg in volunteers did not cause significant changes in heart rate. In Study 08, mean supine heart rates on BUP rose gradually from 80.9 to 87.6/minute; rates on PBO varied from 84.1 at baseline to 82.4 at 21 days and declined to 77.7 at 28 days, a statistically significant difference at that point. In other studies, there was no consistent pattern of BUP effect on heart rate.

b. Blood Pressure: In Study 08, statistically significant differences were found in within-treatment comparisons to baseline on BUP in standing blood pressure, with decreases of 4-9 mm Hg for systolic readings, compared with 1-5 mm on PBO; supine readings were not consistently affected, and diastolic measurements indicated no trend. No consistent changes in supine or erect blood pressure were seen in other studies. Long-term treatment with BUP was associated with either small decreases or no change.

Among patients with a history of clinically significant orthostatic hypotension on tricyclic antidepressants (TCA) who were enrolled and showed no blood pressure effects on PBO, none of 12 who had received ascending doses of BUP (at the time of data cutoff) showed significant changes between PBO and BUP periods. In 86 hypertensive patients, vital signs did not differ significantly from baseline during BUP treatment. Among 156 patients with cardiac disease, symptoms and complaints did not increase during BUP treatment.

c. Respiration: No clinically important increases or decreases in respiratory rate were seen.

d. Temperature: In those instances in which body temperature was measured, no consistent changes were found on BUP.

e. Body Weight: Weight loss of five or more pounds was noted in more BUP patients than PBO patients (23% vs 11%). Weight gain of five or more pounds was only about one-third as likely on BUP as on AMI and only 40% as likely on placebo. Patients whose weights were measured and who gained or lost at least five pounds were as follows:

	BUP			PBO			TCA		
Studies	n	+5	-5	n	+5	-5	n	+5	-5
08, 09, 14	130	6%	23%	81	14%	11%			
15, 21	91	13%	34%				67	39%	9%
35	298	3%	15%						
Total	519	5.7%	20.2%	81	14%	11%	67	39%	9%

2. Adverse Effects on Laboratory Evaluations:

a. EKGs and Cardiac Conduction: 4/304 patients developed abnormalities during BUP treatment. One was noted to have a single premature ventricular contraction (PVC) during BUP; another had abnormal ST-T wave recordings at baseline that

worsened during treatment; the third was a woman aged 61 who had APC and PVC at 5, 12, and 21 days which were still present two weeks after discontinuance; the fourth, a woman aged 58, had newly observed junctional or nodal premature beats.

The overall effect of treatments on ECG recordings is as follows:

	BUP	PBO	TCA
n =	304	123	72

Baseline - Treatment	Percent of Patients		
Normal - Normal	69.7	79.7	65.2
Normal - Abnormal	8.6	3.2	15.3
Abnormal - Normal	5.6	3.2	6.9
Abnormal - Abnormal	16.1	13.8	12.5

One study center provided lead II rhythm strips of 15 seconds taken at double paper speed and voltage for 62 patients; these were to be scored on a blinded basis by the sponsor for the duration of the QRS, P-R, R-R, and the corrected QT intervals (QTc) and the amplitude of the QRS complex; tracings taken on days 14, 21, and 42 were found scorable for 23 BUP and 23 TCA patients. For BUP, there was no statistically significant difference in the length of QRS or P-R intervals developing during treatment; for TCA, these were significantly longer, but the between-treatment comparisons did not show significance.

Overall, there appeared to be no consistent or clearly drug-related on ECG effects of bupropion.

b. Clinical Hematology Evaluations: Decreased hematocrit following a normal baseline value occurred more frequently with BUP than with PBO or TCA treatment. One BUP patient was recorded as having a WBC value of 2300 one day post-treatment in a 42 day study; the result was within the normal range when repeated one week later. BUP was associated with decreases in mean values for hemoglobin (in study 08 at day 14, in study 21 at termination, and in study 26 at 3-8 weeks), hematocrit (in study 21 at termination, and in study 26 at 3-8 weeks), WBC (in study 15 at day 29 and day 92, and in study 17 at 1-2 months and over 6 months), lymphocytes (in study 17 at 1-2 months, in study 08 at day 14, and in study 15 at day 92), monocytes (in study 17 at 3-6 months), and RBC (in study 15 at day 29), and with increased neutrophils (in study 08 at day 14). PBO was associated with increased WBC in one study at termination and with increased neutrophils in another at day 14. TCA was associated with decreased hemoglobin and decreased hematocrit in discrete studies at one point each, and with increased blood glucose (in study 17 at over 6 months, and in study 21 at termination), and increased monocytes (in study 17 at 3-6 months).

Overall, there were no consistent effect of bupropion on hematologic measurements.

c. Clinical Chemistry Evaluations: For liver enzyme values, the pattern of results was similar. Overall, liver enzyme values showed no consistent change during BUP treatment.

BUP was associated with altered mean values for other chemistry examinations at 14 time points during these studies, but the changes appear to occur in a random fashion. PBO was associated with significantly altered mean values in three instances, and AMI in four.

3. Observed Adverse Reactions: The Standard Adverse Experience Listing or the Dosage Record and Treatment Emergent Symptoms (DOTES) Scale was administered at baseline and at intervals during the studies. In listing the data derived from these questionnaires, neither the severity of the reported reaction nor the investigator's judgment of the probability that the event was drug-related has been taken into account.

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 incidence figures cited in the following discussion must be accepted as rather imprecise estimates. They cannot be used to predict 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 calculated incidence estimates cannot reflect the relative severity and/or clinical importance of events. Whether or not an event was severe enough to cause discontinuation of a drug's use is one guide to its importance.

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 the product's premarketing clinical trials. 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, primarily rashes (1.4%). It is important to note, however, that many of these events occurred at doses that exceed the recommended daily dose.

Because the design and duration of a study can influence both the calculated incidence of adverse events and the inferences subsequently drawn, the following discussion provides a separate assessment for each related group of clincal studies.

a. During PBO-Controlled Studies: Data from 222 BUP and 138 PBO patients in studies 06, 08, 09, and 14 were initially combined. Subsequently, the results of another placebo controlled study were added. These results are shown in the attached labeling. The excess of adverse effects in patients on BUP (compared to PBO) was largest for agitation, dry mouth, sweating, and tremor. Other adverse experiences reported more frequently by BUP patients than those on PBO included insomnia, constipation, syncope/dizziness/fainting, weight loss and confusion.

b. During TCA-Controlled Studies: Data from 120 BUP and 83 AMI patients in studies 15 and 21 were combined. There was a notable excess of complaints of increased salivation, nausea/vomiting, headache, and decreased appetite/anorexia in BUP patients, and a numerical excess for complaints of euphoria, numbness, dystonic symptoms, paresthesia, chills, dyspnea, urinary frequency, increased libido, decreased libido/impotence, edema, and dermatologic symptoms compared to AMI patients.

During Long-Term Studies: The percent of 60 patients receiving BUP in studies 17 and 26 who developed symptoms not present at baseline was as follows:

Dry Mouth	28%
Tremor	15%
Menstrual Disturbance	13%
Increased Appetite	13%
Nausea/Vomiting	13%
Syncope/Dizzy/Fainting	13%
Headache	12%
Blurred Vision	12%
Pruritis	11%
Skin Lesion	10%
Agitation/Excitement	10%
Decr Libido/Impotence	8%
Ataxia	6%
Swelling (Testis/Breast)	6%
Peculiar Taste in Mouth	6%

In comparison with the 19 AMI patients in study 17, there was a notable excess of complaints of agitation/excitement, insomnia, and tiredness/fatigue on BUP. (AMI patients had notably more complaints of dry mouth, drowsiness or sleepiness, and constipation than those treated with BUP.)

d. Associated with Discontinuance: Adverse reactions caused discontinuation of BUP treatment in 177 instances. Three patients were receiving both BUP and a neuroleptic under

circumstances in which attribution of the event to either drug is problematic; 6/40 patients in one protocol received doses of more than 750 mg/day, a dose larger than that recommended in the originally proposed labeling, and 2/157 normal volunteers were discontinued after receiving doses larger than those anticipated in the t.i.d. schedule adopted. Excluding these 11 cases, the rates are:

Drug	# Treated	# Discontinued	Percent
BUP	1153	166	14.4
PBO	177	10	5.6
AMI	196	33	16.8

Among subjective, behavioral, or psychological adverse reactions, the one most frequently associated with discontinuance of BUP was excitement/agitation in 9.1%, compared with 6.8% on PBO and 9.2% on AMI. In the nonsubjective, nonbehavioral, or nonpsychological category, the reaction most frequently associated with discontinuance of BUP was dermatologic (usually urticarial or pruritic skin rashes).

e. Post-NDA Exposures: As noted earlier, experience with approximately 1000 additional patients and volunteers was included in the sponsor's final cumulative safety review. In general, no new events or findings that might affect either the approval decision or product labeling were identified that had not been detected in the data submitted with the original NDA.

However, the added experience did affect the precise incidence figures calculated for adverse events and for discontinuations. The revised estimates of incidence are not tabulated herein, but may be found in the attached final product labeling. The safety update, however, did provide greater detail about certain events, especially those that had been described ambiguously. In general, however, the safety update did not substantively alter any conclusion about the safety or relative risk and benefit of bupropion as an antidepressant.

F. Special Safety Considerations:

1. Seizures:

Seizures were first seen in volunteers participating in Phase I studies and the relatively high risk of seizure associated with the use of bupropion is an important determinant of dosing recommendations. The data suggest that high daily dose dose and/or rapid escalation of dose are strong predictors of seizure risk. Prior history of seizures and primary structural brain disease also appear to increase the risk of seizure.

The table below illustrates the relationship between dose, predisposing factors and seizure risk:

INCIDENCE OF SEIZURES IN PATIENTS RECEIVING BUPROPION

BUPROPION Dose mg/day	Total Seizure Incidence (%)	Seizure Incidence in Patients Without Seizure Predisposition (%)
less than 450mg	0.2%	0.0%
450mg	0.3%	0.2%
600mg*	2.3%	1.3%
600mg-900mg*	2.8%	1.9%

*: symbol indicates a dosage exceeding the maximum recommended daily dose.

2. Overdoses, Suicides and Deaths:

In the original NDA, reports described five outpatients who ingested single overdoses in amounts of 900 to 3000 mg BUP during clinical trials. Several vomited, and all recovered without sequellae following hospital admission. (OD-5 ingested an overdose of diphenhydramine 11 days after being restarted on BUP and was terminated from the study at that point.) Three other patients receiving BUP in clinical trials ingested overdoses of other drugs, and one attempted suicide by cutting his wrists.

The safety update included 8 more overdoses, for a total of 13. None had proven fatal, although seizures occurred definitely in one and probably in another. All these patients recovered without "residual impairments."

Fatalities in temporal association with the use of bupropion were reported in 14 patients prior to approval. None are known or believed to be a consequence of treatment with bupropion. Nine deaths were self-inflicted. Three deaths occurred in elderly and/or seriously ill patients.

3. Evaluation of Abuse Potential:

Preclinical studies in rodents suggest weak amphetamine-like effects with respect to locomotor activity and effects on schedule controlled behavior; in animals trained to discriminate amphetamine from PBO, BUP was identified as amphetamine-like.

Data obtained from clinical efficacy studies suggest mild amphetamine-like effects, with increased motor activity. Neither notable anorectic effect nor peripheral sympathomimetic activity was consistently observed with BUP; although, in regard to the former, weight loss in patients was more common than in TCA treated patients.. A dose of 400 mg produced a modest elevation over PBO responses on the morphine benzedrine group subscale of the Addiction Research Center Index (ARCI), and a score intermediate between amphetamine and PBO on the Liking Scale of the ARCI.

VI. Advisory Committee and Foreign Regulatory Agency Actions:

Psychopharmacologic Drugs Advisory Committee (PDAC):

Wellbutrin was presented to the Committee on June 10, 1982, prior to the assessment of the data and reports bearing on its safety. The application was presented to the Committee in an attempt to gain their views about the adequacy of the three week long efficacy trials. The Committee, however, elected to consider the issue of approval.

The Committee reviewer noted that all four PBO-controlled studies showed the common problem of an inordinate drop-out rate at day 21, due to a feature which allowed patients to be removed from the study at that point if favorable therapeutic effects were not apparent.

It was noted that results in study 15 favored AMI over BUP, significantly in some instances. The reviewer concluded that BUP was associated with greater improvement than PBO in the three inpatient studies, based on Ham-D and Clinical Global Severity of Illness scores at day 21.

The Committee recommended approval of bupropion for the treatment of depression, but conditioned their recommendation upon acceptable findings in the then incomplete safety review. The Committee was <u>not</u> aware of the inordinately high risk of seizure at the time its recommendation was made.

MADE IN JAPAN

VII. Conditions for Approval:

Performance of (1) a multiple-dose dose proportionality study covering the drug's recommended dosage range which is to evaluate bupropion and its active metabolites, (2) a multiple-dose pharmacokinetic study in geriatric patients, (3) clinical studies to determine whether or not the antidepressant effect persists beyond three weeks, (4) a program to determine the potential of bupropion to cause seizures, (5) an investigation for an extended period to determine the extent of abuse and diversion of the drug in comparison to other antidepressants will be required after marketing is approved, and (6) the submission of laboratory data collected in the period following the submission of the original NDA.

VIII. Approved Package Insert:

The approved package insert is attached.

MADE IN JAPAN

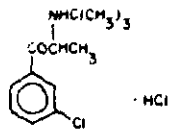
PI

646430
Special Fold 646436

Wellcome

WELLBUTRIN® (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 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) film-coated tablets.

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 (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 tenfold) 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 in patients who fail to respond adequately to or who cannot tolerate alternative antidepressant treatments. Wellbutrin is not recommended as an antidepressant of first choice for most patients because its use at doses approximately one and one-third times greater than the usually required daily dose (450 mg) is associated with a high risk of seizure (see WARNINGS).

The efficacy of Wellbutrin was demonstrated in placebo-controlled clinical trials which enrolled principally hospitalized patients with diagnoses of depressive neurosis or manic-depressive (depressed type) disorder. The depressive illness of the patients studied most closely corresponds 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.

Evidence to demonstrate the sustained effectiveness of Wellbutrin after three weeks of use in placebo-controlled investigations is not presently available.

CONTRAINDICATIONS: Because of its potential to induce seizures, Wellbutrin should not be used in patients with a convulsive disorder.

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:

CONVULSIONS: Wellbutrin appears to possess a greater epileptogenic potential than other marketed antidepressants. While the estimated risk of seizure at doses of 450 mg and below does not appear excessive in comparison to the risk reported for other antidepressant drug products, the estimated risk increases almost fivefold between a dose of 450 and 600 mg a day. Given the wide variability among individuals in their capacity to metabolize and eliminate drugs, this disproportionate increase in seizure incidence with dose incrementation is a cause for concern.

During the period of premarketing evaluation, 25 among approximately 2400 patients treated with Wellbutrin experienced seizures. At the time of seizure, seven (7) patients were receiving daily doses of Wellbutrin at or below the lowest documented effective daily dose of 450 mg. Twelve (12) patients experienced seizures at daily doses of 600 mg; six (6) additional patients had seizures at daily doses between 600 and 900 mg. The risk of seizure appears to be strongly associated with dose and may be increased by predisposing factors (e.g., head trauma, CNS tumor, etc.) or a history of prior seizure. In addition, sudden and large increments in dose may contribute to an increased risk. While many seizures occurred early in the course of treatment, some seizures did occur after several weeks of use at fixed dose.

INCIDENCE OF SEIZURES IN PATIENTS RECEIVING WELLBUTRIN

	Wellbutrin Dose mg/day	Total Seizure Incidence (%)	Seizure Incidence in Patients Without Seizure Predisposition (%)
Within Recommended Dose	<450	0.2%	0.0%
	450	0.3%	0.2%
Above Recommended Dose	600	2.3%	1.3%
	600-900	2.8%	1.9%

DOSAGE AND ADMINISTRATION RECOMMENDATIONS SHOULD BE STRICTLY FOLLOWED TO MINIMIZE THE RISK OF SEIZURE (see DOSAGE AND ADMINISTRATION). Extreme caution should be used when combining Wellbutrin with other agents which lower seizure threshold or when administering Wellbutrin to patients with a history of seizure disorder or cranial trauma.

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 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 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 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.

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.

WELLBUTRIN® (BUPROPION HYDROCHLORIDE) Tablets

Nursing Mothers: It is not known whether Wellbutrin is excreted in the milk of lactating women. Because many drugs are excreted in human milk, caution should be exercised when Wellbutrin is administered to women who are nursing.

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 the product's premarketing clinical trials. 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
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 entire premarketing evaluation of Wellbutrin: During its premarketing assessment, Wellbutrin was evaluated in almost 2400 subjects. 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; and rare were pallor and phlebitis.

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

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, and intestinal perforation.

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 was lymphadenopathy.

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

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 and rate or rhythm disorder.

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.

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.

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: At doses that are one and one-third times the usually required dose (450 mg/day) (see WARNINGS), the observed incidence of seizure increases by as much as tenfold. This predicts a relatively narrow therapeutic ratio for the safe use of bupropion, especially as there is considerable inter-individual variability in the capacity of patients to metabolize drugs.

Consequently, it is particularly important to administer bupropion in a manner that is most likely to minimize the risk of seizure. Retrospective analysis of clinical experience gained during its premarketing development 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 in divided doses to avoid high peak concentrations of bupropion and/or its metabolites, and 3) the rate of incrementation of dose is very gradual.

Wellbutrin should be given t.i.d., preferably with intervals of at least 6 hours between successive doses. Besides its apparent value in lowering the risk of seizure, gradual dose escalation is important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these side effects may be managed by temporary reduction of dose or the transitory administration of a sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment.

The following suggested dosing regimen incorporates the principles described above.

Usual Adult Dosage: A starting dose of 225 mg/day given as 75 mg t.i.d. is recommended. Based on clinical response, this dose may be increased to 75 mg/day no sooner than every three days according to the following schedule, up to a total maximum daily dose of 450 mg/day. Of course, if distressing, untoward effects supervene, dose escalation should be stopped.

	Dosing Schedule 75 mg Tablets			
Treatment Day	Morning	Midday	Evening	Total Daily Dose
1	1	1	1	225 mg
4	2	1	1	300 mg
7	2	2	1	375 mg
10	2	2	2	450 mg

In patients who do not demonstrate an adequate response after an appropriate period of treatment at 450 mg/day, drug should be discontinued.

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 which maintains remission is recommended. The maximum recommended maintenance dose is 450 mg/day. While it is generally recommended that a course of antidepressant drug treatment should continue for several months and many patients have been treated with Wellbutrin in long-term clinical trials of up to 2 years duration, there has been no systematic placebo-controlled evaluation of the efficacy of Wellbutrin for a period beyond three to four weeks.

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).

Store at 15°-25°C (59°-77°F).

*U.S. Patent No. 3819706
U.S. Patent No. 3885046 (Use Patent)

BURROUGHS WELLCOME CO.
Research Triangle Park, NC 27709
Printed in U.S.A.

January 1986

646430
Special Fold 646430

MADE IN JAPAN

MED. REVIEW

File

REVIEW AND EVALUATION OF CLINICAL DATA
NDA 18-644

Sponsor: Burroughs Wellcome

Drug: Wellbutrin (bupropion)

Category: antidepressant

Date of Submission: May 1, 1985

Date of Review: May 16, 1985

This is five volume submission. The first volume is a response to our approvable letter and includes revised labeling. The major difference between the revised labeling and the FDA proposed labeling is in the Indications section and Dosage section. A complete review of the labeling follows the safety update below. The remaining volumes contain the safety update.

Safety Update.

The following areas will be discussed. The material is taken from volumes 9.2 though 9.5.

1. Data Base
2. Serious Events
   a. Deaths (primarily suicides) and bupropion overdoses
   b. Seizures
   c. Terminations (adverse effects and other reasons)
   d. Other (pregnancies)]
3. Lab tests, vital signs, weight, EKG
4. Adverse Events
5. Conclusions

1. Data Base

The data base now includes 2,398 subjects who were given bupropion (1482 females and 1157 males.) In the original NDA submission, there were 1315 subjects exposed to bupropion (735 females and 580 males). Occasionally, the number of exposures (2642) and not the number of patients form the basis for tables.

A number of tables were provided to describe the data base. A listing of each study, the type of study and the number of patients enrolled is provided by the sponsor. There is also a listing of all the investigators by study. In addition, there is a breakdown of the number of patients by dosage (less than or equal 600 mg and greater than 600 mg) for patients and volunteers separately for the NDA and for the total data base (NDA and post NDA). A total of 2182 unique individuals received bupropion up to 600 mg/day and 213 received doses greater than 600 mg/day. Case records for the approximately 1100 new patients have not been submitted. It is noteworthy that study 39, a multicenter humanitarian treatment protocol, contributed 23% of the total patient exposures.

The submission also contains a table of the number of patients in each age category by study for males and females separately and a table of age and sex for the NDA and for the total data base. Fifty-eight percent of patients were females and the median age for all subjects was between 40 and 50 years of age. Nineteen percent (428 patients) were 60 years of age or older.

There is a table of the number of patients for each dosage and duration for the total data base and for the NDA. The highest number of patients received bupropion for 1-4 weeks followed by 5-8 weeks, 13-26 weeks (286 patients), 9-12 weeks (169 patients), 27-52 weeks (147 patients), 53-78 weeks (101 patients) and out to 104 weeks (26 patients).

There are some studies ongoing. The sponsor has included in this submission all adverse experiences "of substantial clinical significance" reported to then through April, 1985.

2. Serious Events

a. Deaths (primarily suicides) & Bupropion Overdoses

Three tables with information on bupropion overdoses, deaths, and suicide attempts were provided by the sponsor and these are included in the following pages (Tables 1, 2, & 3). Table 1 describes 14 deaths which occurred in patients while on bupropion. (Nine of the deaths occurred on the "humanitarian" protocol.) Nine were suicides. None of the deaths involved bupropion directly. Table 2 describes 13 suicide attempts with bupropion (overdoses from 850-9000 mg) none of which had sequellae. The patient who took 9000 mg had a seizure and sinus tachycardia but she had also ingested tranylcypromine. Table 3 details suicides and suicide attempts by means other than bupropion. (This table overlaps partially with Table 1.) There were 14 suicide attempts and 9 deaths. Again, 13 of the 23 cases were from the humantarian protocol.

TABLE 1 (spons 17)

Patient Deaths Which ed While Taking Bupropion

Study	Investigator	Pt #	Sex	Age	Wt (kg)	Race	Daily dose (mg) at time of event	Duration on Bupropion		Related to Bupropion?	Cause of Death/Comments
								Total Days	Days on Dose at which Event Occurred		
16-001		69	M	23	87	C	0	7	5 days post-dose	No	Suicide by asphyxiation Patient had history of prior suicide attempt
17-005		6C	M	80	66	C	250	149	60	No	Septic shock following development of a preforated viscus and peritonitis
29-001		1	F	40	59	C	0	28	4 days post-dose	No	Suicide by overdose of desimipramine, amount unknown
39-001		1026	M	53	81	C	600	14	9	No	Suicide by gunshot
39-002		03	M	52	83	C	600	19	13	No	Suicide by gunshot Prior suicide attempts though not suicidal at study entry
39-022		103H	F	68	59	C	600	656	57	No	Suicide from overdose of Tuinal Patient had made previous suicide attempt with overdose of Tuinal and Dalmane
39-027		1	F	34	54	C	300	195	156	No	Patient went into cardiac arrest the evening following her first chemotherapy treatment for Hodgkin's Disease
39-047		1304-A	F	49	54	C	400	44	13	No	Suicide from overdose of barbiturate, benzodiazepines, Quaaludes, and alcohol, amount unknown
39-047		2529	M	55	95	C	500	343	239	No	Death from metastatic cancer, patient had terminal pre-existing medical condition prior to administration of WELLBUTRIN
39-048		9	F	72	62	C	400	27	20	No	Patient had a brain stem cerebrovascular accident with respiratory arrest and subsequent death
39-048		85	M	53	77	C	0	120	6-21 days post dose	No	Suicide by gunshot Unknown how long patient off bupropion Estimated 1-3 weeks posttreatment
39-086		5	M	46	82	C	0	75	2 days post-dose	No	Overdose with propranolol Patient stopped bupropion (300 mg/day) two days prior to overdose Medical examiner's final anatomic diagnoses 1) acute propranolol poisoning, 2) pulmonary congestion and edema
40-001		32	M	34	83	C	Tapering off 300	73	4	No	Suicide by hanging Patient was schizophrenic with depression Had made suicide attempt prior to study entry (was not suicidal when enrolled)
Trial in France		---	F	Unkn.	-	-	300	---	---	-	Details unavailable at time of this submission

122.85/1126

TABLE 1 (sponsor ... 17)

Patient Deaths Which Occurred While Taking Bupropion

Study	Investigator	Pt #	Sex	Age	Wt (kg)	Race	Daily dose (mg) at time of event	Duration on Bupropion		Related to Bupropion?	Cause of Death/Comments
								Total Days	Days on Dose at which Event Occurred		
16-001		69	M	23	87	C	0	7	5 days post-dose	No	Suicide by asphyxiation Patient had history of prior suicide attempt
17-005		6C	M	80	66	C	250	149	60	No	Septic shock following development of a preforated viscus and peritonitis
29-001		1	F	40	59	C	0	28	4 days post-dose	No	Suicide by overdose of desimipramine, amount unknown
39-001		1026	M	53	81	C	600	14	9	No	Suicide by gunshot
39-002		03	M	52	83	C	600	19	13	No	Suicide by gunshot Prior suicide attempts though not suicidal at study entry
39-022		103H	F	68	59	C	600	656	57	No	Suicide from overdose of Tuinal Patient had made previous suicide attempt with overdose of Tuinal and Dalmane
39-027		1	F	34	54	C	300	195	156	No	Patient went into cardiac arrest the evening following her first chemotherapy treatment for Hodgkin's Disease
39-047		1304-A	F	49	54	C	400	44	13	No	Suicide from overdose of barbiturate, benzodiazepines, Quaaludes, and alcohol, amount unknown
39-047		2529	M	55	95	C	500	343	239	No	Death from metastatic cancer, patient had terminal pre-existing medical condition prior to administration of WELLBUTRIN
39-048		9	F	72	62	C	400	21	20	No	Patient had a brain stem cerebrovascular accident with respiratory arrest and subsequent death
39-048		85	M	53	77	C	0	120	6-21 days post dose	No	Suicide by gunshot Unknown how long patient off bupropion Estimated 1-3 weeks posttreatment
39-056		5	M	46	82	C	0	75	2 days post-dose	No	Overdose with propranolol Patient stopped bupropion (300 mg/day) two days prior to overdose Medical examiner's final anatomic diagnoses 1) acute propranolol poisoning, 2) pulmonary congestion and edema
40-001		32	M	34	83	C	Tapering off 300	73	4	No	Suicide by hanging Patient was schizophrenic with depression Had made suicide attempt prior to study entry (was not suicidal when enrolled)
Trial in France		---	F	Unk.	--	--	300	---	---		Details unavailable at time of this submission

122-85/1126

TABLE 2 (Sponsor's Table 18)

Suicide Attempts by Bupropion Overdose

Study	Investigator	Pt #	Sex	Age	Wt (kg)	Race	Dosage of Bupropion Ingested		Other Chemicals Ingested (Rx = prescribed)	Side Effects	Recovery	Comments
							mg	mg/kg				
6-001		70	F	35	65	C	900	14	None	None	No sequelae	Self treated by emesis
7-001		17	F	27	53	C	3000	57	75 300 mg Dalmane	Nausea, vomiting, headache, drowsiness	No sequelae	Drowsiness possibly related to Dalmane
17-009		07	F	22	52	C	2200	42	None	Dry mouth, lethargy, possible visual hallucinations, serum K⁺ = 3.5, nonspecific T wave changes	No sequelae	History of multiple drug overdose
22-001		36	F	44	53	C	1700	32	Unknown	Unknown	Unknown	None
35-011		01	F	53	79	C	2400	30	140 mg Tranxene	Hostility, slurred speech, dizziness, grogginess, mild sinus tachycardia, serum K⁺ = 2.7	No sequelae	None
39-002		18	M	39	66	C	850 2000	13	400 ml, 12.5% ethanol	Questionable seizure, exhaustible horizontal nystagmus	No sequelae	None
39-002		222	M	43	74	C	2000	27	None	Mild sinus tachycardia, mild coarse tremor, drowsiness, nonspecific T-wave changes	No sequelae, resumed treatment	None
39 032		01	F	---	81	C	1250	15	None	Nausea, vomiting, drowsiness	No sequelae, resumed treatment	None
36-036		10	F	57	98	C	9000	92	300 mg tranylcypromine, unknown quantity acetylsalicylic acid	Sinus tachycardia, tonic-clonic seizure, serum K⁺ = 3.3, vomiting	Initially semi-comatose (due to Valium), recovered subsequently and resumed treatment	Treatment for overdose-10 mg Valium, I.V., 300 mg Dilantin, I.V.
39-056		02	F	27	50	C	4200	84	--50-100 tablets acetaminophen	None	No sequelae	None
39-071		18	F	29	53	C	2250	42	Rx 10 mg/7 days Prolixin Decanoate	Dry mouth, vomiting, feeling cold	No sequelae	None
39-079		08	F	39	82	C	1050	13	Ethanol Rx 6 mg/day Xanax, 5-10 mg/day Provera	None	No sequelae	None
39-123		01-957	F	26	61	C	3000	49	None	Experienced a "high" feeling temporary amnesia	No sequelae	History of phenelzine overdose

ate 3 (Sponsor's Table 19)

Suicides/Attempted Suicides by Means Other Than Bupropion Overdose

Study	Investigator	Pt #	Sex	Age	Wt (kg)	Race	Daily dose (mg) at time of event	Duration on Bupropion		Event	Outcome
								Total Days	Days on Dose at which Event Occurred		
15 001		33	F	24	50	C	300	21	21	Overdose of approximately 6 MinOval and 10 Anacin tablets	Survival
15 001		40	F	33	59	C	450	17	10	Overdose of 26 gm chloral hydrate	Survival
16 001		35	F	50	54	C	[illegible]	3	2	Overdose of Norpramin, amount unknown	Survival
16 001		69	M	23	87	C	0	7	5 days post dose	Suicide by asphyxiation Patient had history of a prior suicide attempt	Death
17 001		8	M	25	68	C	400	8	2	Slashed wrists	Survival
26-01A		43	M	39	87	C	500	426	9	Overdose involving an unknown quantity of alcohol and up to 700 mg of diazepam, ingested during recreational abuse	Survival
26 018		21	M	52	92	C	550	88	28	Patient began drinking heavily and attempted to slit his wrists, lacerations superficial	Survival
29 001		1	F	40	59	C	0	28	4 days post-dose	Overdose of desimipramine, amount unknown	Death
29-006		56	F	51	45	M	150	11	11	Patient eloped from ward and stabbed herself in the stomach	Survival
39 001		1026	M	53	81	C	600	14	9	Suicide by gunshot	Death
39 001		42	F	51	54	C	300	213	20	Overdose with kerosene	Survival
39 001		167	F	2o	---	C	225	16	6	Overdose with Xanax, Mellaril and Restoril, amounts unknown	Survival
39 002		03	M	52	83	C	600	19	13	Suicide by gunshot Prior suicide attempts though not suicidal at study entry	Death
39 022		103H	F	68	59	C	600	656	57	Overdose of Tuinal, amount unknown, prior overdose of Tuinal and Dalmane	Death
39-029		---	F	---	---	---	450	---	5	Overdose of 100 mg Valium (additional demography/dosing unavailable at time of this submission)	Survival
39 043		38003	M	23	101	C	600	36	1	Slashed wrists	Survival
39 047		1304 A	F	49	54	C	400	44	13	Overdose of barbiturates, benzodiazepines, Quaaludes and alcohol, amounts unknown	Death
39-048		85	M	53	77	C	0	120	6-21 days post dose	Suicide by gunshot Unknown how long patient off bupropion, estimated 1-3 weeks post-treatment	Death
39-052		17	F	38	78	C	600	480	129	Slashed wrists	Survival
39 063		45	F	36	87	C	400	71	71	Overdose of dilantin, amount unknown, cut wrists superficially	Survival
39-086		5	M	46	82	C	0	75	2 days post-dose	Overdose of propranalol, amount unknown	Death
39-120		07	F	27	45	C	450	109	6	Overdose of Ludiomil, Ativan, Macrodantin and Aventyl, amounts unknown	Survival
40-001		32	M	34	83	C	Tapering off 300	73	4	Suicide by hanging Patient was schizophrenic with depression Had made suicide attempt prior to study entry (was not suicidal when enrolled)	Death

MS/11.'6

Comment. A rather nigh number of deaths and overdoses have occurred during the premarketing program. However, these did not occur in the controlled trials but during the humanitarian protocol, an open and possibly less well supervised situation.

In summary, bupropion overdoses (850 - 9000 mg) did not result in death. In addition, bupropion did not appear to be directly implicated in the deaths which occurred in patients while on the trials.

b. Seizures

Extensive information was provided on the 26 cases of seizure from the total data base. Table 4 (taken from the sponsor's submission) gives the details on each case. Table 5 (taken from the sponsor's submission) shows the breakdown by dosages and the presence or absence of predisposing factors. The risk is dose dependent in patients without predisposing factors with an escalating incidence above 450 mg daily.

The sponsor has also provided graphs for each individual subject showing the dose, duration of treatment and time of seizure. The sponsor examined the relationship between seizures and duration of treatment. In this analysis, they excluded four patients (brain cancer, overdose, cerebral palsy, and alcohol withdrawal) and found that 9/22 seizures occurred within the initial 1-2 days following a dosage increase, and 18/22 occurred within the first three weeks of a dosage escalation. Seizures also occurred, occasionally, with drug initiation).

Comment. Table 5 is misleading. It combines the one seizure at 9000 mg with the six which occurred at doses from 600 - 900 mg. Since this table also appears in the labeling, I would suggest that the category be changed by moving the one patient at 9000 mg to a separate line. In addition, there is no statement in the labeling indicating the seizures generally follow dosage increases.

c. Terminations

All raw data forms (? case report forms) were reviewed by the sponsor to identify terminations. In the introduction (page 8), a termination was defined as occurring whenever a patient discontinued more than one day prior to study completion. However, this would not apply to the open ended studies (long-term continuation and humantarian protocols). On page 15, it states that subjects from these protocols were included as a termination only if toxicity occurred.

TABLE 4 (Sponsor's Table 20)

Seizures Which Occurred During Bupropion Treatment

Study	Investigator	Vol./Pt. #	Sex	Age	Wt. (kg)	Dose at which seizure occurred	Days on dose at which seizure occurred
01A		1	M	36	66	800	4
01A		8	M	24	67	800	2
09-002		35	M	30	73	900	6
14-001		76	F	38	66	600	1
19-001		3	F	25	50	600	2
21-001		48	M	48	70	450	8
21-001		51	M	31	67	600	2
22-003		2	M	37	97	600	2
23-002		1	F	51	50	600	1
28-001		151	M	35	74	700	40
28-002		203	F	26	66	600	1
34-001		11	M	26	52	750	2
39-001		14H	F	56	53	100	55
39-001		117H	F	37	51	600	20
39-001		161	F	46	46	450	1
39-028		30	F	45	50	700	63
39-036		10	F	57	99	9000	---
39-048		56	F	38	75	600	28
39-052		43	F	31	71	300	18
39-063		45	F	36	87	400	---
39-098		174	F	32	78	600	14
39-098		115810	F	24	63	550	67
39-105		30034	F	45	56	600	14
54-001		4	M	59	66	200	1
55-001		390	F	38	59	600	20
UK-SA*		7	F	29	78	450	7

* US-SA is a study conducted in South Africa by the Wellcome Research Laboratories in England (clinical trial material manufactured in U K.)

Table 5 (Sponsor's Table 21)

Incidence of Seizures During Bupropion Treatment by Dose

Bupropion Dose Mg/Day	# Total Seizures[a]/ # Patients (%)	Seizures in Patients Without Predisposing Factors (%)	PREDISPOSING FACTORS	
			# Seizure Patients with History of Head Trauma or Seizure[b]	# Seizure Patients with Concomitant Agents Which Lower Seizure Threshold[c]
<450	4/2398 (0 17)	0/2398 (0.00)	3/4	2/4
450	3/1281 (0 23)	2/1281 (0.16)	1/3	0/3
>450-600	12/527 (2 28)	7/527 (1.33)	2/12	3/12
>600-9000[d]	7/213 (3 29)	4/213 (1.88)	0/7	3/7

[a] Patient 39-002/18 experienced a questionable seizure subsequent to an overdose of bupropion and is excluded from all seizure analyses.

[b] Patients 21-001/48, 22-003/2, 28-002/203, 39-001/14H, 39-052/43, 39-063/45

[c] Patients 28-001/151, 34-001/11, 39-001/117H, 39-036/10, 39-048/56, 39-052/43, 54-001/4, 55-001/390

[d] >600-9000 mg is outside recommended dosing range

THZZ/85/1132
RB/djm(doh)*

MADE IN JAPAN

Table 5 (Sponsor's Table 21)

Incidence of Seizures During Bupropion Treatment by Dose

Bupropion Dose Mg/Day	# Total Seizures[a]/ # Patients (%)	Seizures in Patients Without Predisposing Factors (%)	PREDISPOSING FACTORS	
			# Seizure Patients with History of Head Trauma or Seizure[b]	# Seizure Patients with Concomitant Agents Which Lower Seizure Threshold[c]
<450	4/2398 (0 17)	0/2398 (0.00)	3/4	2/4
450	3/1281 (0 23)	2/1281 (0.16)	1/3	0/3
>450-600	12/527 (2 28)	7/527 (1.33)	2/12	3/12
>600-9000[c]	7/213 (3 29)	4/213 (1.88)	0/7	3/7

[a] Patient 39-002/18 experienced a questionable seizure subsequent to an overdose of bupropion and is excluded from all seizure analyses.

[b] Patients 21-001/48, 22-003/2, 28-002/203, 39-001/14H, 39-052/43, 39-063/45

[c] Patients 28-001/151, 34-001/11, 39-001/117H, 39-036/10, 39-048/56, 39-052/43, 54-001/4, 55-001/390

[d] >600-9000 mg is outside recommended dosing range

THZZ/85/1132
RB/djm(doh)*

The number and percent of patients dropped from "all clinical trials" and the reasons were as follows:

	Number Treated	Number Dropped: Toxicity	*Therapy Failure	*Clin. Events	*Other	Total Dropped
Bupropion	1734	262 (10.5)	231 (31.3)	23 (3)	298 (40)	737 (43)
Imipramine	48	3 (6.3)	11 (29.7)	3 (8)	20 (54)	37 (77)
Amitriptyline	181	24 (13.3)	15 (16.7)	2 (2)	49 (54)	90 (50)
Doxepin	48	12 (25)	10 (29.4)	2 (6)	10 (29)	34 (71)
Placebo	282	12 (4.3)	83 (55.7)	4 (3)	55 (37)	149 (53)

* Numbers and percent for bupropion in these columns do not include the long-term continuation protocol and the humantarian protocol.

The number of dropouts for toxicity and therapeutic failure in the controlled trials are given in Table 6 taken from the sponsor's submission.

A listing of the specific adverse effects resulting in discontinuation are given in Table 7 (taken from the sponsor's submission. It is not clear why the table does not include the 12 new seizures. What else is excluded? (The total number of patients dropped agrees with the table on page 6.)

Comment. The number of patients dropped from the studies is high. There are some discrepancies in the numbers of patients examined which I am unable to clarify.

TABLE 6 (Sponsor's Table 15)

Patient Discontinuation in Controlled Clinical Trials

Placebo-Controlled Clinical Trials

Number of Patients Treated			Number of Patient Discontinuations (%)			
			Ther. Failure		Toxicity	
Study	PBO	BUP	PBO	BUP	PBO	BUP
06	27	55	8 (29.6)	8 (14.5)	0 (0.0)	2 (9.1)
08	24	42	12 (50.0)	9 (21.4)	0 (0.0)	5 (11.9)
14	40	77	18 (45.0)	17 (22.1)	2 (5.0)	8 (10.4)
09	52	77	17 (32.7)	12 (15.6)	1 (1.9)	14 (18.2)
TOTAL	**143**	**251**	**55 (38.5)**	**46 (18.3)**	**3 (2.1)**	**29 (11.6)**

Amitriptyline-Controlled Clinical Trials

Number of Patients Treated			Number of Patient Discontinuations (%)			
			Ther. Failure		Toxicity	
Study	AMI	BUP	AMI	BUP	AMI	BUP
15	62	150	7 (11.3)	17 (11.3)	5 (8.1)	13 (8.7)
21	82	92	7 (8.5)	12 (13.0)	16 (19.5)	14 (15.2)
TOTAL	**144**	**242**	**14 (9.7)**	**29 (12.0)**	**21 (14.6)**	**27 (11.2)**

Table 7 (Sponsor's Table 16)

Number and Percent of Patients/Volunteers Discontinued
Due to Adverse Experiences

NON-COSTART TERMS

BODY SYSTEM	PREFERRED TERM	N	% TOTAL BUPROPION PATIENTS
Cardiovascular	Cardiac Arrhythmias	3	0.11
	Chest Pain	2	0.07
	Dizziness	7	0.26
	EKG Abnormality	2	0.07
	Hypertension	3	0.11
	Hypotension	3	0.11
CV SUBTOTAL		20	0.75
Dermatologic	Pruritus	7	0.26
	Rash/Lesion	31	1.16
DERM SUBTOTAL		38	1.42
Gastrointestinal	Anorexia	5	0.19
	Appetite Increase	1	0.04
	Colitis	1	0.04
	Constipation	1	0.04
	Diarrhea	1	0.04
	Liver Damage/Jaundice	1	0.04
	Nausea/Vomiting	38	1.42
	Upset Stomach	6	0.22
	Upset Stomach/Gas	2	0.07
	Weight Gain	1	0.04
GI SUBTOTAL		57	2.13
Genitourinary	Impotence	1	0.04
	Painful Ejaculation	1	0.04
	Urinary Retention	5	0.19
GU SUBTOTAL		7	0.26
Musculoskeletal	Arthritis	1	0.04

MADE IN JAPAN

Table 7 (Cont.)

BODY SYSTEM	PREFERRED TERM	N	% TOTAL BUPROPION PATIENTS
Neurological	Ataxia/Incoordination	2	0.07
	Autonomic Disturbance (Salivary Flow)	2	0.07
	Extrapyramidal Abnormalities	3	0.11
	Headache/Migraine	9	0.34
	Myoclonus	3	0.11
	Seizure*	14	0.52
	Sleep Disturbance (Impaired Quality)	1	0.04
	Sleep Disturbance (Insomnia)	8	0.30
	Tremor	4	0.15
NEUROLOG SUBTOTAL		46	1.72
Neuropsychiatric	Abnormal Mental Status	12	0.45
	Cognitive Impairment	1	0.04
	Cognitive Impairment (Attention)	1	0.04
	Delirium	11	0.41
	Mood Disturbance (Agitation)	44	1.65
	Mood Disturbance (Anxiety)	4	0.15
	Mood Disturbance (Hostility)	3	0.11
	Mood Disturbance (Mania)	3	0.11
NEUROPSYCH SUBTOTAL		79	2.96
Nonspecific	Fatigue	3	0.11
Oral Complaints	Glossitis	1	0.04
	Stomatitis	3	0.11
ORAL SUBTOTAL		4	0.15
Respiratory	Upper Respiratory Complaint	1	0.04
Special Senses	Auditory Disturbances	5	0.19
	Visual Disturbances	3	0.11
SS SUBTOTAL		8	0.30
TOTAL		264	9.88†

*Does not include 12 seizures for whom data was not available at the time of the data base cut-off. Details of all seizures reported through April, 1985 are discussed in Section II.F.

†This percentage is based on combined patient and volunteer discontinuations.

3. Vital Signs, Weights, Laboratory Tests

a. Vital Signs

A summary table of vital sign changes (systolic and diastolic blood pressure, supine and standing; pulse rate, supine and standing; and respiratory rate) and a table of changes as a function of baseline measures separately for each drug were provided by the sponsor. Inspection of the tables indicated that there was an overall tendency for blood pressure to decrease (systolic more frequently than diastolic) and it was slightly more marked in patients with higher initial measures. At the same time, there was a slight increase in pulse rate overall, with greater increases in patients with lower baseline pulse rates. There were also decreases in pulse rates in patients with higher initial rates. There did not appear to be any consistent changes in respiration rate.

b Weight

Bupropion produced weight loss in more patients than weight gains. The weight losses tended to occur more frequently in patients with higher initial weights. The greatest number of losses were in the 1-5 pound category (114/341 patients) followed by the 6-10 pound category (77/341 patients). Amitriptyline produced more weight gains in the same two categories.

c. Laboratory Data

No information was provided in the submission.

d. ECG Data

No information was provided in the submission.

4. Adverse Events

The sponsor provided a table of adverse events using COSTART terms giving the percent of patients reporting each event for the NDA and for the NDA-plus-post-NDA patients. Its appears that this table was developed to demonstrate whether there have been new serious effects or increases in frequency of effects since the NDA was submitted. There did not appear to be significant differences between the NDA and NDA-plus-post-NDA percent occurrences. However, it is difficult to evaluate, by inspection, changes in percent of occurrence. This table (Table 8) is included on the following pages. For some reason, the numbers of subjects in the total group is less than the sponsor indicated were used as the data base.

TABLE 8 (Sponsor's Table 10)

OBSERVED ADVERSE EXPERIENCES - PERCENT OF PATIENTS/VOLUNTEERS

REPORTING AND NUMBER REPORTED PER PATIENT

	NDA PLUS POST-NDA (N = 2313; 1296 F, 1017 M)		NDA (N = 1315; 735 F, 580 M)	
Adverse Experience	% Subjects	# Reports Per Subject	% Subjects	# Reports Per Subject
ABSCESS	0.17	1.3	0.30	1.3
ACNE	0.35	3.0	0.00	0.0
AGITATION	28.92	2.0	27.45	2.0
AKATHISIA	3.03	1.7	2.59	1.8
AKINESIA	0.22	1.2	0.38	1.2
ALLERG REACT	0.04	2.0	0.00	0.0
ALOPECIA	0.52	2.2	0.15	1.0
ALTERED HORMON LEVEL	0.04	2.0	0.00	0.0
AMBLYOPIA	10.68	2.2	11.63	2.0
AMNESIA	0.69	1.8	0.84	1.3
ANOREXIA	18.50	1.9	18.40	1.9
ANXIETY	1.90	1.7	2.05	1.7
APPETITE INC	5.62	1.8	5.40	1.4
ARRHYTHMIA	0.09	1.0	0.08	1.0
ARTHRALGIA	4.02	1.7	3.50	1.6
ARTHRITIS	0.04	7.0	0.08	7.0
ASTHENIA	12.62	1.9	9.89	2.0
ATAXIA	0.91	1.3	0.61	1.0
BRONCHOSPASM	0.13	1.3	0.15	1.0
CHILLS	1.38	1.4	0.68	1.0
CNS DEPRESS	0.04	3.0	0.08	3.0
CNS STIMULAT	0.04	1.0	0.08	1.0
CONFUS	5.19	1.8	3.73	1.8
CONJUNCTIVITIS	0.09	1.0	0.08	1.0
CONSTIP	12.36	2.1	12.24	1.9
CONVULS	0.52	1.0	0.53	1.0
COORDINAT ABNORM	1.69	1.4	0.91	1.3
COUGH INC	0.30	1.1	0.15	1.0
CYSTITIS	0.09	1.0	0.00	0.0
DEAF TRANS PART	0.09	1.0	0.00	0.0
DELUSIONS	0.86	1.2	0.15	3.0
DEPERSONAL	0.26	1.2	0.46	1.2
DEPRESSION	1.73	1.6	2.81	1.6
DIARRHEA	3.11	1.4	1.90	1.2
DIZZINESS	8.99	1.6	9.66	1.6
DREAM ABNORM	3.72	1.9	1.75	1.6
DRY MOUTH	17.03	2.0	16.65	2.0
DYSARTHRIA	0.09	1.5	0.00	0.0
DYSKINESIA	0.73	2.1	0.76	2.1
DYSMENORRHEA	0.08	1.0	0.00	0.0
DYSPEPSIA	3.33	1.4	1.83	1.1
DYSPHAGIA	0.17	1.3	0.23	1.0
DYSPNEA	0.17	1.0	0.08	1.0
DYSTONIA	0.48	1.5	0.38	1.2
ECCHYMOSIS	0.17	1.0	0.15	1.0
ECG ABNORM	0.09	3.5	0.15	3.5
ECZEMA	0.04	1.0	0.00	0.0
EDEMA		1.3	0.30	1.0
EDEMA PERIPH		1.0	0.00	0.0

TABLE 8 (CONT'D.)

OBSERVED ADVERSE EXPERIENCES - PERCENT OF PATIENTS/VOLUNTEERS REPORTING AND NUMBER REPORTED PER PATIENT

	NDA PLUS POST-NDA (N = 2313; 1296 F, 1017 M)		NDA (N = 1315; 735 F, 580 M)	
Adverse Experience	% Subjects	# Reports Per Subject	% Subjects	# Reports Per Subject
EDEMA TONGUE	0.04	1.0	0.00	0.0
EEG ABNORM	0.04	1.0	0.00	0.0
EJACULAT ABNORM	0.10	2.0	0.00	0.0
EMOTION LABIL	3.20	1.7	2.59	1.5
EPISTAXIS	0.04	1.0	0.08	1.0
ERUCTAT	0.09	1.0	0.00	0.0
EUPHORIA	1.73	1.7	1.22	1.8
EYE DISORDER	0.17	1.0	0.23	1.0
FACIES MASK	0.17	2.8	0.30	2.8
FECES DISCOLOR	0.04	1.0	0.08	1.0
FEVER	0.13	1.7	0.00	0.0
FEVER CHILLS	0.13	2.7	0.23	2.7
FLATUL	0.65	1.5	0.61	1.0
GAIT ABNORM	0.09	1.0	0.15	1.0
GI DISORDER	0.04	1.0	0.00	0.0
GINGIVITIS	0.04	2.0	0.08	2.0
GLOSSITIS	0.04	1.0	0.00	0.0
GLYCOSURIA	0.04	1.0	0.08	1.0
GYNECOMASTIA	0.86	1.9	0.38	1.8
HALLUCIN	1.56	1.7	1.52	1.7
HEADACHE	16.99	1.9	16.50	1.7
HEMORR GUM	0.04	1.0	0.08	1.0
HOSTILITY	0.13	1.0	0.15	1.0
HYPERKINESIA	0.82	1.8	1.44	1.8
HYPERTENS	0.61	1.6	0.76	1.8
HYPERTONIA	1.04	2.3	1.14	2.6
HYPERVENTIL	0.13	1.0	0.15	1.0
HYPOKINESIA	0.61	1.1	0.99	1.2
HYPOTENS	0.26	1.0	0.15	1.0
HYPOTENS POST	0.13	2.0	0.00	0.0
IMPOTENCE	5.06	2.7	5.70	2.7
INFECT	0.04	2.0	0.00	0.0
INFECT URIN TRACT	0.09	1.0	0.00	0.0
INSOMNIA	21.79	2.0	18.48	2.0
JAUNDICE	0.04	1.0	0.00	0.0
LARYNGITIS	0.17	1.5	0.15	1.5
LEUKEMIA CHRON LYMPHO	0.04	1.0	0.00	0.0
LEUKORRHEA	0.08	1.0	0.00	0.0
LIBIDO DECREASE	2.59	2.2	0.00	0.0
LIBIDO INCREASE	1.30	1.8	0.84	1.5
LIVER FUNC ABNORM	0.04	1.0	0.00	0.0
LYMPHADENO	0.04	1.0	0.00	0.0
MALAISE	0.13	1.0	0.00	0.0
MANIC REACT	0.22	1.0	0.23	1.0
MENOPAUSE	0.08	7.0	0.00	0.0
MENS DISORDER	3.32	1.8	2.59	1.4
MONILIA VAGINA	0.08	1.0	0.00	0.0
MS/MUS	0.04	1.0	0.00	0.0
MYALGIA	0.35	1.0	0.30	1.0

MADE IN JAPAN

TABLE 8 (CONT'D.)

OBSERVED ADVERSE EXPERIENCES - PERCENT OF PATIENTS/VOLUNTEERS

REPORTING AND NUMBER REPORTED PER PATIENT

	NDA PLUS POST-NDA (N = 2313; 1296 F, 1017 M)		NDA (N = 1315; 735 F, 580 M)	
Adverse Experience	% Subjects	# Reports Per Subject	% Subjects	# Reports Per Subject
MYDRIASIS	0.04	1.0	0.08	1.0
MYOCLONUS	0.99	1.3	0.91	1.1
NAUSEA VOMIT	10.55	1.6	9.51	1.7
NERVOUSNESS	0.73	1.2	0.68	1.0
NEUROPATHY	0.04	1.0	0.08	1.0
NEUROSIS	0.17	2.0	0.15	2.0
NOCTURIA	1.34	2.0	1.52	2.0
OTITIS MED	0.04	1.0	0.08	1.0
OVAR DISORDER	0.04	1.0	0.00	0.0
OVERDOSE INTENT	0.04	1.0	0.00	0.0
PAIN	2.72	1.5	1.83	1.3
PAIN ABDO	0.82	1.3	0.61	1.1
PAIN BACK	0.26	1.5	0.23	1.7
PAIN BREAST	0.09	1.0	0.08	1.0
PAIN CHEST	0.61	1.2	0.53	1.3
PAIN EAR	0.09	1.0	0.!	1.0
PAIN EYE	0.04	1.0	0.00	0.0
PAIN NECK	0.13	1.3	0.15	1.0
PAIN TOOTH	0.22	1.2	0.15	1.0
PALLOR	0.04	1.0	0.08	1.0
PALPITAT	4.50	1.6	4.18	1.5
PARANOID REACT	0.04	1.0	0.08	1.0
PARESTHESIA	3.24	2.0	2.59	1.5
PENIS DISORDER	0.10	1.0	0.17	1.0
PERSON DISORDER	2.03	1.6	1.44	1.4
PETECHIA	0.43	1.1	0.00	0.0
PHARYNGITIS	0.22	1.2	0.30	1.0
PHLEBITIS	0.04	1.0	0.00	0.0
PHOTOPHOBIA	0.04	2.0	0.08	2.0
PROCTITIS	0.04	1.0	0.00	0.0
PRURITUS	2.38	1.5	1.52	1.4
PSYCHOSIS	0.30	2.7	0.53	2.7
RASH	2.72	1.4	2.74	1.4
RASH MAC PAP	0.04	1.0	0.00	0.0
RASH PHOTO	0.35	2.4	0.15	3.0
RESPIRAT DISORDER	0.17	1.0	0.08	1.0
RHINITIS	0.69	1.1	0.99	1.1
SALIVA INCREASE	0.78	1.4	0.76	1.5
SINUSITIS	0.13	1.0	0.08	1.0
SKIN DRY	0.09	1.0	0.00	0.0
SOMNOLENCE	10.51	1.6	11.18	1.6
SPEECH DISORDER	0.22	1.0	0.23	1.0
STOMATITIS	0.78	1.2	0.30	1.0
SWEAT	7.26	1.8	6.69	1.8
SYNCOPE	0.61	1.2	0.15	1.0
TACHYCARDIA	0.73	1.4	1.22	1.4
TASTE PERVERS	3.03	1.6	2.36	1.4
THINKING ABNORM	6.79	1.9	4.03	1.6
THIRST	0.13	1.0	0.15	1.0

MADE IN JAPAN

TABLE 8 (CONT'D.)

OBSERVED ADVERSE EXPERIENCES - PERCENT OF PATIENTS/VOLUNTEERS REPORTING AND NUMBER REPORTED PER PATIENT

	NDA PLUS POST-NDA (N = 2313; 1296 F, 1017 M)		NDA (N = 1315; 735 F, 580 M)	
Adverse Experience	% Subjects	# Reports Per Subject	% Subjects	# Reports Per Subject
TINNITUS	2.98	1.6	2.21	1.5
TREMOR	8.73	2.0	7.83	1.9
TRISMUS	0.09	1.5	0.15	1.5
TWITCH	0.17	1.0	0.23	1.0
URIN FREQUENCY	2.85	1.6	1.67	1.7
URIN INCONTIN	0.04	1.0	0.00	0.0
URIN RETENT	1.73	1.9	0.91	1.5
URTICARIA	1.30	1.3	0.91	1.3
VAGINITIS	0.23	1.0	0.41	1.0
VASODILAT	1.77	1.7	1.29	1.6
VERTIGO	0.04	1.0	0.00	0.0
VISION ABNORM	0.04	1.0	0.00	0.0
VOMIT	0.04	1.0	0.00	0.0
VULVOVAGINITIS	0.08	1.0	0.00	0.0
WEIGHT DECREASE	0.04	1.0	0.00	0.0
WEIGHT INCREASE	0.69	1.3	0.76	1.2

NOTE: For the following adverse experiences, the % subjects was calculated using the # females, rather than the # subjects: DYSMENORRHEA, LEUKORRHEA, MENOPAUSE, MENS DISORDER, MONILIA VAGINA, VAGINITIS, and VULVOVAGINITIS. For the following adverse experiences, the % subjects was calculated using the # males: PENIS DISORDER, EJACULAT ABNORM.

Also note that the % subjects was calculated using only the subjects who had at least one treatment period evaluation. Therefore, the number of patients/volunteers used in this analysis (2313) is less than the number of unique patient/volunteer entries (2398). The # reports per subject was calculated as follows: # reports of an event / total # subjects reporting that event.

The incidence of convulsions reflects only those instances in which a seizure was recorded on adverse experience forms and entered into the computerized data base (through August 1, 1984). Details of all seizures reported through April, 1985 are presented in this update (see Section II.F.).

Table 9 gives the most frequent events (greater than one percent). This table was developed by the sponsor from the previous exhaustive list. Table 10 (developed by the sponsor) uses non-COSTART categories (which are not those used in Table 7) to show the incidence for bupropion and placebo in controlled trials. The sponsor also developed a table (by study) where each adverse event that occurred was classified as trivial (requiring no action), of some concern (requiring some action exclusive of discontinuation) and serious (requiring study discontinuation). This table gives head counts but does not give a listing of the actual events. Finally, life table analyses by dosage category of the three most frequent events (agitation, insomnia, anorexia) are provided.

Number and Percent* of Patients Reporting Adverse Experiences

	Number Treated	No Adverse Effects	Trivial	Some Concern	Serious**
Bupropion	2486	404 (16)	1185 (47.7)	635 (25.5)	262 (10.5)
Imipramine	48	3 (6.3)	25 (52.1)	17 (35.4)	3 (6.3)
Amitriptyline	181	4 (2.2)	93 (51.4)	60 (33.1)	24 (13.3)
Doxepin	48	4 (8.3)	15 (31.3)	17 (35.4)	12 (25)
Placebo	282	35 (12.4)	174 (61.7)	61 (21.6)	12 (4.3)

* ( ) = percent
** Serious dropped from the study.

5. Conclusions.

The sponsor has provided an update of serious events, seizures, terminations, adverse events and vital signs. There do not appear to have been any new events or increases in the frequency of known events. The discussion of the seizures identifies the risk factors (dosage changes, higher dosages and, for some, predisposing factors).

The sponsor should submit a cross tabulation of all laboratory results in the tests where there were abnormalities. This should be done for bupropion, placebo and any relevant standard. In addition, a listing of all ECG abnormalities for each treatment should be provided.

MADE IN JAPAN

Table 9 (Sponsor's Table 11)

Adverse Experiences Which Occurred at Frequencies Greater Than One Percent*

Frequency	Adverse Experience	% Patients
> 20%	Agitation	28.9
	Insomnia	21.8
>10% ≤20%	Amblyopia	10.7
	Anorexia	18.5
	Asthenia	12.6
	Constipation	12.4
	Dry Mouth	17.0
	Headache	17.0
	Nausea/Vomiting	10.5
	Somnolence	10.5
>5% ≤10%	Appetite Increase	5.6
	Confusion	5.2
	Dizziness	9.0
	Impotence	5.1
	Sweating	7.3
	Thinking Abnormalities	6.8
	Tremor	8.7
>1% ≤5%	Akathisia	3.0
	Anxiety	1.9
	Arthralgia	4.0
	Chills	1.4
	Coordination Abnormalities	1.7
	Depression	1.7
	Diarrhea	3.1
	Dream Abnormalities	3.7
	Dyspepsia	3.3
	Emotional Lability	3.2
	Euphoria	1.7
	Hallucinations	1.6
	Libido Decrease	2.6
	Libido Increase	1.3
	Menstrual Disorder	3.3
	Nocturia	1.3
	Pain	2.7
	Palpitations	4.5
	Paresthesia	3.2
	Personality Disorder	2.0
	Pruritus	2.4
	Rash	2.7
	Taste Perversion	3.0
	Tinnitus	3.0
	Urinary Frequency	2.9
	Urinary Retention	1.7
	Urticaria	1.3
	Vasodilation	1.8

*Data derived from Table 10.

MADE IN JAPAN

TABLE 10 (Sponsor's Table 12)

ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS*

(Percent of Patients Reporting)

Adverse Experience[1]	Bupropion (n = 218)	Placebo (n = 140)
AUTONOMIC		
Dry Mouth	34.9	27.1
Saliva Increase	3.2	4.3
Constipation	31.2	26.4
Diarrhea	7.8	11.4
Sweat	22.0	19.3
CARDIOVASCULAR		
Tachycardia	12.8	11.4
Palpitation	18.3	15.7
Hypertension	4.6	2.1
Hypotension	3.2	2.9
CNS		
Agitation	28.4	21.4
Anxiety	1.4	0.0
Confusion	6.4	1.4
Emotion Lability	4.6	2.9
Euphoria	1.8	0.0
Insomnia	12.4	12.1
Personality Disorder	4.1	3.6
Somnolence	20.2	20.0
DERMATOLOGIC		
Rash	8.3	7.1
GASTROINTESTINAL		
Anorexia	35.8	44.3
Appetite Increase	2.8	2.1
Dyspepsia	1.8	1.4
Nausea/Vomiting	28.4	23.6
Weight Increase	17.4	30.0
GENITOURINARY		
Urinary Retention	1.8	2.9
Nocturia	5.0	5.7
Menstrual Disorder	11.4	7.8
MUSCULOSKELETAL		
Arthralgia	6.0	5.7

*Studies 06, 08-001, 08-002, 09, 14

LION 301 MADE IN JAPAN

TABLE 10 (Cont.)

ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

Adverse Experience	Bupropion (n = 218)	Placebo (n = 140)
NEUROLOGICAL		
Asthenia	3.7	7.1
Dizziness	31.2	25.7
Dystonia	1.4	0.7
Headache	29.4	20.7
Hyperkinesia	13.8	5.7
Hypertonia	2.3	1.4
Hypokinesia	9.2	10.0
Tremor	17.9	7.1
Paresthesia	2.3	0.7
OCULAR		
Amblyopia	16.1	12.9
RESPIRATORY		
Rhinitis	5.0	12.9
SEXUAL FUNCTION		
Impotence	29.8	23.6
OTHER		
Tinnitus	4.1	1.4
Taste Perversion	2.8	1.4

[1]Events reported by $\geq$1% of bupropion patients are included.

Labeling Changes.

Indications Section. We had suggested that the following statement be included: "However, because experience in clinical studies suggest that Wellbutrin may pose a greater risk of seizure than other antidepressant drug products, Wellbutrin should not generally be considered as the antidepressant of first choice for most depressed patients." Burroughs Wellcome rejected this proposal. Their indications read, "Wellbutrin is indicated for the treatment of depression. The efficacy of Wellbutrin was demonstrated in placebo control clinical trials which enrolled primarily hospitalized patients with diagnoses of depressive neuroses or manic depressive disorder." Our equivalent was, "The efficacy of bupropion was demonstrated in clinical trials of three weeks duration which enrolled, etc." We also had recommended the following, "The only placebo controlled trial of bupropion in depressed outpatients failed to provide unequivalent evidence of its efficacy." The sponsor's equivalent was, "As with other antidepressants, the appropriate treatment duration for patients who have shown a positive clinical response to Wellbutrin is not known. Although many patients have been treated with Wellbutrin in long term clinical trials of up to two years in duration, these studies were not placebo controlled and evidence to demonstrate the sustained effectiveness of Wellbutrin after three weeks of use in placebo controlled investigations is not presently available."

Dosage Section. This section was changed to recommend a lower dosage range. The sponsor is now recommending as the usual adult dosage, a starting dose of 225 mg/day [illegible] as 75 mg t.i.d. "Based on clinical response this dose may be increased by [illegible] mg/day no sooner than every three days according to the following schedule up to a total daily dose of 450 mg/day. Most patients who respond do so at a total daily dose of 450 mg/day or less." There then is a dosing schedule to tell how many tablets of 75 mg to give in the morning, midday and evening. They go on to say that in patients who do not respond at 450 mg., dose escalation may continue in 75 mg/day increments no sooner than every five days to a maximum of 600 mg/day or 4 mg/pd/day which ever is smaller. Similarly a table is given showing how many tablets should be administered at each time of the day.

The sponsor had been requested to show that patients did respond at a dose of 450 mg/day. That is, because the dosage range was changed to a lower range, we requested that an efficacy analysis be carried out for the revised dosage schedule. The sponsor did not provide this. They referred us to studies 06, 08, and 14-01. Dr. Leber has talked to them about this. (See Dr. Leber's memo of May 16, 1985.)

Specific Changes.

The sponsor has made the following possibly significant changes:

1. Under Warnings, the potential for hepatotoxicity was characterized as mild. Since we do not have a laboratory test update, it is not possible to verify this.

2. Under Use in patients with systemic illness, the sponsor added a sentence suggesting that Wellbutrin "was well tolerated in patients who developed orthostatic hypotension on tricyclic antidepressants."

3. Under Adverse Reactions, the sponsor deleted the final paragrapn concerning glucose and LDH changes. They state that the original expanded summary suggests that the percentage of patients who had normal or near normal baseline blood glucose and LDH levels and subsequently experienced significant elevations was approximately the same in the bupropion and placebo groups (2-3%).

Conclusions.

1. Safety Update. The sponsor should submit a cross tabulation of all laboratory results for tests where there were abnormalities. This should be done for bupropion, placebo and any reievant standard. In addition, a listing of all ECG abnormalities for each treatment should be provided.

2. Labeling. A decision should be made about the indications and dosage section. The seizure discussion should be changed by removing the 9000 mg case from the normal dosing group and by including a statement to the effect that they occurred more frequently following dosage increases. Finally, the above "specific changes" must be supported by data.

J. Hillary Lee, Ph.D. (HFN-120)

cc:
Orig:NDA 18-644
HFN 120
HFN-120/Thayes/PLeber
HFN-120/HLee
rd/mb/5/23/85
DOC 0108n

Review andEvaluation of Clinical Data
Proposed Labeling

NDA: 18-644
Sponsor: Burrough s Wellcome Co.
Drug: Wellbutrin
Date of Submission: 1985, Nov. 26, 1985
Date of Review: December 12, 1985

Material Reviewed: Indications, Warnings, Precautions, Drug interactions, and Adverse Reactions. Some sections from earlier submissions in 1985 have also been reviewed again to amplify some issues in the labeling.

1. Indications.

2. Warnings . The table of seizures should be revised as it is misleading. That is, the bottom line (number of seizures occurring between 600 and 9000 mg) should be divided into two lines with one line for dosages between 600 and 900 and the second line for dosages above 900mg. That is, the overdose at 9000 mg should be separated from those seizures occurring within the former prescribed range.

   In addition, the text on the page immediately preceeding the table of seizures should include a statement to the effect that BLANK percent of seizures occurred within two days of a dosage increase.

3. Precautions. Since weight loss is more unusual and potentially more serious than weight gain, I would recommend that the weight loss effect be discussed before the weight gain.

   Under Drug Interactions, reference is made to an interaction with phenylzine in animals. Do we know anything about other MAOI's in animals?

   Should the Information for patients section contain a caution about abrupt withdrawal? I am not aware of problems on withdrawal except for one case of a second seizure during gradual withdrawal from Wellbutrin following the original seizure.

4. Adverse Reactions. In the table of adverse experiences in the placebo controlled trials, I noted that approximately 12 percent of the subjects had akinesia/bradykinesia. When I went to see where this side effect came from, I found that there were four or five cases of akinesia from study 38, a study evaluating the effect of Wellbutrin vs. placebo in schizophrenic patients receiving fluphenazine who showed pseudoparkinsonism. Bradykinesia was not listed as a side effect in any of the earlier submissions. I did, however, find hypokinesis which was listed as an effect occurring in depression studies. I assume this was combined with the akinesia to form the new category. I have two comments. First, I think the table of adverse effects in controlled trials should be limited to trials in depression and this could be stated in the table heading. Second, I wonder if hypokinesis is a BW classification for psychomotor retardation? Perhaps we could ask for clarification on this.

In keeping with my review of the psychiatric side effects, namely, confusion and psychosis(hallucinations), I would recommend these categories be combined and read as confusion/psychosis (hallucinations).

I still find the section following the table confusing. That is, an effect is classified as most frequent yet it does not include effects occurring in the table. Although the section is prefaced with a phrase ("In addition to the events described above"), this could be missed when the reader jumps into the listing. Also, the distinction between most frequent and less frequent is artificial. Perhaps the distinction could be dropped.

Under 'Gastrointestinal',the items for changes in weight are confusing. That is, 33 percent of Wellbutrin and 30 percent of placebo patients have weight loss as an adverse effect while 20 of Wellbutrin and 30 percent of placebo have weight gain as an adverse effect. Could this possibly mean weight change and not an adverse effect? It would be understandable that 60 percent of patients had a weight change. Perhaps we should ask the sponsor to set a minimum change before it would be reported as an adverse effect? It is possible that by reporting all weight changes, they are obscuring large weight losses on Wellbutrin, for example.

Conclusions. The above items are for discussion concerning the final labeling.

J. Hillary Lee

J. Hillary Lee, Ph.D.
Psychologist

18.444
NDA
120/Hlee

Clinical Review of Submission

NDA 18-644

Drug: Wellbutrin (bupropion)

Sponsor: BW

Submission date: 9/18/84

Introduction:

The submission contains a response to our request for evidence supporting the sustained antidepressant efficacy of bupropion beyond three weeks.

To be acceptable as a source of evidence for a given duration of antidepressant effect, we required that any study selected for presentation retain at least 70% of the subjects at the time point of the analysis (vide infra). This rule was used to preclude the presentation of data from trials that were of longer than three weeks duration in name only.

Specifically, we asked the sponsor to conduct an "intent to treat" analysis of 1) all patients and 2) the same cohort excluding those who violated the protocol because of sedative/hypnotic use. Each analysis was to be an "end point" analysis (last observation carried forward or LOCF). The endpoint chosen was to be selected as the latest time for which observations were available at which at least 70% of the subjects randomized to treatment were retained in each treatment group. Importantly, the firm was told explicitly that the time should not be selected as the time when the study, overall, retained 70% of its subjects. This qualification was made to preserve the quality and validity of between groups comparisons when the rate and timing of dropouts varied between treatments.

Using these rules, the sponsor was to analyze the raw data and the change from baseline scores for all treatments on the following items: the Ham-D total, the Ham-D depression item, the Ham-D retardation factor and the two globals (severity and improvement). Power calculations and/or confidence limits for each calculation were to be presented for the between treatment contrasts.

Results of the sponsors presentation:

After examining the trials available, the sponsor concluded that only one study, # 15, an active control trial employing amitriptyline as the standard treatement, satisfied the retention criterion sufficiently far beyond three weeks to deserve analysis.

The salient points of the sponsor's presentation are summarized below:

Point 1: The study 15 Analysis:

Study 15 consists of 6 subcenters or sites. While nominally following the same protocol, the results varied from center to center.

While the sponsor did not present the analysis for the items requested at the single time point requested, he did provide tables and graphical displays which permitted this reviewer to reconstruct the information requested. Using a graphical technique (i.e., dropping a vertical line from the point of 70% retention for the first treatment crossing this retention boundry to the time (X) axis), I estimated the time at which each center and the combined centers met our analysis criteria, that is, the time at which the regular scheduled LOCF analysis could be performed.

For all sub-studies but one, including the combined study, 29 days was the appropriate 'endpoint' analysis point. For study 1502, 43 days was used.

The Hamilton depression scale score change from baseline difference for each center for bupropion and amitriptyline are presented below:

Hamilton total change from baseline score:

Study	Bupropion	Amitriptyline	better	Number bup:ami
1501	- 7.7	-13.6	ami	25:13
1502*	-11.5	- 9.7	bup	11:7
1503	-15.4	-18.9	ami	32:16
1504	-17.2	-17.4	?ami	13:7
1505	-10.6	- 9.2	bup	19:10
1506	- 7.1	-12.9	ami	21:9
all (#)	-11.3	-14.2	ami	121:62

Hamilton Depression item change from baseline scores:

Study	Bupropion	Amitriptyline	better	Number bup:ami
1501	- 1.04	- 1.62	ami	25:13
1502*	- 1.64	- 1.29	bup	11:7
1503	- 1.56	- 1.94	ami	32:16
1504	- 1.85	- 1.71	none	13:7
1505	- 1.32	- 1.2	bup	19:10
1506	- 1.00	- 1.78	ami	21:9
all (#)	- 1.33	- 1.66	ami	121:62

NB: *=day 43, all others day 29; #=weighted analysis.

Although not tabulated here, the global severity and global improvement results generally confirm the findings on the Hamilton Depession Scale.

Several statistically significant differences favoring amitriptyline were found; none favoring bupropion were detected. The times and conditions in the 'all patients analysis' at which statistically significant differences were detected are enumerated. As noted, all favored amitriptyline.

MADE IN JAPAN

For the Ham-D Total:

on observed data: combined unweighted analysis and 15-01, 15-06 barely missed (p-0.073).

on change from baseline data: study 1501, 15-06 was close(p=0.084)

For Hamilton Depression Item:

observed data: combined centers, both equal and weighted, 15-01

change score: combined centers, both equal and weighted, and 15-06

For CGI Severity:

observed: combined centers only, 15-06 was close (p=0.064)

change score: combined centers, only

For CGI Improvements:

observed: combined, both analyses, 15-01
there is no change score for this item

On the Ham-D retardation factor, the combined center results also achieved significance, but no single center did.

Conclusion regarding study 15 and the sponsor's discussion:

Commenting upon the results without benefit of formal statistical consultation, I find little that is of immediate use to us. The results suggest that in some settings, patients assigned to amitriptyline fare better than those on bupropion. Of some interest is the fact that the three largest studies by rank, 03.01 and 06, all favor amitriptyline, the standard drug, a point reflected, I believe, in the larger differences found using the weighted analysis.

Whether or not the results may be explained by agitation caused by bupropion, or the sedation caused by amitriptyline, is irrevelant. Without placebo, there is simply no way to know if the poorer showing of bupropion is meaningful.

In any event, whatever the explanation, I do not find in this data proof that bupropion is effective for twenty-nine days.

Indeed, rather than focusing on the issue of sustained efficacy, the issue that motivated our request for the analysis, the sponsor's discussion of study 15 appears to have an apology for the "poorer" showing of bupropion as its major thrust. For example, the analysis and discussion is not limited to the duration question but attempts to review the entire study including results at

For the Ham-D Total:

on observed data: combined unweighted analysis and 15-01, 15-06 barely missed (p-0.073).

on change from baseline data: study 1501, 15-06 was close(p=0.084)

For Hamilton Depression Item:

observed data: combined centers, both equal and weighted, 15-01

change score: combined centers, both equal and weighted, and 15-06

For CGI Severity:

observed: combined centers only, 15-06 was close (p=0.064)

change score: combined centers, only

For CGI Improvements:

observed: combined, both analyses, 15-01
there is no change score for this item

On the Ham-D retardation factor, the combined center results also achieved significance, but no single center did.

Conclusion regarding study 15 and the sponsor's discussion:

Commenting upon the results without benefit of formal statistical consultation, I find little that is of immediate use to us. The results suggest that in some settings, patients assigned to amitriptyline fare better than those on bupropion. Of some interest is the fact that the three largest studies by rank, 03.01 and 06, all favor amitriptyline, the standard drug, a point reflected, I believe, in the larger differences found using the weighted analysis.

Whether or not the results may be explained by agitation caused by bupropion, or the sedation caused by amitriptyline, is irrevelant. Without placebo, there is simply no way to know if the poorer showing of bupropion is meaningful.

In any event, whatever the explanation, I do not find in this data proof that bupropion is effective for twenty-nine days.

Indeed, rather than focusing on the issue of sustained efficacy, the issue that motivated our request for the analysis, the sponsor's discussion of study 15 appears to have an apology for the "poorer" showing of bupropion as its major thrust. For example, the analysis and discussion is not limited to the duration question but attempts to review the entire study including results at

much later time points, times when the differences favoring amitriptyline are less apparent (and when few patients remain in the study). The sponsor also attempts a refutation of the significance of the statistically significant differences found that favored amitriptyline at the 70% retention endpoint for 15-01 and 15-06 and at virtually all points in the combined study result.

We read the old argument that the size of the mean treatment differences are not clinically significant. I will not get into the issue here, but I would point out that this interpretation of mean differences is a bit specious; indeed, it is the very argument that we refuse to accept as a reason to discard small treatment differences between an experimental drug and placebo when we accept such differences as proof of efficacy.

In any event, I am not prepared to explain why amitriptyline beat bupropion, or what this finding means about the true efficacy of bupropion as an antidepressant. Without placebo as a marker of location, this trial cannot be interpreted in regard to bupropion's absolute efficacy; nevertheless, I must admit, based upon current policy, that the data in study 15 might be used as evidence to support the efficacy of amitriptyline. More to the regulatory point, however, not every drug is good for every patient and bupropion may have advantages not identified in the efficacy relative to amitriptyline (e.g., less anticholinergic properties, less cardiotoxicity, etc.).

Point II: Earlier Evidence on Outpatient Efficacy:

In the course of their reply, the sponsor, anticipating our concern about the lack of evidence on bupropion as an antidepressant in outpatient settings, mentions that a revised analysis of 90-01, one of the two centers of the single placebo controlled outpatient trial, provides evidence that at day 21 Wellbutrin (at a so-called low dose of 150-450 per day) is superior to placebo.

The sponsor correctly notes that the re-analysis was one requested by the agency (we did not like their original analysis of covariance) and the "reanalysis does show that the Ham-D total and CGIs for the 21 day LOCF between groups contrast to be statistically significant (p= 0.053, 0.03 and 0.02 respectively). Unfortunately, in the original analysis of covariance presented by the sponsor, the p values for these very same items at the very same times are quite far from statistical significance (p=0.87, 0.84, 0.81).

Thus, the outcome appears clearly to be dependent upon the type of analysis carried out. A bit surprising, but, without the individual study results on the observed data, there is no intelligent way to respond. Dr. Stein's Novemeber 18, 1982 statistical review had reviewed the reanalysis; in fact, his review tabulates the same data as the sponsor. However, Dr. Stein concludes that that 09 is a study lacking statistical evidence of efficacy. (Incidentally, I do not think the sponsor ever submitted the individual study data for 09-01 or 02; in any event, given the organization of the submission, we can't find it and given the type of information supplied in earlier submissions it is likely that the data will not follow analysis rules we would now use in regard to exclusions, etc.) In any event, the second site, 9-02 fails to confirm the findings in 9-01, even in the "reanalysis."

MADE IN JAPAN

Conclusion:

The sponsor's submission fails to establish that bupropion is effective for more than three weeks in inpatients, or effective at all in outpatients.

The labeling must, therefore, state these limitations on our judgment and/or our basis for that judgment. Full information is critical to the intelligent use of antidepressant drugs.

Paul Leber, M.D.
October 17, 1984

cc: NDA 18-644
HFN-120/Haye indelar/Davis
HFN-713/Stein, Ledger
HFN-120/PLeber/1018/84
Doc. 2495C

MADE IN JAPAN

4193

Clinical Review

of

NDA 18644

I. Sponsor: Burroughs-Wellcome
3030 Cornwallis Road
Research Triangle Park, North Carolina

II. Drug name (Action): bupropion (antidepressant)

III. Trade name: Wellbutrin

IV. Summary:

Sponsor has responded to our letter of September 8, 1983 in which labeling revisions were recommended. The format of this reviewer's comments will be to first address the changes which we proposed in the Sept. 8 letter and then to suggest some additional revisions.

Item 1. We suggested the deletion of the phrase which stated that bupropion is effectiv[illegible] TCA non-responders. Sponsor in its answer has cited a retrospective study of 30 patients which were judged by clinicans to be TCA non-responders. Sponsor has slightly modified its claim to include the fact that the effectiveness of Wellbutrin was seen in a retrospective study.

RECOMENDATION: Delete the claim altogether since a sample of 30 patients is hardly sufficient to establish the claim.

Item 2. We suggested a contraindication of concurrent administration of bupropion with MAOI's. This has been done.

Item 3a. Sponsor was requested to delete the word "small" from the second sentence of the "Carcinogenesis" section. This has been done.

Item 3b. Sponsor was requested to add a statement regarding the weakly positive effects on the Ames Test in the Mutagenesis section. This has been done.

Item 3c. Sponsor was requested to use a Category C pregnancy listing instead of "B". This has not been done. Sponsor has submitted a letter from Dr. James Wilson, a Burroughs consultant (Page 31 of Sponsor's submission).

RECOMMENDATION: A determination should be made by Dr. Leber and the reviewing pharmacologist. Category C is appropriate if the existing data is insufficient to make a clear determination.

Package insert, page 5. (This is Sponsor's change, not our request). The paragraph now reads:

Nursing Mothers: It is not known whether Wellbutrin is excreted in the milk of lactating women. Because many drugs are excreted in human milk, caution should be exercised when Wellbutrin is administered to a nursing women.

RECOMMENDATION: The proposed labeling is inappropriate. Change as follows:

It is not known whether Wellbutrin is excreted in human milk. Because many drugs are excreted in human milk the possibility of fetal risk from the maternal ingestion of Wellbutrin cannot be excluded. Therefore, Wellbutrin should be used in women who are or might become pregnant only if the clinical condition clearly justifies potential risk to the fetus.

Item 4a. We objected to the first of the "Adverse Reaction" section as overtly promotional. Sponsor revised the statement by deleting the phrase "was very well tolerated". The statemment now reads "Wellbutrin produced few significant adverse reactions in clinical trials involving 1153 patients.".

RECOMMENDATION: Delete not only the revised first sentence, but the entire first paragraph as being promotional.

Item 4b. We noted that limiting the presentation of data to patients who received no more than 750 mg per day had the effect of reducing the number of patients reported from 1153 to 361. Sponsor states that this is incorrect and that only 45 patients would fall into this category.

RECOMMENDATION: Sponsor' point seems to be correct and should stand.

Item 4c. We noted that reporting only those reactions which the investigator felt to have at least a 50% probability of relation to drug resulted in underreporting and that raw figures should be presented. Sponsor has added a table showing raw figures.

RECOMMENDATION: Two sets of data are somewhat confusing and the results between the two are disparate. A single set would be better if we and Sponsor can agree on what to use.

Item 5. We questioned the use of a "Comparative Differences" section in which Wellbutrin was compared to other products. Sponsor has removed the heading but not the content (page 9 of package insert).

RECOMMENDATION: It is not appropriate in labeling to list adverse effects which a drug may not produce. This is true whether it is in comparison with another agent or not. The entire paragraph is promotional and should be deleted. If such is allowed, one is opening a "Pandora's Box" for promotion and advertising. I have no doubt that Wellbutrin does not cause hang nail, athletes foot, dandruff, etc. This is true even in cases where other drugs of a class are known to cause a certain reaction and the compound in question does not.

Item 6. A "Drug Abuse and Dependence" section has been added as we requested.

RECOMMENDATION: Drs. Leber and Vocci should decide on the adequacy of this section.

Item 7. In the "Overdosage" section we requested deletion of the sentence dealing with phenytoin and barbiturates. Sponsor has done this.

Package Insert, page 10. (This is Sponsor's change, not one that we requested.). Under "Dosage and Administration" a new second sentence has been inserted. This reads "A dose of 300 mg per day (100 mg T.I.D.) can be given from the outset since the side effects characteristic of other antidepressants are usually minimal with Wellbutrin.".

RECOMMENDATION: Delete the sentence. It is both promotional and redundent. The 300 mg. per day dose is already given in the two paragraphs below. For clarity insert "(100 mg. T.I.D.)" after "300 mg/day" in both of these paragraphs.

Other Suggested Revisions:

These are the reviewer's comments.

1. Under "Indications and Usage" delete all the symptoms listed in parentheses on page 2 of the package insert. Also, Sponsor has apparently used both DSM II and DSM III nomenclature. Probably only DSM III should be used.

2. In the third paragraph of this section Sponsor states that "There is no clinical experience with Wellbutrin in patients with a recent history of myocrdial infarction or unstable heart disease, however." Add to this sentence "and is not recommended in these groups."

3. In the "Overdosage" section Sponsor has given preclinical data (first paragraph). This shold be deleted or placed in a "Preclinical Pharmacology" section on the first page of the package insert.

LION 331 MADE IN JAPAN

Summary of current state of NDA:

The statistical enclosure has been reviewed and found satisfactory by the Division of Statistics. The SBA is about 75 % complete and should be finished soon. The chemistry is still incomplete but the problems seem to be minor and relate to validation methods. The biopharmaceutics seem to be satisfactory.

David M. Davis

David M. Davis
Psychologist, HFN-120

Dist:
Orig: NDA
HFN-120
HFN-120/DDAVIS
Doc# 5189B

TA Hayes 04-30-83

JUL 2 5 1982

25

Clinical Review of NDA 18-644

I. Sponsor: Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park
North Carolina 27709

Telephone (919) 541-9090
Project Officer: Warren Stern, Ph.D.
Head, Psychiatry Section

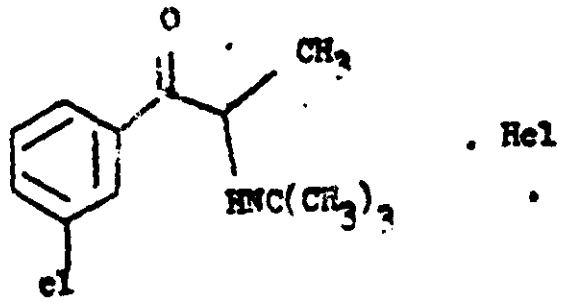
II. Drug Name (Action): bupropion (Presumed Antidepressant)

III Trade Name: Wellbutrin

IV. Summary:

A. Introduction:

Wellbutrin (bupropion HCl) is a new antidepressant compound having the chemical formular C13H18CLNO. Its molecular weight (for the hydrochloride) is 276.21 and has the following chemical structure:



. HCl

Wellbutrin is chemically but not pharmacologically (in Sponsor's view) related to a marketed anorectic, diethylpropion (Tenuate). The compound appears as a white powder with a slight characteristic odor. The marketed formulation would be as a tablet in 3 potencies. These are 50 mg (white), 75 mg (yellow) and 100 mg (read).

Bupropion is an Ameinoketone which is chemically distinct from all marketed antidepressants. It is neither a tricyclic nor MAOI. Moreover, it is dissimilar to the newer antidepressants such as

Trazodone and Merital. The compound is not currently marketed anywhere in the world although a New Drug Application has been filed in Canada concurrently with this one. There is, therefore, no significant body of clinical literature either domestic or foreign.

In preclinical studies the absorption and disposition of Wellbutrin were determined in rats, mice and dogs. Toxicological effects were also investigated.

In an acute toxicity study in mice TTEP/78/0028 (Sponsor's protocol designation) bupropion was administered orally to 2 groups (20 male and 20 female) mice at doses of 400, 500, 600, and 700 mg/ kg. The observed LD/50's were 544 ± 29 mg/kg (males) and 636 ± 23 mg/kg (females).

In a second study, a group of 20 male mice were given IP doses of 200, 225, 250, 275 and 300 mg/kg. The observed LD_{50} in the group was 273 ± 4 mg/kg. All deaths occurred within 17 minutes after dosing.

In an acute toxicity study in rats (TTGP/78/0036) the observed oral LD50's were 606 .9 ± 51 mg/kg (males) and 481.7 ± 91 mg/kg (females). The IP LD_{50} was 263 ± mg/kg (makes only).

Sponsor also conducted a 90 day oral toxicity study in rats (TTGP/70/0009). Twenty rats, 10 per sex, were treated orally for 90 days with doses of 150,300 and 450 mg/kg of bupropion. In the low dose group, one rat died spontaneously, 2 were killed accidentally in the mid dose group. One rat was sacrificed in a moribund condition and one died spontaneously in the high dose group. No specific toxicity was noted although there was a dose related increase in liver growth and an increase in the total serum protein. These findings are regarded as being related to enzyme induction.

There were also 55 week (TTGP/78/0070) and 104 week (TTGP/76/0031) oral toxicity studies in rats. Again, the major findings were dose related increase in liver weights.

Finally, in a 90 day oral toxicity study in dogs (TTGP/70/0001), 4 groups, 2 per sex were treated with doses of lactose (control group), 15, 35, and 75 (increased to 150 after 45 days) mg/kg/day of Wellbutrin. No toxicity was observed in the dogs at any dose level.

Sponsor's proposed maximum human dose of 750 mg/day is approximately 11 mg/kg in a 150 lb (68 kilogram) person.

Absorption and disposition of bupropion in animals:

1. Male and female rats were dosed at 50 mg/kg IP and plasma concentrations were measured over 4 hours. The elimination in male rats was much more rapid than in females. the respective plasma half lives were .95 and 2.3 hours. In a second study, rats were dosed orally or intravenously and plasma and brain concentrations were determined. The dose was 10 mg/kg. A sex difference in bioavailability of the compound was found with the drug being 8% bioavailable in male rats and 21% in females. Also, the br in concentrations over the 4 hours post dose was 10-15 time the serum concentration.

2. In the mouse metabolism studies it appeared that the drug and its metabolites undergo rapid elimination from the entire animal and that the rate of metabolism increases over time.

3. In beagle dogs, bupropion was administered both I.V. and orally at doses of 10 mg/kg. The plasma half-life of I.V. Wellbutrin was 1.7 hours and no sex differences were observed.

Tissue distribution:

1. In the rat, following I.P. administration the greatest concentrations were found in the lung, but following oral administration the greatest accumulation was in the liver. The drug was widely distributed in tissue in both cases. In another study of adult female rats various dose levels produced the greatest concentrations in the liver and kidney followed by the brain and spleen. The tissue concentrations declined significantly after the 6th hour post dose. The tissue plasma ratios were 45 for the liver, 20-30 for the kidney, brain and spleen, 15 in the lung and 10 in the heart. The ratios were similar at 1 and 6 hours after dosing.

2. In a study of pregnant rats bupropion was found in placenta, amniotic fluid as well as the fetus. The fetal levels were lower than levels found in maternal organs.

Teratology:

1. In two teratology studies in rabbits (TTGP/77/0003 and TTGP/77/0004). The key findings were dose related maternal xicity including clonic convulsions at doses of 100 and 150 g/day. there was an increased number of offsprings who had rib formation -- a condition reported to occur ously in the rabbit strains used. There were no drug eratogenic effects.

2. In a rat study, no teratogenic effects were seen.

Carcinogenicity:

Hyperplastic nodules appeared in a 104 week rat study. The animals were given 0, 100, 200 or 300 mg/kg/day. The nodule incidence was dose related. Also dose related were increases in liver weight and hepatocellular hypertrophy associated with hepatic enzyme induction. the incidence of hepatocellular carcinomas did not exceed that which occurs by chance.

Dose MG/KG/Day	N		Nodular Hyperplasia		Hepatocellular Carcinoma	
	M	F	M	F	M	F
0	73	74	2	1	0	0
100	72	68	7	10	1	2
200	70	71	9	10	0	1
300	64	59	0	5	1	0

Bupropion does not elevate prolactin levels in humans and did not cause an increase in the incidence of mammary tumors in rats.

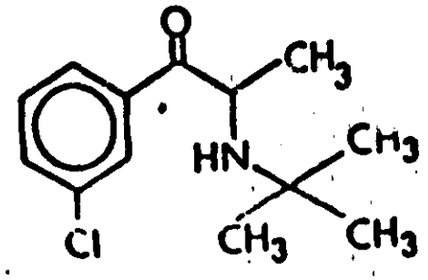
Additional information on preclinical pharmacology is found in the Sponsor's pharmacology Summary (Item L).

B. Clinical Pharmacology

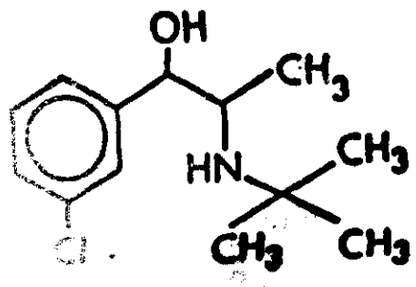
The neurochemical mechanism of Willbutrin is unknown. It has a very slight effect on the inhibition of dopamine and norephinephrine re-uptake.

There is no effect on serotonin or monoamine oxidase. The compound is rapidly absorbed following oral administration. with peak plasma levels typically occurring within 2 hours after dosing. This is followed by a biphasic decline with a half-life of 14 hours (range 9.6-20.9). After 6 hours bupropion plasma levels are almost 30% of peak. The drug is metabolized almost completely and there is no evidence of accumulation. Even so, the metabolic pathway of Wellbutrin in man is not well understood. As in animals, the drug is likely to distribute extensively in tissues. No gender differences were found in the pharmacokinetics of Wellbutrin.

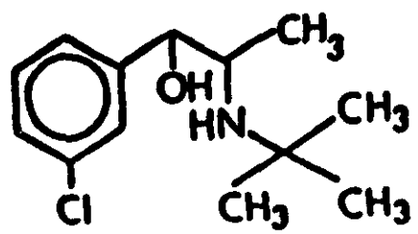
Following the administration of a carbon fourteen labeled dose of Wellbutrin 87% of the radioactivity was recovered in the urine, 10% more was recovered in the feces within 96 hours after dosing. Unchanged bupropion in the urine was .5%. Six urinary metabolites have been identified. These are shown in Figure 1.



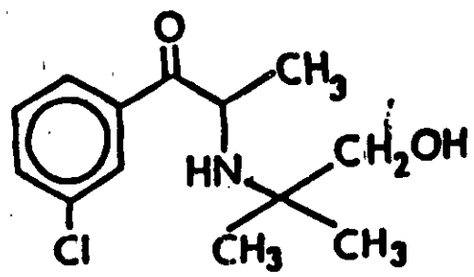
323U66
Bupropion



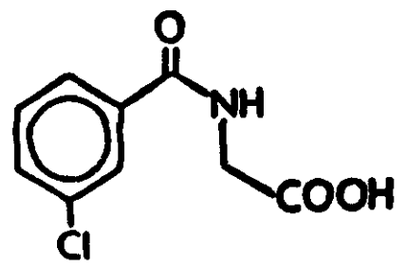
494U73
(+,-)(R*,S*)-2-tert-Butylamino-1-(3-chlorophenyl)propanol



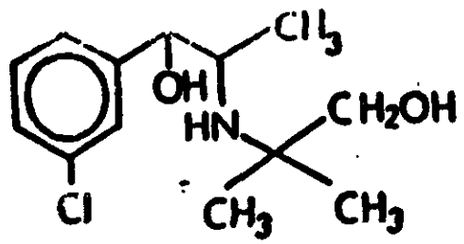
17U67
(+,-)(R*,S*)-2-tert-Butylamino-1-(3-chlorophenyl)propanol



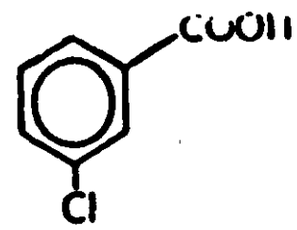
306U77
(+,-)-3'-Chloro-2-(2-hydroxy-1,1-dimethylethylamino)propiophenone



N-(3-Chlorobenzoyl)glycine

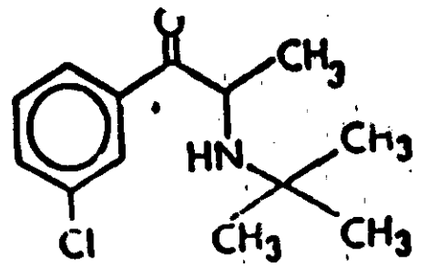


287U73
(+,-)(R*,S*)-1-(3-Chlorophenyl)-2-(2-hydroxy-1,1-dimethylethylamino)propanol

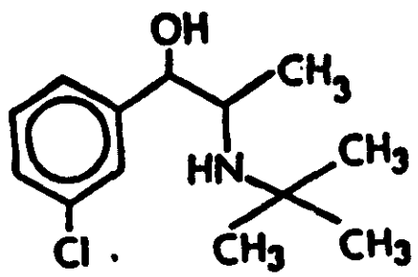


3-Chlorobenzoic acid

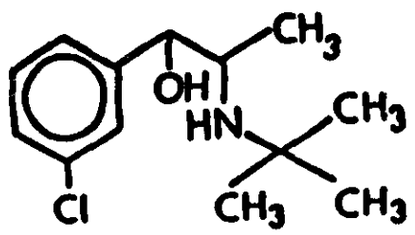
Figure 1: Wellbutrin and its metabolites.



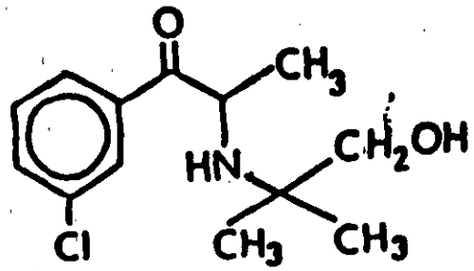
323U66
Bupropion



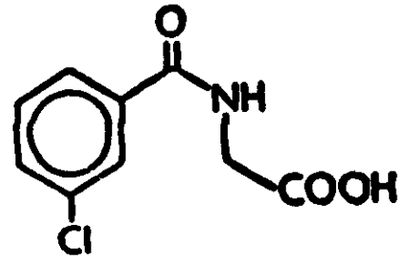
494U73
(±,-)(R*,S*)-2-tert-Butylamino-1-(3-chlorophenyl)propanol



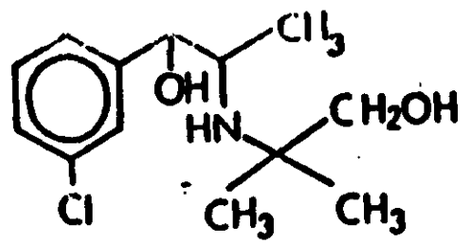
17U67
(±,-)(R*,S*)-2-tert-Butylamino-1-(3-chlorophenyl)propanol



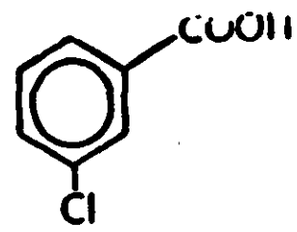
306U77
(±,-)-3'-Chloro-2-(2-hydroxy-1,1-dimethylethylamino)propiophenone



N-(3-Chlorobenzoyl)glycine



287U73
(±,-)(R*,S*)-1-(3-Chlorophenyl)-2-(2-hydroxy-1,1-dimethylethylamino)propanol



3-Chlorobenzoic acid

Figure 1; Wellbutrin and its metabolites.

C. Early Clinical Studies (01A, 02, 03, 04, 05)

A series of 5 exploratory studies were conducted to determine safety and tolerance. Study 01A employed normal volunteers. The remaining 4 employed depressed patients.

1. Study 01A

This was a parallel treatment, double blind, randomized design with placebo control. The dosage was fixed, ascending over a 44 day period. The range was 15-1200 mg/day. the major finding of study 01 were that doses up to 500 mg/day were well tolerated and that the dose was rapidly absorbed.

2. Studies 02, 03, and 04 were open uncontrolled trials of bupropion in hospitalized depressed patients. In study 02 patients had to be adults, free of cardiovascular, renal, hepatic and neurologic disease with no recent history of alcohol or drug abuse. Laboratory exams were given periodically during the 3-4 weeks of treatment. Four subjects participated with a mean daily dose in the range of 600-700 mg. The results showed a moderate effect (HAM D total change of 20-39% from baseline) on depression. Patient 4 who was started at 900 mg per day was tearminated on 5 due to tremors, excitation, restlessness, agitation and confusion. At termination the dose had been decreased to 800 mg/day. Sponsor concluded that 900 mg/day was poorly tolerated.

3. Study 03 patients initially started at 600 mg/day and were rapidly titrated to 900 mg/day. These doses produced agitation, tremulousness, and anxiety. later patients were started at 300 mg/day and increased more gradually to 900 mg/day. This regimen was better tolerated. The HAM-D total and CGI in this study (N=11) showed significant improvement in change from baseline. one patient was discontinued due to urticarial rash and one became overtly psychotic. This patient had a history of paranoid personality.

4. Study 04 was an open 28 day evaluation of bupropion with initial doses of 30 mg/day titrated to 900. Patients were 14 hospitalized depressives of moderate severity. A significant improvement occured within one week on the HAM-D total. No further improvement was noted after the first week (mean change from 28.3 to 20.3 after 3 days). The Zung Depression Scale showed little change, however.

deterioration - 2 (placebo), adverse reactions - 2 (1 each group), intercurrent illness - 1 (Wellbutrin), did not return/eloped/refused treatment - 4 (Wellbutrin), administrative/uncooperative - 3 (2 placebo, 1 Wellbutrin).

The inclusion criteria here and in the other inpatient studies required that patients be non-psychotic and exhibit a depressed mood plus have at least 4 additional symptoms as follows:

a. depressed mood characterized by any of the following: sad, blue, low, despondent, hopeless, gloomy
b. anhedonia
c. poor appetite
d. sleep difficulty (insomnia or hypersomnia)
e. loss of energy, fatigue, lethargy
f. agitation
g. retardation
h. decrease in libido
i. loss of interest in work or usual activities
j. feelings of self-reproach or guilt
k. diminished ability to think or concentrate
l. thoughts of death and/or suicide attempts
m. feelings of helplessness and hopelessness
n. anxiety or tension
o. bodily complaints

Patients were randomly assigned to either bupropion or placebo using a fixed, changing, individualized schedule. In the first week, patients received from 300-400 mg of Wellbutrin (divided t.i.d.). From day 8 to end of study, the dosage could be increased to 600 mg/day.

Assessments were done weekly and included the Hamilton Depression Scale, Hamilton Anxiety Scale, Self-Rating Depression Scale (Zung), Self-Rating Anxiety Scale (Zung), Clinical Global Impressions, Dosage Records and Treatment Emergent Symptoms Scale, and Patient Termination Record.

Results:

The mean dose of Wellbutrin was 450 mg for weeks 2-4. Three placebo and seven bupropion patients received sedative/hypnotic medication at some time during the study. Dalmane (30 mg) was the most commonly used sedative. Analysis of covariance was employed using both age and baseline scores as covariates. There were significant interactions for age by treatment and baseline by treatment (p less than .10). The HAM-D Scale Factors analyzed were 1.

5. Study 05 was a double blind placebo controlled 3 week comparison with a maximum dose of 450 mg/day. the patients were hospitalized depressives. Of the 24 patients starting this study, only 13 were included in the analysis (8 bupropion, 5 placebo). Again, the HAM-D showed improvement, but not the Zung. When comparisons from baseline to termination were made there was no significance in comparison to placebo. This was due, in sponsor's view to low power, and a large placebo response.

Overall conclusions from these studies were that bupropion had minimal anticholinergic and cardiovascular effects. The occurrence of rash was an occasional problem. Agitation and anxiety were the most significant adverse behavioral effect. At the high dose 800 mg (not divided) grand mal seizures occurred in 2 of the subjects. Of course, it was not the point of these studies to establish efficacy.

D. Major Studies to Evaluate Efficacy

Altogether 40 studies at 112 investigational centers have been conducted. Ninety-one of these centers are in the U.S. The remaining centers are located in Canada and the United Kingdom. A total of 1153 patients had been started at the data cutoff date of June 1981. Of these, 359 patients participated in the placebo controlled studies (Sponsor's protocol number 06, 08, 09, 14) and 186 participated in the active drug controlled trial (10c, 15, 21). The total patients then in the major efficacy trials are 545. Three of the placebo controlled trials were inpatient and had a similar design. These were 06, 08, 14. The remaining study, 09, utilized outpatients. Finally, there are 3 supportive studies (17, 26, and 35). The study summaries will follow the ordering above.

1. Study 06, placebo controlled (K. Brodie, W. Zung, L. Fabre, D. Garver).

This was a 28-day, double-blind, placebo-controlled trial which was conducted at 3 centers. A total of 85 inpatients were enrolled and 75 patients were included in the analysis (27 placebo, 48 bupropion). The patients consisted of 16 females and 59 males with an age range of of 21-62 (M=40.7) (placebo) and 18-70 (M=42) (bupropion). The main diagnoses (DSM-II classification) were: manic-depressive (depressed) 55%, depressive neurosis 35%, involutional melancholia 8%, and manic-depressive (circular) 2%. The dropouts occurred for the following reasons: ineffectiveness or clinical course

anxiety/somatization, 2. weight loss, 3. cognitive disturbance, 4. diurnal variation, 5. psychomotor retardation, 6. sleep disturbance. For these factors, only the termination scores were analyzed. There was significance favoring bupropion on anxiety/somatization ($p = 0.17$), cognitive disturbance ($p = .001$), psychomotor retardation ($p = .033$). There was a trend toward less sleep disturbance ($p = .09$). Also, significant were the Hamilton Total Score at day 21 ($p = .004$) and day 28 ($p = .009$). At day 28 the bupropion mean was 14.9 compared to 19.6 for placebo. The CGI ratings also showed Wellbutrin to be superior on the "Severity of Illness" item at day 21 ($P = .009$) and day 28 ($p = .006$). At day 28 the means were 3.20 (Wellbutrin) and 4.06 (placebo). The HAM-A showed a similar superiority for bupropion. On the SDS (Zung) and SAS, trends favored bupropion but were not statistically significant. More detailed summaries are shown in the Study 06 Summary Tables which include Sponsor's Tables #19, 20, 21, 24, 25, 26, 29, and 31.

2. Study 08, placebo-controlled (A. Halaris, W. Fann, D. Dressler):

This was a 5-week (4-week treatment, 1-week followup) study of bupropion versus placebo at 3 centers. 68 patients enrolled, 59 were included in the efficacy analyses (34 bupropion, 25 placebo). There were a total of 40 males and 26 females (sponsor's summary table shows 2 less than listed in his description above). The age ranges were 21-61 with a mean of 40.8 (placebo) and 22-75 with a mean of 42.8 (Wellbutrin). Major diagnoses were depressive neurosis about 60%, manic-depressive (depressed) about 30%, other diagnoses 10%. Dropouts occurred for the following reasons: ineffectiveness - 1 (bupropion), adverse reactions - 3 (bupropion), intercurrent illness - 2 (bupropion), did not return/elapsed/refused treatment - 4 (2 placebo, 2 bupropion).

Inclusion criteria were the same for Study 06, above.

Exclusion criteria for this and other studies were:

a. patients who were actively suicidal
b. schizophrenic
c. organic CNS disease
d. severe dementia
e. incapable of spontaneous conversation or behavior
f. hypersensitivity to drugs
g. abnormal lab or ECG values
h. glaucoma
i. seizure disorders
j. prostatic hypertrophy
k. lactating females who are breastfeeding
l. women of childbearing potential who refused to sign an intent to avoid pregnancy form
m. alcoholism

Results: Doses were started at 300 mg/day and titrated to 750 mg/day by day 11 if the lower dose was well-tolerated.

The mean daily dose of bupropion for weeks 2-4 was about 725 mg. Again, the most commonly used coadministered drug was a sedative, chloral hydrate or flurazepam, which was administered to 30 patients at some time during the study. In addition to the psychiatric rating scales used above, this study also employed the BPRS, the Beck Scale (mainly at center 03), and the POMS at center 01.

The sample sizes at individual centers are rather small and not all scales are included in the major efficacy analyses. Age X treatment interactions were not significant in this study. A treatment by center interaction was found with center 02 (which had enrolled male patients only) showing fewer differences than the other two centers. Baseline X treatment interactions occurred in about half the analyses with more severely ill patients doing relatively better on bupropion than on placebo. On the HAM-D factors, bupropion was significantly better than placebo on anxiety/somatization (p=.002), cognitive disturbance (p=.030), psychomotor retardation (p=.012) and sleep disturbance (p=.035). The HAM-D total was also signi[illegible]nt at day 28 (p[illegible].001). Other findings in favor of Wellbutrin at [illegible]8 were CGI Severity (p=.01), HAM-A total (p=.02), SDS (p less th[illegible].05), SAS (p=.009), BPRS (p=.001). More detailed summaries are shown in the Study 08 Summary Tables which include sponsor's Tables 20, 21, 22, 25, 26, 27, 30, and 32.

3. Study 14, placebo-controlled (J. Feighner, J. Cohn):

This was a two-center study which lasted for 5 weeks (4 weeks treatment, 1 week followup. The followup was to test for withdrawal effects.) There were 117 patients enrolled with 86 being included in the efficacy analysis (26 placebo, 60 bupropion). There were 50 males and 36 females. Center 02 had 1 female and 36 males. Age range was from 23-74 (M=48.2) for placebo and 20-83 (M=45.9) for Wellbutrin. Major diagnoses were depressive neurosis about 50%, and manic depressive (depressed) about 40%. Dropouts were: Ineffective or deterioration - 19 (10 placebo, 9 Wellbutrin), adverse effects - 15 (5 placebo, 10 Wellbutrin), intercurrent illness - 3 (1 placebo, 2 Wellbutrin), did no return/elapsed/refused treatment - 11 (5 placebo, 6 Wellbutrin), administrative - 1 (Wellbutrin).

Results: The initial dosing of bupropion was 300 mg for days 1-4, 400 mg for days 5-7, and 600 mg for days 8-28. All doses were divided and given t.i.d. Adjustment within the limits could be made

by the investigator. The mean dose at days 22-28 was 466.9 mg. The doses at center 02 averaged 546.2 mg compared to 392.1 mg at center 01. The most commonly prescribed concurrent medications were Dalmane and Benadryl which were administered to 10 and 9 patients respectively. Again, the HAM-D and HAM-A, SDS, SAS, and CGI were the rating scales employed.

There were significant baseline by treatment interactions such that bupropion-placebo differences were greater in more severely ill patients. Moreover, while there were no significant age X treatment interactions, there were center by treatment interactions such that there were minimal bupropion-placebo differences in center 02, but marked differences favoring Wellbutrin at center 01. It was therefore decided to analyze the studies separately and accept them as the key analyses for this study.

Briefly, in the combined analysis, sponsor found significance for the HAM-D total, CGI-S and CGI-I at day 28 and in some instances earlier. The HAM-A and SAS showed no significant differences.

Efficacy results for center 14-01: Center 14-01 studied 49 patients, 15 on placebo and 34 on bupropion. There was a significant age X treatment interaction with younger ptients doing relatively better on Wellbutrin compared to placebo than older patients. The baseline by treatment interactions were significant at the 2-week rating only and were dropped from the analysis. On the HAM-D factors, bupropion was significantly better than placebo on anxiety/somatization, cognitive disturbance, psychomotor retardation, and sleep disturbance (p less than .01).

The CGIs were significant in favor of Wellbutrin. The HAM-A total was also significant at day 28. The SDS and SAS showed no significance.

Efficacy results for center 14-02: Center 14-02 included 37 patients in its study (11 placebo, 26 Wellbutrin). There were no significant differences at any time period on any scale. There was a large placebo response in this study. See study 14 Summary Tables which include sponsor's tables 24, 25, 27, 30, 31, 32, 33, 34, 35, 36, 38, 41, 42, 43, 44, and 45.

4. Study 09, placebo-controlled (L. Fabre, J. Mendels): This was the only placebo-controlled outpatient study. In several previous studies subjects who began as inpatients could be released and continue as an outpatient after 14 days.

This was also longer than the previous studies with a one-week placebo treated washout period, six weeks of treatment and a one-week followup. In the prior studies, it does not appear that any washout period was included. In this study, two dose ranges of Wellbutrin were compared with placebo. Each of the 3 groups shared equally in the total sample of 160 patients. Results from 97 patients were included in the efficacy analyses with 40 patients having received the low dose of bupropion, 42 placebo, and 15 the high dose of bupropion. The smaller number in the high dose group reflects sponsor's decision to delete the high dose group during the course of the study. There were 66 females and 31 males included in the efficacy analyses. Age range was 21 to 67 with an average age in the mid to upper thirties. The main diagnoses were manic depressive (depressed) - about 60%, depressive neurosis - about 35%. Dropouts occurred for the following reasons: did not return/refused treatment - 19 (6 placebo 9 low dose bupropion, 4 high dose bupropion), did not meet study criteria - 1 (LD bupropion), ineffectiveness/deterioration - 1 (HD bupropion), adverse reactions - 11 (1 placebo, 6 LD bupropion, 4 HD bupropion).

Inclusion and exclusion criteria are the same as described above.

Regimens: The dosage schedule was fixed/ascending with the low dose/high dose groups starting at 150/300 mg per day and increasing twice weekly as follows 200/400, 300/600 and at day 15 400/800 mg daily. All doses were divided t.i.d. The doses could be adjusted if needed by the investigator. The mean doses ranged from 137-331 and 287-687 my per day.

The usual battery of psychiatric rating scales was included and the Hopkins Symptom Checklist (58 item) was used in addition. The most widely prescribed concomitant medications were antifertility drugs and sedative/hypnotics. The use of sedatives were somewhat lower in this study.

The usual analysis of covariance model was used. There were a number of significant interactions between age and treatment such that low dose Wellbutrin was better in younger patients and the high dose bupropion and placebo was better in older patients.

This was a negative study. The only significant differences on any of the scales were (1) LD bupropion was significantly better than PBO on HAM-D anxiety/somatization factor at day 42 ($p = .027$) and (2) the HSCL total at day 42 showed bupropion to be better than placebo ($p = .028$). The study 09 Summary Tables contain additional information. These include Sponsor's Tables # 18, 19, 20, 21, 24, 25, 26, 30, 32, 34, 35.

E. Major Active Drug Controlled Clinical Trials

1. Study 10 C, imipramine controlled (B. Shopsin)

Fifty-five patients were enrolled in this outpatient single blind study. Twelve were dropped during the first week (placebo treatment period). Forty patients were included in the efficacy evaluations. Patients were divided into 4 groups, 3 dose ranges of Wellbution and imipramine. The groups were divided as follows: 9 received bupropion - 150 mg/day, 10 received 300-450 mg/day, 10 received 300-900 mg/day and 11 received imipramine 75-300 mg/day. There were 21 females and 19 males - age range was from 23-72 with a mean of 45.4. The diagnoses were: manic-depressive psychosis (depressed) - 70%, manic=depressive psychosis (circular) - 25%. Concomitant medication was not systematically employed. Sedatives were used in 10% of the patients.

Study duration was 7 weeks which included the one week placebo treated washout period. Again, assessments were made at baseline and weekly, thereafter. The same efficacy measures were employed. Dropouts occurred for the following reasons: (a) placebo responder - 6 (2 each bupropion 150 and 300-450 mg/day, 1 each bupropion 300-900 mg/day and imipramine, (b) ineffectiveness - 3 (1 bupropion 300-450 ,g/day 2 imipramine) (c) adverse experience - 1 (bupropion 300-900 mg/day), (d) intercurrent illness - 1 (bupropion 300-450 mg/day), did not return/noncompliance - 5 (2 bupropion 150 mg, 1 each in the other 3 treatments).

Results:

The observed average doses received were low dose Wellbutrin - 150 mg/day, medium dose - 360 mg/day, high dose - 785 mg/day, imipramine - 271 mg/day. There were no significant differences between treatments using pair wise comparisons with each of the 3 Wellbutrin doses and imipramine. Sponsor concludes that bupropion was as good as imipramine in reducing depression. Patients on all treatments showed similar improvement with HAM-D total scores being reduced by 1/3 to 1/2 with typical changes from 26 down to 18. See Study 10C Summary of Table #17. Additional information is shown in other tables which includes Sponsor's numbers 17, 18, 19, 20, 21, and 22. Also included are Sponsor's figures # 1-6 inclusive.

2. Study 15, amitriptyline controlled (R. Remick, A. Cooper, J. Mendels, A. Singh, M. Amin, G. Chouinard).

This was a 15 week double-blind six-center comparison of Wellbutrin and amitriptyline. One hundred twenty-four patients were enrolled and 101 patients were included in the efficacy analysis. The dosage schedule was fixed/ascending with placebo being given from days six to 0 (placebo responders were replaced if they showed improvement of 10 or more points on the HAM-D total or had a HAM-D total of 18 or less at day 0. Following the placebo treatment period, patients were given 75 mg of amitriptyline or 300 mg of bupropion for drugs 1-7. After this, the amitriptyline dose was increased to 150 mg and bupropion to 450 mg. Within these limits dosage adjustments were permitted.

The patients in the efficacy analysis included 39 on amitriptyline and 62 on Wellbutrin. The age range was 19-62 (M-about 37). Main diagnoses were; manic-depressive illness (depressed) about 70% and depressive neurosis about 20%. The most commonly prescribed medications that were coadministered were analgesics and sedatives, the latter being given to 17% of the amitriptyline patients and 30% of bupropion patients.

Results:

The observed average doses from days 8-91 were 126 mg of amitriptyline and 392 mg of bupropion.

There were no significant differences between the 2 groups at termination with both groups showing substantial improvement during the course of the study. The average decline in HAM-D total was 15.7 in both groups. See Sponsor's Summary Tables # 21, 22, 23, 25, 26, 27, 29, 30, and 31.

3. Study 21, Amitriptyline Controlled (J. Cohn, R. Miller, J. Ananth, S. Preskorn)

This was an inpatient amitriptyline controlled trial at 4 centers. The plan was to include 160 patients (40 per center, 20 per treatment at each center). The results presented here are from an interim analysis for 92 who had completed the study by October 1, 1980. Results from 65 of these patients are included in the efficacy analysis. The dosing schedule was ascending, individualized with and initial dose of 75 mg of amitriptyline or 300 mg of bupropion. After day 4, doses could be increased to 100 mg of amitriptyline or 450 mg of bupropion.

On day 8 the next increase to 150 mg and 600 mg was permitted. Finally, on day 11 and thereafter, respective doses of 225 and 750 mg were allowed. Study duration was six weeks. There was no washout period. The same efficacy measures were employed with the SCL-90 also being included. Dropouts were as follows: ineffectiveness or deterioration - 7 (6 bupropion, 1 amitriptyline), adverse experiences 7 (3 bupropion, 4 amitriptyline), did not return/refused treatment - 5 (2 bupropion, 3 Endep), administrative - 2 (1 each treatment). The primary diagnoses were = depressive neurosis about 53%, manic depressive psychosis (depressed) - about 25%, psychotic depressive reaction - 12%.

Results:

The observed average doses were 520-620 mg/day of Wellbutrin and 150-170 mg/day of Endep. There were no baseline or age by treatment interactions. The only significant center by treatment interactions occurred on the SCL-90. There were no significant differences between treatments. The average HAM-D total scores declined from 28.3 at baseline to 10.9 at termination for Wellbutrin patients. For Endep patients, the change was from 27.6 to 9.9. See Sponsor's Summary Tables # 22-28 and Figures 1-14 inclusive.

F. Other Efficacy Studies

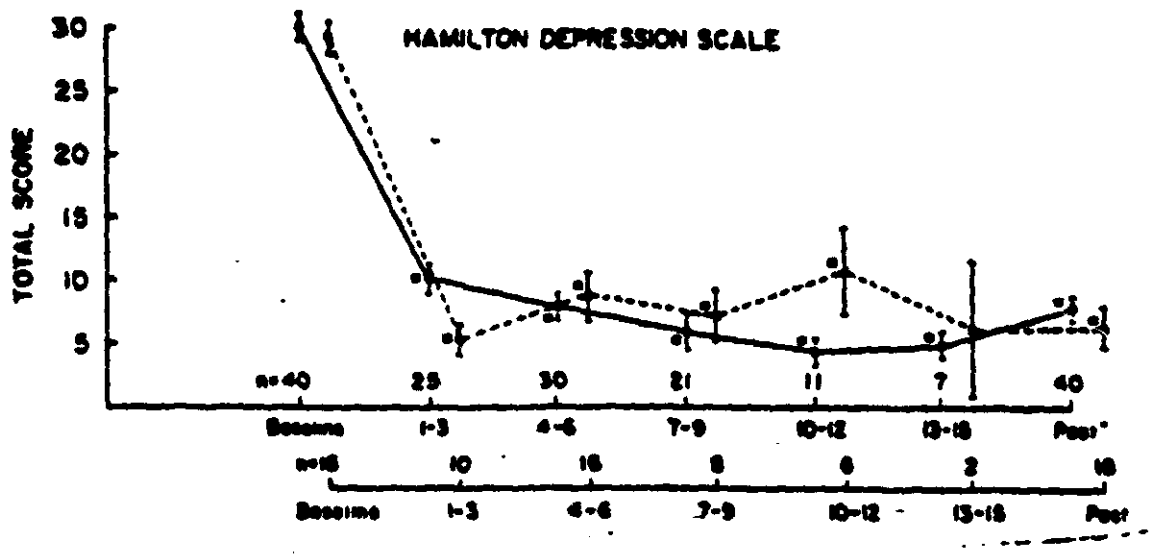
There are three other studies of efficacy which are intended to be supportive rather than primary. Two of these are uncontrolled. The third included an amitriptyline control group.

1. Study 17, amitriptyline controlled (J. Fgighner , J. Cohn, E. Othmer, M. Mandel, R. Remick, G. Chouinard, F Abuzzahab, A. Halaris).

   A total of 74 patients participated in this study which allowed continued treatment with study medication for up to 2 years. Forty-one patients received bupropion, 19 received amitriptyline. Total duration of bupropion therapy ranged from 2 weeks to 1 year. The average duration was 7 months. The "Continued" patients were those that received at least a 35% decrease from baseline on the Hamilton Depression Scale total score during the initial short-term study. In addition, 12 hospitalized patients who had received placebo or bupropion (less than 450 mg/day) were eligible for inclusion in the study and receive bupropion at a higher dose in an open manner. Only the HAM-D total scores and CGIs were included in this interim analysis (see Figure 2). The time periods shown in Figure 2 are

FIGURE 2

SUMMARY OF HAMILTON DEPRESSION SCALE AND CLINICAL GLOBAL IMPROVEMENT (CGI) SCORES



Observed data for each Time Period are expressed as mean values with the standard error bars and number of patients (n) indicated for baseline (start of the initial study), during drug therapy, and after (Post) drug therapy. Solid symbols joined by solid lines signify bupropion data, while open symbols joined by dashed lines signify amitriptyline data. An asterisk (*) indicates a statistically significant ($p < 0.05$) difference from baseline.

months. The solid line is bupropion data. The broken line is data for amitriptyline. The HAM-D total shows significant improvement over time (p less than .05). The CGIs also showed improvement.

2. Study 26, Uncontrolled (E. Gardner)

This was a study to assess the tolerance and effectiveness of Wellbutrin in outpatients who exhibit serious side effects with tricyclics. A total of 40 patients were to have entered the study. Twenty-one patients had entered the study by the data cutoff point. One dropped out prior to receiving drug and 2 received drug for one week or less. Eighteen patients, primarily females (average age 47.7) were included in the analysis. The average HAM-D Total Score dropped from about 11 to 7 during the course of treatment. The CGIs also improved slightly over the course of 30 weeks of treatment. The usual dose range was from 261-477 mg/day.

3. Study 35, Uncontrolled (37 centers)

A total of 380 entered the study. Of these, 359 were included in the efficacy analysis. Study duration was 29 days. The dosing schedule was flexible with a range of 150-450 mg/day. Subjects were outpatients in many private practice settings.

The results showed a significant improvement on the HAM-D total, CGI, and SDS over time. (p less than .001)

G. Discussion

This appears to be a mildly positive NDA with a number of flaws - although perhaps not fatal ones. There are statistical and safety issues which will be discussed briefly here. The full safety and statistical reviews should be consulted for more detail.

There were no comparisons with both active drug and placebo. Such comparisons while not absolutely necessary are useful. A number of studies included no washout period. In general patient rating scales showed little effect. This is a common finding. It is an "interrater reliability problem" of sorts since each patient comes into the study with different attitudes and sets and the physician drings the same sets to bear on each rating. Even so, more support on the patient rating scales would be helpful. After all the scale has presumably been sensitive to drug effects in other studies or it would presumably not be in common use.

MADE IN JAPAN

Figure 3

POSITION

factor structure based on a 1975 analysis of the pretreatment ratings
bjects with diagnoses of neurotic depression. (Table 10).

- Anxiety/Somatization

Anxiety, Psychic
Anxiety, Somatic
Somatic Symptoms, Gastro-Intestinal
Somatic Symptoms, General
Hypochondriasis
Insight

- Weight

Loss of Weight (History)
Loss of Weight (Actual

III - Cognitive Disturbance

Feelings of Guilt
Suicide
Agitation
Depersonalization and Derealization
Paranoid Symptoms
Obsessional and Compulsive Symptoms

INSTRUCTIONS

Work and Activities - Rater may seek information from relatives or ward personnel.

Agitation - This item - printed in the packet as a 3-point scale - should be rated on a 5-point scale as follows:

0 = None
1 = Fidgetiness
2 = Playing with hands, hair, etc.
3 = Moving about, can't sit still
4 = Hand wringing, nail biting, hair pulling, biting of lips

16. Loss of Weight - This is an "either/or" item requiring a response to only part of the item, i.e., 16A or 16B. Actual Weight Changes (16B) is the preferred choice - particularly during the course of a study. It is suggested that Weight by History (16A) be used only at the pretreatment rating.

Factor IV - Diurnal Variation

18A. Diurnal Variation (Time)
B. Diurnal Variation (Severity)

Factor V - Retardation

1. Depressed Mood
7. Work and Activities
8. Retardation
14. Genital Symptoms

Factor VI - Sleep Disturbance

4. Insomnia, Early
5. Insomnia, Middle
6. Insomnia, Late

There is a more difficult statistical problem. Sponsor seems to have conducted covariance analyses on all studies with both baseline severity and age as covariates. Age is not typically used as a covariate and adequate justification for its use here is not presented. In the raw score analyses it appears that most patients disappear at the last rating period. This is a systematic problem that occurs in both placebo and active drug groups.

Individual item analyses for the HAM-D and SDS are not presented. The items making up the HAM-D factors are shown in figure 3. Separate analyses of some individual items such as "depressed mood", "retardation", and "agitation" would also be useful.

In conclusion this appears to be a positive submission, but its ultimate approvability will depend upon the resolution of statistical questions and the determination of whether or not the studies conducted up to this point constitute substantial evidence of efficacy.

David Davis
Psychologist

MADE IN JAPAN

PHARM. REVIEW

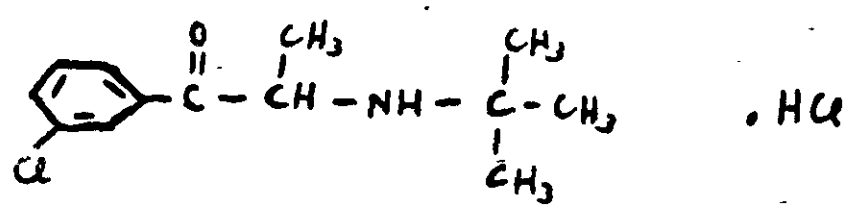
Barry N. Hosloff, Ph.D.
6/15/82

Pharmacologist Review of NDA 18-644
Original Summary

SPONSOR: Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, N.C. 27709

DRUG: Wellbutrin Tablets

generic name: bupropion HCl
Code name: BW 323 U (+ others)
chemical name: 2(-tert-Butylamino)-3'-chloropropiophenone HCl (racemic mixture)



CATEGORY: antidepressant

SPONSOR's INDs For BUPROPION:

PRECLINICAL STUDIES REVIEWED:

		PAGE
1)	Pharmacodynamics	2
2)	ADME; pharmacokinetics	12
3)	Acute toxicity	16
4)	Acute toxic interactions	17
5)	12 wk. p.o. tox. in rat	17
6)	55 wk. p.o. tox. in rat	19
7)	2 yr. carcinogenesis in rat	23
8)	21/22 month carcinogenesis in mouse	29
9)	90 day p.o. tox. in dog	33
10)	1 year p.o. tox. in dog	35
11)	Mutagenicity studies	41
12)	2 generation reprod./fertility in rat	43
13)	Segment II reprod. in rat	46
14)	Segment II reprod. in rabbit (2 studies)	46, 51

All studies were performed by sponsor except the following:

6, 7, 8, 10, and 1 of the 2 segment II studies in rabbits:

International Research & Development Corp.
Mattawan, Michigan

Ames Test:

EG & G Mason Research Institute
Rockville, Maryland

Bone Marrow Chromosome Study:

Hazelton Laboratories America, Inc.
Vienna, Virginia

	PAGE
Summary	54
Evaluation	63
Recommendations	68

PHARMACODYNAMICS

All doses in mg/kg unless otherwise specified. Abbreviations used:

B	bupropion
AMI	amitriptyline
IMI	imipramine
DMI	desmethylimipramine
A	amphetamine
M	methylphenidate
DA	dopamine
NE	norepinephrine
5-HT	serotonin

LEON 301 MADE IN JAPAN

A. CNS ACTIVITY

SPECIES	TEST	RESULTS
MOUSE	Prevention of tetrabenazine-induced sedation	ED 50%: B: 12.5 (i.p.) (lowest active dose = 6.5) and 32 (p.o.) AMI: 3.9 (i.p.) A: 1 (i.p.) M: 12 (i.p.)
RAT	Prevention of tetrabenazine-induced sedation	No consistent D-R effect up to 50 i.p.
MOUSE	Reversal of reserpine-induced hypothermia	B active at 12.5 + i.p. AMI - effect at 5 similar to 25-50 of B
RAT	Porsolt behavioral despair model	Approx. ED 50% (3 doses over 24 hr B: 10 i.p. (inactive at 5) AMI: 12 i.p. IMI: 10 i.p. Effect of B blocked by pre-treatme which depleted brain DA but not by that which depleted brain NE
MOUSE	Potentiation of behavioral effects of pargyline + DOPA	B active at 6.25 + i.p.; IMI equipotent
MOUSE	Locomotor activity	Approx. ED 50%: B: 25 i.p. (increased) (inactiv at 6.25) A: 0.5-1 i.p. (increased) M: 6 i.p. (increased) AMI: 12.5 i.p. (decreased)

RAT	Locomotor activity	B: D-R increase at 5-50 i.p.; ED 50% about 5 A: D-R increase at 0.5-4 i.p.; ED 50% about 0.5 IMI: D-R decrease at 10-20; ED 50 about 10 Effects of B and A blocked by pre-treatment which depleted brain DA but not by that which depleted bra NE Effect of B blocked by reserpine (and slightly by alpha-methylparatyrosine (AMT); effect of A blocked by AMT only; effect of M blocked by R only
RAT	Operant responding on a FI 60/FI 30 schedule	B increased responding during FI (10-50 i.p.); overall pattern of responding more similar to A than IMI
RAT	Operant responding on a DLR-20 schedule	B and A decreased rewards at 25-5 and 0.5 - 2 i.p., resp. (B inactive at 5-10). IMI increa rewards at 5-30. Effect of B and due to increase in early response
RAT	Geller conflict test	No antianxiety effects up to 50 i
RAT	Conditioned avoidance responding	Slight non-dose-related increase avoidance at 10 and 50 (but not a 5 or 25) i.p. for B and at 0.5 - i.p. for A. (IMI - no effect up 20) Number of intertrial crosses (i.e locomotor acitivity) increased by at 10-50 i.p. (No effect at 5) an by A at 0.5 - 2. (IMI - slight decrease at 5 - 20).
RAT	Intracranial self-stimulation	B: dose-related increase at 25- i.p. (inactive at 5; slight increase at 10) A: increased at 0.5-4 i.p.; ef similar magnitude to that of B IMI: slight decrease at 10-30 i.

LION JCI MADE IN JAPAN

RAT	Drug discrimination (Generalization of cues produced by B at 20 i.p.)	Drugs showing generalization: A, cocaine, M, caffeine, phentermine, mazindol, tranylcypromine, viloxazine, nomifensine No generalization: DMI, AMI, TRH, fenfluramine, phenethylamine, scopolamine, diazepam, morphine, pentobarbital, haloperidol, mianserin, trazodone
MONKEY	Self-administration	B produced high rates of self-administration at 1 and 3 per i.v. injection (but not at higher or lower doses); codeine at 0.32 produced lower rates.
RAT	Stereotyped behavior	Increased at 25-100 i.p. (not D-R; no effect at 12.5). Degree considered mild.
MOUSE	Anorexic effect	Active at 50 and 100 (but not at 25) p.o.; fenfluramine at 30 and diethylpropion at 50 had about twice as great effect; also active at 25-50 i.p.
RAT, MOUSE	Brain NE and DA level	No effect up to 100 i.p.
RAT	Brain mitochrondial MAO	No effect up to 10^{-5}M
MOUSE	Brain and liver MAO	No effect in brain up to 100 i.p.; at this dose liver MAO (type A only) inhibited by 25%
RAT	Inhibition of amine uptake into brain slices	IC 50 (μM):

	NE (hypothalamus)	5HT (midbrain)	DA (caudate)
B	32	90	7
AMI	0.3	6.4	5.4

NOT MADE IN JAPAN

RAT	Inhibition of amine uptake into brain synaptosomes	IC 50 (μM): NE (hypothal.) / 5HT (hypothal.) / DA (striatum) B: 6.5 / * / 3.4 AMI: 0.1 / 0.35 / 65 IMI: 0.1 / 0.31 / 19 *10% inhib. at 10 μM
RAT	NE/DA uptake in vivo (block of AMMT -induced depletion of brain NE/DA)	DA (but not NE) depletion blocked a 50 i.p.; DMI at 30 i.p. slightly blocked NE (but not DA) depletion
RAT	NE/DA uptake in vivo (block of 6-hydroxy-DA-induced depletion of brain NE/DA)	DA depletion blocked at 25-100 i.p. D-R (no effect at 12.5); slight effect on NE at 100. DMI blocked NE (but not DA) depletion at 5-30 i.p.
RAT	ATP - Mg++ - stimulated uptake of NE/DA into brain synaptic vesicles	IC 50 (μM): NE: 33 (5 x less potent than in synaptosomes) DA: 60 (20 x less potent than in synaptosomes)
RAT	Spontaneous release of amines from synaptosomes	No effect on NE, DA, or 5 HT at 10^{-4}M
RAT	DA turnover in striatum (AMT method)	Increased at 50 and 75 (but not 25) i.p.
RAT	Binding assays (brain membrane fragments)	Weak inhibition of binding of WB-41((IC 50 = 51 μM vs 0.08 for IMI) and clonidine (60% inhibition at 10(μM). Little or no inhibition of the following ligands at B concentra tions of 100-1000 μM: dihydroalprenolol, dopamine, spiro-peridol, GABA, diazepam, 5-HT
RAT	NE-stimulated adenylate cyclase in cortical slices	No effect at 3000 μM
RAT/MOUSE	Beta receptor desensitization (DHA binding to brain membrane fragments)	Seen with B at 50 i.p. (3x/day for 4 days) in 1/2 of studies; DMI at 10 i.p. (2x/day for 4 days) showed a more consistent effect.

MOUSE	Anticonvulsant	ED 50 = 17 i.p. vs ECS seizures (ED 50 for AMI and DPH = 7 and 9 resp.) ; No effect vs metrazol up to 75 i.p.
RAT	Antagonism of B-induced seizures	Pretreatment with phenobarbital, trimethadione, and chlordiazepoxide (CDP), but not DPH, prevented seizures due to B at 200 i.p.; CDP was most potent (partial protection at 2.5, complete at 5 i.p.) When above drugs given after start of seizures, all (but DPH) shortened the seizure; CDP most potent (activ at 5-10 i.p.)

B. CARDIOVASCULAR/AUTONOMIC

SPECIES	TEST	RESULTS
DOG	Various CV parameters	1) Anesthetized, open chested: at 10-20 i.v., decreases in MAP (20-64% HR (10-20%), CO (15-54%), and right ventricular contractile force (60-70%); effects mostly transient; no effects on above at 5 i.v. 2)-Anesthetized, close-chested: at 5-10 i.v., transient decrease in MAP (40-75%) and transient increase in HR (15-34%). When given as a slower infusion (2 mg/kg/min), effects were of smaller magnitude, and in 1 study a slight increase in MAP (5-10%) was seen with 5 mg/kg. No effect on EKG (arrhythmias, PR, QTc) after 5-10 i.v. (2 mg/kg/min). 3) Conscious dogs: After 20 p.o., 10% and 10-20% increased MAP and HR resp., up to 6 hr.; returned to baseline at next measurement (24 hr.)

CAT	B.P. and H.R. in anesthetized cats; vagi sectioned	1, 2.5, 5, and 10 i.v. (4 min. infusions) given sequentially over 2 hr.; non D-R increases in BP (30%) up to 5 but 31% decrease at 10 (all transient); cumulative increase in HR (23%) with some increase after each dose.
RAT	BP and HR in conscious rats	No effect at 25 p.o.; at 50, HR increased (25%) with gradual return to control by 3 hr., no effect on BP
DOG	Respiratory rats (RR) and minute volume (MV) in anesthetized dogs	At 5 i.v., transient increase in RR (68%) and MV (22%); at 10, transient decrease (39%) followed by longer lasting increase (peak 26%) in MV with large increase in RR (100-150%) which was still elevated (60%) at 1 hr.
RAT/GUINEA PIG	Spontaneously beating right atria (<u>in vitro</u>)	1) RAT: D-R decrease in rate and force of contraction at 10^{-6}M +; ED 50% = 1.4×10^{-4}; complete blockade at 3×10^{-4}. AMI and IMI 5-10 x more potent. 2) GUINEA PIG: D-R decrease in rate of contraction at 10^{-5} M +; ED 50% = 1.5×10^{-4}; complete blockade at 3×10^{-4}.
GUINEA PIG	Isolated left atria (stimulated) (<u>in vitro</u>)	No significant effect up to 10^{-4} M
GUINEA PIG	Evoked action potential (AP) in atria (<u>in vitro</u>)	Decreased amplitude of AP and decreased dv/dt, and increased effective refractory period and AP duration at 10^{-5}M + D-R. Excitation totally inhibited at 5×10^{-4}M; IMI and AMI 10 x more potent.
DOG	Isolated Purkinje fibers (<u>in vitro</u>)	Decreased frequency of spontaneous depolarization at 10^{-6} M + ; complete block at $2\text{-}3 \times 10^{-4}$ (AMI, IMI 10 x more potent). At high doses (10^{-4}M +) decreased amplitude of evoked AP, decreased dv/dt, and increased effective refractory period.

DOG	Isolated papillary muscle (in vitro)	At 10^{-4}M +, decreased amplitude of evoked AP and decreased dv/dt an increased effective refractory period. Blocked excitation at 10^{-3}M (AMI and IMI 12-13 x more potent)
CAT	Isolated papillary muscle (in vitro)	No effect on electrically-stimulate contraction up to 3 x 10^{-5}M.
CAT (anesthetized)	1) Contraction of nictitating membrane by preganglionic stim. of cervical sympathetic nerve. (Measure of sympathetic function)	1, 2.5, 5, and 10 i.v. (4 min. infusions) given sequentially over 2 hrs.: 1) No effect on response to stimula tion; direct contraction occurred in 2 of 5 cats (slight).
	2) Heart rate after vagal stim. (Measure of para-sympathetic function)	2) D-R inhibition; after 10 mg/kg, 50% inhibition with return to baseline after 30-40 min. (In another study, no effect after a single dose of 10).
DOG (anesthetized, vagotomized)	Effect on pressor response to NE and tyramine	D-R potentiation of NE at 0.3 + i.v. (no effect at 0.1); IMI and DMI 10 x more potent and DMI shown to have much longer lasting effect. No consistent effect on tyramine (possible slight inhibition at 9 i.v.) whereas DMI caused 95% inhibition at 1 i.v.
RABBIT	NE uptake into isolated aorta	Weak inhibition; IC 50 = 10 μM (AMI and IMI 50 x more potent)
RAT	Effect on chromodacryorrhea due to methacholine	No effect up to 50 i.p. AMI caused 84% inhibition at 25 i.p. and atro-pine caused complete block at 1 i.p.
MOUSE	Pupil diameter	D-R dilation at 25-200 i.p. ; AMI and Atropine about 5 and 400 x more potent, resp. B did not impair accomodation as did AMI and atropine
GUINEA PIG	Acetylcholine-induced contraction of ileum	2 x shift-to-right of acetylcholine D-R curve at 10^{-4} M; no effect at 10^{-5}. (IMI caused shift-to-right of 10 x and 490 x at 10^{-6}M and 10^{-5}M, resp., and complete block of acetylcholine at 10^{-4}.)

RAT	Acetylcholine-induced contraction of anococcygeus muscle	No effect at 10^{-5}M
GUINEA PIG	Field-stimulated contraction of ileum (Under conditions said to be a measure of acetylcholine release)	Dose-related inhibition at 10^{-5} M +; EC 50% = 3.1×10^{-5}M.
RAT	NE* release from anococcygeus muscle	No effect at 10^{-4}M. Tyramine increased release 150 and 350% at 10^{-5} and 10^{-4}M, resp.
GUINEA PIG	Chronotropic response of atria to NE and isoproterenol	At 10^{-5}M, NE D-R curve shifted 3 x to left; no effect on response to isoproterenol. At 10^{-4}M, no effect on response to NE in electrically driven atria.
CAT	Response of papillary muscle to isoproterenol	No effect at 3×10^{-5}M
GUINEA PIG	NE-induced relaxation of trachea	No effect on NE response (or spontaneous tone) up to 10^{-4}M
RABBIT	NE-induced contraction of aortic strips	50% inhibition at 10^{-5}M; no effect at 10^{-7}M. No direct agonist action at these concentrations
RAT	NE-induced contraction anococcygeus muscle	Potentiation at 10^{-5}M. (Less than 10 x shift of NE D-R curve to the left.)
RAT	5-HT induced contraction of rat fundus and anococcygeus muscle	No effect on fundus response to 5HT at 10^{-5}M (slight direct contraction by B seen at this concentration); slight (about 10x) shift to right of D-R curve for 5HT on anococcygeus muscle at 10^{-4}M.
GUINEA PIG	5-HT induced contraction of ileum	D-R curve for 5-HT shifted to right at 10^{-5} and 10^{-4}M, dose-related. (approx. 10 x and 100 x shift, resp.)
GUINEA PIG	Histamine-induced contraction of ileum	D-R curve for histamine slightly shifted to the right (less than 10 x) at 10^{-4}M.

MADE IN JAPAN

C. MISCELLANEOUS

SPECIES	TEST	RESULTS
GUINEA PIG	Local anesthetic activity (cornea)	Active at 2.5-10 mg/ml; equipotent with cocaine.
MOUSE	Effect of grouping on lethality	No effect on i.p. LD 50 for B; LD for A was decreased. B at 25 i.p. decreased the lethality of A at 2(i.p. in grouped mice; AMI at 5 an(10 i.p. did not have this effect.
VARIOUS	Interactions with phenelzine	No significant potentiation of B effects by doses of P causing significant MAO inhibition were seen in several tests (mice-tetrabenazine-induced sedation; rats - Porsolt test, BP, HR; anesthetized dogs - BP, HR; a spontaneously beating or electrically driven rat atria.)
MOUSE	Body temperature (rectal)	1^{o}(c) decrease at 50 i.p. 4° decrease at 100 i.p. (AMI caus(2° decrease at 12.5, A caused 3° increase at 10).

ADME; PHARMACOKINETICS

A. Plasma levels

1. Rat

After 50 mg/kg i.p., plasma levels of unchanged B (method:HPLC) peaked within 30 minutes and declined with a T 1/2 of 2.3 and 0.95 hr in M and F, respectively. In another study in F, after 30 mg/kg p.o., plasma level of unchanged B (method = RIA) peaked within 30 minutes and declined biphasically, with an initial (within 1 hr.) sharp decline followed by a terminal T 1/2 of 4 hr.; however plasma levels of metabolites were many times higher than those of unchanged drug (5-30 x up to 8 hr.; 100 x at 12 hr.) and declined much more slowly (T 1/2 about 12 hr.). In another study 10 mg/kg was given p.o. and i.v. Serum (and brain) levels of unchanged B (method:RIA) were several fold higher in F than M up to 24 hr. post-dose, although sex differences in T 1/2 were not apparent in this study. Comparison of serum AUC for p.o. and i.v. routes gave a bioavailability of 8 and 21% in M and F, respectively; similar values were found using brain AUC.

In another study, F rats were given 10, 30, or 100 mg/kg orally; plasma levels of unchanged drug increased with increasing doses but slightly less than proportionally at the highest dose; levels of metabolites also increased with increasing dose but less than proportionally at all doses.

2. Mouse

In males, after 50 mg/kg i.p., whole body levels of unchanged drug (method:methyl orange/spectrophotometry) peaked within 15 min. and declined with a T 1/2 of 45 min.; however, metabolite levels remained relatively constant up to 2-4 hr. before declining.

3. Dog

B was given at 10 mg/kg p.c. or i.v. Plasma levels peaked at 1/2 hr. after p.o.; decline in plasma levels by both routes was biphasic with an initial sharp decline within 2 hr. followed by a terminal T 1/2 of about 2 hr. No sex differences in plasma levels were apparent, although N was only 2/sex. A comparison of plasma AUC for i.v. and p.o. gave a bioavailability of 4%.

B. Tissue distribution

Male and female rats were given 50 mg/kg i.p. and sacrificed at 1 hr. Levels of unchanged B (method:methyl orange/spectrophotometry) were highest in lung (25x plasma levels) followed by kidney, and lowest in plasma. After 50 mg/kg given p.o., highest levels were found in liver

(30-33x plasma levels), followed by lung, and lowest in plasma. (Highest level in males was actually in intestine, but it is not clear how much of this was in intestinal contents.) After both routes, brain levels were 10-12x those in plasma; another study showed that B enters brain rapidly with peak level after p.o. administration reached at the same time as peak plasma level (15 min.). After both routes, levels in all female tissues studied were 2-3x those in male tissues.

In another study, female rats were given labelled B orally at 10, 30, or 100 mg/kg and sacrificed at 1 or 6 hr. Unchanged drug was assayed by RIA and metabolites by subtraction (i.e., total label minus unchanged drug). As found above after p.o., highest levels of unchanged drug were found in liver; lowest in plasma. Tissue levels of unchanged drug increased with increasing dose but not always proportionately (sometimes more, sometimes less). At 6 hr., tissue levels of unchanged drug declined to approximately 1/2 - 1/10 those seen at 1 hr. In contrast to unchanged drug, levels of metabolites were generally highest in lung (3-6x plasma). (Levels in liver were 1.5-2x those in plasma except approximately equal to those in plasma after 100 mg/kg). Tissue levels of metabolites increased with increasing doses but generally less than proportionately. The decline of plasma and tissue levels of metabolites over the 1-6 hr. period was usually much slower than that of unchanged drug; occasionally an increase in metabolite level over this time period was seen. Thus levels of metabolites at 6 hr. were generally several fold higher than those of unchanged drug. (Exception: brain, where metabolite level at 6 hr. was ≤ that of unchanged drug). At 1 hr. post-dosing, the level of metabolites in plasma and tissues was also generally greater than that of unchanged drug, but this effect was smaller than that seen at 6 hr. (One exception was brain where levels of unchanged drug were several fold higher than those of metabolites at 1 hr.). In this study pregnant rats also received the same doses of drug on day 16 of gestation, and results were generally similar to those for non-pregnant rats. Fetal levels of unchanged drug were 4-10x those in maternal plasma, and declined in parallel with those in maternal plasma. Fetal levels of metabolites were variable (1/3-3x maternal plasma) with no apparent accumulation during the 1-6 hr. measurement period.

C. Plasma protein binding

(Method: equilibrium dialysis)

SPECIES	CONCENTRATION RANGE (μM)	% Bound
Mouse	3-357	75
Rat	3-298	77
Dog	3-357	81
Man	0.35-8	86
	50-800	82
	1000	75

D. Metabolism

B was shown to be rapidly and extensively metabolized in the species studied. One indication of this is the low oral bioavailability of the drug (above) as contrasted with the high degree of absorption of total label after oral dosing (see excretion studies, below), suggesting a large first-pass effect. In female rats receiving 30 mg/kg p.o., plasma levels of metabolites peaked at the same time (0.5 hr.) as those of unchanged drug, and were greater than those of the latter at all time points measured (5-30x up to 8 hr.; 100x at 12 hr.). Tissue levels of metabolites in rats receiving 10, 30, or 100 mg/kg p.o. were also generally greater than those of unchanged drug at 1 and 6 hr. post-dosing (exception: brain). The rate of decline of metabolites from plasma and tissues was significantly slower than that of unchanged drug in rats.

Twenty-four hour urine and fecal samples from rats were treated with 30 mg/kg p.o. showed only trace amounts of unchanged drug (less than 0.2 % of dose, except for 0.3-2.8% in female urine). Acidic metabolites accounted for 86% of the urine label (71% of dose excreted in urine); no basic metabolites were demonstrated. Twenty-four hour urine from a dog given 50 mg/kg p.o. had 88% and 3% of urine label as acidic and basic metabolites respectively (94% of dose excreted in urine). In contrast, in man, 24 hr. urine had 56% and 45% of label as acidic and basic metabolites, respectively (dose not stated for man.)

Two metabolites were identified (method:HPLC) in 24 hr. rat urines (after 30 mg/kg p.o.): m-chlorohippuric acid (about 25% of dose, or about 1/3 of urine label) and m-chlorobenzoic acid (about 2-3% of dose.) These compounds were also present in 24 hr. feces (2-3% of dose). A conjugate of m-chlorohippuric acid was identified in urine but apparently not quantitated. In 24 hr. dog urine (single dog, 50 mg/kg p.o.) m-chlorohippuric acid and m-chlorobenzoic acid represented about 42% and 4%, respectively, of the dose (45% and 4% respectively, of the urine label).

E. Excretion

1. Rats

30 mg/kg p.o. of labelled B was given; 96 hr. urinary and fecal excretion of label was 78% and 19% respectively, mostly complete by 24 hr. Less than 1% of the dose was found in the carcass at 96 hr. No sex differences were apparent. These results suggest that at least 78% of the drug is absorbed; this figure is probably higher since only trace amounts of unchanged drug was found in feces (above).

2. Dog

One dog received 50 mg/kg p.o. Seven day urinary excretion was 100% of dose (94% in 24 hr.), suggesting complete absorption.

F. Enzyme Induction

1. Plasma and tissue levels of B in rats

Male rats received 0.5, 5, 15, or 50 mg/kg/day, p.o., for 13 days; on day 14 they received 50 mg/kg i.p. and were sacrificed 1 hr later for assay of plasma B. Levels were below acute control (about 50%) at HD only. However, in another study decreases were seen at both 15 and 50 mg/kg (39 and 22% of control level respectively). No effect on liver weight, microsomal protein, or cytochrome P450 was seen. The ability of liver microsomes from these rats to metabolize B and pentobarbital *in vitro* was studied; slight but statistically insignificant increases were seen at the higher doses.

In another study, males and females received 50 mg/kg/day p.o. for 4 days; on day 5 they received 50 mg/kg i.p. and were sacrificed 1 hr. later for assay of tissue B. The levels in the various tissues were about 1/6-1/10 of rats treated acutely.

2. Whole body levels of B in mice

Mice received 50 mg/kg i.p. daily for up to 10 days; whole body B levels were decreased on days 8 and 10 to 63 and 42%, respectively of acute controls. Levels of metabolites were unchanged.

3. Plasma levels of B in dogs

Dogs received 40 or 80 mg/kg/day p.o. for 1 year; on day 366 B levels were 25% and 3-10% of those on day 1 at 40 and 80 mg/kg, respectively. (Levels measured 3 hr. after dosing.)

4. Effect of B on pentobarbital hypnosis (rats, mice)

Doses: 5, 10, 25, 50, 100 or 150 mg/kg/day p.o. for 10 days (latter 2 groups received 50 mg/kg first 5 days). Positive control: phenobarbital at 80 mg/kg. On day 11 animals received a hypnotic dose of pentobarbital.

Results: Rats -- Slight decrease (20%) in sleep time at 100-150 mg/kg; 88% decrease with phenobarbital. No effects on lag time to sleep (slight non-dose-related decrease seen with B).

Mice -- Dose-related decrease in sleep time; 65% decrease at 150 mg/kg (vs 75% for phenobarbital). No effects on lag time to sleep.

MADE IN JAPAN

ACUTE TOXICITY:

A. LD 50

SPECIES	STRAIN	ROUTE	SEX	WEIGHT	LD 50 (mg/kg)
Mouse	CD-1	P.O.	M	22 g	544
		P.O.	F	19 g	636
		I.P.	M	27 g	273
Rat	Long-Evans	P.O.	M	109g	607
		P.O.	F	99 g	482
		I.P.	M	130g	263

B. Observed signs

1. Mouse, p.o.

Dosage range = 400-700 mg/kg; deaths seen at all doses and occurred from 5 min.-2 days post-dose. The following signs were seen at all doses: ataxia, prostration, clonic convulsions, ptosis, compulsive gnawing.

2. Mouse, I.p.

Dosage range = 200-300 mg/kg; no deaths occurred at 200 or 250 mg/kg (1/20 deaths at 225). Deaths occurred within 17 min. post-dose. The following signs were generally dose-related and most were seen at all doses: ataxia, clonic convulsions or opisthotonos followed by prostration, labored breathing, decreased respiration, salivation, ptosis, and compulsive gnawing.

3. Rat, p.o.

Dosage range = 400-700 mg/kg; deaths seen at all doses. Most deaths occurred 1-22 hr. post-dose but some were delayed (4-5 days). Most of the following signs were seen at all doses: ataxia, loss of righting reflex, labored breathing, prostration, salivation, ptosis, arched back, and compulsive gnawing.

4. Rat, I.p.

Dosage range = 175-275 mg/kg; no deaths occurred at 175. Deaths occurred within 10-25 min. post dose. Signs were the same as for p.o.; most were seen at all doses.

MADE IN JAPAN

ACUTE ORAL TOXIC INTERACTION STUDIES (RATS):

A. Bupropion (B) + phenelzine (P)

P, given at highest no-effect and highest non-lethal doses, 3 hr. before B, caused marked decreases in the LD 50 of B. (Degree of decrease hard to calculate from data, but at least 2x). Time to death also decreased. Symptoms potentiated by the combination were salivation, decreased activity, and prostration.

B. Bupropion (B) + 50% ethanol (E)

E given 30 min. after B. The highest non-lethal dose of E decreased the LD 50 of B by 39% in F. The highest non-lethal dose of B caused only very slight decreases in the LD 50 of E (NS in F). No potentiation of toxic signs. (In another study, the highest non-lethal dose of amitriptyline decreased the LD 50 of E by 36% and 20% in M and F, respectively; NS in M).

C. Bupropion (B) + amitriptyline (AMI)

AMI given 3 hr. before B. At 1/2 LD 50 of B + 1/2 LD 50 of AMI, 8/10 and 5/9 deaths were seen in F and M, respectively; thus potentiation occurred in F only. No potentiation of toxic signs.

12 WEEK P.O. TOXICITY IN RATS:

A. Dosage

10 M and 10 F at 0, 150, 300, or 450 mg/kg/day by gavage. (For first 12 days, doses were 100, 200, and 300 mg/kg in LD, MD, and HD, respectively)
Strain: Long Evans

B. Results

1. Observed signs

   a. Urinary incontinence, dose-related
   b. Blood in urine, seen after 5 weeks
   c. Irritability

2. Mortality - 1 LD, 2 HD

3. Body Weight - slightly increased gain in HD F

4. Hematology (post-study)

   a. Hb

   Very slight decrease in all groups, dose-related in F. Maximum mean decrease was to less than 10% below control mean. No extremely low values.

LION 301 MADE IN JAPAN

b. Hct

Slight decrease in all M groups, not dose related. Mean values 10% below control. No extremely low values. No effect in F.

c. MCHC

Very slight dose-related decrease in all F groups; no unusually low values.

5. Blood chemistry (post-study)

a. glucose .

Slightly decreased at MD and HD (about 15% below C); no unusually low values

b. total protein

Dose-related increase in all groups. Mean at HD 9 and 16% above control in M and F, respectively. Most rats were affected but none showed extremely large elevations.

c. Other parameters measured: BUN, SGOT, SGPT, AP

6. Organ weights

a. Liver

Increased absolute and relative weight at MD and HD. At HD, mean relative weight was 48 and 35% above control in M and F, respectively.

b. Kidney

Slight dose-related increase in absolute and relative weight in all groups but LD M. At HD, mean relative weight was 12 and 14% above control in M and F, respectively.

c. Other organs weighed: heart, spleen, testes, brain

7. Gross pathology - no drug effect

8. Histopathology - (H+E stain)

Hyperplasia and/or prominent cellular organelles seen in liver of 0/20 controls, 3/20 LD, 4/20 MD, and 4/20 HD.

<u>55 WEEK P.O. TOXICITY IN RAT:</u>

A. Dosage

60 M + 60 F at 0 (untreated), 0 (vehicle), 25, 50, or 100 mg/kg/day, by intubation. Charles River CD rats used.

B. Results

1. Observed signs

a. Most prevalent: dose-related increase in yellow staining of hair around anogenital region

b. Also seen mainly in treated rats: dry brown material around nose or mouth and moisture around mouth.

2. Mortality

No drug effect. Overall mortality 50-60% in M and 20-25% in F. Most deaths said to be due to intercurrent respiratory disease. Untreated controls had lower mortality than other groups.

3. Bodyweight gain

Very slight decrease in HD M; final weight 5% below vehicle control.

4. Food consumption - no drug effect

5. Ophthalmoscopy

(pre-study and at 12 months in all rats, binocular indirect ophthalmoscope)

No clear drug effect. Cataracts in 2 LD and 2 MD; retinal detachment in 1 LD; neither of these findings at HD

6. Laboratory tests - (10/sex/group at 12 months)

a. Hematology

1. 1 HD M and and 1 HD F had low RBC, Hb, and Hct, and (in F only) high WBC. Group means showed no effect.

2. Other parameters measured: WBC differential.

b. Blood chemistry

1. Glucose

Slight decrease seen in most HD rats (mean 15% below control); slight increases seen in most HD F (mean 18% above control). Values stated to be WNL.

2. BUN

Elevated in 1 MD and 2 HD F (2x control). One HD F had marked focal chronic nephritis; no unusual kidney histopathology in the MD; not examined in the other HD.

3. SGOT/SGPT

Elevations of both seen in 1 LD F and 1 MD M. The M also had slightly decreased albumin (no change in total protein, slightly increased RBC, Hb, and Hct, decreased WBC, slightly increased % neutrophils, and slightly decreased % lymphocytes. No unusual histopathology in the M (kidney and spleen only); not performed in the F.

4. Total protein

Very slight increase in 1 MD F and 1 HD F; moderate increase (50% above control) in 1 HD F (the same rat with elevated BUN and nephritis, above)

5. Other parameters: AP, albumin

c. Urinalysis

1. Color mostly "straw" in control M and F and LD M, and mostly "light straw" in all other groups

2. Other parameters: volume, pH, SG, albumin, glucose, bilirubin, occult blood, ketone, sediment.

7. Organ weight

a. Liver

Absolute weight increased in all groups; dose-related increase in relative weight in all groups (15-18% above control at HD)

b. Kidney

Absolute and relative weight increased in all groups except LD M; effect on relative weight generally dose related, 16 and 7% above C in HD M and HD F, respectively.

c. Thyroid/parathyroid

Increased absolute and relative weight in HD M and HD F (relative weight 57 and 22% above C, respectively)

d. Adrenal

Increased absolute and relative weight in HD M (relative weight 29% above C)

e. Pituitary

Increased absolute and relative weight in HD M when compared to untreated control (relative weight 36% above untreated control); vehicle control value elevated due to one extremely high value.

f. Other organs weighed: testes, brain

8. Gross pathology

No clear drug effect. Enlarged liver seen in 1/29 MD M, 1/24 HD M, and 1/18 HD F which died before termination (vs 0/30 control M and 0/14 control F)

9. Histopathology

(Routine H and E exam in 15/sex in C and HD; spleen and kidney only in 15/sex in LD and MD. Iron stained sections of liver, kidney and spleen in 15/sex/group and bone marrow in 15/sex in C and HD were examined. All rats examined in C and HD were sacrificed at termination, as were 18/30 LD and 23/30 MD, the remainder having died after week 30 except 2 MD M (weeks 20 and 25).

a. Spleen

By H & E stain, increased amount of hemosiderin pigment in red pulp seen in all M groups regarding both incidence and severity and in all F groups regarding severity only (incidence in control F nearly 100%):

		M	F
Incidence:	C	7/15	14/15
	LD	10/15	15/15
	MD	12/15	14/15
	HD	15/15	13/15
Severity: (Sum of severity scores/# of rats affected	C	2.7	3.5
	LD	2.8	3.8
	MD	2.9	3.9
	HD	3.4	4.2

However, by iron staining, hemosiderosis was present in all rats examined with the only pronounced effect on severity seen in HD M with smaller equivocal effects in LD and MD M and HD F:

	M	F
C	3.5	4.6
LD	3.9	4.4
MD	3.8	4.5
HD	4.3	4.8

b. Kidney

1. Increased incidence of yellowish-brown pigment in cytoplasm of proximal convoluted tubule at HD (24/30 vs 9/30 in control); severity also greater.

2. Slightly increased incidence of focal chronic nephritis at HD (14/30 vs 9/30 control); severity slightly increased.

3. Slightly increased severity of hemosiderosis (iron stain) at HD; no effect on incidence (seen in nearly all rats.)

c. Lung

Focal aggregates of alveolar macrophages with hemosiderin pigment seen in all C and HD, but severity slightly greater at HD

d. Liver

Increased incidence of hemosiderosis (iron stain) in HD M (11/15 vs 5/15 control) but no effect on severity.

MADE IN JAPAN

23-24 MONTH RAT CARCINOGENESIS STUDY

A. Dosage

75 M and 75 F at 0, 100, 200, or 300 mg/kg/day, by gavage. HD received 500 mg/kg on days 1-15 and 400 mg/kg days 16-74)

Interim sacrifice (5/sex/group) at 6 months; terminal sacrifice at 23 and 24 months in M and F, respectively

Strain: Charles River CD

B. Results

1. Observed signs

   a. Intermittent convulsions, dose-related (10-20% incidence at HD for the selected weeks shown)

   b. Moisture and red/brown material around mouth, dose-related.

   c. Yellow material on anogenital region, dose-related.

2. Mortality

Dose-related increase in all groups except LD M. One-hundred week survival:

	M	(Week of 50% Survival)	F	(Week of 50% Survival)
C	27/70	(81)	49/70	(> 104)
LD	32/70	(95)	40/70	(> 104)
MD	20/70	(81)	25/70	(90)
HD	3/70	(42)	14/70	(51)

3. Bodyweight

   a. M - decreased gain in all groups (final weight 10, 17, and 16% below control in LD, MD, and HD, respectively.)

   b. F - slight dose-related increased weights seen during most of study (10% above C at HD), although final weights 2-4% below C.

4. Food consumption - very slight increase at HD

5. Ophthalmoscopic exam

(All rats, pre-drug and months 6, 12, 18, 24; binocular indirect ophthalmoscope)

MADE IN JAPAN

Slight increase in incidence of cataracts and/or lens opacity at MD. (Not seen at HD; however this might have been obscured by the high mortality at HD and the fact that most of the findings occurred late in the study.)

6. Laboratory tests

(10/sex/group at months 6, 12, and 23/24 [except only 3 M left at 23 months]).

a. Hematology

No consistent drug effects (RBC, Hct, Hb, WBC, differential)

b. Blood chemistry

1. Glucose - slight decrease in all M groups at months 6 and 23 (but not 12) and in HD F at 24 months

2. Other parameters: BUN, total protein, albumin, AP, SGOT, SGPT

c. Urinalysis

1. Volume - slight dose-related increase in all M groups at 23 months

2. Other parameters: color, appearance, pH, SG, albumin, glucose,, bilirubin, occult blood, ketones, sediment.

7. Organ weight

(5/sex/group at 6 months, plus all surviving animals at termination)

a. Liver

Dose-related increase in absolute and relative weight in all groups. Relative weight at HD 32% and 51% above control at 6 months and termination, respectively.

b. Kidney

1. M - dose-related increased in absolute and relative weight in all groups. Relative weight at HD 21% and 45% above control at 6 months and termination, respectively.

2. F- increased absolute and relative weight at HD at 6 months (relative weight 13% above C) and in all groups at termination (not dose-related; relative weight 16% above C)

8. Gross pathology

(Separate incidence values were presented for deaths at 0-6 months, 6 month interim sacrifice, deaths from 6 months - termination, and terminal sacrifices.)

a. No drug effects at 6 month sacrifice; no effect among deaths 0-6 months aside from increased incidence of bloody oral or nasal discharge at MD and HD (see observed signs).

b. Urine/feces/red material on ventral surface or tail increased in all F groups (see observed signs).

c. Liver

1. Mass/nodule/raised area - slight increase in F at termination (3/43, 8/38, 2/24, 5/12 in C, LD, MD, HD, respectively) but no effect among deaths (6 months-termination) or overall combined.

2. Dark red/brown foci/hemorrhagic foci/area - increase in all groups but LD F at termination:
M: 4/27, 17/31, 11/20, 1/3 in C, LD, MD, HD
F: 7/43, 6/38, 10/24, 3/12 in C, LD,, MD, HD

3. Grey/yellow foci/area - slight increase in F at termination (1/43, 5/38, 2/24, 3/12 in C, LD, MD, HD)

d. Lung

Increased incidence of yellow/white/grey foci in all groups at termination:
M: 9/27, 12/31, 12/20, 3/3
F: 9/43, 17/38, 19/24, 11/12

9. Histopathology

(H&E stain. Complete exam in C, MD, and HD rats which died during the study [except not done in MD which died during first 6 months], in 5/sex in C and HD sacrificed at 6 months, and in all C, MD, and HD which were sacrificed at termination. Exam at LD limited to liver, tumors, and gross lesions suspected of being tumors.)

(Separate incidence values for non-neoplastic findings were presented for deaths at 0-6 months, 6 month interim sacrifice, deaths from 6 months-termination, and terminal sacrifice. One exception to this was liver findings which were presented in 1 overall table; however certain findings were tabulated separately by M.I.T. consultants and will be presented below. Neoplastic findings were also presented in one overall table.)

LION 301 MADE IN JAPAN

a. Neoplastic findings

There were no drug-related increases in either total benign or malignant tumors (corrected for increased mortality in drug groups by use of life-table analyses) or in any specific tumor type. Tumors with the highest incidence were mammary fibroadenoma/adenoma in F and pituitary adenoma; all others generally had an incidence of less than 5%. (Results for hyperplastic nodules in liver, which were increased in drug groups are given below under "non-neoplastic" findings since there is no evidence that these nodules were neoplastic. (See Evaluation.)

b. Non-neoplastic findings

1. Liver

a. Hyperplastic nodules

Increased incidence in all groups. The following incidence values are taken from an M.I.T. consultant report which breaks down the results into incidence at terminal sacrifice vs. incidence among rats which died week 28 and later:

		M	(%)	F	(%)
Terminal Sac:	C	2/27	(7%)	1/43	(2%)
	LD	7/31	(23%)	7/38	(18%)
	MD	7/20	(35%)	5/24	(15%)
	HD	1/3	(33%)	4/11	(36%)
Deaths:	C	0/37	(0)	0/25	(0)
	LD	1/29	(3%)	2/23	(9%)
	MD	0/43	(0)	3/40	(8%)
	HD	0/47	(0)	1/35	(3%)

It can be seen that the majority of nodules were not observed until the terminal sacrifice, suggesting a late appearance.

b. Hepatocellular hyperplasia

Increased at LD and MD. Described mainly as focal and slight or very slight:

M: 10/73, 26/72, 15/70, 2/64 in C, LD, MD, HD
F: 16/74, 29/68, 23/71, 5/59 in C, LD, MD, HD

FUJICON 001 MADE IN JAPAN

c. Hepatocellular hypertrophy

Increased in all groups. Described mainly as focal or multifocal (with some diffuse in MD and HD F), and slight or very slight:

M: 1/73, 6/72, 15/70, 4/64 in C, LD, MD, HD
F: 3/74, 13/68, 31/71, 31/59 in C, LD, MD, HD

2. Lungs

a. dark brown pigment/macrophage accumulation, alveoli

Increased at MD and HD (both sexes) among deaths (6 months-termination) and at termination. Combined incidence = 32/133, 0/2, 66/129, 46/103 in C, LD, MD, HD

b. Interstitial inflammatory/lymphocytic/mononuclear infiltrate

Increased in MD and HD F among deaths (6 months-termination) and at termination. Combined incidence = 15/68, 0/2, 36/65, 18/50 in C, LD, MD, HD.

c. Congestion/edema

Increased incidence at HD among deaths (0 - 6 months) but equivocally among deaths (6 months - termination)

3. Spleen

Hemosiderosis - Increased at MD and HD among deaths (6 months-termination) and (in F only) at termination. Combined incidence:

M: 2/64, 0/2, 15/63, 5/49 in C, LD, MD, HD
F: 4/68, 0/1, 18/64, 14/57 in C, LD, MD, HD

4. Cervical lymph node

Slightly increased incidence of dark brown pigment laden macrophage accumulation at MD and HD among deaths (6 months-termination) and (in M only) at termination. Combined incidence:

M: 3/59, 0/0, 10/53, 5/46 in C, LD, MD, HD
F: 7/65, 0/0, 8/52, 6/45 (deaths only: 1/24, 0/0, 5/32, 5/34) in C, LD, MD, HD

MADE IN JAPAN

5. Mesenteric lymph node

Increased incidence of pigment laden macrophage accumulation/hemosiderosis at MD and HD among deaths (6 months-termination):

M: 1/35, 0/0. 9/43, 7/44 in C, LD, MD, HD
F: 1/24, 0/1, 7/39, 7/33 in C, LD, MD, HD

An equivocal increase also seen at HD at termination

6. Thyroid

Increased incidence of light cell proliferation among deaths (6 months-termination) at HD:

M: 0/37, 0/0, 2/40, 9/46 in C, LD, MD, HD
F: 0/25, 0/0, 0/30, 4/34 in C, LD, MD, HD

7. Kidney

Slightly increased incidence of chronic nephritis at MD and HD among deaths (6 months-termination) and (in F only) at termination.

M (deaths only):	12/37, 0/0, 27/44, 24/48
F (deaths & termination):	17/67, 0/0, 26/64, 20/47

MADE IN JAPAN

21-22 MONTH MOUSE CARCINOGENESIS STUDY

A. Dosage

100 M + 100 F at 0, 50, 100, or 150 mg/kg/day, by intubation.

(MD and HD received 50 mg/kg for first 2 weeks; HD received 100 mg/kg for next 4 weeks.)

Final sacrifice at 21 and 22 months in M and F, respectively.

Strain: Charles River CD-1

B. Results

1. Observed signs

   a. Clonic convulsions at MD and HD, dose-related, throughout the study. At week 92, 11% of HD had convulsions within 3 minutes after dosing.

   b. Increased incidence of moist red substance on urogenital region in all F groups. At week 96: 11, 23, 39, and 50% in C, LD, MD, and HD respectively. (Due to uterine bleeding - see pathology results.)

2. Mortality

   Increased in all M groups, partly dose-related, and slightly at HD F. Survival at termination:

	M	(WEEK OF 50% SURVIVAL)	F	(WEEK OF 50% SURVIVAL)
C	46/99	(91)	28/100	(90)
LD	30/98	(81)	22/100	(89)
MD	33/100	(75)	31/99	(83)
HD	19/100	(66)	20/100	(81)

3. Bodyweight - no drug effect

4. Food consumption - no drug effect

5. Gross pathology

a. Uterus

1. Increased incidence of nodules/masses to about the same extent in all drug groups; seen both at terminal sacrifice and among deaths. Overall incidence = 15/100, 42/100, 41/100, and 41/100 in C, LD, MD, and HD, respectively. According to the text, these masses/nodules were actually extremely dilated veins with thrombosis. (See histopathology, below.)

2. Increased incidence of dark red-grey areas, "highly vascularized/hemorrhagic/red contents," and thickening of uterine wall in all drug groups. The incidence of these findings was generally under 10% and not dose-related except for dark red-grey areas.

b. Spleen

Enlarged spleen seen in all F groups, partly dose-related, both at termination and among deaths. Overall incidence: 16/100, 39/100, 37/100, and 48/100 in C, LD, MD, and HD, respectively.

c. Stomach

Slight increase in red foci/hemorrhagic/bloody contents in all F groups both at termination and among deaths. Overall incidence: 2/100, 5/100, 15/100, 13/100 in C, LD, MD, and HD, respectively.

d. Intestines

Slight increase in hemorrhages/blood/reddish contents in HD M and HD F among deaths: 1/55, 1/75, 6/81, 7/81 in CM, CF, HD M and HD F, respectively.

6. Histopathology

(H + E stain. Routine exam in all C and HD; spleen, uterus, and gross lesions considered possibly neoplastic in LD and MD.)

a. Neoplastic findings

There were no drug-related increases in either total benign or malignant tumors (corrected for increased mortality in drug groups by use of life-table analyses) or in any specific tumor type. The overall tumor rate was low, the highest being for lung adenoma (17% in control, 8% at HD); incidence of all other tumor types was less than 5%.

b. Non-neoplastic findings

1. Uterus

a. Increased incidence of extremely dilated blood vessels, with thrombosis, in all F groups, dose-related, both at termination and among deaths. Overall incidence: 15/100, 37/100, 52/97, and 62/98 in C, LD, MD, and HD, respectively.

b. Increased acute metritis/pyometritis in all F groups, dose-related: 4/100, 12/99, 17/98, and 21/98 in C, LD, MD, and HD, respectively.

c. Slight increase in hemorrhage in all F groups: 1/100, 3/100, 8/97, and 5/98 in C, LD, MD, HD.

2. Spleen

a. Increased hematopoietic activity in all F groups, partly dose-related, among deaths but not at termination. Overall incidence: 17/100, 35/100, 53/99, 52/98 in C, LD, MD, HD.

b. Slight increase in incidence of foamy macrophages in all groups: 0/200, 6/198, 6/199, 7/197 in C, LD, MD, HD.

3. Lymph nodes

Slightly increased incidence of foamy macrophages with cellular debris in HD M and HD F among deaths: 0/45, 0/71, 4/80, and 7/79 in CM, CF, HD M, and HD F, respectively.

4. Liver

a. Slightly increased extramedullary hematopoiesis in HD F, among deaths: 14/79 vs 4/75 in control.

b. Slightly increased incidence of lymphocytic infiltrate in HD F, among deaths: 19/79 vs 6/75 in control.

5. Heart

Increased incidence of thrombus in HD M, among deaths: 7/80 vs 1/55 in control.

6. Lung

Increased incidence of congestion/hemorrhage in HD M both at termination and among deaths. Overall incidence was 34/100 vs 14/99 in control.

MADE IN JAPAN

7. Kidney

Increased incidence of brown pigment in tubule epithelium in HD F, among deaths: 11/79 vs 1/75 in control.

8. Testes

a. Increased incidence of atrophic tubules in HD M both at termination and among deaths; overall incidence = 21/99 vs 6/100 in control. No effect on incidence of aspermatogenesis.

b. Increased incidence of amyloidosis in HD M, among deaths: 31/80 vs 5/55 in control.

9. Stomach, small intestine

Increased incidence of ulcer, congestion, hemorrhage, and inflammation at HD, related to gross findings, above. Very low incidence.

MADE IN JAPAN

90 DAY P.O. TOXICITY IN DOGS

A. Dosage

2M + 2F at 0, 15, 35, or 75→150 mg/kg/day, in capsules. (Dosage increase at HD occurred on day 45.)

Strain: beagle

B. Results

1. Observed signs

No effect. (Preliminary study showed convulsions and death with acute oral doses of 150-400 mg/kg.)

2. Mortality - none

3. Bodyweight - no effect (no data shown)

4. Hematology

(pre-drug and days 45 and 90)

a. Hb

Slight decrease in all groups. Not related to dose or time except greatest effect in HD at 90 days (28% below control). No extremely low values.

b. °Hct

Same as above. Mean in HD at 90 days 21% below control.

c. Other parameters measured: MCHC, platelets, WBC, differential, RBC appearance, clotting time, sedimentation rate, icterus index, osmotic fragility, prothrombin time.

5. Blood chemistry

(pre-drug and days 45 and 90)

No drug effects. One HD F had slightly elevated BUN and creatinine but no associated histopathology. Other parameters measured: glucose, cholesterol, thymol turbidity, AP, SGOT, SGPT, total protein, methemoglobin, Na, K, BSP retention, bilirubin.

LION 301 MADE IN JAPAN

6. Urinalysis

(pre-drug and days 45 and 90)

No drug effects (volume, color, appearance, SG, pH, bilirubin, urobilinogen, albumin, occult blood, sugar, acetone bodies, sediment exam).

7. Fecal exam

(pre-drug and days 45 and 90)

No drug effects (color, appearance, occult blood)

8. Organ weights

a. Liver

Slight increases in absolute and relative weight at HD (Relative weight 18% above control)

b. Other organs weighed: heart, spleen, adrenals, kidney, brain, testes, thyroid

9. Gross pathology - no drug effects

10. Histopathology (H&E stain) - no drug effects

MADE IN JAPAN

52 WEEK ORAL TOXICITY IN BEAGLE DOGS:

A. Dosage

8M + 8F at 0, 40, 80 or 80 → 150 mg/kg/day, in gelatin capsules. Dosage escalation at HD complete by 5 weeks.

At 6 months, 2M + 2F from controls, LD, and MD, and 2M + 1F from HD were sacrificed and necropsied. At 12 months, 4M + 4F per group were sacrificed. All remaining dogs were kept for 2 month withdrawal period, then sacrificed.

B. Results

1. Observed signs

LD - none

MD - ptyalism, emesis, and dry nose and/or mouth noted occasionally

HD

a. Weakness in 4 dogs, mainly first 3 months.

b. Emesis, ptyalism, and dry nose and/or mouth noted occasionally to several times per week.

c. General body trembling noted occasionally in a few dogs.

d. Clonic convulsions in 1 F, week 35. Dosing stopped for 3 weeks; upon re-initiation of dosing, frequent emesis and evidence of convulsions were noted, and death occurred after 4 days.

e. One F died week 17 preceded by body trembling and blood in refuse pan.

2. Mortality

a. 1 MD M, week 35 (No signs prior to death)

b. 1 HD F, week 40 (Signs given above, 1 d)

c. 1 HD F, week 17 (Signs given above, 1 e)

3. Bodyweight gain

Decreased at HD (Overall weight gain = 27% (M) and 19% (F) for controls, and 6% (M) and 7% (F) for HD. During withdrawal period, HD gained more than controls.)

4. Food consumption

   No treatment effect except very slight decrease in HD M.

5. Water intake/urine output (measured pre-drug, and months 3, 6, and 12, over 5 consecutive days, in controls and HD).

   No treatment effects

6. Ophthalmoscopic exam (performed on all dogs pre-drug and months 3, 6, and 12, using binocular indirect ophthalmoscope)

   No treatment effects

7. ECG (measured in all dogs pre-drug and months 3, 6, and 12.)

   ECG tracings for all dogs were included in the appendix. There were apparently no calculations of segment lengths performed. The report states there were no treatment effects.

8. Hematology (measured pre-drug and months 3, 6, and 12; after withdrawal period, only total RBC, Hct, and Hb measured)

   a. Total RBC

      1. Moderate decrease in 1 LD dog, month 6

      2. Slight decrease at MD, month 6

      3. Slight decrease at HD, months 3, 6, and 12, but least effect month 12.

   b. Hct

      1. Moderate decrease in 1 LD dog, month 6

      2. Slight decrease at HD, months 3, 6, and 12, but least effect month 12.

   c. Hb

      1. Moderate decrease in 1 LD dog, month 6

      2. Very slight decrease at MD, month 6

      3. Slight decrease at HD, months 3, 6, and 12, but least effect month 12.

MADE IN JAPAN

d. The above effects on RBC, Hct, and Hb were greatest at HD, but did not appear to be progressive over time. The mean decreases at HD were less at 12 months vs 6 months. Some individual dogs with low values at early times showed normalization at 12 months. The values in treated dogs after the withdrawal period were comparable to controls.

e. Total WBC - increased in 2 HD dogs, month 12

f. Differential WBC

Slight increase in neutrophils and slight decrease in lymphocytes at LD, months 6 and 12, and MD, month 12.

g. No treatment effects on platelet count

9. Blood chemistry (measured pre-drug and months 3, 6, and 12; after withdrawal period, only cholesterol, AP, SGOT, and SGPT were measured)

a. AP (alkaline phosphatase)

Dose-related increase seen at all months. The magnitude of the increase, relative to controls, increased over time. At 12 months, group mean values were approximately 2x, 2x, and 4x that of the controls in LD, MD, and HD, respectively. Most of the treated dogs had elevations. However, none of the recovery animals had elevations after the 2 month withdrawal period.

b. SGPT

1. 3 months - slight elevation in 1 LD and 1 MD; slight to moderate elevation in most HD.

2. 6 months - slight elevation in 1 control, 1 LD, 1 MD, and most HD.

3. 12 months - slight elevations in most MD; slight to moderate elevations in all HD.

4. The magnitude of the elevation was greatest at HD but not clearly related to duration of treatment: The group mean values at HD were approximately 4x, 1.7x, and 3.6x that of controls at 3, 6, and 12 months, respectively. At MD, the largest increase (1.6x control mean) was at month 12. After the withdrawal period, slight elevations were seen in 2 of the 3 dogs at MD and HD (group mean values approximately 1.5x control mean); the elevations in the 2 HD dogs were considerably less than those seen at 12 months.

MADE IN JAPAN

c. SGOT

1. 3 months - moderate elevation in 1 LD; slight elevations in 2 LD, 1 MD, and 6 HD.

2. 6 months - moderate elevation persisted in 1 LD; slight elevations in 1 control and 1 MD.

3. 12 months - slight elevation in 1 MD and most HD (group mean at HD approximately 2x control mean). The elevations in individual MD dogs at 12 months were not significantly different in magnitude than those seen at 3 months.

4. No treatment-related effects seen after withdrawal period.

d. BSP retention

Slight increases in approximately 1/2 HD at month 3, and in most HD at month 12 (mean value approximately 2x control mean). Very slight increase in mean value seen at MD at month 12.

e. Total protein

Slight decrease in most HD dogs at 6 and 12 months

f. Albumin

Very slight decrease in most HD dogs at 6 and 12 months

g. No consistent treatment effects on cholesterol, glucose, BUN, A/G ratio, prothrombin time, bilirubin, Na, K, or creatinine.

10. Urinalysis (measured pre-drug and months 3, 6, and 12)

a. Slight, dose-related decrease in pH in all treatment groups at all months.

b. No consistent treatment effects on urine volume, urine color and appearance, specific gravity, albumin, glucose, bilirubin, occult blood, or sediment.

11. Organ weights

a. Liver - increased absolute and relative weights in all groups at both 6 and 12 months, dose-related. No treatment effects in recovery dogs.

b. Kidney - Increased absolute and relative weights in all groups, dose-related, at 6 months; at 12 months increase in relative weight only, at MD and HD only. After recovery period, no treatment effect on absolute weight; relative weight increased at LD and HD.

c. Ovary - absolute and relative weight increased at HD at 6 months, but decreased at 12 months. No effect at HD after recovery, except slightly increased relative weight due to decreased body weight.

d. Thyroid/parathyroid - Increased absolute and relative weight at HD at 6 months only.

12. Gross pathology

a. 6 month interim sacrifice

1. Slightly yellowish liver in 1 LD

2. In the HD F which died: "Pulmonary edema and congestion and slight hydrothorax in this dog were probably compound related, agonal changes."

b. Terminal sacrifice

1. No treatment-related effects in dogs which were sacrificed at termination or after the withdrawal period.

2. In the MD M which died: hemorrhages in tracheal and bronchial mucosa and scattered hemorrhages in lung

3. In the HD F which died: hemorrhages in mucosa of stomach and small intestine, and congestion and/or hemorrhages in several other organs.

13. Microscopic pathology (H and E was only stain used, except for Giemsa-Wrights for bone marrow)

a. Liver

1. At the terminal sacrifice, the hepatocytic cytoplasm was described as having a finely granular "ground glass" appearance in 7/8 MD and 8/8 HD. (0/8 in controls and LD). The severity of this was described as slight to moderate, and was not related to dose. This finding was not reported among dogs sacrificed at 6 months, or after the recovery period. It was not reported for the 3 dogs which died during the study.

2. At 6 months, greenish-brown pigment in Kupffer cells seen in 0/4 controls, 2/4 LD, 1/4 MD, and 1/4 HD (severity was very slight to slight, not dose-related.) At termination, brown pigment in Kupffer cells was seen in 1/8 controls, 0/8 LD, 2/8 MD, and 1/8 HD; however, dark brown pigment (very slight to slight) located in "phagocytic cells, portal areas" was seen in 4/8 HD but not in other groups. In addition, at termination, fine dark brown pigment in hepatocytes was seen at 4/8 MD (very slight to slight) and 2/8 HD (slight), and in 0/8 in controls or LD. No findings of liver pigment were seen in the 3 dogs which died during the study. Among the recovery animals, dark brown pigment in Kupffer cells (very slight) was seen in 1/4 controls, 1/4 LD, 0/3 MD, and 1/3 HD, and fine brown pigment in hepatocytes was seen in 0/4 controls, 1/4 LD, 1/3 MD, and 3/3 HD (severity very slight to slight, not dose-related).

3. Slight coarse vacuolation of periportal hepatocytes was seen in 3/8 HD at terminal sacrifice. Hepatocytic vacuolation was also seen in the MD dog which died during the study. At the 6 month sacrifice, centrolobular hepatocytic vacuolation was found in 1/4 LD (slight) and 1/4 MD (moderate), but not found in the 4 control or HD dogs. Vacuolation was not seen in any of the recovery dogs.

4. Hyaline droplets in hepatocytes (very slight to slight) was seen in 3/8 HD at terminal sacrifice; it was not seen in other groups. In the recovery dogs, however, it was seen in 2/4 controls, as well as in 3/4 LD, 0/3 MD, and 1/3 HD. It was not reported in dogs sacrificed at 6 months or in dogs which died during the study.

5. Bile duct proliferation was seen at the 6 month sacrifice in 0/4 controls, 0/4 LD, 2/4 MD (very slight to slight), and 2/4 HD (slight). At termination, it was seen in 5/8 HD (very slight to slight), not seen in other groups. After recovery period, seen in 1/4 controls (very slight), 2/4 LD (very slight), 0/3 MD, and 2/3 HD (very slight to slight). It was not seen in the 3 dogs which died during the study.

b. Kidney - At termination, brown pigment in tubular epithelium was seen in 3/8 controls, 6/8 LD, 5/8 MD, and 7/8 HD. The severity was greater (very slight to moderate) in the treatment groups, but not dose related. It was not seen at the 6 month sacrifice, or in dogs which died during the study. Among recovery dogs, it was seen in 3/4 controls, 2/4 LD, 3/3 MD, and 3/3 HD, the severity being very slight in controls and LD, slight to moderate in MD, and ranged from very slight to marked at HD.

c. Among the 3 dogs which died during the study, congestion and/or hemorrhage was found in several organs.

MUTAGENICITY

A. Ames Test

1. Plate Incorporation Assay

Salmonella strains TA 98, 100, 1535, 1537 and 1538 were used. Drug levels were 60-6000 μg per plate, with and without metabolic activation (Aroclor - induced rat liver S9 preparation). Bupropion was weakly positive in the following strains:

a. TA 100, without metabolic activation: at all doses, dose-related; largest increase about 2x control. Positive control (1, 3 propane sultone, 0.04 μg per plate) caused 6.5x increase.

b. TA 100, with metabolic activation: at all doses, roughly dose related; largest increase less than 2x control. (Similar results in 2 separate studies). Positive control (2 aminoanthracene, 1 μg per plate) caused 9x increase.

c. TA 1535, with metabolic activation: in one study, dose-related increase starting at 300 μg, greatest effect 2x control; in a second study, non-dose-related increase at all doses, greatest effect 3x control. Positive control (2 aminoanthracene, 1 μg per plate) caused 10x increase.

2. Preincubation assay

Same Salmonella strain as above. Drug levels used were 15-1800 μg per plate (25-3000 μg/ml), with and without metabolic activation. Bupropion was weakly positive in the same strains in which it was positive in the plate incorporation assay, above:

a. TA 100, without activation: dose-related increase at 300-900 μg (1800 μg apparently bacteriotoxic); largest effect less than 1.5x control. Positive control (1,3 propane sultone, 0.04 μg per plate) caused 8x increase.

b. TA 100, with activation: generally dose related increase at 150 μg and above; largest effect less than 1.5x control. (Similar results in 2 separate studies.) Positive control (2 aminoanthracene, 1 μg per plate) caused 6x increase.

c. TA 1535, with activation: non dose-related increase at 150 μg and above; largest increase about 2x control. (Similar results in 2 separate studies.) Positive control (2 aminoanthracene, 1 μg per plate) caused 6x increase.

B. Rat Bone Marrow Chromosome Study

5M + 5F were given 0, 100, 200, or 300 mg/kg/day for 5 days by gavage. Positive control: 5M + 5F at 0.4 mg/kg i.p. triethylenemelamine.

No significant effects seen at LD and MD. At HD there was an increase in all types of chromosomal aberrations tabulated, with no sex differences noted. The % of aberrant cells was 4.6, 5.8, 5.3, and 9.3 in C, LD, MD, and HD, respectively. In contrast, the positive control produced 27.0% aberrant cells. The average number of aberrations per cell was also increased at HD: 0.050, 0.062, 0.067, and 0.140 in C, LD, MD, and HD, respectively. The value for positive control was 0.926. The mitotic index was decreased at HD (1.2 vs 2.4 in control) but this was stated to be not statistically significant.

C. DNA Binding

Rats were given either bupropion-C^{14} (100 mg/kg p.o.) or 2-AAF-C^{14} (20 mg/kg p.o.) and sacrificed 24 hr. later. The degree of covalent binding to liver DNA, RNA, and protein was then assessed. On a specific activity basis, 20x more 2-AAF equivalents were bound to DNA than that found for bupropion (despite the 5x higher dose of bupropion). A covalent binding index was calculated and compared with literature values for known hepatocarcinogens and non-hepatocarcinogens, and the value for bupropion was more similar to those in the latter category. The degree of binding to protein or RNA was not greatly different between bupropion and 2-AAF. It was concluded that the binding of bupropion to DNA, RNA, and protein was minimal and probably non-specific.

TWO GENERATION REPRODUCTION AND FERTILITY STUDY IN RATS

A. Method

1. Strain: Long-Evans

2. Dosage: 15 M and 30 F at 0 (2 groups - one vehicle treated, one untreated), 100, 200, or 300 mg/kg/day, by gavage, from day 60 pre-mating through mating (M) or from 15 days pre-mating through either day 13 of gestation (1/2 F) or day 21 postpartum (remaining F).

3. Procedure: Mating ratio was 2 F/M of the same dosage group. One of the 2 F mated to each M was sacrificed day 13 of gestation; the other F was allowed to deliver normally. Pup weights and survival were monitored to day 21 PP. At 12 weeks of age, these F1 generation pups were mated (1 F per litter mated to an intragroup M, but not a brother) and allowed to rear young (F 2 generation) to day 21 PP, during which time pup weights and survival were monitored.

B. Results

1. Observed signs

No drug effect in M; 1/30 MD F and 1/29 HD F had wobbly gait on days 1-2 of premating period only

2. Mortality

1 LD M, 1 MD M, and 1 HD F (dosing accidents), and 1 untreated control

3. Bodyweight

a. M - All drug treated groups gained more weight than vehicle controls, but not dose-related.

b. F - All drug teated groups gained slightly more weight than controls during mating period (not dose-related); this difference persisted through pregnancy and lactation periods.

4. Mating performance

a. M - No drug effect

b. F - No drug effects (pregnancy rate = 26/29, 24/30, 24/28, 22/30, and 23/29 in untreated controls, vehicle controls, LD, MD, and HD respectively).

MADE IN JAPAN

5. Post-mortem uterine findings in F

   a. F sacrificed day 13 of pregnancy - no drug effects on number of total, live, or dead implants/dam, number of CL, or CL/implantation ratio.

   b. F which had not delivered by day 26 of gestation (4 vehicle controls, 3 LD, 3 MD, and 3 HD) - all had failed to implant (no implant scars seen).

   c. Pup - bearing F sacrificed day 21 PP - No drug effects on number of uterine scars.

6. Term deliveries

   No drug effects on number of live pups per dam. Slight increase in number of dead and live + dead pups per dam at HD.

7. Pup survival (F 1 generation)

   No drug effects through day 21 PP

8. Pup weight (F 1 generation)

   No drug effects through day 21 PP

9. Observed signs (F 1 generation)

   Results given up to 12 weeks of age - no drug effects

10 Bodyweight (F 1 generation)

   a. M - Slightly higher than vehicle controls at LD and HD (measured up to 12 weeks of age).

   b. F - No drug effect up to 12 weeks of age. During pregnancy, weight gain at HD was slightly decreased. No drug effect during lactation period.

11. Reproductive performance in M (F 1 generation)

   No drug effect on percent of M mating (100% in all groups) or siring litters (93, 64, 82, 82, and 90% in untreated controls, vehicle controls, LD, MD, and HD, respectively).

12. Gross necropsy in F 1 males at 12 weeks of age.

   No drug effects.

13. Reproductive performance in F (F 1 generation)

    a. No drug effect on pregnancy rate (7/11, 9/11, 9/12, and 9/11 in vehicle controls, LD, MD, and HD, respectively)

    b. No drug effect on length of gestation

    c. Slight decrease in mean number of live pups at HD compared to vehicle but not untreated controls; no drug effect on number of dead pups.

    d. Slight decrease in number of implant scars at HD.

14. Gross necropsy findings in F (F 1 generation).

    No drug effects among F not selected for mating (sacrificed at 12 weeks of age) or among pup-bearing F (sacrificed day 21 PP). No drug effect among F which were mated but had not delivered by day 26 of gestation - all were not pregnant and had no implant scars.

15. Pup survival (F 2 generation)

    No drug effects through day 21 PP.

16. Pup weight (F 2 generation)

    Mean weights slightly higher than controls at most days measured in all drug groups, not dose-related.

17. Number of pups with both eyes open on day 14 PP (F 2 generation)

    No drug effects.

18. Gross necropsy of F 2 pups (day 21 PP) - no drug effects.

SEGMENT II REPRODUCTION STUDY IN RATS

A. Method

1. Strain: Long-Evans

2. Dosage: 22 F at 0, 20 at 150, 20 at 300, and 23 at 450 mg/kg/day, by gavage, from days 6-15 of gestation. (Group numbers refer to number of pregnant dams whose offspring were examined for abnormalities; the number which were started on the study cannot be determined from the data presented).

3. Procedure: Dams sacrificed day 20 of gestation, laparotomies performed. All fetuses examined for external malformations, approximately 1/3 for visceral defects (Wilson method), and approximately 2/3 for skeletal defects (Alizarin Red S staining)

B. Results

1. Observed signs in dams

Ataxia, urinary incontinence, and gnawing on cage and/or forepaws seen in 3/28 MD and 24/53 HD.

2. Dam tality

24/53 HD died on or before day 17 of gestation (one due to dosing accident; 19 exhibited signs as stated above).

3. Bodyweight of dams

Weight loss in all treated groups after first dose, but then caught up and slightly surpassed mean control values.

4. Number of CL and implantations

Slight increase in CL/dam and slight decrease in implantations/dam in all treated groups, not dose related.

5. Number of live and dead fetuses per dam

No drug effects

6. Number of resorbed fetuses per dam

Slight increase in LD and HD, mainly due to 1 dam in each group.

7. Fetal weights

Slight decrease in all drug groups, not dose-related

8. Fetal lengths

Very slight decrease in all groups, not dose related.

9. Fetal abnormalities

a. Number of fetuses examined

	C	LD	MD	HD
gross	209	193	197	220
visceral	70	66	69	77
skeletal	139	127	128	143

b. Gross and visceral abnormalities - no drug effects

c. Skeletal abnormalities

The sponsor concludes that there were no significant treatment effects; however, the incidence tables show a trend toward decreased ossification of several structures at the higher doses, for example:

% with reduced ossification

	C	LD	MD	HD
interparietals	10.1	7.9	14.8	14.0
parietals	12.9	7.2	10.9	16.1
supraoccipital	14.4	11.8	27.3	21.0

The incidence of unossified second sternebrae was increased at LD and HD (5.8%, 19.7%, 8.6% and 22.4% in controls, LD, MD, and HD, respectively). However, the incidence of unossified 5th sternabrae appears to be decreased at MD and HD (about 1/2 contro' incidence).

The number of total skeletal findings per number of fetuses examined was increased in all treated groups: 3.6, 4.0, 4.2, and 4.3 in controls, LD, MD, and HD, respectively. The number of fetuses with skeletal findings per number of fetuses examined was not affected by drug, in that virtually all fetuses examined had at least one finding.

II REPRODUCTION STUDY IN RABBITS (1 OF 2 STUDIES IN RABBITS)

hod

Strain: New Zealand White

Dosage: 21 F at 0, 22 at 50, 21 at 100, and 24 at 150 mg/kg/day, by gavage, from days 6-18 of gestation.

Procedure: Does artifically inseminated. Ovulation induced naturally via mounting by bucks. Does sacrificed day 29 of gestation. All fetuses examined for external malformation, approximately 1/3 for visceral defects (Wilson method), and approximately 2/3 for skeletal defects (Alizarin Red S staining).

ults

Observed signs in does

a. Slight to severe clonic convulsions in 1/21 MD and 8/24 HD. One HD died during, and 1 MD survived, an opisthotonic convulsion.

b. ber of does failing to eat all of daily food ration (100 g) 1 or more days: 11/21, 15/22, 16/21, and 24/24 in controls, , MD, and HD, respectively.

Doe mortality

a. Deaths: 1 control and 2 LD (uncertain cause), 2 MD (dosing accidents), and 1 HD (following opisthotonic convulsion).

b. Sacrifices prior to delivery: 1 LD (broken back), and 2 MD (1 broken back, 1 aborted day 25 of gestation).

. Bodyweight of does - no drug effect.

. Number of does pregnant at day 29 of gestation: 17, 18, 16 and 17 in controls, LD, MD, and HD, respectively.

. Number of abortions, live fetuses/doe, dead + resorbed fetuses, and total implants

No drug effect

. Mean fetal weight

Slight decrease in all drug groups, dose-related

. Mean fetal length

Very slight decrease at HD

8. Fetal abnormalities

a. Number of fetuses examined

	C	LD	MD	HD
gross	140	135	114	140
visceral	45	46	37	47
skeletal	95	89	77	93

b. Percent incidence of malformations (number of malformations X 100/number fetuses examined)

	C	LD	MD	HD
1) gross	0	0	0.9	2.1
2) visceral	0	8.7	5.4	6.4
3) skeletal	2.1	5.6	0	6.5
4) percent of does with malformed fetuses of any type	5.9	33.3	12.5	41.2

The sponsor states that although there does appear to be a drug-related increase in malformations, it is not considered biologically significant primarily because no pattern of abnormalities was seen, i.e., except in one instance not more than one fetus per group had any given abnormality, and there was little overlap of types of abnormalities among the different groups. The sponsor also states that all abnormalities seen in the drug groups that were not seen in the concurrent controls have been reported to occur spontaneously.

c. Incidence of common variants

1. Visceral - no drug effect

2. Skeletal

a. The percent of fetuses examined having unilateral or bilateral supernumerary 13th ribs was as follows:

C 26.3
LD 41.6
MD 45.5
HD 55.9

The percent of does with fetuses having this finding was:

C	58.8
LD	72.2
MD	68.8
HD	94.1

The sponsor states that supernumerary ribs are considered to be a normal skeletal variant in rabbits with incidences as high as 75-100%. The increased incidence in the drug groups was considered by the sponsor to be secondary to maternal toxicity.

b. There was a slight increase in incidence of decreased ossification of the palate in all drug groups, not dose-related (8.4, 14.6, 14.3, and 14.0% in controls, LD, MD, and HD, respectively). The incidence of decreased ossification of other bones was not increased by treatment.

SEGMENT II REPRODUCTION STUDY IN RABBITS (1 OF 2 STUDIES IN RABBITS)

(Performed by International Research and Development Corporation)

A. Method

1. Strain: New Zealand White

2. Dosage: 20 F at 0, 20 at 25, 28 at 50, 20 at 100, and 20 at 150 mg/kg/day, by gavage, from days 6-18 of gestation. (The group numbers refer to the numbers of pregnant does whose offspring were examined for abnormalities; the numbers which were started on the study cannot be determined from the data presented.) Thirteen F of the 50 mg/kg group were accidentally given 100 mg/kg on 1 day.

3. Procedure: Chorionic gonadotropin was given i.v. to stimulate ovulation after mating. Fetuses were delivered by cesarean section on day 29 of gestation. All fetuses were examined for external anomalies, dissected and examined for visceral anomalies, and cleared and stained with Alizarin Red S and examined for skeletal anomalies.

B. Results

1. Observed signs in does

a. LD and MD - no drug effect

b. M-HD - slight hypoactivity

c. HD - slight hypoactivity plus (in 9 does) convulsions, ataxia, tremors, loss of righting reflex, hyperpnea, and muscle spasms.

2. Doe mortality

Number dying or sacrificed due to injury = 0, 1, 1, 2, and 1 in controls, LD, MD, M-HD, and HD, respectively.

3. Bodyweight of does

Weight gain at M-HD and HD less than controls (very slight effect at M-HD)

4. Mean number of CL and implantation sites, and number of live, dead, or resorbed fetuses per doe.

No drug effects

5. Mean fetal weight

Very slight dose-related decrease in all drug groups except LD.

6. Fetal abnormalities

a. Number of fetuses examined:

C	149
LD	146
MD	210
M-HD	142
HD	145

b. Incidence of anomalies

The table on the following page, taken from the IND, shows a trend toward increased incidence of gross, soft-tissue, and skeletal anomalies in the treated groups, which tended to be dose related in some instances.

The increase in gross and soft-tissue anomalies was not statistically different from controls ($\alpha = .05$), and was not discussed by the sponsor. From the table which gives the findings in individual fetuses, it does not appear that there was any pattern showing an increase in any specific anomaly in the treated groups.

Regarding skeletal anomalies, statistically significant drug effects were found for 2 anomalies which are considered common variants: accessory rib(s) (incidence = 29, 49, 51, 48, and 49% in controls, LD, MD, M-HD, and HD, respectively), and delayed ossification of the fifth phalanx of the forelimb (incidence increased at HD only; incidence = 3.4% in controls, and 10.1% at HD). In addition to these findings, a few fetuses in each drug group had "barbell" shaped thoracic centra (incidence = 0, 2.7, 1.0, 0.7, and 4.1% in controls, LD, MD, M-HD, and HD, respectively). The sponsor concludes that these skeletal findings are secondary effects of maternal toxicity in the drug-treated groups.

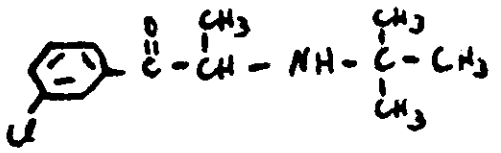
	C	LD	MD	M-HD	HD
Fetuses with Gross Anomalies (%)	1 (0.7)	5 (3.4)	5 (2.4)	4 (2.8)	9 (6.1)
Fetuses with Soft-tissue Anomalies (%)	4 (2.7)	4 (2.7)	4 (1.9)	6 (4.2)	8 (5.5)
Fetuses with Skeletal Anomalies (%)	79 (53.0)	107 (73.3)	135 (64.3)	85 (59.9)	102 (68.9)*
Fetuses Showing One or More Gross Anomalies (%)	1 (5.0)	3 (15.0)	2 (7.1)	2 (10.0)	2 (10.0)
Fetuses Showing One or More Soft-tissue Anomalies (%)	3 (15.0)	4 (20.0)	4 (14.3)	2 (10.0)	6 (30.0)
Litters Showing One or More Skeletal Anomalies (%)	20 (100.0)	19 (95.0)	26 (92.9)	18 (90.0)	20 (100.0)

* Significantly higher than control group (α = .05)

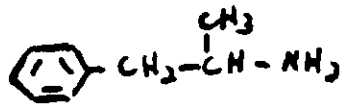
SUMMARY

A. Pharmacology

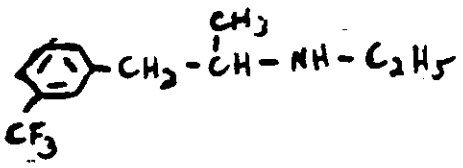
Bupropion (B) is structurally similar to amphetamine, fenfluramine, diethylpropion, and other phenethylamine derivatives.



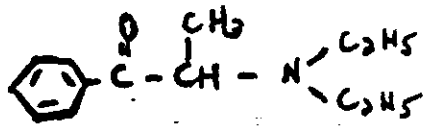
BUPROPION



AMPHETAMINE



FENFLURAMINE



DIETHYLPROPION

its pharmacological profile is that of a CNS stimulant with several similarities to amphetamine. B was active in 3 types of tests which are predictive of antidepressant activity: prevention or reversal of tetrabenazine/reserpine effects in mouse, decreased immobility in the Porsolt behavioral despair test in rats, and potentiation of the behavioral effects of pargyline + DOPA in mice. In these studies B had an i.p. ED 50% of 10-12 mg/kg (32 mg/kg p.o. in 1 study); activity was sometimes seen at doses as low as 6.5 mg/kg i.p. The potency of B in these tests ranged from 3-5x less potent to equipotent with classical tricyclics. B produced dose-related CNS stimulation in rats and mice as evidenced by increase in locomotor activity as well as by performance in several operant behavioral tests; the potency of B was generally 10-50x less than that of amphetamine in these studies. The ED 50% for increased locomotor activity in mice was approximately 2x that for antitetrabenazine effect whereas the reverse was true for amphetamine and methylphenidate, suggesting a more specific "antidepressant" effect for B. However, some increase in locomotor activity was seen with B at all doses but the lowest which were effective in the antitetrabenazine test. Data in rats further suggested that there is little or no separation of CNS-stimulating and "antidepressant" doses.

B was shown to be a relatively weak blocker of the uptake of NE and 5 HT into brain and peripheral nerve compared with classical tricyclics. It was somewhat more potent in blocking DA uptake although the dose in rat (40 mg/kg i.p.) needed to produce serum levels high enough to cause 50% inhibition of DA (or NE) uptake into brain synaptosomes was 4x greater than the ED 50% in the Porsolt test; thus the blockade of DA (or NE) uptake is probably not involved in the "antidepressant" effect of B. (The reverse holds true for imipramine regarding the potency ratio for "antidepressant effect" and NE uptake blockade.) However, destruction of dopaminergic neurons with 6-hydroxydopamine + DMI blocked the effect of B in the Porsolt test in rats, suggesting that DA neurons are involved in some way.

B did not inhibit MAO or elevate brain NE or DA at relatively high doses.

Many similarities between the pharmacological profiles of B and amphetamine (and other CNS stimulants) were noted,, along with some differences. These may be summarized as follows:

1. B, amphetamine, and methylphenidate all had dose-related antitetrabenazine effects and caused dose-related increases in locomotor activity in mice. However, the ratio of the i.p. ED 50% values these 2 effects was approximately 1:2 for B and 2:1 for amphet e and methylphenidate. (In contrast, classical tricyclics cause <u>decreased</u> locomotor activity above "antidepressant" doses.)

2. Amphetamine and methylphenidate reversed tetrabenazine-induced sedation in mice whether given before or after the tetrabenazine; B was only active when given before.

3. Selective depletion of brain DA blocked the locomotor effects of both B and amphetamine; selective depletion of NE had no effect on either drug.

4. The locomotor effect of B and methylphenidate depends primarily on a storage (reserpine-sensitive) pool of catecholamines, whereas that of amphetamine depends primarily on newly synthesized (alpha-methyltyrosine sensitive) catecholamines.

5. B caused an increase in stereotyped behavior in rats; no direct comparison to amphetamine was made.

6. Several behavioral (operant) tests showed the profile of B to be more similar to amphetamine than to classical tricyclics.

7. B had an anorexic effect in mice. (Oral potency at least 2x less than that of fenfluramine and diethylpropion; amphetamine not used.)

8. Drug discrimination studies in rats showed similarities between B and several CNS stimulants (e.g., amphetamine, methylphenidate, caffeine, cocaine) as well as to the newer antidepressants viloxazine and nomifensine.

9. At high doses B caused hypothermia in mice whereas amphetamine caused hyperthermia.

10. Grouping of mice caused an increase in the i.p. lethality of amphetamine but had no effect on that of B; B decreased the lethality of amphetamine in grouped mice.

Cardiovascular studies showed rather large but generally transient decreases in CO and right ventricular contractile force, and both increases and decreases in heart rate and blood pressure, at i.v. doses of 1-20 mg/kg in anesthetized dogs and cats. (It is not clear if these results were corrected for vehicle effects). In conscious dogs, 20 mg/kg p.o. caused slight increases in HR and BP (lasting at least 6 hr.); in conscious rats 50 mg/kg caused a slight increase in HR (lasting 3 hr). Comparison drugs were not used in these studies so that the relative potency of B in causing these changes is not known. No effect on EKG (aside from increased HR) was seen in dogs at 10 mg/kg i.v. (2 mg/kg/min). In dogs, 5-10 mg/kg i.v. caused rather large increases in respiratory rate and smaller increases in minute volume. A relatively weak depressant effect on cardiac tissue in various <u>in vitro</u> preparations was noted which may have been due to the local anesthetic properties of B (equipotent with cocaine in guinea pig cornea); the potency of B was generally 5-15x less than that of imipramine and amitriptyline.

Several studies were performed to assess the anticholinergic effects of B. Effects were generally weak or absent (except for dose-related mydriasis in mice, although it is not clear if this represents an anticholinergic or sympathomimetic effect), and B was significantly less potent than amitriptyline and imipramine when compared. Antagonist actions at other receptors (adrenergic, serotonergic, histaminergic) were generally weak or absent; however reference drugs (which could have validated the systems as well as estimated the relative potency of B) were not used. Likewise, binding studies showed little or no interaction of B with a variety of receptors, but no reference drugs were used.

B. <u>ADME/Pharmacokinetics</u>

ADME/pharmacokinetic studies were performed in rat, mouse, and dog. After oral dosing, plasma levels of B peaked rapidly (within 1/4-1/2 hr) and declined rapidly with a T 1/2 in the 1-4 hr. range. Over a dosage range of 10-100 mg/kg/ p.o. in rats, plasma levels increased with increasing dose but slightly less than proportionately at the highest dose. Studies comparing plasma AUC after i.v. and p.o. dosing showed a bioavailability of 8-21% in rats and 4% in dogs; however, excretion studies using labelled drug showed complete absorption in dogs and a high if not complete degree

of absorption in rats after p.o. dosing. B was widely distributed to tissues in rats; levels were highest in liver and lung after p.o. and i.p. dosing, respectively; lowest levels were in plasma. B was shown to be rapidly and extensively metabolized, which is in agreement with the low oral bioavailability of the drug. Plasma and tissue levels of metabolites were generally substantially higher than those of unchanged drug (exception: brain). Very little unchanged B was found in rat or dog urine; acidic metabolites (m-chlorohippuric and m-chlorobenzoic acids, and a conjugate of the former, were identified), presumably arising from side chain oxidation, were predominant. This is in contrast to human urine, where acidic and basic metabolites were present in nearly equal amounts. Plasma and tissue levels of metabolites declined much more slowly than those of unchanged drug (e.g. in 1 study the plasma T 1/2 for metabolites appeared to be about 12 hours). This suggests that whereas the parent drug is unlikely to accumulate with repeated dosing due to its short T 1/2, metabolites may. However, in one mouse study, 10 days dosing did not lead to an accumulation of metabolites; such a tendency may have been counteracted by an enzyme - induction effect (levels of unchanged B were decreased).

The ability of B to induce liver microsomal metabolic enzymes was demonstrated in rat, mouse, and dog. In rat, pre-treatment with 15-50 mg/kg/day p.o. for 13 days decreased the rise of B in plasma seen after an acute dose of 50 mg/kg i.p., and 50 mg/kg/day p.o. for 4 days decreased the rise of B in tissues seen after an acute dose of 50 mg/kg i.p. In mouse, 50 mg/kg i.p. for 8 or 10 days decreased the rise in whole body level of B seen after an acute dose of 50 mg/kg. In dog, plasma levels after 1 year treatment at 40 or 80 mg/kg/day p.o. were significantly less than those seen on day 1. Studies on pentobarbital sleep time in mice showed a decrease after 5-150 mg/kg/day p.o. for 10 days (effect at HD slightly less than effect of phenobarbital pretreatment at 80 mg/kg/day); in rats a slight decrease was seen at high doses (100-150 mg/kg/day) only. It is possible that part or all of these effects on pentobarbital sleep time were due to CNS stimulation by B; thus while it appears that B can induce its own metabolism, the ability to induce the metabolism of other compounds has not been clearly demonstrated.

Excretion of B + metabolites was shown to be primarily urinary in rats (78%) and dogs (100%).

Over concentration ranges that were stated to be "normally found in animals and during clinical studies in man," B was 75-85% bound to plasma proteins from mouse, rat, dog, and man. Binding was generally constant over the concentration ranges used, although it tended to fall off in man at the highest concentration (1000 μM).

There appears to be some sex differences in the disposition of B, at least in rats. Plasma and tissue levels of unchanged drug, plasma AUC, and oral bioavailability were several-fold greater in F; T 1/2 was greater in F in one rat study but apparently not in another. There did not appear to be

any important sex differences in metabolic pattern or excretion, although data on these points were limited. No sex differences in plasma levels in dogs were apparent although only 2 dogs per sex were used. The acute toxicity of B in rats was slightly greater in F than M, but the reverse appeared to be true in the chronic rat toxicity studies.

C. Toxicology

The acute oral LD 50 was 544 (M) and 636 (F) mg/kg in mouse and 607 (M) and 482 (F) mg/kg in rat. Acute i.p. LD 50 was 273 and 263 mg/kg in male mice and male rats, respectively. Prominent acute signs included: mouse - ataxia,, convulsions, prostration, ptosis, and compulsive gnawing by both routes, plus labored breathing, decreased respiration, and salivation after i.p. only; rat - ataxia, loss of righting reflex, labored breathing, prostration, salivation, ptosis,, arched back, and compulsive gnawing by both routes.

Acute p.o. toxic interaction studies were performed in rats. Phenelzine (at highest no-effect and highest non-lethal doses) caused a marked decrease in the LD 50 of B. (However, no pharmacodynamic interactions were seen in several tests at lower doses). Only a slight potentiation of the lethality of B was caused by treatment with ethanol at its highest non-lethal dose; this was seen in F only. Lethal potentiation was noted between B and amitriptyline (each given at 1/2 LD 50), in F only.

The following oral subacute/chronic toxicity studies were performed (daily dose in mg/kg in parentheses):

1. Rat - 3 month (150, 300, 450)
2. Rat - 55 week (25, 50, 100)
3. Rat - 2 year (100, 200, 300)
4. Mouse - 21-22 month (50, 100, 150)
5. Dog - 3 month (15, 35, 75→150)
6. Dog - 1 year (40, 80, 150)

The principal findings are summarized as follows:

1. Rat

Increased mortality, associated with convulsions, was seen in the 2 year study at all doses (except LD M), and was marked at HD (300 mg/kg). No effect on mortality was seen in the 55 week study (HD = 100); in the 3 month study 2/20 died at 450. Observed signs included urinary incontinence/urine staining (all studies, all doses), dried blood around nose/mouth (55 wk and 2 yr studies, all doses), and convulsions (2 yr study, all doses). Slight decreases in bodyweight gain were seen in all M groups in the 2 yr study. Slight decreases in blood glucose were seen above 100-150 mg/kg. The most prominent post-mortem findings were as follows:

a. Liver

In the two-year study there was an increase in incidence of hyperplastic nodules and hepatocellular hypertrophy at all doses; hyperplasia was increased at LD and MD only. (In a consultant report many of the hyperplastic nodules were reclassified as "foci or areas of altered hepatocytes"). The incidence of these findings is underestimated in the drug groups in a dose-related fashion due to the increased mortality and the late appearances of the lesion. (Most hyperplastic nodules were found at the terminal sacrifice, and almost all were found after 90 weeks). There was no increase in the incidence of hepatocellular carcinoma; the observed incidence (0/147, 3/140, 1/141, and 1/123 in control, LD, MD,, and HD, respectively) is within the historical control range. Similar findings were not seen in the 55 week study (HD = 100); in the 3 month study a low incidence of hyperplasia and "prominent cellular organelles" was seen at all doses. Increased liver weights were seen in all studies at all doses except LD in the 3 month study. Grossly, in the 2 yr. study slight increases in the incidence of masses/nodules/raised area (F only) and dark red/brown/hemorrhagic foci were seen at all doses at termination but not among deaths. The sponsor suggests that these proliferative changes in liver may represent either (1) an indication of microsomal enzyme induction or (2) an adaptive response to hepatic injury. Regarding the former, B has been shown to induce its own metabolism (see above). Regarding the latter, no other indication of hepatic damage (including blood chemistry) was obtained in rats, although some indications of liver damage were obtained in dogs.

b. Hemosiderosis

In the 55 week study an increase in hemosiderosis (as determined either by H + E stain, iron stain, or presence of pigment-containing macrophages) was seen in spleen, kidney, lung, and liver. This was seen primarily at HD, although lower doses were not examined in lung and liver. Likewise, in the two year study, evidence of increased hemosiderosis was seen in spleen, lung, and lymph nodes at MD and HD. (LD not examined in these organs). No other pathological findings were present to help explain the increased hemosiderosis. Hematology did not reveal any striking abnormalities. (2/20 HD in the 55 week study had low Hb, Hct, and RBC; no effect in two year study; slight decreases in Hb and Hct seen in the 3 month study but no hemosiderosis reported).

c. Kidney

Slight increases in the incidence of chronic nephritis were seen in the 55 week study (HD only) and in the two-year study (MD and HD; LD not examined). There were no consistent effects on lab tests indicative of renal function; in the 55 week study there were elevations of BUN in 3 of 40 rats at MD and HD. Kidney weights were elevated in all studies at all doses.

d. Neoplasia

There were no drug-related increases.

2. Mouse

In the 22 month study mortality was increased in all M groups and HD F. There was no effect on weight gain. As in rats, convulsions were seen (MD and HD). Laboratory studies were not performed. The most prominent postmortem findings were seen in uterus, consisting of a dose-related increased incidence of extremely dilated blood vessels, with thrombus, in all F groups. This increase was seen both among mice which died and those which survived to termination, suggesting a lack of association with lethality. Grossly there was an increased incidence of uterine nodules/masses; according to the text these were actually extremely dilated veins with thrombosis. The red urogenital staining noticed during the in-life phase was probably also related to these changes. Also seen in uterus was increased incidence of acute metritis/pyometritis in all drug groups (dose-related) and slightly increased incidence of uterine hemorrhage in all drug groups (not dose-related). Splenomegaly and hematopoiesis in spleen and liver were also seen in F; the pathology report considered these to be secondary to the uterine blood loss although an independent analysis by the sponsor did not show a good correlation between the uterine and spleen/liver changes. Changes similar to those in uterus were not clearly seen in other organs, although a low incidence of hemorrhage and ulcer in stomach and small intestine was noted, primarily at HD, the incidence of thrombus in heart was increased in HD among deaths but not at termination, and the incidence of congestion/hemorrhage in lung was increased in HD M. An increased incidence of atrophic tubules in testes at HD was also seen in this study, although there was no effect on the incidence of aspermatogenesis. As in the rat study, there was no effect on the incidence of neoplastic changes.

3. Dog

No significant toxic effects were seen in the 90 day study (HD = 75→150); a slight increase in liver weight was seen with no associated pathology. In the 1 year study the HD (150) produced 3/16 deaths. This dose also produced convulsions in 1 dog and body trembling in

several dogs. Emesis and ptyalism were seen at both MD and HD. Bodyweight gain was decr eased at HD. Values for RBC, Hb, and Hct tended to be decreased at the higher doses but this did not progress with time and no effect was seen in recovery dogs. (Slight decreases in Hb and Hct were also seen in the 90 day study.) There was a dose-related elevation of serum alkaline phosphatase in all groups at all months measured, and the magnitude increased over time; no effect seen in recovery dogs. Elevations of SGOT and SGPT were also seen mainly at the higher doses, starting at 3 months but not clearly progressive over time. Some recovery dogs still had elevated SGPT after the recovery period, but of smaller magnitude. Slight increases in BSP retention were seen at MD and HD. Liver weights were increased in all groups (dose-related) at both 6 and 12 months but not at recovery. Microscopic exam of liver showed several drug-related changes including finely granular "ground glass" cytoplasm (MD and HD, seen at 12 months but not at 6 months or after recovery period), dark brown pigment in hepatocytes and phagocytic cells (MD and HD, seen at 12 but not at 6 months, and seen at all doses after recovery period), slight coarse vacuolation of hepatocytes (seen in HD at 12 months and in LD and MD at 6 months and in the 1 MD which died; not seen after recovery period), and bile duct proliferation (very slight to slight) (seen at MD and HD at 6 months and at HD at 12 months, also seen after recovery period in 2/4 LD and 2/3 HD but also in 1/4 control and 0/3 at MD). Kidney weight was elevated in all groups at 6 months; however at 12 months an increased relative weight only was seen (MD and HD only). Histologically, the incidence and severity of brown pigment in tubular epithelium was increased in all groups at termination. The incidence of this finding among recovery dogs was similar across groups although severity was greater at MD and HD. No clear abnormalities of renal function were seen in this study.

D. Mutagenicity

B was weakly positive in some Salmonella strains in the Ames Test. (TA 100, both with and without metabolic activation, and TA 1535, with activation only). Greatest effects were 2-3 x control revertant count; positive controls caused 6-10 x increases. In a rat bone marrow chromosome study, an increase in aberrations was seen at 300 but not 100-200 mg/kg p.o., given for 5 days; the increase was 2-3 x control compared to 6-19 x for the positive control. In a study of binding to rat liver DNA after oral administration, it was found that the binding of bupropion (+ metabolites) was much lower than that of known hepatocarcinogens and was concluded to be nonspecific.

E. Reproduction

A 2 generation reproduction and fertility study was performed in rats. Both M and F (of the F0 generation only) were drug treated, dosages = 100, 200, and 300 mg/kg/day. Except for wobbly gait in 1 MD and 1 HD, no

drug-related signs were observed. Body weight gain was slightly increased in all treated groups, but not dose-related. There was no drug-related increase in mortality. No drug effects on M or F mating performance, on F fertility or reproductive parameters, or on pup (F 1 generation) survival and body weight were seen. There were no significant effects on mating or reproductive performance of the F 1 generation. Pup survival (F 2 generation) was not affected by treatment, although F 2 pups in all drug groups had slightly increased body weight.

Segment II reproduction studies were performed in rats and rabbits. In rats (dosages = 150, 300, and 450 mg/kg/day), signs including ataxia, urinary incontinence, and gnawing were seen primarily in HD dams. Mortality was increased at HD (24/53 = 45%). Bodyweights were transiently decreased in all drug groups after the first dose. There was a slight decrease in fetal weight and length in all drug groups, not dose-related. There were no drug-related effects on gross or visceral fetal abnormalities. A slightly increased incidence of reduced or absent ossification of some bones was seen at MD and HD and to a smaller extent at LD; this was reflected in a slight increase in total skeletal findings in all drug groups.

Two segment II reproduction studies were performed in rabbits, 1 by the sponsor's lab and 1 by International Research and Development Corporation. Dosages were 25 (latter study only), 50, 100, and 150 mg/kg/day. Does displayed slight hypoactivity at 100 and 150 mg/kg, and convulsions, ataxia, tremors, and hyperpnea were seen in some does at 150 (convulsions also seen in 1 doe at 100 mg/kg). In one study, decreased dose food consumption on individual days was seen in all drug groups, but no overall effects on body weight were seen; however, the other study showed reduced weight gain at 100 and 150 mg/kg. There was no drug-related increase in mortality in either study. Fetal weight was slightly reduced in all drug groups at 50 mg/kg and above, dose-related. Fetal length (reported in 1 study) was slightly reduced at 150 mg/kg. There was a trend toward an increase in gross, visceral, and skeletal abnormalities in fetuses of all drug groups, which was partly dose-related. The increase in gross and visceral abnormalities does not appear to be biologically significant in that no pattern of abnormalities was seen, i.e. there was no significant increase in any particular type of abnormality, and the overall percent of fetuses affected was relatively low. Regarding skeletal abnormalities, a significant increase in supernumerary ribs occurred in all drug groups which was dose-related in 1 study but not in another. In addition, one study showed an increase in reduced ossification of the palate (all drug groups, not dose-related), and the other study showed an increase in delayed ossification of the 5th phalanx of the forelimb at HD only as well as a low incidence of barbell shaped thoracic centra in all drug groups. Reduced ossification (also seen in rat study) and supernumerary ribs are considered to be normal variations, and it is concluded that the above skeletal findings, as well as the findings of decreased fetal weight and length, were secondary consequences of maternal toxicity.

EVALUATION:

The preclinical data submitted for bupropion (B) adequately characterizes the pharmacoicgical and toxicological profile o: this drug.

B, unlike classical antidepressants, is a CNS stimulant in animals, with a potency of about 1/50-1/10 that of amphetamine in causing CNS stimulation in various tests in mice and rats. Although it was shown that, unlike for amphetamine, the ED 50$ for increased locomotor activity in mice was greater than that for an "antidepressant" (i.e. antitetrabenazine) effect, it appeared that there was acutally little separation of doses producing "antidepressant" effects from those producing at least some CNS stimulation. Several pharmacological similarities between B and amphetamine (and other CNS stimulants) were noted, including self-administration by monkeys, raising the question of possible abuse. Studies addressing this question have been conducted in man.

The sponsor claims that B has less anticholinergic and adverse cardiovascular effects than classical antidepressants. The animal data appear to support the former: in several tests anticholinergic activity was generally weak or absent (except for dose-related mydriasis in mice, although this may represent a sympathomimetic effect) and B was significantly less potent than imipramine and amitriptyline when compared. Regarding adverse cardiovascular effects, however, the relative potency of B and classical antidepressants is difficult to determine based on the data presented. Acute I.v. doses of 1-20 mg/kg in anesthetized cats and dogs produced large but generally transient effects on blood pressure, heart rate, cardiac output, and right ventricular contractile force. In conscious dogs, 20 mg/kg p.o. caused slight increases in blood pressure and heart rate, and in conscious rats 50 mg/kg p.o. caused a slight increase in heart rate. No adverse EKG effects were seen either with a slow I.v. infusion of up to 10 mg/kg in anesthetized dogs or in a 1 year toxicity study in dogs with a maximum daily dose of 150 mg/kg p.o. However, comparison drugs were not used in these studies; a more informative study would have used other antidepressants, and pushed up doses until adverse EKG/cardiovascular effects were seen so that the relative potency of B could be estimated. (In in vitro studies, B was approximately 5-15 x less potent than imipramine or amitriptyline regarding cardiodepressant effects but this cannot be readily extrapolated to in vivo conditions). The sponsor points out that doses and concentrations causing cardiovascular effects in the above studies were 10-100 x greater than clinically therapeutic plasma levels (and plasma levels in mice after administration of the "antidepressant" ED 50); however this does not address the question of possible overdose effects.

Pharmacokinetic studies showed a sex difference in rats, i.e. higher blood and tissue levels were found in females. (The acute toxicity of B in rats is greater in F than M, although this did not appear to be true regarding chronic toxicity). The drug appears to undergo extensive first-pass

HON 301 MADE IN JAPAN

metabolism in animals and has a short T 1/2 (1-4 hr., but much longer for metabolites), however human studies have shown a longer T 1/2 of 14 hr. B was shown to induce its own metabolism, presumably VIA an effect on liver microsomal enzymes, in rat, mouse, and dog.

Segment II reproduction studies, performed in rats and rabbits, showed a tendency toward delayed ossifications and supernumerary ribs, findings which are relatively common in drug studies and are thought to result from maternal stress/toxicity and/or fetal immaturity (although it should be noted that some of these skeletal findings were seen at the lower doses which did not clearly induce other overt toxic effects). In the rabbit studies overall gross and visceral abnormalities were increased at all doses, although the percent of fetuses affected was relatively low and no increase in any specific type of abnormality was seen. A consultant report by Dr. James G. Wilson, an acknowledged expert in teratology, concluded that there were "no major indications of embryo-fetotoxicity observed ... at any dosage."

Carcinogenesis studies in rats (23-24 months) and mice (21-22 months) did not reveal any increase in neoplasia (maximum daily dose = 300 and 150 mg/kg, resp.), despite the fact that B was weakly positive in some strains in the Ames Test and at 300 mg/kg in a rat bone marrow chromosome study.

The major toxicological findings having possible implication for man were the following:

1) Convulsions - seen in rat, mouse, dog, and rabbit, primarily at the higher doses. Studies in rats suggested that chlordiazepoxide was the most effective antagonist of B-induced seizures. (Other benzodiazepines were not tested).

2) Hyperplastic nodules in liver

These were seen in the 2 yr rat (but not mouse) study. (In the 1 year dog study, "ground glass" and vacuolated cytoplasm were seen but it is not clear if these were similar to "foci of cellular alteration" which have been described in rats and have been considered to be related to [possible precursors of ?] hyperplastic nodules). Nodules were seen at all doses (100, 200, 300 mg/kg) in the 2 year rat study, and thus no "no-effect" dose was established. (Nodules were not seen at 25, 50, or 100 mg/kg in the 55 week rat study; however, they did not appear until around 90 weeks in the 2 year study, and thus might have possibly developed at these lower doses had the rats lived long enough). (For comparison, acute ED 50% for antidepressant activity was approximately 10 mg/kg i.p. in rats, and 12.5 mg/kg i.p. and 32 mg/kg p.o. in mice). The toxicological implications of hyperplastic nodules are not clear. The sponsor suggests that they may represent either (1) a reflection of liver microsomal enzyme induction or (2) an adaptive response to hepatic injury. Regarding the former, B has been shown to induce its own metabolism although the ability of B to induce the metabolism of other compounds was not clearly demonstrated. Regarding the latter, no other indication of hepatic damage (including blood chemistry) was seen in rats, although some indications of liver damage were obtained in dogs. There has been much controversy in recent years concerning the possible role of hyperplastic nodules in the development of hepatocarcinomas. Several years ago some pathologists suggested that such lesions should be considered "pre-neoplastic" or "neoplastic" in that it was hypothesized that they could progress to malignant tumors (Squire and Levitt, Cancer Res. 35: 3214, 1975; Williams, Biochem. et Biophys. Acta 605: 167, 1980). These pathologists thus suggested replacing the term "hyperplastic nodule" with "neoplastic nodule". (It has also been suggested that "foci of cellular alteration" are also "pre-neoplastic" in the sense that they might progress to neoplastic nodules or possibly directly to malignant tumors). However, this area was recently the subject of a symposium (Rodent Liver Nodules - Significance to Human Cancer Risk?, Int'l Symposium of the Society of Toxicologic Pathologists, May 10-12, 1982, Reston, VA; proceedings to be published) at which these

earlier hypotheses were challenged. Data was presented showing that in several cases nodules and foci of cellular alteration regressed after cessation of treatment, suggesting that they are not necessarily on an irreversible pathway to malignancy. It has also been shown that nodules are not necessarily transplantable. Based on these observations of a lack of autonomy of these proliferative lesions, an informal consensus was reached agreeing with the proposition that the term "neoplastic nodule" was a misnomer and that such lesions do not necessarily progress irretrievably to malignancy. However, even though these proliferative lesions may not be autonomous and do not necessarily progress irretrievably to malignancy, it is possible that they would progress under the influence of continued drug administration, or alternatively they may simply be "markers" for malignancy (i.e. if a drug produces such lesions it is an indication that the drug is also likely to produce malignancies). Again, based on an informal vote a majority of pathologists present at this symposium believed that the production of nodules or foci of cellular alteration in liver by a chemical was not sufficient evidence to establish that chemical as a hepatocarcinogen. Although several potent hepatocarcinogens have been shown to produce nodules and foci of cellular alteration, several examples were given of chemicals, dietary regimens, and surgical manipulations which produced nodules or foci but did not produce malignancies despite prolonged treatment. (B would also be an example of this). In summary, I believe that given the state of the art in this area, there is not enough evidence at this time to label B a hepatocarcinogen. It is not known if the proliferative lesions produced by B were autonomous since no studies on reversibility or transplantability were performed. However, these lesions did not progress to malignancy despite continued drug administration in a lifetime rat study. In addition, the nodules were very late appearing (most seen at terminal sacrifice; almost all after 90 weeks), in contrast to the effects of established hepatocarcinogens. On the other hand, in view of the still lingering uncertainty in this area (as well as the weakly positive mutagenicity results), I believe that the findings of an increase in proliferative lesions in liver should be mentioned prominently in the labeling, at least until the issue of the carcinogenic significance of these lesions is resolved.

3) A marked toxic interaction between B and phenelzine was demonstrated in rats (although no pharmacodynamic interactions were seen in several tests at lower doses). Thus, as with classical tricyclic antidepressants, the combined use of B and MAO inhibitors in man should proceed cautiously if at all.

Other findings of more questionable or unknown significance to man were the following:

MADE IN JAPAN

1) Increased hemosiderosis in several organs in the 55 week and 2 year rat studies, primarily at the higher doses. No other pathological findings were present to explain this; RBC, Hct, and Hb were decreased in 2 of 20 HD rats in the 55 week study but no effect seen in the 2 year study; a slight decrease in Hb and Hct was seen in the 3 month study but no hemosiderosis was reported. (A dark brown pigment was seen in liver and kidney in the 1 year dog study and in kidney in the 2 year mouse study; the pigment was not characterized; decreases in RBC, Hct, and Hb were seen in dogs).

2) Increased incidence of extremely dilated uterine blood vessels with thrombus, uterine bleeding, and acute metritis/pyometritis seen at all doses in the 2 year mouse study. It was considered to be an accentuation of a spontaneous lesion; time of onset was not affected. Similar findings were not seen in other species.

3) Some evidence of liver toxicity was seen at all doses in the 1 year dog study, including elevated AP, SGOT, SGPT, and BSP retention. Liver histopathology included findings of pigment, vacuolation, "ground glass" cytoplasm, and bile duct proliferation; necrosis was not reported. Most of these changes were reversible upon cessation of treatment.

MADE IN JAPAN

RECOMMENDATIONS:

This NDA is approvable based on the preclinical data submitted, with the following recommendations:

1) Regarding the 2 year rat and mouse carcinogenicity studies, the sponsor should indicate how often the drug solutions for dosing were prepared, and what the drug stability was under these conditions, in order to assure that the actual doses administered were what they were stated to have been.

2) The findings in uterus in the 2 year mouse study (extremely dilated blood vessels with thrombus, bleeding, metritis/pyometritis) should be brought to the attention of the clinical reviewer. The relevance of this finding, seen only in mouse, to man is not clear; a review of adverse reactions in this area would be helpful. Post-marketing monitoring as well as inclusion of the mouse results in the labeling should also be considered.

3) The clinical reviewer should consider making combined use of Wellbutrin and monoamine oxidase inhibitors a contraindication (as with other antidepressants) in view of the toxic potentiation noted in rats. (The sponsor mentions this finding in the "Drug Interactions" section of the labeling).

4) The following recommendations concern the proposed labeling:

a) Carcinogenesis section

The word "small" in the sentence "In rats there was a small increase in nodular proliferative lesions of the liver..." should be eliminated. The incidence of this finding in the drug groups was several times that in controls.

b) Mutagenesis section

The weakly positive effects noted in the Ames Test should be mentioned.

c) Pregnancy section

The findings of an increase in fetal anomalies (aside from supernumerary ribs and delayed ossifications) in the rabbit studies should be mentioned. Although there was no strong evidence that the drug was teratogenic (i.e. there was no increase in any specific type of anomaly and the number of fetuses affected was relatively small), the data do raise a suspicion which should be mentioned.

APR 21 1982

Review and Evaluation of the Pharmacology & Toxicology Data of
NDA 18-644
New NDA of 12/23/81
Drug Abuse Staff Consult

Background:

Wellbutrin (Bupropion) is an antidepressant drug which Burroughs-Welcome has submitted for marketing approval (NDA 18-644). The drug differs from a classic phenethylamine structure in three ways: it has a meta-chloro substituent on the phenyl ring, a B-keto group on the ethyl side chain, and a t-butyl substitution on the nitrogen atom. The similarity of bupropion to amphetamine and diethylpropion was recognized during the drug's development and, consequently, a battery of neuropharmacologic and behavorial tests were performed to address issues relating to abuse potential.

Preclinical pharmacology:

Bupropion lacks the peripheral sympathomimetic effects of amphetamine. Large i.v. and oral doses were without sustained cardiovascular effects in dogs and had only weak transient effects on the pressor response to exogenous norepinephrine and tyramine. Doses of 25 or 50 mg/kg, p.o. did not affect systolic blood pressure or heart rate. No significant effects were observed on α or β-adrenergic mediated responses. Further, in isolated tissue preparations, bupropion did not release catecholamines.

Bupropion was compared to amphetamine in terms of appetite suppression, CNS stimulation and stereotypy responses. The drug produced a mild decrease in food consumption in food-deprived mice. Milk consumption in mice was disrupted but the confounding effect of increased motor activity makes it difficult to determine the specificity of the anorectic response. In terms of increased locomotor activity, bupropion was approximately 1/10 as potent as amphetamine. The effects of either compound could be blocked by prior destruction of central catecholamine neurons, lesioned by 6-hydroxydopamine.

Buproprion's and amphetamine's actions on locomotor activity could be differentiated by pretreatment with reserpine or α-methyl paratyrosine (α-MPT). While reserpine blocked the locomotor activity of bupropion, amphetamine's actions were unaffected. Conversely, while the stimulant activity of amphetamine was antagonized by α-MPT treatment, the action of bupropion was unchanged.

High doses of amphetamines produce a well defined stereotypy response consisting of intense sniffing, licking and chewing movements. Bupropion (25 mg/kg, i.p.) produced a partial replication of amphetamine stereotypy in that sniffing movements were observed but licking and chewing movements were absent.

The ability of a compound to reverse tetrabenazine-induced sedation is a preclinical screening test for antidepressant activity. Both bupropion and amphetamine pretreatment prevented tetrabenazine-induced sedation but only amphetamine reversed the sedation when given after tetrabenazine.

Amphetamine and bupropion were tested for effects on schedule controlled behavior in rodents. The effects of bupropion were qualitatively similar to amphetamine; i.e., bupropion increased low rates of responding and decreased high rate of responding in a number of operant tasks.

In another series of behavioral experiments, animals were trained to discriminate bupropion from saline. Several psychomotor stimulants, including caffeine and amphetamine, and the antidepressant viloxazine cross-generalized to the discriminative stimulus of bupropion. In animals trained to discriminate amphetamine from saline, bupropion generalized to amphetamine whereas viloxazine did not.

In a study conducted in codeine lever-trained rhesus monkeys, parenteral administration of bupropion at the unit doses of 0.3 and 1.0 mg/kg produced response rates which exceeded those maintained by codeine and approached those maintained by the optimal unit dose of amphetamine.

Bupropion differed from amphetamine in <u>in vitro</u> synaptosomal preparations in the following ways: (1) it did not release catecholamines; and (2) the action to block accumulation of catecholamines was unaffected by prior reserpinization (amphetamine was enhanced.)

Clinical studies:

Psychomotor stimulation, or lack thereof, can be inferred from symptom checklists used in placebo controlled studies. Four studies were identified in which patients received treatment for 4-6 weeks: <u>06</u>, 100-200 mg, t.i.d.; <u>08</u>, 100-250, t.i.d.; <u>09</u>, 50-150 mg, t.i.d.; and <u>14</u>, 100-200 mg, t.i.d. Consistent measures in these studies included the symptoms of agitation/excitement, increased motor activity, decreased appetite, insomnia, drowsiness/sleepiness and hallucinations. In study 06, bupropion increased scores on the agitation/excitement parameter. In study 08, bupropion increased agitation/excitement and increased motor activity relative to the placebo scores. No definite trends were observed for insomnia, decreased appetite and drowsiness. Additionally, there were no reports of anti-fatigue effects, abnormal elation, racing thoughts, heightened sensory perception or hallucinations.

In two studies (#09 and #14), a weight loss of about two pounds occurred in the bupropion groups. This difference was statistically significant from placebo at $p < 0.05$. In another clinical study (#17), longer treatment (6 months) with bupropion produced a slight weight gain.

Bupropion (100, 200 and 400 mg) was tested against amphetamine (15 and 30 mg) for anorectic activity in a double-blind, placebo controlled fashion. Bupropion had no anoretic effect, nor did it produce a decrease in calorie intake.

Analysis of post-treatment (withdrawal) periods failed to note any systematic changes in symptoms associated with amphetamine withdrawal.

Behavioral, physiological and subjective effects of bupropion were compared to amphetamine in three placebo controlled, double-blind studies. In the first two studies (11 UK and 37 UK) d-amphetamine (10 mg) and placebo were compared to 100 or 200 mg doses of bupropion. Amphetamine increased auditory vigilance, decreased reaction time, increased heart rate and systolic blood pressure, increased pupil diameter, increased attention and subjective measures of alertness, elation and energy in normal volunteers. Bupropion at doses up to 200 mg did not affect any of the behavioral or subjective measures. A 12% increase in heart rate was observed with the 200 mg bupropion dose.

The third st[illegible] (#24) evaluated the effects of single dose of bupropion (100, 200 or 400 [illegible] or amphetamine (15 or 30 mg) on a number of behavioral, physiological and subjective rating scales in multiple drug abusers. The study design was placebo-controlled, double-blind crossover type with a latin square to correct for order effects. Subjective effects were measured on the Addiction Research Center Inventory (ARCI) and the Amphetamine Self-Rating Scale (ASRS). Subjects were also administered a single dose questionnaire and the Liking Scale (a rating of degree of preference).

Behavioral measures rated were appetite, caloric intake at lunch and supper and an estimate of quality and duration of sleep.

Physiological indeces obtained were pulse rate, blood pressure, and body temperature, respiratory rate and pupillary diameter.

Thirteen subjects completed the crossover design. Measurements were obtained at 0.5, 1, 2, 3, 4, 5, 12, and 24 hours following each dose.

Amphetamine produced dose-related effects on the amphetamine, benzedrine and morphine benzedrine group scales. Bupropion could not be differentiated from placebo on the amphetamine or benzedrine subscales; the 400 mg bupropion dose registered above placebo values on the morphine benzedrine group scale. On the Single Dose Questionnaire, bupropion was identified more often as a placebo. Further, the identifications of bupropion as benzedrine occurred no more often than placebo was identified as benzedrine. On the Liking Scale, amphetamine was clearly differentiated from placebo and bupropion. The 400 mg dose produced a slight elevation of the liking score relative to the placebo response.

On the behavioral measure, amphetamine reduced appetite and caloric intake whereas bupropion could not be differentiated from placebo. Further, amphetamine decreased total sleep time, quality of sleep and feelings of freshness in the morning and increased feelings of tiredness during the day. Bupropion did not affect sleep indeces.

Amphetamine increased systolic and diastolic blood pressure in a dose-related fashion. The 30 mg dose of amphetamine increased pulse rates at a number of time points. There was a trend for amphetamine to increase body temperature. Bupropion had no significant effect on the physiological parameters.

Evaluation:

The sponsor has submitted preclinical and clinical data which address the relative stimulant effects of bupropion vs. amphetamine. Preclinical data in rodents suggest some weak amphetamine-like effects wth respect to locomotor activity, effects on schedule controlled behavior and cross-generalization to amphetamine in a discriminative stimulus paradigm. Further, self-administration data in the rhesus monkey suggest that intravenous administration of bupropion at unit doses of 0.3 and 1.0 mg/kg maintains response rates equivalent to amphetamine.

Neurochemistry and pharmacology data suggest that amphetamine and bupropion act on catecholaminergic neurons but the two substances act on different pools of norepinephrine. Amphetamine appears to interact with a reserpine-insensitive (newly synthesized?) pool whereas bupropion may intereact with a reserpine sensitive (granule storage?) pool.

Data obtained from clinical efficacy studies suggest mild amphetamine-like activity with respect to increased motor activity. However, no anorectic effect of note was observed with bupropion. Further, no peripheral sympathomimetic activity was consistently observed with bupropion.

On the behavioral and subjective rating scales, doses of 10 to 30 mg of amphetamine had their expected effects of increased vigilance, decreased fatigue, elation, insomnia, etc. On the ARCI subscales, amphetamine scored highly on the amphetamine, benzedrine, and morphine benzedrine subscales whereas the 400 mg dose of bupropion produced only a modest elevation over placebo responses on the morphine benzedrine group scale. On the Liking Scale, amphetamine produced significant elevations whereas the 400 mg doses of bupropion produced a score intermediate to amphetamine and placebo.

There is an apparent discrepancy between the preclinical and clinical data with respect to the amphetamine-like activity of bupropion. Several explanations are conceivable. It may be that bupropion would have more amphetamine-like activity if higher oral doses or parenteral doses were administered. For ethical reasons, neither of these possibilities was

investigated. It appears that 400 mg of orally administered bupropion may have some threshold amphetamine-like activity. Higher doses may produce a more reliable, intensive amphetamine-like effect. The sponsor's argument is that 800 mg of bupropion may produce seizures, thus limiting the abusable dose range of the compound from a threshold dose of 400 mg to the toxic single dose of 800 mg.

Conclusion:

The abuse potential of bupropion by the oral route appears to be minimal. Therapeutic doses lack subjective amphetamine-like activity and higher doses appear to have weak amphetamine-like activity. The abusable dose range appears to be between 400 and 800 mg, p.o.

The abuse potential of bupropion by the parenteral route appears to be greater than that observed with the oral route. The animal data do not permit a conclusion with respect to reinforcement efficacy vis a vis amphetamine. No human parenteral experience has been documented with this substance. However, given the animal data, it is tempting to speculate that bupropion may be amphetamine-like in man if administered intravenously.

The issue now becomes what to do with the available data on bupropion's abuse potential. I do not believe that bupropion warrants scheduling under the Controlled Substances Act. Rather, I believe the available data should be incorporated into a Drug Abuse and Dependence Section in the labeling.

Recommendation:

1. The sponsor should incorporate a Drug Abuse and Dependence Section into the labeling which incorporates the following data:

[redacted]

(2) In operant behavioral paradigms, bupropion has effects on behavior similar to those observed with psychomotor stimulants;

(3) In animals trained to discriminate amphetamine from placebo, bupropion was identified as amphetamine-like;

(4) In rhesus monkeys, bupropion was self-administered at rates above those maintained by codeine and approximating rates maintained by amphetamine.

b. Clinical studies

(1) In clinical trials, oral doses of up to 250 mg t.i.d. had mild effects on an agitation/excitement parameter in a symptom checklist. No reports of amphetamine-like effects were observed at these doses;

(2) In psychopharmacology studies, single oral doses of up to 200 mg of bupropion were indistinguishable from placebo. Amphetamine had its usual effects of increased vigilance, elation and increased sociability. Single oral doses of 400 mg bupropion had mild amphetamine-like activity as measured by the morphine-benzedrine scale of the Addiction Research Center Inventory and Liking Scores. Higher doses were not tested as 800 mg may produce seizures;

(3) tolerance did not develop to the antidepressant effect of bupropion;

(4) the bupropion post-treatment period was not associated with rebound phenomena thought to constitute an amphetamine withdrawal syndrome; e.g., somnolence, hyperphasia, depression.

Frank T. Vocci Jr, Ph.D.
Frank J. Vocci, Jr., Ph.D.

cc:
NDA Orig
HFD-180
HFD-120
HFD-120/FVocci/3/25/82
FT:dcm/3/26/82
DOC #1806B

Cleared 4-26-82

LION 801 MADE IN JAPAN

CHEM. REVIEW

LION 301 MADE IN JAPAN

REVEIW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA/[redacted] # 18-644

File

Division: HFD- (HFN-120)
Chemist Review #3
Reviewing Chemist: P. A. Zinsitz

Applicant: Burroughs Wellcome
Sponsor: Research Triangle Park
Address: North Carolina 27709

Date Completed: 5/24/85

Product Name(s):
Proprietary: Wellbutrin (USA) Amfebutamone (INN, NFN)
Non-proprietary: bupropion hydrochloride
Compendium:
USAN: bupropion hydrochloride
Code name/number: [redacted]
Drug Classification: 1C

Dosage Form(s) and Route(s) of Administration: Tablets - oral

Pharmacological Category and/or Principal Indication: Antidepressant

Structural Formula & Chemical Name:

Initial Submission: December 28, 1981
Amendment(s): 5/21/85 (Rec'd. in HFN-120 5/21/85 and for Rev. 5/23.85) (see Chem. Rev. dated 6/9/83 for amends.
Related Documents: See prior Chem. Rev. for related docs.

Conclusions and Recommendations.

The application remains approvable pending receipt of FPL and concurrence with the Division of Biopharmaceutics regarding the dissolution specifications and test as cited above.

Francis A. Zinsitz 5/24/85
Chemist

cc: IND/NDA Original
HFD-120/Kumkumian (only Chemist's Review #1)
HFD-Division File
HFD- DIV./drafter/date/typist/date

R/D Initialed by:

Print entire Page

MADE IN JAPAN

ANALYTICAL METHODS

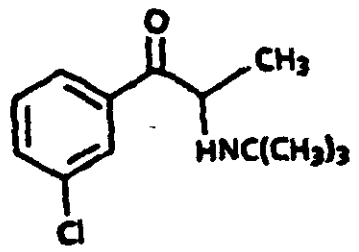
STABILITY CONTROLS

MADE IN JAPAN

BURROUGHS WELLCOME CO. ANALYTICAL STANDARD

NAME. Bupropion Hydrochloride				ITEM NO. or STOCK NO. [redacted]
PAGE 1 OF 3	DATE ISSUED [redacted] DATE EFFECTIVE [redacted]	SUPERSEDES [redacted]	MF'. BY: CDL	APPROVED BY: J.E. Gillikin
COPY TO: Distribution List				OFFICIAL IN: [redacted]

SPECIFICATIONS



• HCl

$C_{13}H_{18}ClNO \cdot HCl$ Mol. Wt. 276.21

PHYSICAL EXAMINATION: [redacted] White powder with a slight characteristic odor.

COLOR AND CLARITY:

A. [redacted] A 2 percent aqueous solution has [redacted]

B. [redacted] A 2 percent aqueous solution has [redacted] than the Reference Standard.

IDENTIFICATION:

A. Infrared: [redacted] The infrared absorption spectrum of a potassium bromide dispersion of the sample exhibits maxima and minima only at the same wavelengths with the same relative intensities, as that of the Reference Standard similarly run.

For revision refer to [redacted]

CONFIDENTIAL - NOT TO BE COPIED [redacted]

NAME: Bupropion Hydrochloride	DATE ISSUED [redacted]

B. HPLC: [redacted] The retention time for the bupropion peak in the sample chromatogram agrees with that of the Reference Standard.

RELATED SUBSTANCES:

I) TLC:

2-Bromo-3'-chloropropiophenone: [redacted] Not more than [redacted]

3'-Chloropropiophenone: [redacted] Not more than [redacted]

3-Chlorobenzoic acid: [redacted] Not more than [redacted]

[redacted] Not more than [redacted]

II) HPLC:

2-(tert-Butylamino)-propiophenone HCl [redacted] Not more than [redacted]

2-(tert-Butylamino)--2'-chloropropiophenone HCl: [redacted] Not more than [redacted]

III) [redacted] The total related substances found is not more [redacted]

LOSS ON DRYING: [redacted] Not more th[redacted]

WATER: [redacted] Not more than [redacted]

CONFIDENTIAL - NOT TO BE COPIED

[redacted]

[redacted] 301 MADE IN JAPAN

BURROUGHS WELLCOME CO. ANALYTICAL STANDARD [redacted] PAG[redacted]

NAME: Bupropion Hydrochloride	DATE ISSUED [redacted]

CHLORIDE: [redacted] Not less th[redacted] and not more than [redacted]

ASSAY: [redacted] (HPLC) Between [redacted] and [redacted]

CONFIDENTIAL - NOT TO BE COPIED

BURROUGHS WELLCOME CO. ANALYTICAL STANDARD

NAME: Bupropion Hydrochloride				ITEM NO. or STOCK NO. [redacted]
PAGE 1 OF 7	DATE ISSUED: [redacted] DATE EFFECTIVE:	SUPERSEDES [redacted]	MFD. BY: CDL	APPROVED BY: Jesse Gillikin
COPY TO: Distribution List				OFFICIAL IN: [redacted]

TESTING INSTRUCTIONS

PHYSICAL EXAMINATION: Examine a portion of sample on a clean sheet of white paper, report the color, odor and form.

COLOR AND CLARITY:

Sample Preparation: Transfer 1.0 g of sample into a 50-ml color comparison tube, dissolve in and dilute to volume with water, and mix.

A. Color - Proceed as directed in the General Method entitled "APHA Color of Solutions" [redacted], comparing the sample to APHA Standard 20.

[redacted]

B. Clarity - Compare the sample with the Reference Suspension, 5 minutes after preparation, in matched 50-ml color comparison tubes in diffused daylight, viewing vertically against a black background. The diffusion of light must be such that the Reference Suspension can readily be distinguished from water. [redacted]

Reagents:

Hydrazine Sulfate Solution - Dissolve 1.0 g of hydrazine sulfate (ACS reagent grade) in water and dilute to 100.0 ml with the same solvent. Allow to stand 4 to 6 hours.

Hexamethylenetetramine Solution - Dissolve 2.5 g of hexamethylenetetramine (ACS reagent grade) in 25.0 ml water in a 100-ml glass-stoppered flask.

Primary Opalescent Suspension - Add to the Hexamethylenetetramine Solution in the flask 25.0 ml of Hydrazine Sulfate Solution. Mix and allow to stand for 24 hours. This solution [redacted] provided it is stored in a glass container free from surface defects.

For revision refer to [redacted]

CONFIDENTIAL - NOT TO BE COPIED

[redacted]

NAME: Bupropion Hydrochloride | DATE ISSUED: [redacted]

The suspension must not adhere to the glass and must be well mixed before use.

Standard of Opalescence - Dilute 15.0 ml of the Primary Opalescent Suspension to 1000.0 ml with water. This suspension must be [redacted]

Reference Suspension - Add 5.0 ml of Standard of Opalescence to a 100-ml volumetric flask and bring to volume with water. Mix thoroughly and transfer 50 ml into a 50-ml color comparison tube.

IDENTIFICATION:

A) Infrared - Determine the infrared absorption spectrum of a potassium bromide dispersion of a portion of sample using a suitable infrared spectrophotometer and compare it to the Reference Standard similarly run. Use a vibrating ball mill to grind the sample and standard with the potassium bromide prior to pressing it into a disk.

B) HPLC- Obtain the chromatograms of the Standard and Sample Preparations in the ASSAY below, and compare the retention times for the bupropion peak in each. Report the results.

RELATED SUBSTANCES:

RELATED SUBSTANCES:

I. TLC

Standard Preparation:

Stock Solutions:

CAUTION: 2-bromo-3'-chloropropiophenone is a pungent lachrymator. Handle with gloves and goggles. Use in a fume hood whenever possible.

(A) Transfer 25 mg of 2-bromo-3'-chloropropiophenone, accurately weighed, into a 25-ml volumetric flask, dissolve in and dilute to volume with methanol.

(B) Transfer 25 mg of 3'-chloropropiophenone and 25 mg of Bupropion Hydrochloride Reference Standard, accurately weighed, into a 5-ml volumetric flask, dissolve in and dilute to volume with methanol.

CONFIDENTIAL - NOT TO BE COPIED [redacted]

NAME: Bupropion Hydrochloride	DATE ISSUED [redacted]

(C) Transfer [redacted] of 3-chlorobenzoic acid, accurately weighed, into a [redacted] volumetric flask, dissolve in and dilute to volume with methanol.

Standard 1 Preparation: Pipet [redacted] of the Stock Solutions B and C into separate [redacted] volumetric flasks, dilute to volume with methanol and label B' and C'. Into a 10-ml volumetric flask, pipet [redacted] of Stock Solution A, [redacted] of diluted Solution B', and [redacted] of diluted Solution C'. Dilute to volume with methanol and mix. This solution represents the following concentrations [redacted] bupropion sample concentration:

[redacted]
2-bromo-3'chloropropiophenone
3'-chloropropiophenone
3-chlorobenzoic acid
bupropion hydrochloride

Standard 2 Preparation: Into a [redacted] volumetric flask, pipet [redacted] each of the Stock Solutions A, B, and C, dilute to volume with methanol, and mix. This solution represents the following concentrations relative to a [redacted] bupropion sample concentration:

[redacted]
2-bromo-3'-chloropropiophenone
3'-chloropropiophenone
3-chlorobenzoic acid
bupropion hydrochloride

Sample Preparation: Transfer 500 mg of sample, accurately weighed, into a [redacted] volumetric flask, dissolve in and dilute to volume with methanol.

Analysis: Spot 5 µl of the Sample and Standard Preparations, separately, about 1 cm from the bottom of a Silica Gel with fluorescent indicator TLC plate which has been washed with the mobile phase and dried in an oven. Develop the chromatogram in a chamber previously equilibrated for 30 minutes, using a solvent system of toluene:cyclohexane:acetic acid [redacted] until the solvent front has traveled about [redacted] above the origin. Remove the plate, air dry, and locate the spots under both long and short wavelength ultraviolet light. Plates should be viewed immediately since the spots can evaporate with time.

NOTES: 1. Camag Nanomat® used for spotting, spot diameter [redacted]
2. Merck Silica Gel 60 F-254 plates were employed.

C O N F I D E N T I A L - N O T T O B E C O P I E D
[redacted]

NAME: Bupropion Hydrochloride | DATE ISSUED. [redacted]

Approximate R_f Values

Compound	Approximate R_f Value
Bupropion hydrochloride	[redacted]
3-Chlorobenzoic acid	
3'-Chloropropiophenone	
2-Bromo-3'-Chloropropiophenone	

II) HPLC - See ASSAY

LOSS ON DRYING:

Dry about 1.0 g of sample, accurately weighed, for [redacted] and calculate as follows:

$$\text{Percent Loss on Drying} = \frac{\text{Net Loss in Weight}}{\text{Initial Sample Weight}} \times 100$$

WATER:

Proceed as directed in the General Method entitled "Moisture Determination by Karl Fischer" [redacted]

CHLORIDE:

NOTE: Use water from the same container to prepare the Standard and Sample Preparations and for the blank.

Standard Preparation: Transfer approximately [redacted] accurately weighed, of dry sodium chloride into a [redacted] volumetric flask. Dissolve in and dilute to volume with water and mix. This solution contains [redacted] of chloride per ml.

Sample Preparation: Transfer approximately [redacted] of sample, accurately weighed, into a [redacted] volumetric flask. Dissolve in and dilute to volume with water and mix.

Acid Reagent: Carefully transfer [redacted] of nitric acid and [redacted] of glacial acetic acid into a [redacted] volumetric flask containing [redacted] of water and mix.

C O N F I D E N T I A L - N O T T O B E C O P I E D

[redacted]

NAME: Bupropion Hydrochloride	DATE ISSUED [redacted]

Gelatin Reagent: Transfer 1.24 g of a dry mixture containing gelatin [redacted]; soluble thymol blue 1 part; and thymol 1 part; by weight into a 500-ml beaker. Add 200 ml of water and heat on a steam bath with stirring until the solution is clear. Pour about 10-ml portions into small glass vials, stopper [redacted]

Procedure: Proceed as directed in the [redacted] entitled [redacted], employing [redacted] of the Standard and Sample Preparations, 2.0 ml of the Acid Reagent and [redacted] Run a blank determination using [redacted] of water instead of the sample or standard.

[redacted]

Run blanks, samples, and standards in duplicate. Correct for the blank and determine the percent chloride as follows: [redacted]

% Chloride =

$$\frac{\text{Sec SPL-Sec blank}}{\text{Sec STD-Sec blank}} \times \frac{\text{Conc STD* mg/ml} \times \text{ml STD} \times 100 \text{ ml} \times 100}{\text{Wt SPL(mg)} \times 2.0 \text{ ml}}$$

* [redacted] $\times \frac{\text{Wt Sodium Chloride (mg)}}{500 \text{ ml}}$

[redacted]

NOTE: Care must be taken that all transfers and dilutions are done quantitatively.

ASSAY:

Related Substances Standard Preparation: Transfer [redacted] accurately weighed, of each of the following into [redacted] volumetric flask: 2-(tert-butylamino)propiophenone hydrochloride, 2-(tert-butylamino)-2'-chloropropiophenone hydrochloride, and 3-chlorobenzoic acid. Add a mixture of methanol:water [redacted] and bring to volume with mixing.

Standard Preparation: Transfer approximately 60 mg of Bupropion Hydrochloride Reference Standard, accurately weighed, into a 100-ml volumetric flask. Transfer 1.0 ml of the Related Substances Standard Preparation to the flask and add a mixture of methanol:water [redacted] to volume with mixing to dissolve the bupropion hydrochloride. [redacted]

CONFIDENTIAL - NOT TO BE COPIED

[redacted]

NAME: Bupropion Hydrochloride | DATE ISSUED [redacted]

[redacted]

Sample Preparation: Transfer approximately 60 mg of sample, accurately weighed, into a 100-ml volumetric flask and add a mixture of methanol:water [redacted] to volume with mixing to dissolve the sample. Sonication may be necessary to effect the complete solution of the bupropion hydrochloride.

Procedure: Obtain the chromatograms for the Standard and Sample Preparations using the Instrumental Conditions listed below. Chromatograph the preparations so that duplicate samples are both preceded and followed by standards (STD, SPL, SPL, STD). Report the individual assay results and the average values.

Instrumental Conditions+:

Instrument:	Suitable HPLC with a 10-µl sampling loop
Column:	30 cm x 3.9 mm I.D. Waters Assoc. µBondapak® C18 or 25 cm x 4.2 mm I.D. Whatman Partisil®-10 ODS-3
Mobile Phase:	Methanol:pH 7 Phosphate Buffer++ (65:35); filter through 0.8 micron alcohol resistant filter and degas
Flow Rate:	[redacted]
Detection:	UV, 240 nm, [redacted]
Retention Times:	[redacted]
	3-chlorobenzoic acid: [redacted]
	2-(tert-butylamino)propiophenone: [redacted]
	2-(tert-butylamino)-2'-chloropropiophenenone:
	bupropion:

+Instrumental Conditions may be varied so that the requirements of the System Suitability Test (below) are met.

++pH 7 Phosphate Buffer Preparation: Transfer 27.22 g of monobasic potassium phosphate (KH_2PO_4) into a 1000-ml volumetric flask, dissolve in and dilute to volume with water and mix. Prepare fresh every two days. Then transfer 250.0 ml of this solution and 100.0 ml of 0.291N sodium hydroxide into a 1000-ml volumetric flask, dilute to volume with water, and mix. [redacted]

CONFIDENTIAL - NOT TO BE COPIED

[redacted]

NAME: Bupropion Hydrochloride	DATE ISSUED [redacted]

Calculations: (weights in mg)

a) percent 2-(tert-butylamino)propiophenone hydrochloride =

$$\frac{\text{SPL Pk Ht or Area}}{\text{Avg** STD Pk Ht or Area}} \times \frac{\text{STD Wt}}{100} \times \frac{1}{100} \times \frac{100}{\text{SPL Wt}} \times \frac{100}{(100-\%LOD)} \times 100$$

b) percent 2-(tert-butylamino)-2'-chloropropiophenone hydrochloride =

$$\frac{\text{SPL Pk Ht or Area}}{\text{Avg** Std Pk Ht or Area}} \times \frac{\text{STD Wt}}{100} \times \frac{1}{100} \times \frac{100}{\text{SPL Wt}} \times \frac{100}{(100-\%LOD)} \times 100$$

c) percent bupropion hydrochloride (dry basis) =

$$\frac{\text{SPL Pk Ht or Area}}{\text{Avg** STD Pk Ht or Area}} \times \frac{\text{STD Wt}}{100} \times \frac{100}{\text{SPL Wt}} \times \frac{100}{(100-\%LOD)} \times 100$$

[redacted]

System Suitability Test:

Six replicate injections of the Standard Preparation give relative standard deviations of [redacted] and peak retention times of the bupropion peaks. The resolution (R_s) of the bupropion peak from the 2-(tert-butylamino)-2'-chloropropiophenone peak in the Standard Preparation chromatogram [redacted] The retention time for bupropion [redacted]

[redacted]

[redacted]

CONFIDENTIAL - NOT TO BE COPIED

[redacted]

ION 301 MADE IN JAPAN

SUPPLEMENTS

MADE IN JAPAN

JAN 14 1986

NDA 18-644/S-001
/S-002

Burroughs Wellcome Co.
Attention: Donald A. Knight
Drug Regulatory Affairs
3030 Cornwallis Road
Research Triangle Park, N.C. 27709

Dear Mr. Knight:

We acknowledge the receipt on January 14, 1986 of your supplemental new drug applications (S-001, S-002) dated January 14, 1986 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Wellbutrin^{R} (bupropion hydrochloride).

The first submission (S-001) provides for final printed labeling agreed upon in the meeting of December 20, 1985, between Burroughs Wellcome and this Agency. In addition, your second submission (S-002) contains a change in this labeling which was discussed in a January 9, 1986 teleconference between Dr. Allen Cato of Burroughs Wellcome and Dr. Paul Leber of this Agency. The change provides for the removal from the Dosage and Administration section of the statement, "While no systematic study of withdrawal has been conducted, it seems prudent to recommend gradual tapering of drug over a period of a week".

We have completed the review of these supplemental application (S-001, S-002) and they are approved. Our letter of December 30, 1985 detailed the conditions relating to the approval of this application.

Should you have any questions please contact Mr. Tony DeCicco, Consumer Safety Officer at (301) 443-4020.

Sincerely yours,

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

cc:
Orig NDA
HFN-120
HFN-120/TLaughren/PLeber
TDeCicco
ad/1/17/86/1/23/86
DOC 1466x

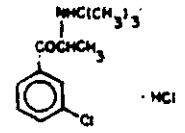
WELLBUTRIN® TABLETS - PACKAGE INSERT

646430
Special Feld 646436

Wellcome

WELLBUTRIN® *(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 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 50 mg (white), 75 mg (yellow-gold), and 100 mg (red) film-coated tablets.

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-distribution) phase is approximately 14 hours, with a range of 8 to 24 hours. Six hours after a single dose, plasma bupropion concentrations are approximately 50% 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 (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 in patients who fail to respond adequately to or who cannot tolerate alternative antidepressant treatments. Wellbutrin is not recommended as an antidepressant of first choice for most patients because its use at doses approximately one and one-third times greater than the usually required daily dose (450 mg) is associated with a high risk of seizure (see WARNINGS).

The efficacy of Wellbutrin was demonstrated in placebo-controlled clinical trials which enrolled principally hospitalized patients with diagnoses of depressive neurosis or manic-depressive (depressed type) disorder. The depressive illness of the patients studied most closely corresponds 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 tiredability, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and suicidal ideation or attempts.

Evidence to demonstrate the sustained effectiveness of Wellbutrin after three weeks of use in placebo-controlled investigations is not presently available.

CONTRAINDICATIONS: Because of its potential to induce seizures, Wellbutrin should not be used in patients with a convulsive disorder.

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:

CONVULSIONS: Wellbutrin appears to possess a greater convulsogenic potential than other marketed antidepressants. While the estimated risk of seizure at doses of 450 mg and below does not appear excessive in comparison to the risk reported for other antidepressant drug products, the estimated risk increases almost fivefold between a dose of 450 and 600 mg a day. Given the wide variability among individuals in their capacity to metabolize and eliminate drugs, it is disproportionate increase in seizure incidence with dose accommodation is a cause for concern.

During the period of premarketing evaluation, 25 among approximately 2400 patients treated with Wellbutrin experienced seizures. At the time of seizure, seven (7) patients were receiving daily doses of Wellbutrin at or below the lowest documented effective daily dose of 450 mg. Twelve (12) patients experienced seizures at daily doses of 600 mg; six (6) additional patients had seizures at daily doses between 600 and 900 mg. The risk of seizure appears to be strongly associated with dose and may be increased by predisposing factors (e.g., head trauma, CNS tumor, etc.) or a history of prior seizure. In addition, sudden and large increments in dose may contribute to an increased risk. While many seizures occurred early in the course of treatment, some seizures did occur after several weeks of use at fixed dose.

INCIDENCE OF SEIZURES IN PATIENTS RECEIVING WELLBUTRIN

	Wellbutrin Dose mg/day	Total Seizure Incidence	Seizure Incidence in Patients Without Seizure Predisposition (%)
Within Recommended Dose	<450	0.2%	0.0%
	450	0.3%	0.2%
Above Recommended Dose	600	2.3%	1.3%
	600-900	2.8%	1.9%

DOSAGE AND ADMINISTRATION RECOMMENDATIONS SHOULD BE STRICTLY FOLLOWED TO MINIMIZE THE RISK OF SEIZURE (see DOSAGE AND ADMINISTRATION). Extreme caution should be used when combining Wellbutrin with other agents which lower seizure threshold or when administering Wellbutrin to patients with a history of seizure disorder or cranial trauma.

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 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 Concomitant 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 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 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 in 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.

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.

WELLBUTRIN® TABLETS - PACKAGE INSERT

WELLBUTRIN® (BUPROPION HYDROCHLORIDE) Tablets

Nursing Mothers: It is not known whether Wellbutrin is excreted in the milk of lactating women. Because many drugs are excreted in human milk, caution should be exercised when Wellbutrin is administered to one who is nursing.

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 the product's premarketing clinical trials. 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 judgment, 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	3.6
DERMATOLOGIC		
Pruritus	2.2	0.0
Rash	9.0	6.5
GASTROINTESTINAL		
Anorexia	18.3	18.4
Appetite Increase	3.7	2.7
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	3.1
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	9.0	8.6
Cutaneous Temperature Disturbance	1.9	1.6
Dry Mouth	27.6	18.4
Excessive Sweating	12.3	14.6
Headache/Migraine	25.7	22.2
Impaired Sleep Quality	4.0	1.6
Increased Salivary Flow	3.4	3.8
Insomnia	19.5	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	3.1
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	3.6
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 entire premarketing evaluation of Wellbutrin: During its premarketing assessment, Wellbutrin was evaluated in almost 2400 subjects. 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; and rare were pallor and phlebitis.

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

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, and intestinal perforation.

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 was lymphadenopathy.

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

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 and rate or rhythm disorder.

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.

WELLBUTRIN (BUPROPION HYDROCHLORIDE) Tablets

DRUG ABUSE AND DEPENDENCE:

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

Physical Dependence: Withdrawal symptoms were not observed upon abrupt discontinuation of WELLBUTRIN. Studies in animals and in humans have not revealed evidence of psychological dependence, withdrawal symptoms, or other behavioral changes following abrupt discontinuation of bupropion.

OVERDOSAGE:

Human experience: Overdosage with bupropion has been documented in patients who took as much as 9 grams. Seizures were observed in approximately 1% of patients who took more than 900 mg/day. Other symptoms observed with overdosage included hallucinations, loss of consciousness, tachycardia, and changes in EKG consistent with cardiac conduction disturbances such as bundle branch block and QRS prolongation.

Management of overdosage: Treatment should be directed toward the elimination of unabsorbed drug and symptomatic support. Induction of emesis is not recommended. Gastric lavage should be performed only by experienced personnel with immediate availability of assistance in endotracheal intubation. Activated charcoal should be administered. Vital signs and ECG should be monitored. A cardiac arrhythmia should be treated with appropriate antiarrhythmic therapy. Hemodialysis is not likely to be helpful because only a very small fraction of the dose administered is removed by dialysis. For the most current information on management of any drug overdose, contact your regional Poison Control Center. Telephone numbers for these centers can usually be obtained from directory assistance, the operator, or the local Emergency Room.

DOSAGE AND ADMINISTRATION:

Bupropion should be given to patients undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines), because withdrawal symptoms may precipitate seizures. Withdrawal symptoms have also been reported following abrupt discontinuation of bupropion.

Bupropion should not be used in patients with a seizure disorder.

Bupropion should not be used in patients with a current or prior diagnosis of bulimia or anorexia nervosa, because a higher incidence of seizures was observed in clinical trials of bupropion in patients with these disorders.

Bupropion should not be used in patients undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines), because withdrawal symptoms may precipitate seizures

NDA 18-644/S-003

MAY 30 1989

Burroughs-Wellcome Comp.
Attention: Loren Miller, M.D.
Drug Regulatory Affairs
3030 Cornwallis Road
Research Triangle Park, North Carolina 27709

Dear Dr. Miller:

Please refer to your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Wellbutrin^{R} (bupropion hydrochloride) tablets.

Please also refer to your submission of May 10, 1989 in which you proposed several changes in the Wellbutrin labeling. In particular, you suggested alternative wording in the Indications and Usage section, the Warnings section, the Dosage and Administration section, and in the Nursing Mothers subsection of the Precautions section. We also refer to conversations between Dr. Lineberry of Burroughs-Wellcome and Dr. Leber of FDA on May 23, 1989, in regard to additional changes in the Indications and Usage and Warnings sections.

We agree to your proposed changes in the Dosage and Administration section and the Nursing Mothers subsection. We also agree with the wording for the initial paragraphs of the Indications and Usage and Warnings sections, as developed by Drs. Leber and Lineberry:

1. Initial paragraph of Indications and Usage section:

   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 four fold. This relative risk is only an approximate estimate because no direct comparative studies have been conducted.

2. Initial paragraph of Warnings section:

   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 four fold. This relative risk is only an approximate estimate because no direct compatative 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.

Consequently, the supplement, S-003, incorporating the revisions described, is APPROVED effective as of the date of this letter.

These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as requested, in the product's final printed labeling (FPL) may render the product misbranded and an unapproved new drug. Please submit twelve copies of the revised FPL when it is available. This submission should be designated for administrative purposes an "FPL Supplement" to the approved NDA. Approval of the supplement by FDA is not required before the labeling is used.

In the future, we anticipate that you will be receiving spontaneous reports of adverse events. Current Wellbutrin labeling does not contain an appropriate category under which to tabulate these reports. You could possibly include them in the pre-approval Other Events Observed subsection of the Adverse Reactions section, but we believe this would be ill-advised because the latter contains carefully monitored data for which quantitative estimates of incidence have been calculated. A better possibility, in our view, would be for you to construct a new subheading of Adverse Reactions, entitled, "Post-Approval Reports." This subsection would enumerate events that could not be more appropriately included in the Warnings or Precautions sections. Ordinarily, then, such events would be those estimated to occur at rates close to those observed in patients not under treatment, or, would be events of little clinical significance. Moreover, these would often be events for which a causal link to treatment is problematic. You need not include this subsection in the final printed labeling to be submitted prior to marketing.

Should you have any questions pleasn contact Mr Tony DeCicco, Consumer Safety Officer at (301) 443-3504.

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc
NDA/IND ORIG.
HFD-100
HFD-100/Temple
HFD-120
HFD-120/CLeber/TLaughren/TDecicco
rd/ad/5/19/89
ft/ad/5/24/89

DOC 3810c

5/26/89

TTFax'd Signed by Dr Laughren (Thomas made is not submission since are related to clinical safety or efficacy. Therefore Wellbutrin can go forward without his signature.

MADE IN JAPAN

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 18-644/3-003

Sponsor: Burroughs Wellcome

Drug: Wellbutrin (bupropion)

Drug Catagory: Antidepressant

Material Submitted: Alternative proposals for selected sections of the proposed labeling for Wellbutrin.

Correspondence Date: May 10, 1989

Date Received: May 10, 1989

Background

These proposals follow a meeting held between staff from Burroughs Wellcome and FDA on May 2, 1989. The primary disagreement identified at this meeting involved the wording in the Indications section. The current submission contains alternative wording for the Indications section, the Warnings section the Dosage and Administration section, and the Breastfeeding subsection of the Precautions section.

Proposed Changes

1. Indications and Usage Section

Burroughs Wellcome proposes the following as the initial paragraph of the Indications and Usage section:

> 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 within an approximate incidence of 0.4% (4/1000). This incidence of seizures may exceed that of other marketed antidepressants which may have seizure incidences as low as 0.1% (1/1000)(See Warnings).

Comment

This proposed wording is very close to our last proposed initial paragraph which we faxed to Burroughs Wellcome on May 4, 1989. The major difference is in the last sentence. In our proposed version, we emphasized the relatively greater rate of seizure in patients taking Wellbutrin compared to other marketed antidepressants by suggesting that the seizure rate for Wellbutrin may exceed that of other antidepressants by as much as four fold. Burroughs Wellcome, on the other hand, wishes to avoid a direct comparison, and alternatively, simply states that the rate for other antidepressants maybe as low as 0.1%.

I think we have already modified our position substantially, essentially by backing off from the requirement that Wellbutrin would be labeled as a second line antidepressant, i.e., only for patients nonresponsive to or intolerant of standard antidepressant therapy. While I think it is acceptable to drop this requirement for second line status, I do think it is important to inform physicians of the relatively greater risk of seizure with Wellbutrin compared to other antidepressants. Furthermore, I believe that the estimate of a four fold higher rate of seizure associated with Wellbutrin use is the most valid estimate available. Consequently, I recommend that we retain this relative risk estimate in the final sentence of this paragraph.

2. Warnings Section

In our March 24, 1989 letter, we had proposed that the first paragraph from our originally approved product labeling be retained. Burroughs Wellcome has alternatively proposed the following as the first paragraph:

> 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 which may have seizure rates as low as 0.1% (1/1000). The estimated risk for Wellbutrin increases almost tenfold between a dose of 450 and 600 mg/day, which is twice the usual 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.

Comment

I think this proposed version is close to being adequate, but again, it is flawed in its failure to emphasize the relative risk of seizure for Wellbutrin compared to other antidepressants. Consequently, I recommend a slight modification of the ~~first~~ sentence of this paragraph to focus more definitively on this relative risk.

3. Dosage and Administration Section

Burroughs Wellcome has proposed the following alternative first sentence of the "General Dosing Considerations" subsection:

> It is particularly important to administer Wellbutrin in a manner most likely to minimize the risk of seizure (See Warnings).

Comment

I have no objection to this alternative wording.

MADE IN JAPAN

4. Nursing Mothers Subsection

Based on results from the first patient in a study of bupropion and its metabolites in breast milk, which suggested that a significant amount of bupropion and one metabolite are transmitted in breast milk, the sponsor has proposed a stronger statement regarding nursing in mothers concomitantly taking Wellbutrin.

Comment

I agree with the sponsor's proposed alternative statement.

Recommendations

I recommend the following comments be conveyed to the sponsor in a letter:

In your May 10, 1989 letter, you have proposed several changes in the Wellbutrin labeling, i.e., Indications and Usage section, Warnings section, Dosage and Administration section, and the Nursing Mothers subsection of the Precautions section.

We agree to your proposed changes in the Dosage and Administration section and the Nursing Mothers subsection. However, we disagree on a major issue reflected in your alternative wording for the Indications and Usage section and the Warnings section. We feel it is important to warn physicians of the relatively greater risk of seizure associated with Wellbutrin use, compared to other marketed antidepressants. Consequently, we ask that you retain in both of these sections the estimate of a four fold greater seizure risk for Wellbutrin compared to other antidepressants.

Therefore, we ask that you incorporate the following as the initial paragraph of the Indications and Usage section:

> 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 four fold.

MADE IN JAPAN

In addition, we ask that you incorporate the following as the initial paragraph of the Warnings section:

> 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 four fold. The estimated risk 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.

Thomas P. Laughren 5/19/89

Thomas P. Laughren, M.D.

cc:
Original NDA
HFD-120/Laughren/Leber/DeCicco
tt/ejs/5/19/89
DOC#1004s

MADE IN JAPAN

ARCHIVAL COPY

Burroughs Wellcome Co.

Wellcome

May 10, 1989

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

S-cs/BM
S-003
NDA SUPPLEMENT

NDA 18-644/3-003
WELLBUTRIN® Tablets

Dear Dr. Leber:

Reference is made to our meeting with you, Dr. Laughren, Mr. DiCicco and Dr. Temple on May 2, 1989, and to your telephone conversation with Dr. Lineberry on May 5, 1989 concerning labeling for WELLBUTRIN (bupropion hydrochloride) Tablets. Reference is also made to your letter of March 24, 1989 to Dr. Miller and our letter to you of April 4, 1989 from Dr. Lyon.

On the basis of the meeting of May 2 and the telephone conversation of May 5, we appear to be very close to agreement on the Indications statement, and believe the only issue to be resolved is the "four-fold" comparative statement. We are submitting, herewith, proposed revisions for Indications and Usage, Warnings, and Dosage and Administration based on these recent discussions. In addition, we propose revised wording for the subsection on breast feeding, based on data from a single subject showing significant excretion of bupropion and metabolites in breast milk.

Indications and Usage

In your telephone conversation with Dr. Lineberry on May 5, 1989, you expressed your preference for including in Indications and Usage a statement that the incidence of seizures with Wellbutrin "may exceed that of other marketed antidepressants by as much as four-fold." While we appear close to agreement on the rest of the wording in this section, we have a major concern with the use of a ratio to compare seizure rates in this instance. In order to make statistically valid comparisons of adverse event rates among different treatments, it is essential that estimates of rates be derived from study samples that are comparable in patient characteristics, dosing levels, treatment durations, methods of detecting events, physician judgements, etc. This is best accomplished in prospective, randomized, double-blind, head-to-head comparative studies where these factors can be controlled and held equal across different treatment groups. No such studies have been done comparing Wellbutrin with other agents. Thus, any comparison of rates must rely on data from separate studies conducted under conditions that in all probability differed widely from study to study.

In our meeting of May 2, we discussed our differing views on the incidence of seizure with various antidepressants. We reviewed reports of seizure incidences in the literature which suggest that the seizure rate for other antidepressants is in the range of 0.1% to 1.0%, depending on the agent, dose, treatment duration, and other factors. We further indicated that, because of methodological flaws, it is probable that these studies significantly underestimated the rate of seizure, and in our opinion a more accurate estimate of the true range would be 0.4% to 0.6%. Your view, based on data available to the FDA from control groups in IND studies with other agents, is that the lowest rate is approximately 0.1%. Given these different views, it is apparent that there is not a concensus regarding the true rate of seizure for most antidepressants.

MAY 1 0 1989
RECEIVED

Nevertheless, while we do not agree with your estimate of 0.1% for other antidepressants, we have agreed to include it in the Indications and Usage statement. We have also agreed to include in the last sentence of the first paragraph of the Indications and Usage statement proposed above, a comparative statement that the incidence of seizures with Wellbutrin may exceed that of other marketed antidepressants. We are, however, reluctant to include a ratio to compare seizure rates in this instance, since that would imply a level of precision and comparability between rates that is not justified on statistical grounds.

We propose the following to be included as the initial paragraph:

"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 which may have seizure incidences as low as 0.1% (1/1000) (see Warnings)."

Warnings

In your letter of March 24, 1989, you requested we reinstate the first paragraph of the Warnings section from the labeling originally approved in 1985. Based on our recent discussions, some of the wording in that paragraph may no longer be appropriate. We propose a paragraph which is similar to the first paragraph of the 1985 Warnings section, but contains new statements about the rate of seizure for Wellbutrin and other antidepressants which are compatible with statements currently proposed for the Indications and Usage section.

We propose the following for the first paragraph under Warnings:

"WARNINGS: 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 which may have seizure rates as low as 0.1% (1/1000). The estimated risk for Wellbutrin increases almost tenfold between a dose of 450 and 600 mg a 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 in their capacity to metabolize and eliminate drugs, this disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing."

Dosage and Administration

In your letter of March 24, you proposed the following sentence be incorporated as the initial sentence under General Dosing Considerations: "Since there is an almost 10-fold increase in seizure risk associated with a dose increase from 450 mg/day to 600 mg/day, it is necessary to administer this drug in a manner most likely to minimize the risk of seizure (see Warnings)."

While total daily dose is one factor to be considered in the safe use of this drug, there are several others described under Recommendations for Minimizing the Risk of Seizure in the Warnings Section. We would prefer a general reference to the full discussion of this issue under Warnings, because we are concerned this may imply that dosing within the recommended range is the only factor to be considered in minimizing the risk of seizure.

We propose the following to be included as the first sentence under General Dosing Considerations:

"General Dosing Considerations: It is particularly important to administer Wellbutrin in a manner most likely to minimize the risk of seizure (see Warnings)."

MADE IN JAPAN

Nursing Mothers

We propose the following revised wording in the section on Nursing Nothers under Precautions: "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."

This revision is based on the results of an assay of breast milk samples from a single patient in Study 85 (protocol submitted to FDA on December 3, 1985), which was designed to determine bupropion and metabolite concentrations in plasma and breast milk of nursing mothers after a single, oral dose of 100 mg of buropion HCl. The study was terminated for administrative reasons after this patient was entered.

Significant amounts of bupropion (up to 150 ng/ml), the threo-aminoalcohol metabolite (up to 70 ng/ml), and the morpholinol metabolite (up to 55 ng/ml) were found. Although no firm conclusions can be made regarding amounts of bupropion and metabolites excreted in breast milk based on experience in a single patient, it appears clear that significant amounts are excreted via this route.

We anticipate that the differences remaining can be quickly resolved. The Indications and Usage section, as written above, accurately states the scientific data in a valid way. We feel that a direct comparison of seizure rates, as in your proposed "four-fold" wording, denotes a degree of comparability of these rates that does not exist. If resolution of this point cannot be accomplished rapidly, we would like to request a meeting as soon as possible with appropriate FDA personnel.

Sincerely,

George M. Lyon, Jr., M.D.
Director
Drug Regulatory Affairs

GML/mg*
TRZO/89/0379

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-644/S-003

MAR 24 1989

Burroughs-Wellcome Company
Attention: Loren Miller, M.D.
Drug Regulatory Affairs
3030 Cornwallis Road
Research Triangle Park, North Carolina 27709

Dear Dr. Miller:

Please refer to your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Wellbutrin^{R} (bupropion hydrochloride) tablets.

Please also refer to your submissions of October 7, 1988, December 19, 1988 (S-003), January 11, 1989, and January 13, 1989, providing the results of the bupropion seizure study (86A) and the efficacy study utilizing the 300mg dose (84A). We have reviewed the data from study 86A and we agree that these data provide confirmation that the crude seizure rate associated with Wellbutrin use at doses of 450 mg/day or less is approximately 0.4%. We have also reviewed the data from study 84A, and we agree that these data provide support for the antidepressant efficacy of Wellbutrin at a dose of 300 mg/day in moderately depressed outpatients. However, we do not agree with all of your proposed revisions of the labeling for Wellbutrin. Consequently, while S-003 is Approvable, its final approval will be contingent upon your submitting final printed labeling containing our additional revisions to the labeling, which we have detailed in the remaining sections of this letter. We have commented on your proposed revisions to the labeling and we have proposed alternative wording in the instances where we disagree. These comments and alternative wording proposals are provided on a section by section basis, as follows:

1.0 Indications and Usage

1.1 Proposed Changes

You have dropped the reference to Wellbutrin being a drug of second choice, and alternatively, you have proposed that it should be indicated simply for the treatment of depression. You have also added a reference to the fact that Wellbutrin has now been demonstrated to be effective in a trial of 6 weeks duration in outpatients with depression. Finally, you have dropped the sentence referring to the lack of evidence for effectiveness beyond 3 weeks.

1.2 Comment

We disagree with a first line status for Wellbutrin. Although it is true that we do not have reliable seizure estimates from comparably designed studies for any of the marketed antidepressants, it is generally believed that the seizure

incidence for imipramine and most other tricyclic antidepressants is approximately 0.1%. You cite the recently marketed Prozac as having a crude seizure rate of 0.2%. However, it is important to note that this estimate includes all premarketing events that could possibly have been considered seizures (i.e., 16/8000). In fact, only 10 of these events could confidently be considered seizures, yielding a rate of 10/8000, i.e., approximately 0.1%. [Note: Your estimate of crude seizure rate for Wellbutrin, based on Study 86A, includes only well documented seizures, and would be somewhat higher if questionable cases were included.] Thus, the crude seizure rate for Wellbutrin at doses of 450 mg/day or less is probably 4-fold the rate for most marketed antidepressants. At the time of the original approval of Wellbutrin as a second line antidepressant drug, the estimate of seizure incidence for patients receiving doses of 450 mg/day or less was 0.33%, so we now are seeing an observed incidence which is actually slightly higher. Consequently, we do not believe that there is adequate justification for dropping the second line status for this drug.

It is also important to note that, although you have now generated data suggesting the antidepressant efficacy of Wellbutrin at a dose of 300 mg/day, this study (84A) was done in depressed outpatients. The other data upon which the original approval of Wellbutrin was based come from depressed inpatients, many of whom were dosed at 450 mg/day. It is possible that some patients may need doses up to 450 mg/day, and the labeling will have to reflect this fact. Thus, even if you could demonstrate that the seizure rate is substantially lower at 300 mg/day, we would still not be inclined to accept a first line status for Wellbutrin. Alternatively, you would need to show that Wellbutrin has some specific therapeutic advantage over other antidepressants, in which case it could be a first line drug for whatever subgroups seem to differentially benefit.

We agree that the labeling can now indicate that Wellbutrin has been demonstrated to be effective in a 6 weeks trial in depressed outpatients, but your proposed wording implies that efficacy has been demonstrated in 6-week trials in both inpatients and outpatients, and this needs to be clarified. In addition, there still needs to be some discussion of the lack of evidence beyond 6 weeks. We think that, in regard to longer term use, the standard language used in the labeling for Prozac would be appropriate here as well.

1.3 Recommendations

We recommend that the first paragraph in the currently approved PPL be retained, with changes only in the multiples of the doses at which the seizure risk increases, as follows:

"Wellbutrin is indicated for the treatment of depression. Generally, its use should be reserved for patients who fail to respond adequately to, or who cannot tolerate, alternative antidepressant therapy. Wellbutrin is not recommended as an antidepressant of first choice for most patients because its use at doses of 450 mg/day and below is associated with a seizure rate of 0.4%, a rate believed to be approximately four-fold higher than the rate for other marketed antidepressants (see Warnings)."

We recommend the following as the second paragraph:

"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."

The third paragraph, defining major depression, can remain as is.

For the fourth paragraph, we recommend the following:

"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."

2.0 Contraindications

2.1 Proposed Changes

You have modified this section by adding a contraindication for the use of Wellbutrin in patients with a current or prior diagnosis of bulimia or anorexia nervosa. Otherwise, this section is unchanged.

2.2 Comment and Recommendations

We agree with your revision of this section of the labeling.

3.0 Warnings

3.1 Proposed Changes

The language in the first paragraph of your revised Warnings section diminishes the strength of the warning. This section eliminates the seizure incidence table, but does retain the incidence estimates that suggest a steep dose response curve, and it adds the seizure incidence estimate from the recently completed open study (86A). It retains a modified version of the paragraph linking risk to dose and to predisposing factors. It eliminates the paragraph referring to adherence to dosing recommendations, and alternatively, it expands this paragraph by including the specific dosing recommendations that had previously been in the original Dosage and Administration section.

3.2 Comment

While we agree that your revised Warnings section is generally an improvement over the original, we believe that it goes too far in diminishing the impact of the original first paragraph.

3.3 Recommendations

We ask that you retain the original first paragraph in the currently approved FPL for Wellbutrin. The remaining paragraphs of your revised Warnings section are acceptable.

4.0 Dosage and Administration

4.1 Proposed Changes

You have rearranged this section of the labeling by putting the actual dosing recommendations first, followed by a general discussion of the rationale for using caution in dose escalation. Of note, you have removed all references to the occurrence of seizure in this discussion. Also, as noted earlier, all of the specific recommendations regarding dosing strategies to decrease the possibility of seizure have now been moved to the Warnings section. There is also a revision of the "Maintenance" subsection.

4.2 Comments

We agree with your rewording of the two subsections giving actual dosing recommendations, i.e., "Usual Dosage for Adults" and "Increasing the Dosage Above 300 mg/day." However, we think that it would be preferable to have the "General Dosing Considerations" subsection first, to provide the rationale for the actual recommendations. We also think that there should be some mention of the seizure problem in this general discussion section, with a reference to "Warnings" for more complete details. We have no objection to the revised "Maintenance" subsection.

4.3 Recommendations

We ask that you put the "General Dosing Considerations" section at the start of the Dosage and Administration section. In addition, this introductory section should begin with the following:

"Since there is an almost 10-fold increase in seizure risk associated with a dose increase from 450 mg/day to 600 mg/day, it is necessary to administer this drug in a manner most likely to minimize the risk of seizure (see Warnings)." In addition, the sentence beginning "gradual escalation ..." should be modified by adding "also" after "is," i.e., "gradual escalation in dosage is also important ...," in order to emphasize that these are secondary reasons for using caution.

This introductory section can then be followed by your two paragraphs giving actual dosing recommendations and your revised "Maintenance" subsection.

LION 301 MADE IN JAPAN

Should you have any questions please contact Mr. Tony DeCicco, Consumer Safety Officer at (301) 443-3504.

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

MADE IN JAPAN

WD/
INFO

JAN - 2 1987

Dear Mr. Mason:

I am responding to your recent letter that expresses your distress about the possibility that Wellbutrin (bupropion) may not be marketed.

To begin, it is important for you to understand that the FDA has not rendered a final decision about the marketability of Wellbutrin and it currently allows Burroughs Wellcome to distribute the drug under a compassionate IND program to physicians for use in patients who have a documented need for it.

It is also important to understand that the FDA is fully aware of the potential benefits that Wellbutrin may offer to selected patients. Indeed, if the FDA had considered Wellbutrin to be simply another 'me-too' antidepressant, it would not have approved it for marketing last year. Let me explain.

Despite its potential advantages, Wellbutrin is a potentially dangerous drug; at doses only slightly greater than those required to produce its antidepressant effect, it causes an unacceptably high incidence of generalized convulsions (seizures). A generalized convulsion is not a trivial side effect. Depending upon the circumstances (e.g., driving a car, operating complex machinery) in which it occurs, a seizure can cause serious injury, even death; worse, the injury may involve others besides the the patient taking the drug. At the very least, even a single seizure followed by full recovery may have profound effects upon an individual's personal life; a full and costly medical workup may be necessary, driving privileges may be lost, etc.

Thus, a high risk of seizure is ordinarily an absolute barrier to the approval of a new drug. However, the FDA was mindful of the problems confronting the depressed patient unresponsive to or intolerant of existing antidepressant treatment and an effort was made to find a way to allow Wellbutrin's marketing under circumstances that might reduce the risk of seizure.

The FDA's initial review of the records of patients who experienced seizures while taking Wellbutrin suggested that the risk of seizure was probably affected by the total amount of drug given daily and the rate at which the daily dose was changed. On the basis of this analysis, the FDA agreed to the marketing of Wellbutrin, but only upon the condition that its labeling 1) advise against its use as an antidepressant of first choice, and 2) prominently warn about the relationship between total daily dose and seizure incidence.

In the spring of 1986, shortly after approval had been granted but before full scale marketing of Wellbutrin had begun, additional reports of seizures occurring within the dose range recommended in the product's labeling (i.e., the supposedly safe dose range) were received. An analysis of the reports indicated that Wellbutrin might be associated with a much higher risk of seizure than earlier evidence had indicated. Both the firm and the FDA were alarmed by these findings and both agreed that additional data was needed to settle the question; clearly, there is an incidence of seizure that can not be accepted in a marketed drug product no matter how cautionary its labeling.

The decision to delay marketing and carry out a large scale clinical study to estimate the actual risk of seizure among patients taking the drug at the recommended dose was reviewed and endorsed by an independent board of experts, FDA's Psychopharmacologic Drugs Advisory Committee.

Setting up a complex study takes time and over the past five months, FDA staff and representatives of Burroughs Wellcome have engaged in iterative negotiations to develop proper testing conditions and protocols. It appeared that agreement was close on all but minor issues when, in mid-September, the firm announced that it had decided to discontinue its development of Wellbutrin.

Clearly, this is an unfortunate decision and the FDA shares your hope that the it will be reconsidered. The firm has been encouraged to continue to provide Wellbutrin, under their compassionate treatment program, to physicians. You can be assured that the FDA will continue to cooperate with Burroughs Wellcome to seek to find a way to continue development of this promising drug product.

Sincerely yours,

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

cc:
HFN-120/PLeber
/DeCicco
ft/mb/12/31/86
DOC 0447c

NDA 18644

Howard J. Schaeffer, Ph.D.
Burroughs Wellcome Company
Vice President
Research, Development and Medical
3030 Cornwallis Road
Research Triangle Park, North Carolina 27709

Dear Dr. Schaeffer:

I am writing in response to your letter of September 17, 1986 announcing Burroughs Wellcome's 'voluntary withdrawal' of Wellbutrin.

Clearly, I am not aware, nor should I be, of all the factors that entered into your decision to abandon Wellbutrin. A statement in your letter, however, suggests that your decision, in part at least, may have been based on a misinterpretation of a critical aspect of our exhaustive negotiations. If my inference is correct, I'd like to set the record straight because it would indeed be unfortunate if a decision to discard a potentially useful drug was based on a misunderstanding of a key point.

Your letter states that your decision to abandon Wellbutrin was based on the failure of our negotiations to reach agreement about 'requirements for (the) commercial marketing' of Wellbutrin. Actually, agreement was reached that Wellbutrin could be marketed if the 95% upper bound of seizure incidence associated with its use at recommended doses could be shown prospectively not to exceed 7 events per thousand patients exposed for a six week interval. It is important to emphasize that agreement on this matter came after months of negotiation and took into consideration advice and counsel offered by both your own expert advisors and our Psychopharmacologic Drugs Advisory Committee. Moreover, during the course of negotiations we also agreed that the incidence of seizure with Wellbutrin is very high, unexplained on a pathophysiologic basis and may exceed that associated with other antidepressants by an order of magnitude. Nonetheless, a high relative incidence of seizure (i.e., circa 4 or 5/1000) was judged to be tolerable because, if marketed, 1) Wellbutrin would not be recommended as an antidepressant of first choice, 2) its labelling would prominently describe the risk and the linkage between dose and seizure incidence and 3) there is reason to believe that Wellbutrin might provide a unique advantage to certain selected depressed patients (e.g., those exhibiting severe orthostatic responses to marketed antidepressants, those failing to respond to other antidepressants, etc.).

In my view, therefore, it is inaccurate to suggest that negotiations faltered over a disagreement about the requirements for marketing. In my view, negotiations actually became deadlocked over the nature and the extent of the guarantee that the division felt it could offer, before the fact, about its probable interpretation (vis a vis marketing) of the study that you had proposed to conduct to estimate the upper bound of seizure risk. In short, negotiations failed when we could not offer you the degree of 'before the fact' assurance that you felt you needed to initiate the proposed trial. This

As I repeatedly emphasized during the course of our protracted negotiations, the division ordinarily avoids making formal agreements about how it will interpret the results of clinical trials intended to document the safety of a drug. It has been our experience that Nature is capricious; the unexpected and unanticipated occurs frequently. Consequently, we consider it prudent to make regulatory decisions affecting the marketing of products with all evidence in hand. In those rare instances when we do elect to make a 'before the fact' commitment, we want to be more than reasonably certain that we will be able to honor it. Thus, in negotiating a set of 'before the fact' rules governing our future behavior, we necessarily assume a conservative posture. Clearly, after an experiment has been conducted and analyzed, it can be evaluated on an ad hoc basis taking into account factors and issues that cannot possibly be considered in advance.

I want to be certain that you fully understand our position on this point because it raises the very real possibility that if you were to conduct a study of the sort you last proposed (i.e., in your August 11, 1986 submission), and submit the results, they might prove sufficient to convince the Agency that the agreed upon marketing requirements had been met. Indeed, I intended to convey this point in my letter of September 5, 1985. Upon rereading the letter now, however, I am concerned that I was not sufficiently explicit or encouraging about this alternative approach.

In any case, whatever your final decision, patients currently using Neiloutrin on a 'compassionate' basis certainly should be allowed to continue to have access to it. Clearly, there is no mechanism other than an IND to permit this sort of distribution. I would hope, therefore, that Burroughs Wellcome will continue to maintain a compassionate use IND. If the cost is prohibitive, and you do not intend further clinical development, you might develop arguments to gain agency permission to recover your costs for supplying the drug product.

I, of course, would be happy to discuss any issue related to this matter.

Sincerely yours,

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Product
Office of Drug Research and Review
Center for Drugs and Biologics

cc:
Robert J. Temple
HFN-120
HFN-120/MLeber/9/19/86
Katz, Laughren, Kapit
DOC 393/p

DUPLICATE

SUPPL NEW CO

Burroughs Wellcome Co.

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

Wellcome

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

September 17, 1986

Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 18-644
WELLBUTRIN® Tablets

Dear Dr. Leber:

Since our voluntary withdrawal of WELLBUTRIN on February 28, 1986, we have been engaged in continuing negotiations with the Division of Neuropharmacological Drug Products regarding their requirements for commercial marketing. We have been unable to reach agreement. It is therefore the decision of Burroughs Wellcome Co. to terminate all WELLBUTRIN studies under IND and to discontinue all further development efforts.

As you may be aware, there are currently more than 700 patients receiving WELLBUTRIN under provisions of compassionate plea. For these patients and others who are nonresponsive to currently available antidepressants, we feel it would be in the public interest for WELLBUTRIN to be made commercially available for humanitarian use. Burroughs Wellcome Co. is willing to make WELLBUTRIN commercially available under restrictive labeling. We hope you will consider this possibility.

We believe Burroughs Wellcome Co. has acted responsibly and in the public interest as demonstrated by our voluntary withdrawal of WELLBUTRIN, our subsequent proposals for resolution of the outstanding issues, and our offer for humanitarian availability. We appreciate all the efforts of the FDA in this matter.

Sincerely,

Howard J. Schaeffer

Howard J. Schaeffer, Ph.D.
Vice President
Research, Development and Medical

RECEIVED
NATIONAL
SEP 17 1986
FOR DRUGS &
BIOLOGICS

HJS/cc/XD3
TRZO/86/0664

cc: Robert J. Temple, M.D.

MADE IN JAPAN

NDA 18-644

12:03:51 2/28/1986 WELLBUTRIN:

got call relayed via Tony DiCicco about seizures and wellbutin.

Called Lineberry back with Tony, Tom and Rich. Kapit.
The story: now four seizures (generalized convulsions) as of 2/27/86 among a sample of approximately 50 so called normal weight bulimics.

First seizure was seen on 1/7, the second on 1/11 and the third on 2/10. At that point they changed the upper dosing limit in the study, DID NOT NOTIFY US HOWEVER, and continued to enroll patients.

On 2/27/86, the 4th seizure occurred. They called us!

DATA TABLE: Four patients among approximately 50

date	age	sex	dose(mg)	days at dose	total days	weight(kg)	mg/kilo
1/7	23	f	375/d	9d	19d	39+	9.4mg/k
1/11	25	f	375/d	1d	7d	71.7	5.3mg/k
2/10*	42	f	375/d	7d	14d	46.3	8.1mg/k
2/27	27	f	300/d	20d	?	50.8	5.9mg/k

Approved upper mg/kg dose based on 450mg and 50kg is 9mg/k-bs
* upper permitted dose changed as of this date.
NB. NO CASES OF SEIZURE OBSERVED AMONG 20-30 PLACEBO PATIENTS IN STUDY!

Firm proposes:
To Contraindicate drug in Bulimia. They believe this is a 'special' group because in their compassionate extension protocol 20 depressed SS with bulemic symptoms did not have seizure. They suggest that bulemics may be a differnt breed because it has been suggested that they really have a subcoritical seizure disorder (i.e., driving their episodic binges).

They had intended to go ahead with 'launch' of product which is scheuduled for mid-March. They really want us to rapidly agree to the proposed labeling revision.

My comments:
first, I asked them why, on 2/10 when they had altered the protocol of their study, indicating their concern that the drug may have an increased risk not previsouly appreciated, that they failed to call us. They made some lame excuse.

I advised them strongly not to go ahead with the 'launch.'
I reminded them that the approval of Wellbutrin had been a very close decision based upon the apparent safety of doses below 450mg.

I pointed out that the sharp transition between the risk at 450 and 600 mg had never made much sense and it was quite possible that the observations in the so called normal weight bulimics (in my mind a somewhat dubious entity biologically) could not prudently be limited to the group.

HON 301 MADE IN JAPAN

At the very least, I noted, the agency would require time to review and reconsider the approval and the proposed alternative labeling changes. I noted that I did not have the authority to make any direct demand myself and needed time to contact the appropriate staff and agency personnel. I, however, reiterated my advice that they hold the launch!

I asked them to inform me ASAP what they would do about their launch. Mr. Lineberry told me that he had no authority to act, either, but he would discuss my suggestion and get back to me.

We also agreed that they would forward a summary of what they had told us immediately.

As an after thought, I asked Diccicco to call firm to make sure that all trials with bulemica patients had been suspended, just in case their hypothesis was correct.

12:36:40 2/28/1986 end memo

Paul Leber, M.D.

file NDA 18-644
HFN-120: Leber
Kapit
Katz, Laughren
Diccico

LION 301 MADE IN JAPAN

3:34:42 2/28/1986 TELCON: LEBER AND ALLEN CATO OF BW
SUBJECT: WELLBUTRIN AND SEIZURES.

Reached Allen Cato instead of Lineberry; put me on speaker phone. Company has decided on voluntary withdrawal of Wellbutrin through pharmacy level--I agree for the moment that this seems sufficient given their claim that there is very little distribution and virtually no prescribing as most physicians don't know that product is available.

They are emphasizing that the additional four cases, applied to the general population denominator, do not increase overall rate very much. I then went over some of the factors that led me to be less sanguine about their limited extrapolation of the events observed in bulimics.

Promised to get back to them if RT had any substantive new information.

Paul Leber, M.D.

cc: NDA 18-644
HFN-100: Temple
120: Leber, Laughren, Kapit, Katz
DiCicco
301: G Koustenis

MADE IN JAPAN

OTHER CORR. MEMOS ETC.

Department of Health and Human Services
Public Health Service
Food and Drug Administration

Memorandum

Date:

To: File NDA 18-644

Director
Office of Drug Research and Review, HFN-100

From: Director
Division of Neuropharmacological Drug Products, HFN-120

Subject: Approval Package

Introduction:

Almost a year ago, an approvable letter for NDA 18-644, Wellbutrin, issued to Burroughs-Wellcome. The letter conditioned the agency's final approval of the NDA upon the firm's agreement to:

1) revise, as directed, the product's proposed labeling,

2) submit a comprenensive safety update on adverse reactions and laboratory findings. (An especially elaborate update effort was required because the firm's previous tabulations of adverse events employed idiosyncratic rules [e.g., events recorded before drug administration began were included in the list of possible ADRs], entailed repeated categorizations of events, and employed redundant terminology making it difficult to obtain reliable estimates of the incidence of various untoward events associated with the product's use. Thus, before final labeling could be drafted, a systematic re-analysis of ADR incidence was needed. Incidentally, the Division went to considerable lengths to provide the sponsor with concrete examples of an adverse event enumeration strategy, including the creation, de novo, of a glossary of terms organized by body system.),

3) commit to conduct, after approval, a series of clinical studies including:

   a) a study to assess the sustained antidepressant efficacy of bupropion at intervals beyond three weeks. (Three weeks was the maximum effective duration of any clinical trial providing persuasive evidence of antidepressant efficacy.)

   b) a study or studies to assess the efficacy of bupropion in the outpatient population. (Bupropion's efficacy was not demonstrated in adequate and well-controlled investigations employing outpatients; only the inpatient trials provided persuasive evidence of efficacy).

MADE IN JAPAN

NDA 18-044

FEB 19 [illegible]

Burroughs Wellcome Company
Attention: D. A. Knight
3030 Cornwallis Road
Research Triangle Park, North Carolina 27709

Gentlemen:

Attached is a Glossary of Adverse Reaction terms that I developed from the file COSTART.DTA provided by Dr. Starbuck. In addition to the hardcopy printout (Glossary.dta/appendix two), I have also enclosed an electronic copy as an ASCII file that was created using the nondocument mode of WORDSTAR©.

Because of the amount of effort involved, I could not find the time to duplicate my effort with COSTART2.DTA. I will assume that your staff physicians can, using my Glossary as an example, categorize the terms reported in COSTART2.DTA and use them, if required to expand the glossary.

In general, I attempted to take the terms in colum one of COSTART.DTA and categorize them within clinically logical clusters. Obviously, working without the benefit of case reports, the classification of many individual terms had to be arbitrary. Nonetheless, the resulting glossary terms can be used in a between treatment comparison of untoward event incidence. The reliability of the contrast will be enhanced if your staff, using case report data, ensures the appropriate classification of each patient under each glossary term. (see below)

Unfortunately, the list of terms is still far too large. I suggest, therefore, that any between group incidence enumeration be partially data conditioned. After a final glossary is generated, the number of individuals suffering each glossary event under each treatment condition should be enumerated. Again, as agreed, suffering an event means developing or experiencing the event for the first time after drug assignment or experiencing a worsening of the phenomena if it was present at baseline.

There should be two general analyses; one with patients in controlled trials, the other with patients in open extended studies.

For example, events sustained by individuals who participated in all controlled studies employing either placebo or active drug should be tabulated by glossary category for each treatment type (placebo, bupropion, amitriptyline, etc.). To make the tabulation meaningful, your staff will have to examine individual case reports to determine if the classification is appropriate. For example, your staff will have to find out, in some way, if a report of chest pain represented angina, dyspepsia, or anxiety.

I see little reason to do statistical analyses on this information. At this point, we are still looking for signals. For example, is the incidence of

MADE IN JAPAN

psychosis higher with bepropion? Once we've had a chance to look over detailed the results of this enumeration, we might, again jointly, examine related categories in greater detail. For example, bad dreams, sleep disorders, hallucinations of the hypnopompic and hypnagogic type and psychosis might require further investigation at the case report level.

One technical matter: In laying out the glossary format, I placed general system terms at the far left. At the first level of indentation, I generally placed the specific glossary term that I believed was of clinical interest. On the far right, I placed specific examples of individual report terms that I thought should be subsumed under terms to the left. My layout, however, is not uniform. In some instances, I further subdivided a glossary. For example, under Neurological events, I have a category of ataxia/incoordination. I have only partially subsumed the terms Dysarthria and Nystagmus in this broader category. This reflects my interest in seeing two levels of enumeration in this setting. One in which ataxia/incoordination includes reports of dysarthria and nystagmus; the other in which it does not. There are other examples of this approach in my layout and your staff may wish to attempt similar breakouts themselves on other glossary categories.

One final note: In some cases, simply because I became tired of using the cumbersome Wordstar editor, I elected not to complete the editing of the file, leaving the section as it had originally appeared (e.g., section on pain). The further classification of the terms appearing in these sections is, however, obvious from the context of the file.

In any event, despite its obvious limitations, I believe that the glossary will be a useful starting point for the tabulation and comparison of adverse events reported in the clinical trials with bupropion.

Please contact me, if you have any questions about the procedure or strategy that I used.

Sincerely yours,

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

Orig. NDA File
~~HFN-120~~
HFN-120/TAHaves
HFN-120/PLeber/2/15/85
Doc. #0071p

LION 301 MADE IN JAPAN

GLOSSARY.DOC APPENDIX TWO

GLOSSARY

PREFERRED TERM OR SUB TERM	SECONDARY TERM
CARDIOVASCULAR SYSTEM:	
ANGINA	CHEST PAIN (NOTE JUDGEMENT REQUIRED TO DISTINGUISH BETWEEN ANGINAL/CARDIOVASCULAR SIGNS/SYMPTOMS AND THOSE RELATED TO ANXIETY:SOB, DYSPNEA, TIGHTNESS,ETC. CLASSIFICATION SHOULD RELY UPON INVESTIGATOR'S JUDGMENT!)
ARRHYTHMIAS	CARDIAC ARRHYTHMIA PALPITATIONS PALPITATIONS/SINUS ARRYTHMIA
CONGESTIVE HEART FAILURE	
(NOTE/EDEMA HAS MANY CAUSES, EACH CASE WILL REQUIRE APPROPRIATE CLASSIFICATION AS TO CAUSE. i HAVE SIMPLY LISTED SOME POSSIBLE CHF RELATED COMPLAINTS; OBVISOUSLY, OTHER EXPLANATIONS FROM VARICOSITIES TO PROTEIN LOOSING ENTEROPATHIES ARE POSSIBLE!)	
FOOT SWELLING	
FSWELLING OF EXTREMITIES	
LPERIPHERAL EDEMA	
LEDEMA,FACIAL & FEET	
SWOLLEN ANKLES AND FEET	
EDEMA PEDAL	
EDEMA-2+ FEET	
PEDAL EDEMA +2	
DIZZINESS/SYNCOPE/FAINTING	FAINTING/DIZZINESS LIGHTHEADED LIGHTHEADEDNESS LIGHTHEADEDNESS W/ STANDING
EKG ABNORMALITY	
HYPERTENSION	

LION 501 MADE IN JAPAN

	HYPERTENSION
	ELEVATED BLOOD PRESSURE
	INCR BLOOD PRESSURE
	INCR'D BP
	INCR'D DIASTOLIC BLOOD PRESSURE
	INCREASED BLOOD PRESSURE
HYPOTENSION	
ORTHOSTATIC HYPOTENSION	
	BLD PRESSURE DROPS
	BLOOD PRESSURE DECREASED
	HYPOTENSION
	ORTHOSTATIC HYPOTENSION
	POSTURAL HYPOTENSION
DERMATOLOGIC	
ALOPECIA	ALOPECIA
	HAIR LOSS
HIRSUITISM	
RASH/LESION:	PSORIASIS
	NEURODERMATITIS
	PHOTOSENSITIZATION
	ABSCESS
	ACNE
	PETECHIAE
	BRUISING
	ECCHYMOSES
	LARGE BRUISE LEFT LEG
	ECZEMA
	ECZEMA OF FOREHEAD
	FOREHEAD ECZEMA
	EDEMA
	LIP SWELLING
	SWOLLEN NECK & THROAT
	URTICARIA
PRURITUS	ITCHING
	ITCHING OF ANY BODY PART,ETC.
	BURNING SENSATION
DRY SKIN	
	DRY LIPS

LION 301 MADE IN JAPAN

DESQUAMATION OF SKIN ON PALMS

FOREHEAD DRYNESS
ROUGH/DRY SKIN

HAIR DISCOLORATION

NAIL CHANGES(FINGERS OR TOES)

BRITTLE NAILS
RIDGING FINGER NAILS

ENDOCRINE

GLYCOSURIA

GYNECOMASTIA (UNLESS LINKED TO PRIMARY DISEASE)

GASTROINTESTINAL SYSTEM:

ANOREXIA

DECREASED APPETITE

APPETITE INCREASE

OVEREATING
INCREASED APPETITE

BLEEDING

MELENA
HEMATEMESIS

COLITIS

CONSTIPATION

DIARRHEA

INCREASED # OF BOWEL MOVEMENTS

DYSPHAGIA

CHOKING
DIFFICULTY SWALLOWING
DIFFICULTY TO SWALLOW
SWALLOWING DIFFICULTY
LUMP IN THROAT
LUMP IN THROAT 2HRS POST DOSE

LIVER DISEASE/JAUNDICE

NAUSEA/VOMITING

LION 301 MADE IN JAPAN

ULCER/INTESTINAL PERFORATION

UPSET STOMACH/GAS

RT

DRY HEAVES

ULCERS(PEPTIC)

DYSPESIA
HEARTBURN
HEARTBURN 3HRS POST DOSE
BURNING IN STOMACH
GASTRIC REFLUX
INDIGESTION
POSTPRANDIAL EPIGASTRIC DISCOMFO

EPIGASTRIC PAIN

"UNSETTLED FEELING IN STOMACH"

UPSET STOMACH
ELEVATED GAS
FLATULENCE
GASTRIC DISTENSION
INTESTINAL GAS
BLOATING
FLATUS
GAS PAIN
GAS-BURPING & FLATUS
GAS/CRAMPS
"GAS"

FILLING IMPRESSION AFTER DRUG INTAKE FLATUL DIG/GEN

WEIGHT LOSS

WEIGHT GAIN

WEIGHT DECREASE
LOSS OF WEIGHT

WEIGHT INCREASE
WEIGHT GAIN-40 LBS
WT GAIN

GENITOURINARY

ENDOMETRIOSIS

HEMATURIA

IMPOTENCE

LION 301 MADE IN JAPAN

MENSTRUAL COMPLAINTS

MENSTRUAL CRAMPS
DYSMENORRHEA

NOCTURIA

PRIAPISM/PAINFUL ERECTION

PROSTATIC ENLARGEMENT

SEXUAL APPETITE DISTURBANCE (DISTINGUSH DIRECTION)

(NOTE: DISTINGUISH THIS FROM 'IMPOTENCE')

MASTURBATION?

URINARY FREQUENCY/DYSURIA

POLYURIA

URINARY RETENTION

DIFFICULTY TO VOID
URINARY HESITANCY

URINARY INCONTINENCE

FG/VAG	VAGINAL IRRITATION/INFECTION	VAGINITIS	UG/
FG/VAG	VAGINAL BLEEDING HEAVY VAGINAL DISCHARGE	LEUKORRHEA	UG/

HEMATOLOGIC/ONCOLOGIC

LYMPHADENOPATHY

MUSCULOSKELETAL SYSTEM:

ARTHRITIS/ARTHRALGIA

JOINT PAIN/STIFFNESS
ARTHRITIS IN BOTH KNEES
ARTHRITIS-KNEES

NEUROLOGICAL

ATAXIA/INCOORDINATION

DECR COORDINATION
INCOORDINATION
INTERNAL SHAKINESS & UNSTEADINESS
UNSTEADINESS

LION 361 MADE IN JAPAN

DISEQUILIBRIUM

DYSARTHRIA
HESITANT SPEECH
SLURED SPEECH
STUTTERING

NYSTAGMUS

AUTONOMIC NERVOUS SYSTEM COMPLAINT

CUTANEOUS TEMPERATURE REGULATION DISTURBANCE:
COLD
COLD/CLAMMY FEELING
INTOLERANCE TO COLD TEMP
HOT AND COLD SPELLS
HOT SPELLS/FLASHES
FEELS WARM
FLUSHING
FLUSHED FEELING
FLUSHED FEELINGS
HOT,FLUSHED FEELING

MYDRIASIS

DILATED PUPILS
MYDRIASIS

SALIVARY FLOW DISTURBANCE:

DECREASED SALVATION/DRY MOUTH
INCREASE SALVATION/DROOLING

EXCESSIVE SWEATING

LIP & EYE PERSPIRATION
SWEATING
SWEATY PALMS

COMA

LOSS OF CONSCIOUSNESS

(DISTINGUISH BETWEEN SYNCOPE,SEIZURE,ETC.!)

EEG ABNORMALITIES

EXTRAPYRAMIDAL ABNORMALITIES

AKATHISIA

AKINESIA/BRADYKINESIA

LION 301 MADE IN JAPAN

CHOREOATHETOSIS	
DYSTONIA	
PSEUDOPARKINSONISM	COGWHEELING INCREASE TONE MASKED FACIES RIGIDITY
DYSKINESIA/TARDIVE DYSKINESIA	JAW MOVEMENTS
HEADACHE/MIGRAINE	HEADACHE HOLLOW FEELING IN HEAD PRESSURE IN EYES
MUSCLE SPASM	TIGHTENING OF FACIAL MUSCLES EYE TWITCH TWITCH IN RT EYE MUSCLE SPASMS IN BACK MUSCLE SPASMS IN NECK MUSCLE TWITCHING TWITCHING OF FACIAL MUSCLES
MYOCLONUS	
SEDATION:	SLEEPINESS DIFFICULTY STAYING AWAKE DECREASED ALERTNESS CALM FEELING DROWSINESS/SLEEPINESS GROGGINESS SOMNOLENCE
SLEEP DISTURBANCE:	
INSOMNIA	
	REDUCED NEED FOR SLEEP

LION 301 MADE IN JAPAN

BAD DREAMS
NIGHTMARES
DREAMS
TALK IN SLEEP

TALKING IN SLEEP
TALKING IN SLEEP ONCE
SLEEP TALKING

SENSORY DISTURBANCE

SENSITIVE FINGER TIPS
PARESTHESIAS
TINGLING IN SCALP
BURNING SENSATION IN EXTREM
COLD EXTREMITIES
LOSS OF FEELINGS
NUMBNESS
PARESTHESIA
SHRINKING SENSATION IN GONADS
TINGLING
LEGS TINGLING
"TICKLY FEET"

SEIZURE

CONVULSION

TREMOR

VERTIGO

NEUROPSYCHIATRIC

ABNORMAL MENTAL STATUS

DELUSIONS

HALLUCINATIONS

FLASHING LIGHTS
HALLUCINATIONS
LIGHT FLASHES
VISUAL SPOTS

ION 301 MADE IN JAPAN

MISPERCEPTIONS

FORMAL THOUGHT DISORDER

DIFFICULTY THINKING
LOOSE ASSOCIATIONS
RACING MIND
RACING THOUGHTS

PARANOIA

IDEAS OF REFERENCE
REFERENTIAL THINKING

DELIRIUM

CONFUSION
CONFUSIONAL STATE
CONFUSION/DISORIENTATION
TOXIC CONFUSION STATE

PSYCHOSIS

COGNITIVE IMPAIRMENT

ATTENTION DEFICIT

DISTRACTIBILITY
DAY DREAMING

MEMORY IMPAIRMENT

AMNESIA
DECR'D MEMORY
DECREASED MEMORY
DECREASED SHORT-TERM MEMORY
MEMORY DECREASE
MEMORY LOSS
POOR MEMORY
SPOTTY MEMORY
FORGETFULNESS
FORGETFULLNESS
ABSENT-MINDEDNESS

MOOD DISTURBANCE:

AGITATION:

AGITATION
AGITATION/EXCITEMENT
EXCITEMENT/AGITATION

LION 301 MADE IN JAPAN

RESTLESSNESS
(BE CERTAIN TO DISTINGUISH RESTLESSNESS AND AKATHISIA!)

ANXIETY:

ANXIETY
ANXIOUS
ACUTE ANXIETY
INCR ANXIETY
INCR IN ANXIETY
SOME INCR ANXIETY

DISTRESS
SLIGHT "ANXIOUS" FEELING IN AE
TREMULOUS FEELING
FEELS TIGHT & TENSE
INCREASED ANXIETY
FLUTTERY FLNG IN EPIGASTRIUM,NOT NAUSEA
INNER RESTLESSNESS
JITTERY FEELING
NERVOUSNESS

DEPERSONALIZATION/DEREALIZATION

DEPRESSION:

APATHY
MALAISE

CRYING
CRYING SPELL
CRYING SPELLS

HOSTILITY/IRRITABILITY:

IRRITABLE
IRRITABILITY
INAPPROPRIATE AGGRESSION

MANIA/HYPOMANIA

MOOD ELEVATION
EUPHORIA
MANIC REACTION

MOOD INSTABILITY

EMOTIONAL LABILITY

MADE IN JAPAN

INCR'D RAPIDITY OF MOOD SWINGS
MOOD SWINGS
RAPID CHANGE IN MOOD
RAPID MOOD SWINGS
RAPID MINOR MOOD SWINGS
RAPID SWINGS IN MOOD

SUICIDAL ATTEMPT/GESTURE/

SUCIDAL IDEATION (CAREFULLY DISTINGUISH FROM ATTEMPT OR ACT)

SUICIDAL IDEAS
INCR SUICIDAL IDEATION
SUICIDAL IDEATION

ORAL COMPLAINTS

SL SWELLING OF TONGUE
SWOLLEN TONGUE
GUM SWELLING
BRUXISM
GRINDING TEETH
CLENCHING TEETH
INTENSE MOUTH INFECTION
MUCOUS MEMBRANE RASH
SORES IN MOUTH
STOMATITIS
MUCOUS MEMBRANE LESION

RESPIRATORY ILLNESS

BRONCHITIS
BRONCHOSPASM
WHEEZING/ASTHMA
COUGH
COUGHING

UPPER RESPIRATORY COMPLAINTS,MINOR

HEAD COLD
RHINITIS
COLD-HAY FEVER
COMMON COLD
NASAL CONGESTION
NASAL STUFFINESS
SNEEZING

SINUS CONGESTION
SINUS BLOCK
HEAD & SINUS CONGESTION
DRY NOSE
DRYNESS OF NOSE
EPISTAXIA
NASAL BLEEDING
NOSE BLEEDING
ERYTHEMA OF THE LARYNX
HOARSENESS
ENLARGED TONSILS WITH EXUDATE

SORE THROAT

TONSILLITIS

SHORTENESS OF BREATH/DYSPNEA

BREATHLESSNESS
DYSPNEA
EXERTIONAL DYSPNEA
SHORTNESS OF BREATH
SIGHING
DIFFICULTY BREATHING

RESPIRATORY RATE OR RHYTHM DISTURBANCE:

/GEN	HYPERVENTILATING	HYPERVENTIL	RES
/GEN	HYPERVENTILATION	HYPERVENTIL	RES
/GEN	IRREGULAR BREATHING	HYPERVENTIL	RES
/GEN	RAPID BREATHING	HYPERVENTIL	RES

SPECIAL SENSES

AUDITORY

HEARING DEFICIT
DEC HEARING RT EAR
EARS BLOCKED
EARS POPPING
BUZZING IN THE EARS
TINNITUS
TINNITUS,BILAT
TINNITUS,ONE DAY
BUZZING IN EAR
CLICKING NOISE (R) EAR
EAR-RINGING
RINGING IN EARS
RING(ING) EARS
"RINGING" IN EARS

LION 301 MADE IN JAPAN

	GUSTATORY	LOSS OF SENSE OF TASTE PECULIAR TASTE (IN MOUTH) PECULIAR TASTE(IN MOUTH) UNPLEASANT TASTE IN MOUTH	
	OLOFACTORY	ALTERED SENSE OF SMELL SENSE OF SMELL CHANGED	
	VISUAL DISTURBANCE	BLURRED VISION JERKY VISION DRY EYES	

		GLASSY EYES SQUINTING EYES	
		BILATERAL CONJUNTIVITIS CONJUNCTIVITIS EYES TEARING SCRATCHY EYE	
	DOUBLE VISION	DIPLOPIA	
	PHOTOPHOBIA		
HMRG	SUBCONJUNCTIVAL HEMORRHAGE	HEMORR EYE	SS/EYE/GEN/

NONSPECIFIC SYSTEMIC COMPLAINTS:

	BODY ODOR STRONG B.O.	
	FATIGUE	

LION 361 MADE IN JAPAN

MUSCLE WEAKNESS
PHYSICAL WEAKNESS
"WEAK SPELLS"
TIREDNESS
TIREDNESS/FATIGUE
WEAKNESS
YAWNING

FEVER/CHILLS

FEVER

FEVER OF UNKNOWN ORIGIN
FEVERISH
TEMPERATURE ELEVATION
CHILLS

B	HERPES	HERPES SIMPLEX	SKIN/DERM/V
B	HERPES SIMPLEX	HERPES SIMPLEX	SKIN/DERM/V
B	HERPES SIMPLEX,IN MOUTH	HERPES SIMPLEX	SKIN/DERM/V

B	HERPES-FACE & MOUTH	HERPES SIMPLEX	SKIN/DERM/V
B	FEVER BLISTERS	HERPES SIMPLEX	SKIN/DERM/V
B	COLD SORE	HERPES SIMPLEX	SKIN/DERM/V
B	COLD SORE X2 DAYS	HERPES SIMPLEX	SKIN/DERM/V

FLU LIKE SYMPTOMS/GENERAL MALAISE (NOT PART OF DEPRESSION)
FLU-LIKE SYMPTOMS
GENERAL BODY ACHES
BODY ACHES
GENERAL DISCOMFORT
MUSCLE PAIN/STIFFNESS
MUSCLE PAINS
VIRAL ILLNESS

INFECTION	INFEC	BODY/GEN

PAIN

(THE INTERPRETATION OF PAIN BY NOMINAL BODY REGION IS VALUELESS. BECAUSE THE MEANINGFUL INTERPRETATION DEPENDS UPON ANCILLARY INFORMATION, THIS ENTIRE SET OF COMPLAINTS MUST BE ANALYZED AFTER IT IS RECATAGORIZED ON THE BASIS OF PROBABLE PATHOGENESIS, TAKING INTO ACCOUNT THE CLINICAL SETTING,ETC. THIS IS NOT A SUGGESTION TO GUESS AT WHETHER OR NOT DRUG CAUSED THE EVENT! IT IS A

LION 301 MADE IN JAPAN

GALL BLADDER DISEASE, ESOPHAGITIS, AND FUNCTIONA
MANIFESTATIONS OF ANXIETY.)

ACHE IN JAW	PAIN	BODY/HEAD
ARM PAIN	PAIN	BODY/UE
ARM PAIN (LT)	PAIN	BODY/UE
BURNING IN MOUTH	PAIN	DIG/BUC
CRAMPS	PAIN	BODY/UE
CRAMPS IN FINGERS	PAIN	BODY/UE
GUM IRRITATION/PAIN	PAIN	DIG/BUC
HIP PAIN	PAIN	BODY/LE
PAIN IN HIP	PAIN	BODY/LE
LEG PAIN	PAIN	BODY/LE
LEG/HIP PAIN	PAIN	BODY/LE
MOUTH PAIN	PAIN	DIG/BUC
PAIN ACROSS FACE	PAIN	BODY/HEAD
PAIN IN HAND	PAIN	BODY/UE
PAINFUL SCAR	PAIN	BODY/GEN

PRESSURE IN NECK, EYES, & ARMS	PAIN	BODY/GEN
RECTAL PAIN	PAIN	DIG/REC
SENSATIONS AS OF "QUICK SHOCKS" IN LEGS	PAIN	BODY/UE
SHARP PAINS	PAIN	BODY/GEN
SHIN SPLINTS	PAIN	BODY/LE
SORE FEET	PAIN	BODY/LE
SORE FINGER	PAIN	BODY/UE
TENSION	PAIN	BODY/GEN
TIGHT MUSCLES	PAIN	MS/MUS
TRIGEMINAL NEURALGIA	PAIN	BODY/HEAD
LEG PAIN -- "SCIATICA"	PAIN	BODY/LE
LEG PAIN "SCIATICA"	PAIN	BODY/LE
ABDOMINAL CRAMPS	PAIN ABDO	BODY/ABDO
ABDOMINAL PAIN	PAIN ABDO	BODY/ABDO
ABDOMINAL PAIN.NEW ONSET	PAIN ABDO	BODY/ABDO
ABDOMINAL PAIN/CRAMPS	PAIN ABDO	BODY/ABDO
GASTRIC PAIN	PAIN ABDO	BODY/ABDO
STOMACH PAIN/CRAMPS	PAIN ABDO	BODY/ABDO
INCREASED ABDOMINAL DISCOMFORT	PAIN ABDO	BODY/ABDO
STOMACH PAIN	PAIN ABDO	BODY/ABDO
'TUMMY ACHE'	PAIN ABDO	BODY/ABDO
BACK ACHE	PAIN BACK	BODY/BACK
BACK PAIN	PAIN BACK	BODY/BACK
BACK PAINS	PAIN BACK	BODY/BACK
BACKACHE	PAIN BACK	BODY/BACK
LUMBAR-SACRAL BACK PAIN	PAIN BACK	BODY/BACK
LUMBAR-SACRAL BACKPAIN	PAIN BACK	BODY/BACK
NAGGING PAIN IN RT ILIAC REGION	PAIN BACK	BODY/BACK
SCIATICA	PAIN BACK	BODY/BACK
TIGHTNESS LOWER BACK	PAIN BACK	BODY/BACK

LION 301 MADE IN JAPAN

BREAST PAIN	PAIN BREAST	UG/FG/BRST
BREAST TENDERNESS	PAIN BREAST	UG/FG/BRST
SORE NIPPLES	PAIN BREAST	UG/FG/BRST
CHEST PAIN	PAIN CHEST	BODY/THOR
CHEST PAINS	PAIN CHEST	BODY/THOR
CHEST PAINS-2D	PAIN CHEST	BODY/THOR
FUNCTIONAL CHEST PAIN	PAIN CHEST	BODY/THOR
THORACIC PAIN	PAIN CHEST	BODY/THOR
TIGHT CHEST	PAIN CHEST	BODY/THOR
TIGHTNESS IN CHEST	PAIN CHEST	BODY/THOR
CHEST PRESSURE QAM & QHS	PAIN CHEST	BODY/THOR
CHEST TIGHTNESS	PAIN CHEST	BODY/THOR
RETROSTERNAL PAIN	PAIN CHEST SUBSTERN	BODY/THOR
SUBSTERNAL TIGHTNESS "LIKE A LUMP"	PAIN CHEST SUBSTERN	BODY/THOR
EARACHE	PAIN EAR	SS/EAR/GEN
EAR ACHE	PAIN EAR	SS/EAR/GEN
EYE ACHE	PAIN EYE	SS/EYE/GEN
EYE ACHES	PAIN EYE	SS/EYE/GEN
EYES ACHING	PAIN EYE	SS/EYE/GEN
NECK/BACK INJURY	PAIN NECK	BODY/NECK
NECK ACHE	PAIN NECK	BODY/NECK
NECK PAIN	PAIN NECK	BODY/NECK
TENSE NECK MUSCLES	PAIN NECK	BODY/NECK
TIGHTNESS IN NECK MUSCLES	PAIN NECK	BODY/NECK
TOOTHACHE	PAIN TOOTH	DIG/BUC

END PAIN TERMS

THIRST

COMPULSIVE DRINKING
POLYDIPSIA
THIRST
INCREASED THIRST
INCR'D THIRST
INCREASED THIRST-NOT DRY MOUTH

161

Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, N. C. 27709

Wellcome

cables & telegrams
Tabloid Raleigh, N. C.
TWX510927[illegible]
tel. 919 248-3000

Tech

April 4, 1989

NEW CORRESPONDENCE

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

RECEIVED
NAT... CENTER
APR 0 5 1989
HFN-120
FOR DRUGS &
NDA 18-64[illegible]
WELLBUTRIN® Tablets

Dear Dr. Leber:

Reference is made to Dr. Temple's letter of March 24, 1989 as well as my telephone conversation with you on March 29, 1989 concerning labeling for WELLBUTRIN (bupropion hydrochloride) Tablets.

The letter of March 24 from Dr. Temple indicates agreement with the conclusions of our recent clinical studies with WELLBUTRIN establishing efficacy at 300 mg per day and confirming a seizure rate of approximately 0.4% within the recommended dosing range. These conclusions are based on our recent submissions of October 7 and December 19, 1988, which included reports for studies 84A (efficacy study) and 86A (surveillance study), respectively. Based on the results of these studies, we have submitted labeling revisions for the following sections of the package insert: Indications and Usage, Contraindications, Warnings, and Dosage and Administration. The letter of March 24 summarizes the Agency review of our proposed labeling and provides specific recommendations. Our response to these recommendations follows.

Contraindications

As you suggest, the revisions for this section proposed in our submission of December 19, 1988 will be incorporated in the final printed labeling.

Warnings

We agree to add the original first paragraph to this section, but would like to discuss possible modifications to the wording in this paragraph.

Dosing and Administration

We agree to begin this section with "General Dosing Considerations" and will insert the word "also" into the sentence beginning with "Gradual escalation". Concerning the proposed first sentence for "General Dosing Considerations," we would like to discuss the wording in this sentence in the context of other references to seizures in the final printed labeling.

Indications and Usage

We agree to incorporate the second, third and fourth paragraphs as you suggest.

We disagree, however, with the proposed first paragraph. While we continue to share your concern that physicians be fully informed about the seizure risk associated with the use of WELLBUTRIN, the first paragraph is unduly restrictive and is not justified by what is known about the relative rates of seizure for other antidepressants. We view this labeling as excessively alarming compared to labeling for all other antidepressants, and believe it will prevent physicians from making accurate risk/benefit assessments. As a result, many patients who may benefit from WELLBUTRIN therapy will be deprived of this therapeutic alternative because of inappropriate physician concerns generated by the indications statement.

An accurate assessment of risk/benefit for WELLBUTRIN can be made only if the seizure risk is balanced fairly against the important safety advantages associated with its use. Suicide, for example, is a primary concern for physicians treating depressed patients with currently available products. Tricyclics, the antidepressants prescribed for the vast majority of depressed patients, are the most common cause of death in overdose. WELLBUTRIN, with its relative safety in overdose, will provide a reasonable alternative for the treatment of patients with suicidal ideation or intent, and its use could have a significant impact on reducing mortality and morbidity in suicide attempts. The safe cardiovascular profile of WELLBUTRIN also provides a treatment for depressed patients with cardiovascular disease or orthostatic hypotension, who otherwise would receive subtherapeutic doses of other antidepressants or no treatment at all. In addition, patients with weight gain and intolerable anticholinergic effects from other antidepressants could benefit from WELLBUTRIN. While we do not wish to minimize the importance of the seizure issue, we do want physicians to be able to make informed decisions about the use of WELLBUTRIN so that these safety advantages can be properly utilized in the population of patients who require treatment for depression. This will be precluded by unduly restrictive labeling.

MADE IN JAPAN

Accordingly, we propose that the indication for WELLBUTRIN should remain as proposed in our December 19, 1988 submission, "WELLBUTRIN is indicated for the treatment of depression." The multiple, prominent seizure warnings in other sections of the revised labeling greatly exceed the warnings for any other antidepressants despite marginal differences in seizure rates. These differences in labeling will assure a clear distinction between WELLBUTRIN and other antidepressants, and will meet our mutual goals of fully informing physicians.

As discussed in our telephone conversation, we would like to request a meeting with you, your staff, and Dr. Temple to discuss the above revisions to the WELLBUTRIN labeling.

Sincerely,

George M. Lyon, Jr., M.D.
Director
Drug Regulatory Affairs

ORIGINAL COPY

LION ... MADE IN JAPAN

Burroughs Wellcome Co.

Wellcome

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

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel 919 248-3000

January 13, 1989

SCS/85
-003
NDA SUPPL AMENDMENT

Paul Leber, M.D., Director
Division of Neuropharmacological
Drug Products
Office fo Drug Research and Review
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville MD 20857

RE: NDA 18-644
Wellbutrin® (bupropion) Tablets

Dear Dr. Leber:

Reference is made to telephone calls from Dr. Gene Levine of your Division to George Lyon, M.D. of our Department and to Andy Johnson, Pharm. D. of our Medical Division on January 12, 1989 regarding a request for some additonal statistical analyses.

Enclosed is the following information related to the Hamilton Depression, Depressed Mood, Item 1 Analyses:

Appendix A - T-tests for the differences between Wellbutrin and placebo on observed change scores by site for assessment days 7, 14, 21, 28, 35 and 42.

Appendix B - Results of tests for treatment-by-site interactions for assessment days 7, 14, 21, 28, 35 and 42.

If you have any questions regarding the submission, please contact Loren Miller, Ph.D., Drug Regulatory Affairs at (919) 248-4151.

Sincerely,

D. A. Knight
Associate Director
Drug Regulatory Affairs

RECEIVED
NATIONAL CENTER
JAN 13 1989
HFN-130
FOR DRUGS & BIOLOGICS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-644/S-003

MAR 24 1989

Burroughs-Wellcome Company
Attention: Loren Miller, M.D.
Drug Regulatory Affairs
3030 Cornwallis Road
Research Triangle Park, North Carolina 27709

Dear Dr. Miller:

Please refer to your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Wellbutrin^{R} (bupropion hydrochloride) tablets.

Please also refer to your submissions of October 7, 1988, December 19, 1988 (S-003), January 11, 1989, and January 13, 1989, providing the results of the bupropion seizure study (86A) and the efficacy study utilizing the 300mg dose (84A). We have reviewed the data from study 86A and we agree that these data provide confirmation that the crude seizure rate associated with Wellbutrin use at doses of 450 mg/day or less is approximately 0.4%. We have also reviewed the data from study 84A, and we agree that these data provide support for the antidepressant efficacy of Wellbutrin at a dose of 300 mg/day in moderately depressed outpatients. However, we do not agree with all of your proposed revisions of the labeling for Wellbutrin. Consequently, while S-003 is Approvable, its final approval will be contingent upon your submitting final printed labeling containing our additional revisions to the labeling, which we have detailed in the remaining sections of this letter. We have commented on your proposed revisions to the labeling and we have proposed alternative wording in the instances where we disagree. These comments and alternative wording proposals are provided on a section by section basis, as follows:

1.0 Indications and Usage

1.1 Proposed Changes

You have dropped the reference to Wellbutrin being a drug of second choice, and alternatively, you have proposed that it should be indicated simply for the treatment of depression. You have also added a reference to the fact that Wellbutrin has now been demonstrated to be effective in a trial of 6 weeks duration in outpatients with depression. Finally, you have dropped the sentence referring to the lack of evidence for effectiveness beyond 3 weeks.

1.2 Comment

We disagree with a first line status for Wellbutrin. Although it is true that we do not have reliable seizure estimates from comparably designed studies for any of the marketed antidepressants, it is generally believed that the seizure

incidence for imipramine and most other tricyclic antidepressants is approximately 0.1%. You cite the recently marketed Prozac as having a crude seizure rate of 0.2%. However, it is important to note that this estimate includes all premarketing events that could possibly have been considered seizures (i.e., 16/8000). In fact, only 10 of these events could confidently be considered seizures, yielding a rate of 10/8000, i.e., approximately 0.1%. [Note: Your estimate of crude seizure rate for Wellbutrin, based on Study 86A, includes only well documented seizures, and would be somewhat higher if questionable cases were included.] Thus, the crude seizure rate for Wellbutrin at doses of 450 mg/day or less is probably 4-fold the rate for most marketed antidepressants. At the time of the original approval of Wellbutrin as a second line antidepressant drug, the estimate of seizure incidence for patients receiving doses of 450 mg/day or less was 0.33%, so we now are seeing an observed incidence which is actually slightly higher. Consequently, we do not believe that there is adequate justification for dropping the second line status for this drug.

It is also important to note that, although you have now generated data suggesting the antidepressant efficacy of Wellbutrin at a dose of 300 mg/day, this study (84A) was done in depressed outpatients. The other data upon which the original approval of Wellbutrin was based come from depressed inpatients, many of whom were dosed at 450 mg/day. It is possible that some patients may need doses up to 450 mg/day, and the labeling will have to reflect this fact. Thus, even if you could demonstrate that the seizure rate is substantially lower at 300 mg/day, we would still not be inclined to accept a first line status for Wellbutrin. Alternatively, you would need to show that Wellbutrin has some specific therapeutic advantage over other antidepressants, in which case it could be a first line drug for whatever subgroups seem to differentially benefit.

We agree that the labeling can now indicate that Wellbutrin has been demonstrated to be effective in a 6 weeks trial in depressed outpatients, but your proposed wording implies that efficacy has been demonstrated in 6-week trials in both inpatients and outpatients, and this needs to be clarified. In addition, there still needs to be some discussion of the lack of evidence beyond 6 weeks. We think that, in regard to longer term use, the standard language used in the labeling for Prozac would be appropriate here as well.

1.3 Recommendations

We recommend that the first paragraph in the currently approved FPL be retained, with changes only in the multiples of the doses at which the seizure risk increases, as follows:

"Wellbutrin is indicated for the treatment of depression. Generally, its use should be reserved for patients who fail to respond adequately to, or who cannot tolerate, alternative antidepressant therapy. Wellbutrin is not recommended as an antidepressant of first choice for most patients because its use at doses of 450 mg/day and below is associated with a seizure rate of 0.4%, a rate believed to be approximately four-fold higher than the rate for other marketed antidepressants (see Warnings)."

MADE IN JAPAN

We recommend the following as the second paragraph:

"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."

The third paragraph, defining major depression, can remain as is.

For the fourth paragraph, we recommend the following:

"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."

2.0 Contraindications

2.1 Proposed Changes

You have modified this section by adding a contraindication for the use of Wellbutrin in patients with a current or prior diagnosis of bulimia or anorexia nervosa. Otherwise, this section is unchanged.

2.2 Comment and Recommendations

We agree with your revision of this section of the labeling.

3.0 Warnings

3.1 Proposed Changes

The language in the first paragraph of your revised Warnings section diminishes the strength of the warning. This section eliminates the seizure incidence table, but does retain the incidence estimates that suggest a steep dose response curve, and it adds the seizure incidence estimate from the recently completed open study (86A). It retains a modified version of the paragraph linking risk to dose and to predisposing factors. It eliminates the paragraph referring to adherence to dosing recommendations, and alternatively, it expands this paragraph by including the specific dosing recommendations that had previously been in the original Dosage and Administration section.

3.2 Comment

While we agree that your revised Warnings section is generally an improvement over the original, we believe that it goes too far in diminishing the impact of the original first paragraph.

3.3 Recommendations

We ask that you retain the original first paragraph in the currently approved FPL for Wellbutrin. The remaining paragraphs of your revised Warnings section are acceptable.

4.0 Dosage and Administration

4.1 Proposed Changes

You have rearranged this section of the labeling by putting the actual dosing recommendations first, followed by a general discussion of the rationale for using caution in dose escalation. Of note, you have removed all references to the occurrence of seizure in this discussion. Also, as noted earlier, all of the specific recommendations regarding dosing strategies to decrease the possibility of seizure have now been moved to the Warnings section. There is also a revision of the "Maintenance" subsection.

4.2 Comments

We agree with your rewording of the two subsections giving actual dosing recommendations, i.e., "Usual Dosage for Adults" and "Increasing the Dosage Above 300 mg/day." However, we think that it would be preferable to have the "General Dosing Considerations" subsection first, to provide the rationale for the actual recommendations. We also think that there should be some mention of the seizure problem in this general discussion section, with a reference to "Warnings" for more complete details. We have no objection to the revised "Maintenance" subsection.

4.3 Recommendations

We ask that you put the "General Dosing Considerations" section at the start of the Dosage and Administration section. In addition, this introductory section should begin with the following:

"Since there is an almost 10-fold increase in seizure risk associated with a dose increase from 450 mg/day to 600 mg/day, it is necessary to administer this drug in a manner most likely to minimize the risk of seizure (see Warnings)." In addition, the sentence beginning "gradual escalation ..." should be modified by adding "also" after "is," i.e., "gradual escalation in dosage is also important ...," in order to emphasize that these are secondary reasons for using caution.

This introductory section can then be followed by your two paragraphs giving actual dosing recommendations and your revised "Maintenance" subsection.

LION 301 MADE IN JAPAN

Should you have any questions please contact Mr. Tony DeCicco, Consumer Safety Officer at (301) 443-3504.

Sincerely yours,

Robert Temple

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

MADE IN JAPAN

MAR 22 1989

MEMORANDUM

DATE: March 22, 1989

FROM: DIRECTOR, DNDP

TO: FILE NDA 18-644/S-003
and
DIRECTOR, OFFICE OF DRUG EVALUATION I, HFD-100

SUBJECT: WELLBUTRIN APPROVAL ACTION, MEMORANDUM OF 3/16/89 FROM THE OFFICE DIRECTOR TO DR. LEBER and THE MEMORANDUM OF 3/20/89 FROM THOMAS LAUGHREN.

First, I agree to the revision suggested for the Indications Section by Dr. Temple.

In hindsight, it seems sensible to consider why we failed to include a more explicit statement about Wellbutrin's relative epileptogenic potential in the Indication Section of the labeling we approved in December of 1985. As I recall, we were certainly very concerned about the possibility; in fact, the wording of both the Warnings and Dosage and Administration Sections of the originally approved labeling clearly conveys our concern that inter-individual variation in drug metabolism and/or susceptibility might make Wellbutrin a very risky drug for some patients at the dose recommended.

A review of the data then available will reveal why we did not make a more definitive statement in the labeling about Wellbutrin's relative risks. At the time, the point estimates available for the incidence of Wellbutrin associated seizure were, on face, not that disconcerting, especially if viewed in isolation. For doses less than 450 mg, the estimated incidence was 0.2%; moreover, among "patients without a seizure predisposition," the point estimate of incidence at a dose of 450 mg sa day was only 0.2%. To be clear, we were not especially reassured as these estimates were based on crude proportions of patients uncorrected for the time at which patients were exposed. Moreover, we did not have reliable data on seizure incidence for marketed antidepressants which we guessed to be about 0.1%. Thus, while we clearly feared that the risk at the recommended dose might be higher, the most we could do responsibly was to point out the 'steepness' of the relationship between seizure incidence and dose.

The results of study 86A, however, now document that the incidence of seizure is 0.4% among a population of patients, (importantly, patients without a seizure predisposition) treated with doses of Wellbutrin within the range recommended in product labeling 300-450/day). This point estimate is higher than that upon which our original approval action was based. Moreover, we now are aware that the risk of seizure with fluoxetine seems likely to be very close to 0.1% Thus, with Study 86A in hand, I feel much more

comfortable in following Dr. Temple's suggestion and asserting explicitly in the Indications Section that Wellbutrin is more epileptogenic than other antidepressants.

On the other hand, nothing in the newly submitted data has reduced my concerns about the potential risks associated with the marketing of a drug that is potently epileptogenic at doses only 1.5 to 2 fold greater than those required to produce a therapeutic result. In this respect, I disagree with Dr. Temple's analysis and would personally favor retaining some statement noting the steepness of the dose response relationship in the revised Indications Section. However, my preference stated, I am quite willing to accept the revision proposed because the Warnings Section still provides adequate notification about the dramatic increase in seizure incidence associated with only small increases in daily dose.

Paul Leber, M.D.
March 22, 1989

cc: Orig NDA 18-644
HFD-120
cc:Laughren
DeCicco
Katz

CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 20, 1989

FROM: Thomas Laughren, M.D.
Group Leader, Psychiatric Drug Products

SUBJECT: Wellbutrin, NDA 18-644/S-003

TO: Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products (HFD-120)

I was not really involved with Wellbutrin at the time of its approval, and in preparing the current approvable package, I may have misunderstood the basis for our decision to originally approve Wellbutrin only as a second line antidepressant. I thought our decision was based both on the steepness of the seizure dose-response curve and on the somewhat high absolute estimate of seizure incidence, i.e., relative to other antidepressants. While I believe that both of these issues are still relevant, I am now inclined to agree with Dr. Temple that steepness of the seizure dose-response curve can no longer be a basis for recommending Wellbutrin only as a second line drug. Study 86A does reassure us that, when Wellbutrin is used as recommended, it is associated with an acceptable crude seizure incidence, even if that incidence is somewhat higher than that seen with other marketed antidepressants. Nevertheless, while I do believe that the seizure rate of 0.4% is acceptable for approving Wellbutrin for marketing, I do think that this rate is too high to recommend Wellbutrin as an antidepressant of first choice.

I do feel a little uncomfortable with the absolute seizure estimate of 0.1% for TCAs, since we don't have data of the same quality as the Wellbutrin data to support this estimate. The estimate of 0.1% is the rate often cited in the literature, but it represents more a belief than a fact. Probably the best data come from a prospective study by Jick, et al involving several TCAs and yielding a seizure incidence estimate of 0.06%. The 0.1% rate for fluoxetine is based on the data in the NDA. It's worth noting that BW had an opportunity to do a head-to head comparison with a TCA, indeed, they were strongly encouraged to do so both by us and the PDAC. Unfortunately, they chose not to. In any case, maybe we can put a quantitative estimate about relative seizure rate in labeling in a somewhat softer form, e.g., we might say Wellbutrin has a risk of seizure that is believed to four-fold that for other marketed antidepressants.

MADE IN JAPAN

indications section to address the issue [illegible] proposed that the relatively greater risk of seizure associated with Wellbutrin use compared to other marketed antidepressants is the basis for second line status, rather than the steepness of the seizure dose-response curve. I have also hedged this section a bit more. While this hedging should make the labeling more acceptable to BW and less burdensome for clinicians who want to use Wellbutrin as an antidepressant of first choice, I think it still conveys the message that Wellbutrin should not be the drug of first choice for most patients. I have made no other changes in the letter.

Thomas P. Laughren
3-20-89

Thomas P. Laughren, M.D.

cc:
Orig. NDA 18-644
HFD-120
HFD-120/TLaughren
/TDeCicco
ft/pjb/3/20/89
doc 3138k

MEMORANDUM

DATE: March 5, 1989

FROM: DIRECTOR, DNDP

TO: DIRECTOR, ODE I

SUBJECT: WELLBUTRIN EFFICACY SUPPLEMENT [NDA 18-644/S-003]

Background:

In early 1986, within weeks of gaining FDA's approval of the NDA for Wellbutrin (bupropion), Burroughs Welcome Co. elected to suspend plans for its marketing of this 'second generation' antidepressant drug product. The decision not 'to launch' their commercial marketing program was 'voluntary' and was taken in the face of emerging evidence that added to already existing concerns and uncertainties about bupropion's high, and until then presumably dose related, potential to cause generalized convulsions.

The evidence that kept bupropion from being immediately marketed arose from a small clinical study evaluating the effects of bupropion in normal weight, otherwise healthy, bulimics. At the time the FDA was first informed of the situation, four of approximately 40 young female subjects in the on-going study had experienced generalized convulsions while on daily doses of Wellbutrin below the maximum recommended in the product's recently approved labeling. The importance of this cluster of seizures was that it raised serious doubts about two fundamental assumptions upon which approval of the Wellbutrin NDA had been based: 1) that seizure incidence was reliably predicted by dose and 2) that under the conditions of use recommended in the labeling, seizure incidence would be no more than 2 or 3 fold that presumed for other already marketed antidepressant drugs.

It is important to emphasize, as the passage of time may cause us to forget, that the agency's original decision to approve Wellbutrin had been especially close. Although widely touted as a potential therapeutic advance because of its lack of anticholinergic side effects and relative inability to cause orthostatic hypotension, the evidence to support the actual advantages of the bupropion in use was largely testimonial. Thus, the case for Wellbutrin's superiority to marketed antidepressants was, although theoretically sound, hardly proven. Furthermore, bupropion had several potential disadvantages including an unusual capacity, compared to antidepressants marketed at the time (fluoxetine has changed matters somewhat) to cause agitation, insomnia, weight loss, even psychotic phenomena and was thought by some to have a potential for abuse as a stimulant substance. Most alarming, of course, was the drug's capacity to cause seizure at a very high incidence at doses only slightly higher than those required to document its effectiveness. Indeed, it was only after we became convinced that seizure incidence was reliably predicted

MEMORANDUM

DATE: March 5, 1989

FROM: DIRECTOR, DNDP

TO: DIRECTOR, ODE I

SUBJECT: WELLBUTRIN EFFICACY SUPPLEMENT [NDA 18-644/S-003]

Background:

In early 1986, within weeks of gaining FDA's approval of the NDA for Wellbutrin (bupropion), Burroughs Welcome Co. elected to suspend plans for its marketing of this 'second generation' antidepressant drug product. The decision not 'to launch' their commercial marketing program was 'voluntary' and was taken in the face of emerging evidence that added to already existing concerns and uncertainties about bupropion's high, and until then presumably dose related, potential to cause generalized convulsions.

The evidence that kept bupropion from being immediately marketed arose from a small clinical study evaluating the effects of bupropion in normal weight, otherwise healthy, bulimics. At the time the FDA was first informed of the situation, four of approximately 40 young female subjects in the on-going study had experienced generalized convulsions while on daily doses of Wellbutrin below the maximum recommended in the product's recently approved labeling. The importance of this cluster of seizures was that it raised serious doubts about two fundamental assumptions upon which approval of the Wellbutrin NDA had been based: 1) that seizure incidence was reliably predicted by dose and 2) that under the conditions of use recommended in the labeling, seizure incidence would be no more than 2 or 3 fold that presumed for other already marketed antidepressant drugs.

It is important to emphasize, as the passage of time may cause us to forget, that the agency's original decision to approve Wellbutrin had been especially close. Although widely touted as a potential therapeutic advance because of its lack of anticholinergic side effects and relative inability to cause orthostatic hypotension, the evidence to support the actual advantages of the bupropion in use was largely testimonial. Thus, the case for Wellbutrin's superiority to marketed antidepressants was, although theoretically sound, hardly proven. Furthermore, bupropion had several potential disadvantages including an unusual capacity, compared to antidepressants marketed at the time (fluoxetine has changed matters somewhat) to cause agitation, insomnia, weight loss, even psychotic phenomena and was thought by some to have a potential for abuse as a stimulant substance. Most alarming, of course, was the drug's capacity to cause seizure at a very high incidence at doses only slightly higher than those required to document its effectiveness. Indeed, it was only after we became convinced that seizure incidence was reliably predicted

by dose that the NDA was finally approved, and then, with very strong labeling advising the product not be used as a treatment of first choice.
Thus, the evidence emerging from the bulimia study was especially alarming. An incidence of seizure of 8% per six weeks exposure was totally inconsistent with the presumption that Wellbutrin, administered at the doses recommended in labeling, would be associated with an incidence of only 0.3% per treatment episode. In short, the emerging evidence raised the possibility that our assumptions about dose and seizure were terribly inaccurate; in fact, in the worse case, they might be off perhaps by an order of magnitude.

Incidentally, it is important for reasons of historical context to realize that all of this was taking place <u>para passu</u> with the worldwide marketing withdrawal of Merital, an antidepressant we had approved only a year earlier.

In any case, prudence dictated caution. The agency and firm simultaneously initiated programs to reassess the question of seizure and sought the counsel of our Advisory Committee. What happened thereafter is briefly recounted in the Background Section of Tom Laughren's 2/14/89 review. His account is generally complete, but it fails to capture the extent and cost of the effort involved in gaining the firm's agreement to pursue the study that has now been completed. Indeed, many quarters gratuitously criticized the agency for its caution and this generally added to the difficulty we had in securing agreement from the firm.

I mention all of this because I believe the data presented in the current Supplement prove the wisdom of our policy.

Conclusions:

The evidence submitted in S-003 confirms that Wellbutrin has a greater potential than other antidepressants to cause generalized convulsions. Critically, however, the data amassed in Study 86A documents that the incidence of seizure at doses of 450mg a day or less is within limits deemed acceptable in a marketed antidepressant. Interestingly, the point estimate of approximately 0.4% is slightly higher than that originally estimated from the incomplete sources of data available at the time of the NDA's original approval. Thus, Wellbutrin, although reasonably safe for marketing is not a drug with ideal properties. It must be used with caution, and should remain a treatment that is reserved for patients who have failed to respond to less risky antidepressants. This conclusion is essentially identical to the one I reached more than 3 years ago; if anything, it makes more sense today given the marketing of Prozac (fluoxetine), an antidepressant which is proving to be a treatment with fewer risks than older antidepressants and a profile of benefits not unlike

those claimed for Wellbutrin.

The fact that the firm has now adduced evidence in a controlled trial (Study 84A) that Wellbutrin can be effective when administered at a dose of 300 mg a day does NOT affect this conclusion. Seizure incidence is clearly dose related, but we have no way of determining from the data in hand just how much the risk of seizure will be affected by the revised recommendation to use the drug at doses of 300mg a day.

In my judgment, it is most prudent to take a wait and see approach. Let the firm market the drug under the labeling revisions proposed by Dr. Laughren. If the risk of seizure associated with Wellbutrin, as judged by voluntary post-marketing reporting rates, is eventually observed to be essentially identical to the risk of seizure inferred for Prozac, I would be favorably inclined toward allowing removal of the restrictive indication. (Incidentally, my willingness to rely on post-marketing reporting may seem unusual as I am not ordinarily in favor of using reporting rates ratios to estimate the relative risk of products to cause ADRs. However, generalized convulsions are, like death, relatively easy events to count and classify; thus, the exception.

Closing Comment:

Some might be tempted to argue that the results of study 86A show that the delay in Wellbutrin's marketing was not worthwhile. Indeed, they might be tempted to argue that the agency's conservatism kept a valuable drug out of reach for three years. Perhaps, but the delay had clearly beneficial effects as well. Indeed, it will lead to the introduction of the drug under conditions that will allow it to be used more effectively and efficiently, and perhaps safely.

Specifically, the delay gave the firm the chance to carry out a controlled study of Wellbutrin in ambulatory depressed patients. Its results document that Wellbutrin can be used effectively at a dose considerably lower than that recommended in the labeling with which Wellbutrin was initially approved. Considering the fact that dose predicts not only seizure, but probably a whole series of troubling side effects, the delay can be viewed as beneficial, not only for the patients who would have suffered side effects at higher doses, but for the product's reputation, and perhaps chance for success in the marketplace.

LION 301 MADE IN JAPAN

Recommendation:

Issue the approvable letter attached to this package.

Paul Leber, M.D.
March 5, 1989

cc: Original NDA 18-644
HFD-120
HFD-120/P. Leber/T. Laughren/CSO
HFD-713/J. Levine

LION 301 MADE IN JAPAN

Burroughs Wellcome Co.

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

Wellcome

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

GUS

NDA SUPPL AMENDMENT
5 CS/BS
002

January 11, 1989

Paul Leber, MD, Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Review
Office of Drug Review 1
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 18-644
Wellbutrin®(bupropion) Tablets

Dear Dr. Leber:

Reference is made to a telephone conversation between Dr. Thomas Laughren of your Division and Dr. Charles Lineberry of our Medical Division on January 6, 1989 regarding a request for additional statistical analyses on study data contained in our supplemental NDA submitted on December 19, 1988.

We are submitting herewith the requested tabular summaries, statistical analyses and figures.

If there are any questions regarding this material, please contact Loren Miller,PhD at (919) 248-4151.

Sincerely,

Donald A. Knight
Associate Director
Drug Regulatory Affairs



LION 301 MADE IN JAPAN

Wellcome

Burroughs Wellcome Co.

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

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

Food and Drug Administration
Document Control Section, HFN-46
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Dear Sir or Madam:

Pursuant to 21 CFR 314.80, this is to advise that no reports have been received and no actions taken with regard to the twelfth quarterly Periodic ADR Report for WELLBUTRIN® Tablets for the time period September 1, 1988 through November 30, 1988. WELLBUTRIN was not marketed during this quarter.

A copy of the current labeling is attached.

NDA 18-644

Sincerely,

Donald A. Knight
Associate Director
Drug Regulatory Affairs

RECD
HFN-20
DRUGS AND BIOLOGICS

MEMORANDUM

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 6, 1989

FROM: Thomas P. Laughren, M.D.
Group Leader, Psychiatric Drug Products Group
Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: Minutes of Teleconference between FDA staff (Dr. Laughren, Jay Levine, Tony DeCicco) and Burroughs Wellcome staff (Dr. Lineberry, Dr. Miller, and statistical staff), regarding additional information needed to assist us in our review of two recent submissions (October 7 and December 19, 1988), held on January 6, 1989.

TO: NDA 18-644 (Wellbutrin)

Summary of Meeting

Study 86A

1. Dosing Information

We indicated that summary dosing information was rather sparse for this study, consisting only of figure 1, which enumerated patients participating in the 3 cohorts by week for the initial 8 weeks of the study. We requested that they provide more detailed information, and suggested they present the data in the form of a dose-duration matrix, as described in our supplementary suggestions for preparing an integrated safety summary. They apparently do not have a copy of these suggestions, but a representative of BW will visit the Division next Tuesday to pick up a copy.

2. Life-Table Analysis

We noted that in their life table analysis for seizure incidence they calculated the cummulative incidence only out to 56 days, and thus included only 8 of the 13 seizures. We asked that they complete this analysis out to the duration for the latest occurring seizure, which happened to be at approximately 11 months. However, they indicated that duration data beyond 56 days are not yet entered into their database. Consequently, it would not be possible to generate the requested analysis without putting in a large amount of additional data.

LION 301 MADE IN JAPAN

Study 84A

For the efficacy study, we asked that they provide one additional analysis, i.e., for the HAM-D Depression Item. We asked for complete details of this analysis, including the 2-way analysis of variance for treatment by center interaction. For all 3 of the critical efficacy variables, i.e., HAM-D Total Score, HAM-D Depression Item and CGI Severity Score, we asked for plots of the treatment by center interactions in the instances where they were felt to be significant.

Thomas P. Laughren 1-10-89

Thomas P. Laughren, M.D.

16.1

Review and Evaluation of Clinical Data

NDA 18-644/S-03

Sponsor: Burroughs Wellcome Co.

Drug: Wellbutrin (bupropion tablets)

Drug Catagory: Artidepressant

Material Submitted: Original Supplement (S-03), December 19, 1988, containing 1) the final study report for study 86A, "Prospective Open Evaluation of the Seizure Incidence with Bupropion Hydrochloride," and 2) revised labeling, including a removal of the "not drug of first choice" restriction, as well as a recommendation for dosing at 300 mg/day; January 11, 1989 amendment to S-03, containing requested additional analyses for study 84A; this review will also cover the full study report for study 84A, dated October 7, 1988, and entitled "Multicenter Evaluation of the Efficacy and Safety of a 300 mg Daily Dose of Wellbutrin vs. Placebo in Depressed Outpatients."

Background

At the time of the original approval of Wellbutrin in December, 1985, the estimates of seizure incidence, based on a total exposed population of N=2398, were as follows: for doses less than or equal to 450 mg, 0.33%; for 600 mg, 2.3%; for 600 to 900 mg, 2.8%. However, prior to the marketing of Wellbutrin, an unexpectedly high incidence of seizure was observed (4 out of 55 patients) in a study of bulimic patients being treated with Wellbutrin at doses of less than 450 mg. This finding raised concern about the validity of the earlier estimates of seizure incidence. Since there was no persuasive explanation for this finding, we asked the sponsor to delay marketing until we could discuss this issue at the Psychopharmacologic Drugs Advisory Committee (PDAC). In preparation for the PDAC, the seizure rates were updated (April, 1986) to include an additional N=1583 patients. The revised rate in this combined population of N=3981 for doses of less than or equal to 450 mg was 0.40%.

The PDAC was held on April 25, 1986. The Committee agreed that Wellbutrin should not be marketed until the seizure rate could be confirmed in a prospective study. They recommended that the company conduct a large scale study comparing bupropion and imipramine. Despite this recommendation, the sponsor subsequently proposed a limited marketing of Wellbutrin, along with the conduct of this proposed comparative study.

However, we persisted in our view that Wellbutrin should not be marketed prior to the conduct of a prospective study, and the sponsor eventually agreed. Over the summer of 1986, we held several meetings with the sponsor regarding the design of an appropriate study to estimate seizure incidence. As a result

MADE IN JAPAN

of these meetings, we agreed on a decision rule for the marketing of Wellbutrin, i.e., Wellbutrin could be marketed if, in an appropriately designed and conducted study, the upper 95% confidence limit of seizure incidence associated with the use of Wellbutrin at recommended doses could be shown not to exceed 7/1000 patients exposed for 6 weeks. The problem was that we could not agree on the details of the appropriate study, in particular, the definition of the patient cohort. In September, 1987, the sponsor indicated its intent to abandon any further study of Wellbutrin.

After an extended period of relative inactivity, the sponsor informed us in June, 1987, that they planned to proceed with a large, open, uncontrolled study of Wellbutrin to assess the risk of seizure. Without providing any prior agreement regarding how we would interpret the outcome of such a study, we encouraged them to proceed with what was now being referred to as study 86A. Also at that time they informed us that they planned to conduct study 84A, a comparison of Wellbutrin 300 mg/day and placebo in depressed outpatients.

This review will focus on:

1. The safety data from study 86A, with an emphasis on seizure incidence

2. Efficacy and safety data from study 84A

3. Proposed labeling revisions for Wellbutrin

Safety Data from Study 86A

1.0 Investigators/Locations

Although 106 sights were registered for this study, four sites contributed no patients. Therefore, 102 sites contributed the total of N=3341 patients who participated.

2.0 Study Plan

2.1 Objectives/Rationale

The primary objective of the stuoy was to determine the incidence of seizure in patients treated with bupropion under the conditions of general clinical practice.

2.2 Population

The original plan was to recruit a total of 3,000 patients from 60 to 100 sites. Patients were to be a minimum of 18 years of age and were required only to have a clinical diagnosis of "depression," as defined by the individual investigators. Exclusion critera included: seizure disorder or predisposition (history of head trauma, brain tumor, history of any seizures, or concomitant medication that might lower seizure threshold); concurrent use of MAOIs; prior bupropion treatment; diagnosis of bulimia or anorexia nervosa; pregnancy, lactation or unacceptable method of contraception in any women of childbearing potential.

2.3 Design

This was planned as a 56 day, open, prospective, multicenter evaluation of seizure incidence in depressed outpatients or inpatients who were treated with bupropion. There were to be three phases: screening; acute treatment phase; continuation phase. After screening to ensure compliance with inclusion and exclusion criteria, patients were to be entered into the acute treatment phase. Bupropion was supplied in 75 mg tablets. The following dosing regimen was to be followed: 75 mg tid on days 1 - 3; 150 mg in the morning and 75 mg at midday and early evening, on days 4 - 7; 150 mg in the morning and at midday, and 75 mg in the early evening, on days 8 - 10; 150 mg tid on days 11 - 56. Investigators were encouraged to proceed to the 450 mg dose, but not if the patient was intolerant of this high dose or if the patient responded adequately at a lower dose. Patients were instructed to return their unused medications at each visit, and the investigator was to conduct a pill count in order to assess compliance. There was no fixed requirement regarding the frequency of return visits. However, investigators were to have contact at least every two weeks, even if only by phone.

At every treatment visit, investigators were to use the Verbal Probe Procedure to assess for seizures and any other major adverse events. This procedure involved a standard opening question and a specific protocol for follow-up evaluation in the event of a positive response. Otherwise, investigators were to provide routine psychiatric care. They were also asked to provide a global evaluation of response to bupropion and tolerance to bupropion.

For patients deemed appropiate, investigators could continue bupropion treatment beyond 56 days. Again, visit frequency was to be determined by the investigator, but the Verbal Probe Procedure was to be used at each contact. Otherwise, follow-up involved routine clinical care.

2.4 Analysis Plan

The sample size of 3,000 was chosen to provide a minimum of 1,500 patients who completed eight weeks of treatment and were 90% compliant with the 450 mg/day regimen. Compliance for the individual patient was defined as the number of pills taken during the 56 day acute treatment phase (or whatever the actual treatment interval was if less than 56 days) divided by the number of pills prescribed for that acute treatment interval.

The plan provided for calculating several seizure rates. First, an observed rate for all patients participating in the acute treatment phase was to be calculated, and secondly an overall study rate for all seizures during the combined acute treatment and continuation phases. There was also a plan to do a survival analysis to determine the cumulative seizure rate for eight weeks of acute treatment in a cohort of patients dosed within the range of 300 to 450 mg per day, i.e., the dose range considered to be effective in the treatment of depression. This cohort was to be defined as the patients who received a minimum of 90% of the total cumulative dose required for the 300 mg/day regimen, for either the 56 days of acute treatment, or for whatever lesser interval patients actually participated. The life table method of Lee (1980) was to be used, as provided by SAS.

All other adverse advents reported were to be converted into preferred terms and tabulated.

3.0 Study Conduct/Outcome

3.1 Patient Disposition/Exclusions

Patients were recruited from 102 sites and the total participation was N=3341. Of these, 62 were excluded from all safety analyses, yielding a sample of N=3279 for the safety analysis. Of the 62 exclusions, 57 never received bupropion. For three others, it was unknown if they had received medication but it should be noted that no ADR's were reported for these patients. Two of these three patients refused further follow-up, and one was simply lost to follow-up. [Note: It is interesting that this is the only patient out of 3,341 who was lost to follow-up, a remarkable outcome, given the fact that 102 different sites contributed patients.] Finally, two patients of Robert Fox, M.D., were not included, due to a concern for the reliabilty of his data. Neither patient had any important ADR's. [Note: Apparently, Dr. Fox had fabricated data for 12 fictitious patients, and, of course, none of these patients were included either.]

In addition, other patients were excluded from some tabulations and analyses for various violations, missing data, etc., but were included in the safety analyses. One of these patients did not have a diagnosis of depression. Two had prior treatment with bupropion. Three had been pregnant. However, it should be noted that the two patients who had been previously treated with bupropion were excluded from the denominator of the seizure incidence calculation, yielding a total sample for seizure incidence of N=3,277. [Note: Neither of these two patients had a seizure.]

3.2 Demographics

The female to male ratio was 59/41. The mean age for males was 44 (range: 18-88), and the mean age for females was 43 (17-87). Ninety-six percent of patients were white. Seventy-three percent of patients met DSM III criteria for major depression, 8% for bipolar disorder, depressed type, and 18% had other affective diagnoses. Only 1% of patients had non-affective disorder diagnoses.

3.3 Dose/Duration of Use Information

Although 3,279 patients were known to have taken bupropion in the study, compliance determinations could be made only on N=3267, due to inadequate records. Overall, the mean compliance across patients (i.e., tabs taken/tabs prescribed) was 92.5%. Of these patients, 77% had individual compliances of at least 90%.

As noted above, 3,277 patients were included in the overall seizure denominator. Of these, 2,708 met the requirements for entry into the 300-450 mg/day cohort (as defined above). The sponsor's figure 1 (appendix 1) is a histogram display enumerating patients in each of the three cohorts (300, 375 and 450 mg) at various points over the course of the 56 day acute treatment phase. The predominant dose was clearly 450 mg. The total cohort diminished from 2,708 at baseline to 1,835 at day 56 (67%). The sponsor also provided [as Table A (see appendix 2)] a dose/duration matrix (for up to 56 days) for the total sample of N=3267 patients for whom dose/duration data were available. [Note: This display does not extend beyond 56 days because the continuation phase is still ongoing, and these data have not yet been entered into the data base.] Of the total sample, approximately 60% completed 56 days of treatment, and of these, approximately 81% went on to the continuation phase. For the total sample, approximately 40% had a mean dose greater than or equal to 405 mg/day, and approximately two-thirds had a mean dose greater than or equal to 337 mg/day.

3.4 Seizure Incidence

Overall, 13 seizures occurred among the 3277 patients exposed to bupropion for the first time, yielding a crude seizure rate of 0.40% (upper one-sided 95% confidence limit=0.58%). [Using an "exact" approach for calculating two sided confidence limits for seizure incidence (i.e., the Clopper-Pearson method), Jay Levine (Division of Biometrics) obtained a 95% upper confidence limit of 0.68%, i.e., still under the upper limit we previously agreed upon as acceptable.] Eight of these seizures occurred in the acute treatment phase while 5 occurred in the continuation phase. [Note: The sponsor contacted all 102 sites between December 1 and December 9, 1988 to ensure complete ascertainment up to this point in time.] The sponsor's table 17 (appendix 3) provides a brief summary of each seizure. All were grand mal and all patients recovered fully. Eight of the patients were considered by the sponsor to have predisposing factors, including hyponatremia, recent withdrawal from benzodiazepines or alcohol, abnormal EEG, history of head trauma, history of infantile seizures and recent use of amitriptyline. Ten of the seizures occurred at a dose of 450 mg/day, two at 375 mg/day and one at 300 mg/day. Ten of the seizures occurred within one to four hours after the last bupropion dose. It should be further noted that three of the 13 patients with seizures had multiple seizures, i.e., two patients had three seizures each, and one patient had two seizures.

The sponsor also did a life table analysis, but included only the 8 seizures occurring during the acute phase for the n=2708 patients who met the requirements for being in the 300-450 mg/day cohort. The cumulative seizure rate at 8 weeks was 0.36% (upper one-sided 95% confidence limit=0.57%). A plot of the cumulative rate and the details of the life tables analysis are provided in the sponsor's figure 6 and appendix 6 (see appendices 4 and 5).

3.5 Other Major Adverse Events

Treatment Phase

The sponsor identified 82 patients having a total of 84 adverse events other than seizure during this phase. Fifty-six (67%) of these events were psychiatric, and 28 (33%) were medical. The psychiatric events included 10 suicide attempts, 4 of which resulted in death. Bupropion apparently was not

directly involved in any of the attempts. In addition, there were 2 other deaths. Patient #139-07 died from an apparent pulmonary embolus. Patient #153-08 left the study after 2 days for migraine HA, and then died 7 days later with the cause of death listed as "polypharmacy." In retrospect, this patient was noted to be a drug abuser, and had been abusing a variety of psychoactive substances, including several narcotics, and this patient's death could most reasonably be attributed to this combination of drugs.

Two patients experienced events in the acute treatment phase that might have been considered seizures. Patient #125-36 had bizarre episodes characterized by an electrical sensation across the tongue associated with stuttering and loss of concentration. The seizure work-up was entirely negative and these events were thought to be most ikely "functional." The second patient, #152-15, had a syncopal episode. A work-up revealed intermittent ectopic atrial rhythm and frequent PVCs that may have caused the syncopal episode. In neither case was the event classified as seizure, and I agree with the decision not to include these cases among the seizures.

I reviewed the sponsor's summary of the remaining major adverse events occurring in the acute treatment phase. In my view, they could either not be reasonably attributed to bupropion use, or those that could were already noted in the bupropion labeling. However, there was one event that I think does need to be added to the labeling. This event was a rash occurring in patient #118-10. This was a 34 year old male who, after 6 days of bupropion at 225 mg/day, became febrile and had hallucinations, continuing for 2 days. The bupropion was continued for 2 more days and then stopped, following which the fever diminished, but an erythematous rash appeared. The patient took Benadryl and prednisone beginning 3 days later, and 5 days following this, the patient was noted to have an SGPT of 448. The Benadryl and prednisone were continued. The rash gradually subsided and the SGPT returned to normal.

Continuation Phase

The sponsor's summary of major adverse events occurring in the continuation phase consisted of details for cases that were the subject of IND safety reports (including 1 death), 2 other deaths, and a report on 1 patient with an event that could possibly have been considered a seizure. One of the deaths was an overdose with Cardizem (patient #134-14). The second death was a result of breast cancer (patient #142-01). The third death apparently resulted from a cardiac arrythmia and aspiration. This patient was taking bupropion for approximately 9 months. She suddenly developed chest pain associated with vomiting, following which she aspirated and died. The autopsy revealed significant coronary artery disease with left ventricular hypertrophy and dilitation, which probably was the cause of death. Patient #161-26 experienced a loss of memory for her activities during a period of time in the continuation phase. There were no concomitant symptoms suggestive of seizure. However, she did have a history of "blackouts" on other psychotropic drugs. The seizure work-up revealed occasional right frontal polar spike-wave epileptiform discharges. An EEG several weeks after discontinuation of bupropion was normal. While seizure could not be definitely ruled out, the sponsor decided not to include this as an instance of seizure. Although I might have included this case as a possible seizure, this one additional case would not have changed the seizure incidence estimate significantly.

There were 2 other serious medical events occurring in patients in the continuation phase. Patient #116-80 was a 61 year old female who developed pancytopenia. She has currently been diagnosed as having myelodysplasia and refractory anemia, which is felt to probably represent early leukemia. The hematology consultant has doubted any relationship to bupropion. A second patient, #115-19, is a 51 year old male who had a myocardial infarction. A cardiac work-up has revealed 3 vessel occlusive disease, and consequently the MI cannot be reasonably attributed to bupropion.

3.6 Patient Discontinuations

Overall, 39% of patients discontinued prior to completing 56 days of treatment, including 613 (19%) who discontinued due to an adverse clinical event. The most common symptoms among discontinuing patients included nausea, agitation, anxiety, headache, insomnia and rash. Of the 1986 patients completing 56 days of treatment, 81% (n=1616) went on to the continuation phase.

3.7 Conclusions from Study 86A

The estimate for seizure incidence of 0.4% derived from study 86A is comparable to the estimates of 0.3-0.4% derived from the earlier data. In addition, the profile of ADRs associated with bupropion use is consistent with that seen in earlier studies. However, the possible occurrence of rash associated with fever and increased liver enzymes should be added to the labeling.

Efficacy and Safety Data from Study 84A

1.0 Investigators/Location

This was a five center study including patients from the following five investigators/sites:

84A-01, John S. Carman, M.D., Smyrna, Georgia
84A-02, Eric Dessain, M.D., Danvers, MA
84A-03, Richard A. Weisler, M.D., Raleigh, NC
84A-04, John P. Feighner, M.D., La Mesa, CA
84A-05, Robert P. Granacher, Jr., M.D., Lexington, KY

2.0 Study Plan

2.1 Objectives/Rationale

The objective of the study was to evaluate the efficacy and safety of a 300 mg dose of bupropion compared to placebo in outpatients with moderate to severe depression.

MADE IN JAPAN

2.2 Population

The plan was to recruit a total of 224 outpatients (48 in each of three centers and 40 in the other two). Inclusion critera included: age 18 or older; current diagnosis of depression (either single or recurrent, DSM IIIR); duration of current depressive episode ranging from 4 weeks to 2 years; HAM-D total score of at least 20 at screening and at baseline. Exclusion criteria included: predisposition to seizure; unstable concurrent medical disorder; pregnancy, lactation or unwillingness to use contraceptive methods in women of childbearing potential; recent use of psychoative medication; prior Wellbutrin use; history of alochol or substance abuse; diagnosis of bulimia or anorexia nervosa; active suicidal ideation.

2.3 Design

This was planned as a double-blind, parallel group randomized study of bupropion (N=112) vs. placebo (N=112) in depressed outpatients. Patient screening assessments included: medical history, physical examination, vital signs, routine lab, ECG (if indicated), psychiatric evaluation, and initial psychiatric ratings. Patients who passed the screening were given a one week, single-blind placebo run-in. Patients still satisfying the entry criteria at the end of the single-blind phase were randomized to either bupropion or placebo and treated on a double-blind basis for a maximum of 6 weeks. Bupropion dosing was with 100 mg. tablets, on a bid basis for days 1 - 3, and then 100 mg tid for days 4 - 42.

Efficacy assessments, conducted at each weekly visit, included: 21 item HAM-D, Montgomery Asberg Depression Scale, CGI (both severity index and global improvement). Safety assessments included: vital signs (q week); physical examination and routine lab (baseline and termination); adverse drug experience assessments (q week), using a Verbal Probe Procedure; and ECG (if needed).

2.4 Analysis Plan

The sponsor identified the HAM-D total score as the primary efficacy measure. It should be noted that this decision was not a result of prior discussion with FDA staff. Statistical testing was to be done using a two-sided alpha=0.05 for between group comparisons and alpha=0.10 for treatment by center interaction. The sponsor planned in advance to analyze intent-to-treat samples, defined as all patients randomized who received at least one dose of medication and who had efficacy assessments at baseline and at least one follow-up time. They also planned to do both observed cases analyses and last observation carried forward analyses at each visit. The primary model for analysis proposed by the sponsor was analysis of variance on change from baseline. This study was planned from the start as a multicenter study.

MADE IN JAPAN

3.0 Study Conduct/Outcome

3.1 Patient Disposition

Due to slow enrollment at two sites, enrollment was expanded at other sites, but was still limited overall to a total sample of N=224. Of this sample, N=112 were randomized to bupropion and N=112 to placebo. Enrollment per study center was as follows: Carman (55); Dissain (29); Weisler (48); Feighner (55); Granacher (37). Of the 224 patients randomized, 216 were included in the efficacy analysis (110 for bupropion and 106 for placebo), and 219 in the safety analysis (110 for bupropion and 109 for placebo). Eight patients were excluded from the efficacy analysis because they had no usable follow-up efficacy evaluations (6 placebo, 2 bupropion). Similarly, five patients were excluded from the safety analysis because they had no follow-up safety evaluations.

The sponsor's table 18 (appendix 6) provides a breakdown of the patients who were prematurely terminated from treatment, catergorized by treatment group and by reason for termination. Overall, 28.6% of placebo patients terminated early, compared to 22.4% of bupropion patients.

3.2 Demographics and Baseline Ratings/Group Comparability

The pooled bupropion patients were comparable to the pooled placebo patients on all demographic variables and on all baseline efficacy assessments. The mean age for the bupropion patients was 42, compared to 41 for placebo patients. Approximately 65% of patients were female in both treatment groups and approximately 95% were white. All patients had DSM III diagnoses of major depression, with 76% of bupropion patients having the recurrent subtype, compared to 83% of the placebo patients. 87% of the bupropion patients were moderately depressed (the rest being severe), compared to 91% of placebo patients. Approximately 82% of bupropion patients had current depressive episodes of 3 months or greater duration, compared to 80% of placebo patients. Most of the patients had one or more episodes of depression, i.e., 83% of bupropion patients compared to 76% of placebo patients.

The mean efficacy scores at baseline were as follows:

Rating Scale	Bupropion	Placebo
HAM-D Total	27	27
HAM-D Depression Item	2.9	3.0
MADS	31	30
CGI Severity Index	4.3	4.3

3.3 Dosing Information

The sponsor's table 16 (appendix 7) provides the mean bupropion dose from days 4 - 42, by center. For all centers combined, the mean bupropion dose was 287 mg, and placebo patients took a comparable number of tablets. Overall, these doses represent a compliance rate of 95% for placebo and 96% for bupropion patients.

3.4 Concomitant Medications

Use of nonpsychiatric drugs was common, but comparable in both treatment groups. There was a small amount of psycotropic medication use, in violation of the protocol, but again this use was comparable for both treatment groups.

3.5 Efficacy Results

HAM-D

The mean HAM-D total score, combined across all five centers in the observed cases analyses, dropped from approximately 27 at baseline for both treatment groups to 12.6 for bupropion and 16.1 for placebo, at day 42. For the last observation-carried-forward analysis across all centers at day 42, the combined mean HAM-D total score dropped to 14.5 for bupropion compared to 18.4 for placebo. The combined site analyses for the observed cases were positive at visits 35 and 42, and for the last observation-carried-forward analyses at visits 28, 35 and 42. However, there were significant treatment by center interactions at several visits for both the observed cases and the last-observation-carried forward analyses, due to essentially negative results for centers 1 and 3, and equivocal results for center 5. Therefore, this review will focus on the individual center analyses for this variable.

The sponsor's tables 21 and 22 (appendices 8 and 9) provide summary results for t-testing of change scores on the HAM-D total for both the observed cases analyses and the last-observation-carried-forward analyses, by center. Both centers 1 and 3 show a substantial placebo response, with comparable change in the bupropion group, resulting in findings of no difference. Centers 2 and 4 are strongly positive in favor of bupropion over placebo from 3 - 4 weeks to the end of the study, for both the observed cases analyses and last observation carried forward analyses. Center 5 has more equivocal findings, essentially making it on the observed cases-analysis at day 42, but not on the last-observation-carried-forward analysis, perhaps because of the carrying forward of high scores on several bupropion patients who dropped out early in the trial.

HAM-D Depression Item (#1)

The mean HAM-D Depression Item, combined across all five centers in the observed cases analysis, dropped from baseline to day 42 as follows: Placebo- 3.0 to 1.65; Wellbutrin- 2.9 to 1.25. For the last observation carried forward analysis across all centers at day 42, the combined mean HAM-D Depression Item dropped to 1.96 for placebo and to 1.43 for Wellbutrin. The combined site analyses for the observed cases were positive at visits 35 and

42, and for the last observation carried forward analyses also at visits 35 and 42. [See sponsor's Table 25 (appendix 10).] There were no significant treatment by center interactions for this variable. As with the other critical variables, especially for the last observation carried forward analyses, centers 2 and 4 favored Wellbutrin over placebo, while centers 1 and 3 found no difference. [See sponsor's Tables C and D (appendices 11 and 12).]

CGI-Severity Index (SI)

The mean CGI-SI total score, combined across all five centers in the observed cases analysis, dropped from approximately 4.3 at baseline for both treatment groups to 3.1 for the placebo group and 2.7 for the bupropion group, at day 42. For the last-observation-carried-forward analysis across all centers at day 42, the combined CGI-SI score dropped to 3.4 for the placebo group and 3.0 for the bupropion group. The combined site analyses were positive for the observed cases analyses at visits 28, 35 and 42, and for the last-observation carried-forward analyses at visits 21, 28, 35 and 42. However, there were significant treatment by center interactions at several visits for both the observed cases anylses and the last-observation-carried-forward analyses, again due to the essentially negative results for center 1 and 3 and the equivocal results for center 5. Therefore, this review will focus on the individual center analyses for this variable.

The sponsor's tables 35 and 36 (appendices 13 and 14) provide summary results for t-testing of the CGI-SI change scores for both the observed cases analyses and the last observation-carried-forward analyses, by center. Both centers 1 and 3 again show a substantial placebo response, with comparable change in the bupropion group, resulting in findings of no difference. Centers 2 and 4 are strongly positive in favor of bupropion over placebo from 3 - 4 weeks to the end of the study, for both the observed-cases analyses and the last-observation carried forward analyses. Center 5 is more equivocal, making it on the observed cases, but not on the last-observation-carried-forward analysis, again, perhaps because of the carrying forward of high scores in several bupropion patients who dropped out early.

Other Measures

Although this review will not provide details of the analysis of other variables, i.e., the MADS and the CGI-Global Improvement, it should be noted that the results for these analyses are essentially the same, i.e., they provide support for the efficacy of bupropion in centers 2 and 4.

Efficacy Conclusions

The sponsor's table 41 (appendix 15) provides a summary of the statistically significant findings for both the observed cases analyses and the last observation-carried-forward analyses, for all variables, by center, as well as for the combined analyses. In my view, these results provide substantial support for the antidepressant effectiveness of bupropion at 300 mg/day in moderate to severely depressed outpatients.

MADE IN JAPAN

3.6 Safety Results

Vital Signs and Weight

Bupropion patients decreased from a mean weight of 167 pounds at baseline to 163 at day 42, compared to an increase in placebo patients from a mean weight of 167 at baseline to 168 at day 42. Overall, 10.2% of bupropion patients had a weight loss greater than 5 pounds, compared to 8.5% of placebo patients. Regarding weight gain, 5.6% of bupropion patients had a weight gain of greater than 5 pounds, compared to 9.4% of placebo patients.

The following are the mean values for blood pressure and pulse rate, at baseline and day 42, for placebo and bupropion patients:

Vital Signs Variable	Treatment Group	Day 0	Day 42
systolic blood pressure	placebo	119	122
systolic blood pressure	bupropion	119	121
diastolic blood pressure	placebo	77	81
diastolic blood pressure	bupropion	78	77
pulse rate	placebo	74	73
pulse rate	bupropion	76	75

While there were individual instances of possibly clinically important changes in blood pressure and/or pulse rate, these were relatively infrequent and appeared to be equally distributed among bupropion and placebo patients. No bupropion patients were discontinued for changes in weight or vital signs.

Laboratory

Overall, there was no pattern of important changes in blood chemistry or hematology values in either treatment group over the course of treatment. While some individual patients had changes of possible clinical significance, these were relatively infrequent and appeared to be equally distributed among bupropion and placebo patients.

ECG

Only one bupropion patient with a normal ECG at screening had an abnormal ECG at termination, i.e., T-wave inversion, occurring three days after stopping bupropion. The ECG was repeated at 6 and 33 days after treatment and was normal. The relationship of this finding to bupropion use is unknown.

Physical Examination

There were no physical examination findings relavant to drug treatment.

Adverse Drug Experiences

There were 4 adverse drug experiences for which the reporting rate was higher in bupropion patients than in placebo patients by 5% or more: insomnia (15%), headache (12%), dizziness (9%), impotence (5%).

Premature Terminations

A total of 11 patients were discontinued prematurely for adverse drug experiences (6 on bupropion, 5 on placebo). None of these were serious events.

Safety Conclusions

No serious adverse drug experiences occurred in any patients receiving bupropion in this study. The slight weight decrease associated with bupropion use was expected, as was the finding of a higher incidence of insomnia in bupropion patients compared to placebo patients.

Proposed Labeling Revisions for Wellbutrin

The sponsor's December 19, 1988 supplement includes extensive revisions to the FPL for Wellbutrin. I have included the sponsor's proposed changes as appendix 16. I will discuss the proposed changes on a section-by-section basis.

1.0 Indications and Usage

1.1 Sponsor's Proposed Changes

The sponsor has dropped any reference to Wellbutrin being a drug of second choice, and alternatively has proposed that it should be indicated simply for the treatment of depression. They have also added references to the fact that Wellbutrin has now been studied and demonstrated to be effective in trials of 6 weeks duration, and in both outpatients and inpatients with depression. Finally, they have dropped the sentence referring to the lack of evidence for effectiveness beyond 3 weeks.

1.2 Comment

I disagree with a first line status for Wellbutrin. Although it is true that we do not have reliable seizure estimates from comparably designed studies for any of the marketed antidepressants, it is generally believed that the seizure incidence for imipramine and most other tricyclic antidepressants is approximately 0.1%. The sponsor cites the recently marketed Prozac as having a crude seizure rate of 0.2%. However, it is important to note that this

estimate includes all premarketing events that could possibly have been considered seizures (i.e., 16/8000). In fact, only 10 of these events could confidently be considered seizures, yielding a rate of 10/8000, i.e., approximately 0.1%. [Note: The sponsor's estimate of crude seizure rate for Wellbutrin, based on Study 86A, includes only well documented seizures, and would be somewhat higher if questionable cases were included.] Thus, the crude seizure rate for Wellbutrin at doses of 450 mg/day or less is probably 4-fold the rate for most marketed antidepressants. At the time of the original approval of Wellbutrin, the estimate of seizure incidence for patients receiving doses of 450 mg/day or less was 0.33%, so we now are seeing an observed incidence which is actually slightly higher. Consequently, I do not believe that there is adequate justification for dropping the second line status for this drug.

It is also important to note that, although the sponsor has now generated data suggesting the antidepressant efficacy of Wellbutrin at a dose of 300 mg/day, this study (84A) was done in depressed outpatients. The other data upon which the original approval of Wellbutrin was based come from depressed inpatients, many of whom were dosed at 450 mg/day. It is possible that some patients may need doses up to 450 mg/day, and the labeling will have to reflect this fact. Thus, even if the sponsor could demonstrate that the seizure rate is substantially lower at 300 mg/day, I would still not be inclined to accept a first line status for Wellbutrin. Alternatively, the sponsor would need to show that Wellbutrin has some specific therapeutic advantage over other antidepressants, in which case it could be a first line drug for whatever subgroups seem to differentially benefit.

I agree that the labeling can now indicate that Wellbutrin has been demonstrated to be effective in a 6 weeks trial in depressed outpatients, but the proposed wording implies that efficacy has been demonstrated in 6-week trials in both inpatients and outpatients, and this needs to be clarified. In addition, there still needs to be some discussion of the lack of evidence beyond 6 weeks. I think that, in regard to longer term use, the standard language used in the labeling for Prozac would be appropriate here as well.

1.3 Recommendations

I recommend that the first paragraph in the currently approved FPL be retained, with changes only in the multiples of the doses at which the seizure risk increases, as follows:

"Wellbutrin is indicated for the treatment of depression in patients who fail to respond adeaquately to or who cannot tolerate alternative antidepressant treatments. Wellbutrin is not recommended as an antidepressant of first choice for most patients because its use at doses approximately two times the usually required dose (300 mg/day) and one and one-third times greater than the maximum recommended dose (450 mg) is associated with a high risk of seizure (see Warnings)."

I recommend the following as the second paragraph:

"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."

The third paragraph, defining major depression, can remain as is.

For the fourth paragraph, I recommend the following:

"Effectiveness of Wellbutrin in long-term use, that is, for more than 6 weeks, has nct 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."

2.0 Contraindications

2.1 Sponsor's Proposed Changes

The sponsor has modified this section, essentially by adding a contraindication for the use of Wellbutrin in patients with a current or prior diagnosis of bulimia or anorexia nervosa. Otherwise, this section is essentially the same.

2.2 Comment and Recommendations

I agree with the sponsor's revision of this section of the labeling.

3.0 Warnings

3.1 Sponsor's Proposed Changes

The language in the first paragraph of the revised Warnings section diminishes the strength of the warning. This section also eliminates the seizure incidence table, but does keep the important incidence estimates indicating a steep dose response curve. This section also adds the seizure estimate from the recently completed open study (86A). It retains a modified version of the paragraph linking risk to dose and to predisposing factors. It eliminates the paragraph referring to adherence to dosing recommendations, and alternatively, expands this paragraph by moving in the specific dosing recommendations that had previously been in the original Dosage and Administration section.

3.2 Comment

I think that the sponsor's Warnings section is generally an improvement over the original, except that it goes too far in diminishing the impact of the original first paragraph.

3.3 Recommendations

I recommend that we retain the original first paragraph in the currently approved FPL for Wellbutrin. Otherwise, I recommend that we accept the subsequent modifications.

4.0 Dosage and Administration

4.1 Sponsor's Proposed Changes

The sponsor has rearranged this section of the labeling by putting the actual dosing recommendations first, followed by a general discussion of the rationale for using caution in dose escalation. Of note, they have removed all references to the occurrence of seizure in this discussion. Also, as noted earlier, all of the specific recommendations regarding dosing strategies to decrease the possibility of seizure have now been moved to the Warnings section. There is also a revision of the "Maintenance" subsection.

4.2 Comments

I agree with the sponsor's rewording of the two subsections giving actual dosing recommendations, i.e., "Usual Dosage for Adults" and "Increasing the Dosage Above 300 mg/day." However, I think that it would be preferable to have the "General Dosing Considerations" subsection first, to provide the rationale for the actual recommendations. I also think that there should be some mention of the seizure problem in this general discussion section, with a reference to "Warnings" for more complete details. I have no objection to the revised "Maintenance" subsection.

4.3 Recommendations

I would recommend putting the "General Dosing Considerations" section at the start of the Dosage and Administration section. In addition, this introductory section should begin with the following:

"Since there is an almost 10-fold increase in seizure risk associated with a dose increase from 450 mg/day to 600 mg/day, it is necessary to administer this drug in a manner most likely to minimize the risk of seizure (see Warnings)." In addition, the sponsor's sentence beginning "gradual escalation ..." should be modified by adding "also" after "is," i.e., "gradual escalation in dosage is also important ...," in order to emphasize that these are secondary reasons for using caution.

This introductory section can then be followed by the sponsor's two paragraphs giving actual dosing recommendations and the sponsor's revised "Maintenance" subsection.

Thomas P. Laughren 2-14-89

Thomas P. Laughren, M.D.

cc: Orig.NDA 18-644
HFD-120
HFD-120/TLaughren/PLeber
rd/llt/12/29/88/rd/pjb/1/10/89
ft/pjb/2/14/89
DOC#2955k

NDA SUPPL FOR Control

Burroughs Wellcome Co.

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

Wellcome

Cables & Telegrams
Tabloid Raleigh, N.C.
TWX 5109270915
tel. 919 248-3000

December 19, 1988

RECEIVED
CENTER FOR DRUG EVALUATION AND RESEARCH
DEC 19 1988
P.H.
CENTRAL DOCUMENTS ROOM

Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products
Office of Drug Review I
Center for Drug Evaluation and Review
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Wellbutrin® (bupropion) Tablets
NDA No. 18-644

Dear Dr. Leber:

Reference is made to our New Drug Application for Wellbutrin (bupropion) Tablets (NDA No. 18-644) which was approved on December 30, 1985, and to our meeting with you, Commissioner Frank Young, and other FDA staff on January 7, 1987.

This submission contains the Final Study Report for Study 86A, "Prospective Open Evaluation of the Seizure Incidence with Bupropion Hydrochloride (WELLBUTRIN)". This is the large, multi-center study designed to determine the seizure rate when Wellbutrin is used in a psychiatric out-patient setting. The observed seizure rate confirmed that reported in our original studies, and is within the range reported for other, marketed anti-depressant medications.

Reference is also made to the Final Study Report for Study 84A, submitted on October 7, 1988, which demonstrates safety and efficacy of Wellbutrin in the treatment of depression for up to six weeks in out-patients at a dose level of 300 mg/day (100 mg, t.i.d.).

Based upon the results of these two studies, as well as the database which was submitted with the original New Drug Application, we are submitting revised Labeling. Information which has become available since our initial approval clearly suggests that newly marketed, as well as older, therapies for depression produce seizures at a rate similar to that observed for Wellbutrin. This, coupled with our evidence for efficacy at a lower dose level, justifies removal of the "not drug of first choice" from the Labeling. Accordingly, the revised Labeling now indicates Wellbutrin for the treatment of depression. In view of the high incidence of seizures in bulimia, Wellbutrin is now contraindicated in patients with bulimia or anorexia nervosa. In addition, the Warnings Section has been revised to include new information from Study 86A. Finally, the Dosage and Administration Section has been revised to provide for dosing at 300mg per day, and to reflect the efficacy established in out-patients for up to six weeks.

RECEIVED FOR REC'D DEC 21 1988 DRUGS

LION 301 MADE IN JAPAN

There have been minor alterations in Wellbutrin's Adverse Drug Reaction profile based upon the lower dosage levels used and wider experience gained by these clinical trials. Based upon these observations we feel that changes in the tabular presentation of adverse reaction are warranted. We have not made these changes in this draft Labeling, preferring to wait until we have had the opportunity to discuss the changes with you and your staff and reach agreement upon appropriate inclusion and display criteria.

We look forward to discussing all of these points with you and your staff.

Sincerely,

George M. Lyon, Jr., M.D.
Director,
Drug Regulatory Affairs

15-1

TRANSMITTAL OF ANNUAL REPORTS FOR DRUGS FOR HUMAN USE *(21 CFR 314.81)*	DATE SUBMITTED 11/4/88	*Form Approved: OMB No. 0910-0001*

NOTE: This report is required by law *(21 USC 355; 21 CFR 314.81)*. Failure to report can result in withdrawal of approval of the New Drug Application.

INSTRUCTIONS

Complete a transmittal form for each application for which an annual report is being submitted. Retain the carbon copy labeled "applicant." Submit the remaining copies of the transmittal form along with two copies of the annual report to FDA.

If any part of the annual report applies to more than one application, list in item 7 all other applications to which such parts apply.

1. NDA OR ANDA NUMBER: N 1 8 6 4 4

2. Report No. *(FDA Complete)*: R- 0 0 2

APPLICANT NOTE: Reference NDA and R numbers *(entered on Acknowledgment Copy)* in any subsequent correspondence regarding report.

3. CFR SECTION NUMBER *(Antibiotic only)*:

4. APPLICANT: Burroughs Wellcome Co.

5. DRUG NAME: WELLBUTRIN® Tablets

6. TYPE OF REPORT *(Check one)* *(10)*: ☒ ANNUAL ☐ OTHER

7. OTHER NDA/ANTIBIOTIC APPLICATION NUMBERS *(List all numbers if any part of report applies to more than one number.)*

8. PERIOD COVERED BY REPORT

FROM *(11-14)*		TO *(15-18)*	
YEAR	MONTH	YEAR	MONTH
86	12	88	11

(Fold Line)

9. REPORT INFORMATION REQUIRED *(See §314.81 for description)*
(Enter an "X" in Column A if you have nothing to report. Enter identification of type of information attached in Column C.)
(ALWAYS INCLUDE INFORMATION REQUIRED UNDER "b" AND "c".)

NONE A	TYPE OF INFORMATION B	IDENTIFICATION *(Volume No.(s)/Tab(s)/Page(s) of Report)* C
(19)	a. SUMMARY OF SIGNIFICANT NEW INFORMATION	Tab A
	b. DISTRIBUTION DATA	
	c. LABELING *(Whether or not previously submitted)*	Tab C
X (20)	d. CHEMISTRY MANUFACTURING AND CONTROLS CHANGES	
(21)	e. NONCLINICAL LABORATORY STUDIES	Tab E NAI. B. Podoff 12/15/88
(22)	f. CLINICAL DATA	Tab F
(23)	g. STATUS REPORT-POST MARKETING STUDIES	Tab G
X (24)	h. STATUS OF OPEN REGULATORY BUSINESS *(optional)*	

(Fold Line)

TYPED NAME AND TITLE OF RESPONSIBLE OFFICIAL OR AGENT
Donald A. Knight
Associate Director
Drug Regulatory Affairs

SIGNATURE

APPLICANTS RETURN ADDRESS *(Type within the window envelope tic marks)*

Burroughs Wellcome Co.
3030 Cornwallis Rd.
Research Triangle Park, NC 27709

ATTN: D.A. Knight

FDA USE ONLY

10. DATE OF RECEIPT: 8 8 1 1 0 7

11. REPORT FILED IN NDA NO.: N 1 5 6 4 4

12. DIV CODE (78) ... CARD

13. FDA ACKNOWLEDGEMENT SENT

REC'D NOV 07 1988 HFN-120 DRUGS AND BIOLOGICS

FORM FDA 2252 (9/88) PREVIOUS EDITION IS OBSOLETE. ...PACKET

N.Y. 301 MADE IN JAPAN

15.1

Burroughs Wellcome Co.

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

Wellcome

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

NDA ANNUAL REPORT

November 4, 1988

11/23/88

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

Re: NDA 18-644
WELLBUTRIN® Tablets
ANNUAL REPORT

Dear Dr. Leber:

Pursuant to 21 CFR 314.81, we are submitting herewith our Annual Report for WELLBUTRIN Tablets.

Sincerely,

Donald A. Knight
Associate Director
Drug Regulatory Affairs

CENTER FOR
REC'D
NOV 0 7 1988
HFD-120
DRUGS AND BIOLOGICS

LION 501 MADE IN JAPAN

GXIG 15.1

Burroughs Wellcome Co.

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

Wellcome

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

11-29-88

October 10, 1988

Food and Drug Administration
Document Control Section, HFN-46
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Dear Sir or Madam:

Pursuant to 21 CFR 314.80, this is to advise that no reports have been received and no actions taken with regards to the 11th quarter Periodic ADR Report for WELLBUTRIN® Tablets for the time period June 1, 1988 through August 31, 1988. WELLBUTRIN Tablets were not marketed during this quarter.

A copy of the current labeling is attached.

NDA 18-644

Sincerely,

D. Greg Robbins, Ph.D./fm

Donald A. Knight
Associate Director
Drug Regulatory Affairs

CENTER FOR
RECD
OCT 20 1988

P011

ORIGINAL

12

LION 301 MADE IN JAPAN

CRIG

REPORTS

Burroughs Wellcome Co.

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

Wellcome

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

July 28, 1988

RECEIVED
CENTER FOR DRUG EVALUATION
AUG 02 1988

Food and Drug Administration
Document Control Section, HFN-46
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20852

Dear Sir or Madam:

Pursuant to 21 CFR 314.80, this is to advise that no reports have been received and no actions taken with regards to the tenth quarter Periodic ADR Report for WELLBUTRIN® Tablets for the time period March 1, 1988 through May 31, 1988. WELLBUTRIN Tablets were not marketed during this quarter.

NDA 18-644

Sincerely,

Donald A. Knight
Associate Director
Drug Regulatory Affairs

RECEIVED
NATIONAL CENTER
AUG 03 1988
HFN-120
FOR DRUGS & BIOLOGICS

P010
ORIG

120

ION 30' MADE IN JAPAN

ORIG P 009

REPORTS

Burroughs Wellcome Co.

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

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

March 28, 1988

RECEIVED
APR - 5 1988
DOCUMENTS DESK

Noted
4-13-88

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Dear Sir or Madam:

Pursuant to 21 CFR 314.80, this is to advise that no reports have been received and no actions taken with regards to the ninth quarterly Periodic ADR Report for WELLBUTRIN® Tablets for the time period December 1, 1987 through February 29, 1988.

NDA 18-644

Sincerely,

Donald A. Knight
Associate Director
Drug Regulatory Affairs

RECEIVED
NATIONAL
APR 8 1988
FOR
BDL

ORIGINAL

P009

12C

LION 301 MADE IN JAPAN

ORIG 14.1 REPORTS

Burroughs Wellcome Co.

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

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

December 29, 1987

RECEIVED
CENTER FOR DRUG EVALUATION
JAN 5 1988
CENTRAL DOCUMENT ROOM

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Dear Sir or Madam:

Pursuant to 21 CFR 314.80, this is to advise that no reports have been received and no actions taken with regards to the Periodic ADR Report for WELLBUTRIN® Tablets for the time period September 1, 1987 through November 30, 1987.

NDA 18-644

Sincerely,

J. Greg Rhyne, Ph.D./fa

Donald A. Knight
Associate Director
Drug Regulatory Affairs

RECEIVED
NATIONAL CEN
JAN 07 1988

ACE

120

LION 601 MADE IN JAPAN

ORIGINAL

REPORTS

Burroughs Wellcome Co.

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

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

October 12, 1987

Noted only one periodic report enclosed 39-44-109 Lenzure Case #

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Dear Sir or Madam:

Pursuant to 21 CFR 314.80, enclosed is the Periodic ADR Report for WELLBUTRIN® Tablets.

The time period covered by this report is June 1, 1987 through August 31, 1987.

NDA 18-644

Sincerely,

Donald A. Knight
Associate Director
Drug Regulatory Affairs

RECEIVED
NATIONAL CENTER
OCT 20 1987
HFN-120
FOR DRUGS & BIOLOGICS

RECEIVED
OCT 19 1987

120

LION 301 MADE IN JAPAN

120

REPORTS

ORIGINAL

Burroughs Wellcome Co.

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

Wellcome

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

Need seen in IND 9-24-87

September 17, 1987

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Dear Sir or Madam:

Pursuant to 21 CFR 314.80, enclosed is an Initial 15-Day FDA 1639 Report for WELLBUTRIN® Tablets.

WELLBUTRIN	Motor and sensory changes, tongue numbness, facial and arm tremors, tonic-clonic shaking of body

Report received as part of structured clinical trial of WELLBUTRIN.
Previously sumbitted to IND 13,845 on August 28, 1987.

NDA 18-644

Sincerely,

Donald A. Knight
Associate Director
Drug Regulatory Affairs

RECEIVED
NATIONAL CENTER
SEP 25 1987
HFN-120
CENTER FOR DRUGS & BIOLOGICS

1987 SEP 22 AM 11:37

...AL REPORTS 14-1

Wellcome

Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, N. C. 27709

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

July 13, 1987

RECEIVED
...BIOLOGICS
JUL 22 1987
CENTRAL DOCUMENTS ROOM

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Dear Sir or Madam:

Pursuant to 21 CFR 314.80, this is to advise that no reports have been received and no actions taken with regards to the Periodic ADR Report for WELLBUTRIN® Tablets for the time period March 1, 1987 through May 31, 1987.

WELLBUTRIN Tablets were not marketed during this report period.

NDA 18-644

Sincerely,

Donald A. Knight
Associate Director
Drug Regulatory Affairs

ADR PERIODIC REPORT

120

MADE IN JAPAN

ORIGINAL 14-1

SUPPL NEW CORRES

Wellcome

Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, N. C. 27709

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

April 30, 1987

Noted
Copied
1-28-87

Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products
Office of Drug Research and Review
Centers for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 18-644
WELLBUTRIN® (Bupropion) Tablets

Dear Dr. Leber:

Recently, there has been considerable press coverage of results from the WELLBUTRIN sexual dysfunction trials. Since you may be receiving inquiries on this issue, it may be helpful for you to be aware of our corporate position. Therefore, we are enclosing a copy of our prepared response which will be used for inquiries which we receive from reporters and patients. We hope this is helpful.

Sincerely,

J. Greg Perkins

J. Greg Perkins, Ph.D.
Associate Director
Drug Regulatory Affairs

RECEIVED
CENTER
MAY 05 1987
HFN-120
FOR DRUGS & BIOLOGICS

MADE IN JAPAN

14-1

TRANSMITTAL OF ANNUAL REPORTS FOR DRUGS FOR HUMAN USE
(21 CFR 314.81)

DATE SUBMITTED
April 9, 1987

Form Approved: OMB No. 0910-0001
Expiration Date: May 31, 1986.

NOTE: This report is required by law *(21 USC 355; 21 CFR 314.81)*. Failure to report can result in withdrawal of approval of the New Drug Application.

INSTRUCTIONS

Complete a transmittal form for each application for which an annual report is being submitted. Retain the carbon copy labeled "applicant." Submit the remaining copies of the transmittal form along with two copies of the annual report to FDA.

If any part of the annual report applies to more than one application, list in item 7 all other applications to which such parts apply.

1. NDA OR ANDA NUMBER

1	2	3	4	5	6
N	1	8	6	4	4

2. Report No. *(FDA Complete)*

R-	7	8	9	
	0	0	1	Q

APPLICANT NOTE
Reference NDA and R numbers *(entered on Acknowledgement Copy)* in any subsequent correspondence regarding report.

3. CFR SECTION NUMBER *(Antibiotic only)*

4. APPLICANT
Burroughs Wellcome Co.

5. DRUG NAME
WELLBUTRIN® Tablets

6. TYPE OF REPORT *(Check one)* *(10)*
☒ ANNUAL ☐ OTHER

(Fold Line)

7. OTHER NDA/ANTIBIOTIC APPLICATION NUMBERS *(List all numbers if any part of report applies to more than one number.)*

8. PERIOD COVERED BY REPORT

FROM (11-14)		TO (15-18)	
YEAR	MONTH	YEAR	MONTH
85	12	86	11

9. REPORT INFORMATION REQUIRED *(See §314.81 for description)*
(Enter an "X" in Column A if you have nothing to report. Enter identification of type of information attached in Column C.)
(ALWAYS INCLUDE INFORMATION REQUIRED UNDER "b" AND "c".)

NONE A	TYPE OF INFORMATION B	IDENTIFICATION *(Volume No.(s)/Tab(s)/Page(s) of Report)* C
(19)	*a.* SUMMARY OF SIGNIFICANT NEW INFORMATION	Tab A
	b. DISTRIBUTION DATA	Tab B
	c. LABELING *(Whether or not previously submitted)*	Tab C
X *(20)*	*d.* CHEMISTRY MANUFACTURING AND CONTROLS CHANGES	
(21)	*e.* NONCLINICAL LABORATORY STUDIES	Tab E
(22)	*f.* CLINICAL DATA	Tab F
X *(23)*	*g.* STATUS REPORT-POST MARKETING STUDIES	
X *(24)*	*h.* STATUS OF OPEN REGULATORY BUSINESS *(optional)*	

Waiver Request 4-24-87

NAI. Barry Routh 6/3/87

(Fold Line)

TYPED NAME AND TITLE OF RESPONSIBLE OFFICIAL OR AGENT
Donald A. Knight
Associate Director
Drug Regulatory Affairs

SIGNATURE

APPLICANTS RETURN ADDRESS *(Type within the window envelope tic marks)*

Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, NC 28809

FDA USE ONLY

10. DATE OF RECEIPT

24	25	26	27	28	29
0	4	1	7	8	7

11. REPORT FILED IN NDA NO.

30	31	32	33	34	35
N	1	8	6	4	4

12. DIV CODE *(78)*

13. TYPE CARD *(80)* S

14. FDA ACKNOWLEDGEMENT

1

FORM FDA 2252 (7/85) **PREVIOUS EDITION IS OBSOLETE.**

LION 301 MADE IN JAPAN

Burroughs Wellcome Co.

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

cables & telegrams
Tabloid Raleigh, N.C.
TWX5109270915
tel. 919 248-3000

April 9, 1987

Paul D. Leber, M.D., Director
Division of Neuropharmacological
Drug Products, HFN-120
Office of Drug Research and Review
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: WELLBUTRIN® Tablets
NDA 18-644
ANNUAL REPORT

Dear Dr. Leber:

Pursuant to 21 CFR 314.81, we are submitting herewith our Annual Report for WELLBUTRIN Tablets.

Sincerely,

Donald A. Knight
Associate Director
Drug Regulatory Affairs

RECEIVED
NATIONAL
CENTER
APR 17 1987

MADE IN JAPAN

14-1

RECORDS

Wellcome

Burroughs Wellcome Co.

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

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

March 17, 1987

Noted
RWKnapp
3-1-87

RECEIVED
CENTER FOR DRUGS & BIOLOGICS
MAR 24 1987
CENTRAL DOCUMENTS ROOM

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Dear Sir or Madam:

Pursuant to 21 CFR 314.80, this is to advise that no reports have been received and no actions taken with regards to the Periodic ADR Report for WELLBUTRIN• Tablets for the time period December 1, 1986 through February 28, 1987.

NDA 18-644

Sincerely,

Donald A. Knight
Associate Director
Drug Regulatory Affairs

ADR PERIODIC REPORT

120

LION 301 MADE IN JAPAN

14.1

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE: April 7, 1987
FROM: A.W. DeCuno		OFFICE
TO: File NDA 18-644		DIVISION
SUBJECT: Submission of March 4, 1987		

SUMMARY

Spoke to Wayne Turner in regards to this submission. He agreed with the document, they had sent him a copy and was content with their reporting procedure

A.W. DeCuno

SIGNATURE	DOCUMENT NUMBER

FORM FD 2034 (6/76)

SUPPL NEW CORRES

Orig

Burroughs Wellcome Co.

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

Wellcome

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

March 4, 1987

NAT
4-7-87

Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 18-644
WELLBUTRIN® (Bupropion) Tablets

Dear Dr. Leber:

Prior to January 31, 1986, all adverse reactions occurring in clinical trials with WELLBUTRIN were reported to IND On January 31, 1986, Mr. Tony DeCicco in a phone conversation with me indicated that all serious adverse reactions should be reported to both the IND and NDA. This has resulted in adverse reaction reports being filed to the NDA and forwarded by your office to the FDA Office of Epidemiology and Biostatistics. A phone conversation between Dr. Loren Miller of Drug Regulatory Affairs, Burroughs Wellcome Co., and Wayne Turner of the Office of Epidemiology and Biostatistics has indicated that adverse reactions reported to the NDA should be forwarded to his office through the Central Documents room.

Regulation 21 CFR 314.80 indicates that only serious unlabeled or labeled reactions which represent an increase in incidence are to be reported to the NDA on a 1639 form within 15 days of their identification by the manufacturer. FDA Guidelines for Postmarketing reporting of adverse drug reactions further specify that adverse reactions occurring during the course of an IND clinical trial should be submitted to the NDA on a 1639 form only if they qualify as serious and unlabeled or represent a labeled increase in frequency. All other adverse reactions should be reported to the IND only.

LION 301 MADE IN JAPAN

Thus, to ensure regulatory compliance and to eliminate further confusion, adverse reactions occurring in WELLBUTRIN® clinical trials, if covered by labeling will be reported to the IND only. Serious unlabeled adverse reactions will be reported to both the IND (Division of Neuropharmacology) and NDA (Central Documents room - 1639 form).

If there are any questions concerning this procedure, please contact Loren Miller, Ph.D., Drug Regulatory Affairs, at (919) 248-4151.

Sincerely,

Donald A. Knight
Associate Director
Drug Regulatory Affairs

LION 301 MADE IN JAPAN

Burroughs Wellcome Co.

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

Wellcome

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

January 23, 1987

Noted Correspondence 2-3-87

Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products, HFN-120
Office of Drug Research and Review
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 18-644
WELLBUTRIN® Tablets

Dear Dr. Leber:

Reference is made to our letter of November 30, 1986 concerning a patient (#211) who experienced acute somnolence while enrolled in clinical study 39, "A WELLBUTRIN Treatment Protocol," being conducted by .

We are submitting herewith a follow-up to that report.

Sincerely,

J. Greg Perkins

J. Greg Perkins, Ph.D.
Associate Director
Drug Regulatory Affairs

RECEIVED
NATIONAL
JAN 29 1987
FOR DRUGS & BIOLOGICS

LION ... MADE IN JAPAN

Burroughs Wellcome Co.

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

Wellcome

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

January 15, 1987

1-9-87
Rec'd. NDT.

Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 18-644
WELLBUTRIN• Tablets

Dear Dr. Leber:

At the January 7, 1987 meeting between representatives from the Food and Drug Administration and Burroughs Wellcome Co., you suggested to that an improvement could be made on the recently submitted table entitled "Number of Unique Patients/Volunteers by Maximum Daily Bupropion Dose and Treatment Duration." Enclosed is a revised table incorporating your suggestion concerning dosing categories. We agree that this format provides a better representation of the data. Thank you for your input.

Sincerely,

Donald A. Knight
Associate Director
Drug Regulatory Affairs

RECEIVED
NATIONAL CENTER
JAN 21 1987
FOR DRUGS & BIOLOGICS

MADE IN JAPAN

PERSONALLY SUBMITTED BY

Burroughs Wellcome Co.

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

Wellcome

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

January 6, 1987

Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products, HFN-120
Office of Drug Research and Review
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

18-644

Re: NDA
WELLBUTRIN® Tablets

Dear Dr. Leber:

As discussed with Mr. Prettyman on December 12, 1986, regarding our forthcoming meeting with Commissioner Young on January 7, 1987, we are providing herewith the following information:

1. An update of information regarding patient numbers, duration of treatment, and incidence of seizures since the NDA was approved in December 1985.

2. A paper by _____ et al. regarding their total experience with bupropion in cardiovascular patients.

3. A manuscript by _____ et al. on the cardiovascular effects of imipramine and bupropion in depressed patients with congestive heart failure.

While we realize that this material cannot be thoroughly reviewed before the meeting, we hope that it might serve as additional information for use during our discussions.

Sincerely,

for

George M. Lyon, Jr., M.D.
Director
Drug Regulatory Affairs

MADE IN JAPAN

Burroughs Wellcome Co.

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

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

December 30, 1986

Noted
Will await
the report
RM Kapur
1-8-87

Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products, HFN-120
Office of Drug Research and Review
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 18-644
WELLBUTRIN® Tablets

Dear Dr. Leber:

We are submitting herewith an adverse experience report on a patient who experienced acute somnolence while enrolled in clinical study 39, "A WELLBUTRIN Treatment Protocol." The patient, #211, was a 52-year-old male being treated by .

The protocol for this study was submitted to FDA on June 18, 1984 and amended on January 31, 1985, February 6, 1985, September 3, 1985 and December 17, 1985. I was registered to conduct this study on March 17, 1981.

We will forward any additional data we receive on this patient.

Sincerely,

J. Greg Perkins

J. Greg Perkins, Ph.D.
Associate Director
Drug Regulatory Affairs

RECEIVED
JAN 5

MADE IN JAPAN

REPORTS

Burroughs Wellcome Co.

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

Wellcome

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

December 10, 1986

Noted
1-8-87

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Dear Sir or Madam:

Pursuant to 21 CFR 314.80, this is to advise that no reports have been received and no actions taken with regards to the Periodic ADR Report for WELLBUTRIN• Tablets for the time period September 1, 1986 through November 30, 1986.

NDA 18-644

Sincerely,

Donald A. Knight
Associate Director
Drug Regulatory Affairs

RECEIVED
NATIONAL CENTER
FOR DRUGS & BIOLOGICS

RECEIVED
CENTER FOR DRUGS & BIOLOGICS
DEC 16 1986
CENTRAL DOCUMENTS ROOM

ADR PERIODIC REPORT

12C

MADE IN JAPAN

REPORT

Burroughs Wellcome Co.

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

Wellcome

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

September 19, 1986

RECEIVED
CENTER FOR DRUGS & BIOLOGICS
SEP 23 1986
CENTRAL DOCUMENTS ROOM

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Dear Sir or Madam:

Pursuant to 21 CFR 314.80, this is to advise that no reports have been received and no actions taken with regards to the Periodic ADR Report for WELLBUTRIN• Tablets for the time period June 1, 1986 through August 31, 1986.

NDA 18-644

Sincerely,

Donald A. Knight
Associate Director
Drug Regulatory Affairs

Noted Adequate Quarterly Report 10-7-86

RECEIVED
SEP

ADR PERIODIC REPORT

12

SUPPL

Burroughs Wellcome Co.

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

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

September 17, 1986

Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 18-644
WELLBUTRIN® Tablets

Dear Dr. Leber:

Since our voluntary withdrawal of WELLBUTRIN on February 28, 1986, we have been engaged in continuing negotiations with the Division of Neuropharmacological Drug Products regarding their requirements for commercial marketing. We have been unable to reach agreement. It is therefore the decision of Burroughs Wellcome Co. to terminate all WELLBUTRIN studies under IND and to discontinue all further development efforts.

As you may be aware, there are currently more than 700 patients receiving WELLBUTRIN under provisions of compassionate plea. For these patients and others who are nonresponsive to currently available antidepressants, we feel it would be in the public interest for WELLBUTRIN to be made commercially available for humanitarian use. Burroughs Wellcome Co. is willing to make WELLBUTRIN commercially available under restrictive labeling. We hope you will consider this possibility.

We believe Burroughs Wellcome Co. has acted responsibly and in the public interest as demonstrated by our voluntary withdrawal of WELLBUTRIN, our subsequent proposals for resolution of the outstanding issues, and our offer for humanitarian availability. We appreciate all the efforts of the FDA in this matter.

Sincerely,

Howard J. Schaeffer

Howard J. Schaeffer, Ph.D.
Vice President
Research, Development and Medical

RECEIVED
SEP 17 1986
FOR DRUGS & BIOLOGICS

SUPPL

Burroughs Wellcome Co.

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

Wellcome

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

September 17, 1986

Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 18-644
WELLBUTRIN® Tablets

Dear Dr. Leber:

Since our voluntary withdrawal of WELLBUTRIN on February 28, 1986, we have been engaged in continuing negotiations with the Division of Neuropharmacological Drug Products regarding their requirements for commercial marketing. We have been unable to reach agreement. It is therefore the decision of Burroughs Wellcome Co. to terminate all WELLBUTRIN studies under IND and to discontinue all further development efforts.

As you may be aware, there are currently more than 700 patients receiving WELLBUTRIN under provisions of compassionate plea. For these patients and others who are nonresponsive to currently available antidepressants, we feel it would be in the public interest for WELLBUTRIN to be made commercially available for humanitarian use. Burroughs Wellcome Co. is willing to make WELLBUTRIN commercially available under restrictive labeling. We hope you will consider this possibility.

We believe Burroughs Wellcome Co. has acted responsibly and in the public interest as demonstrated by our voluntary withdrawal of WELLBUTRIN, our subsequent proposals for resolution of the outstanding issues, and our offer for humanitarian availability. We appreciate all the efforts of the FDA in this matter.

Sincerely,

Howard J. Schaeffer

Howard J. Schaeffer, Ph.D.
Vice President
Research, Development and Medical

RECEIVED
SEP 17 1986
FOR DRUGS & BIOLOGICS

NDA 18-544

SEP 3 1986

Burroughs Wellcome Co.
Attention: Donald A. Knight
3030 Cornwallis Road
Research Triangle Park, North Carolina 27709

Dear Mr. Knight:

We have reviewed your submission of August 11, 1986 to your NDA for Wellbutrin (bupropion) in which you have responded to our earlier comments (July 9, 1986) and have provided a detailed protocol for a study to estimate the risk of seizure associated with the use of bupropion.

While we are now in agreement on several of the design and analysis issues, there remain several areas of important disagreement.

1. Identification of Cohort at Risk

While we are sympathetic to the problem of obtaining 100% compliance, your proposal for defining a cohort falls short of the requirements we specified in our earlier letter for defining what we will now refer to as the "critical cohort." We would be willing to accept a rate of non-compliance on the order of 10%, defined in terms of individual patients, i.e., patients meeting the assigned dose and duration requirements could be included in the cohort for seizure estimation if they ingested 90% of their assigned doses during their treatment intervals.

However, our requirements for defining the critical cohort must also be met, i.e., a minimum of 3000 patients who remain in continuous treatment for a minimum of 6 weeks, to include 1500 assigned to a minimum dose of 375 mg and 1500 assigned to a 450 mg dose. We would allow for 10% noncompliance for patients in this group, i.e., each of the 1500 patients assigned to a minimum dose of 375 mg would need to ingest 0.9 x 375 mg/d x 56d = 18900 mg and each of the 1500 patients assigned to a 450 mg dose would need to ingest 0.9 x 450 mg/d x 56d = 22680 mg in order to be included in the cohort.

Patients meeting the minimum dosage requirements, but not the 6 week duration, could be included in a survivor analysis. However, patients not meeting the dosing requirement (either because of assignment to lower doses or greater than 10% noncompliance at an acceptable dose) could not be included in the critical cohort. These cases would be included in the "other group."

2. Estimation of Seizure Risk in the Identified Cohort

We acknowledge your decision to utilize survival methodology in estimating the cumulative seizure risk for 6 weeks of exposure. However, we ask that you provide additional details of the exact method of calculation.

3. Adjustments for Cases Lost from Cohort where Status is Unascertained

We are in clear disagreement with you regarding this issue. While our 2% rule for declaring the study invalid is arbitrary, we feel it is both necessary and reasonable, given the risk of missing seizures in cases lost to follow-up. The only alternative would be to declare all lost cases as seizures, and we feel this would be unreasonable. We also believe that our 8% rule for declaring seizures among cases lost to follow-up is appropriate, since it is based on the worst case we are aware of, i.e., 4/50.

4. Patient Monitoring

We acknowledge your plan to utilize pill counts and to require 2 week contacts with patients. We agree with this plan, but we ask that you specify what information would be obtained at these contacts. In particular, will seizures be ascertained at these contacts?

5. Decision Rule for Marketing of Wellbutrin

We acknowledge your agreement with our proposed decision rule to permit the marketing of Wellbutrin if the upper bound of the 95% confidence interval for cumulative risk of seizure at the end of 6 weeks is no greater than 7/1000 for the critical cohort. However, we disagree with your proposal for deciding on the acceptability of the seizure rate in the "other group" on the basis of a one-sided hypothesis test between the "critical cohort" and the "other group." For the very reasons you cite, i.e., a possibly wide confidence interval, this test would not be reliable. You apparently misinterpreted our suggestion that the incidence of seizure among these patients could not exceed 4/1000 as an upper limit of a confidence interval, rather than as a point estimate, which is what we intended.

In any case, while we generally agree that the seizure rate for this "other group" must be lower than the rate for the "critical cohort," we prefer not to precommit ourselves to any specific approach to ruling on the data from this "other group."

6. Stopping Rule

Finally, we disagree with your proposed stopping rule. While your rule provides acceptable limits at smaller sample sizes, as the sample size increases, it is much too liberal. Indeed, as the sample size approaches 1000, your rule would permit the continuation of the study even after the number of seizures occurring exceeded the number of seizures that would result in our refusal to agree to the marketing of Wellbutrin.

As an alternative, we propose a stopping rule based on the likelihood of observing an overall incidence of seizure in the study that would be judged acceptable. For example, at any point during the study, if the number of seizures observed makes it improbable that an acceptable seizure rate will subsequently be obtained, the study should be terminated. Specifically, in a study of 3000 patients, the largest number of seizures that would satisfy the confidence interval criterion is 13. If X seizures are observed in the first N patients, then at most 13-X seizures can be observed in the remaining 3000-N patients. We propose that you stop the study after X seizures in N patients if, given a true incidence rate equal to 0.0045, the probability of completing the study with no more than 13 seizures is less than 0.10. This stopping rule yields the following table for the number of seizures at various sample sizes that would result in a decision to stop the study:

N	X
200	6
400	7
600	7
800	8
1000	9
1200	9
1400	10
1600	11
1800	11
2000	12
2200	13
2400	13
2600	14
2800	14
3000	14

Unfortunately, despite your statement that the protocol submitted in your August 11, 1986 amendment represents your final draft, we clearly are not yet in sufficient agreement that we can give you a precommitment regarding this study. As we have stated previously, we do not feel that it would be prudent for Wellbutrin to be marketed without first determining a reasonably reliable estimate of the upper bound of the seizure risk. We do not believe that your study design could provide the information we require to make a prudent judgement about the future status of Wellbutrin. While you feel that you have compromised as much as you can, we likewise feel that our comments in this letter represent our final position. You are, of course, free to conduct your proposed study without a prior agreement with the Agency about how to interpret its outcome.

Should you have any questions, please contact Mr. Tony DeCicco, Consumer Safety Officer at (301)443-4020.

Sincerely yours,

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

IRON 01 MADE IN JAPAN

ORIGINAL Mary Lou Schenck
PERSONALLY SUBMITTED BY
SUPPL NEW DRUG

Wellcome

Burroughs Wellcome Co.

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

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

August 11, 1986

Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 18-644
Wellbutrin® (bupropion) Tablets

Dear Dr. Leber:

Thank you for your prompt response (July 9, 1986) to our recent proposal concerning the large scale study (Wellbutrin Study #86) intended to estimate the risk of seizure associated with the use of bupropion in depressed patients. Included herein are a detailed protocol (Attachment A) and our recommended rules for stopping the study based on sequential analyses of seizure rate (Attachment B). In your telephone conversation with Dr.
on July 23, you discussed several issues raised in your letter of July 9, regarding the analysis and interpretation of the results of the planned study. Outlined below is our proposed strategy for data analysis and interpretation:

1. Identification of Cohort at Risk

We propose to conduct a trial which will enroll a minimum of 3000 patients treated with Wellbutrin for up to 8 weeks. In your letter of July 9, you recommended a cohort consisting of patients continuously exposed at fixed dose levels of 375 or 450 mg/day for a period of at least 6 weeks. While we recognize the importance of dosing and length of treatment criteria in establishing the appropriate cohorts for analysis of seizure incidence, we are concerned that your proposed criteria may not be attainable given that 100% compliance in chronic, outpatient studies of this nature is rarely, if ever, obtained. It therefore seems impractical to expect that very many patients could achieve a mean daily dose equal to their prescribed dose across a 6 week period.

RECEIVED
NATIONAL CENTER
AUG 12 1986
HFN-120
FOR DRUGS & BIOLOGICS

MADE IN JAPAN

ORIGINAL Mary Lou Schenck

SUPPL NEW CORR

Wellcome

Burroughs Wellcome Co.

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

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

August 11, 1986

Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 18-644
Wellbutrin® (bupropion) Tablets

Dear Dr. Leber:

Thank you for your prompt response (July 9, 1986) to our recent proposal concerning the large scale study (Wellbutrin Study #86) intended to estimate the risk of seizure associated with the use of bupropion in depressed patients. Included herein are a detailed protocol (Attachment A) and our recommended rules for stopping the study based on sequential analyses of seizure rate (Attachment B). In your telephone conversation with Dr.
on July 23, you discussed several issues raised in your letter of July 9, regarding the analysis and interpretation of the results of the planned study. Outlined below is our proposed strategy for data analysis and interpretation:

1. Identification of Cohort at Risk

   We propose to conduct a trial which will enroll a minimum of 3000 patients treated with Wellbutrin for up to 8 weeks. In your letter of July 9, you recommended a cohort consisting of patients continuously exposed at fixed dose levels of 375 or 450 mg/day for a period of at least 6 weeks. While we recognize the importance of dosing and length of treatment criteria in establishing the appropriate cohorts for analysis of seizure incidence, we are concerned that your proposed criteria may not be attainable given that 100% compliance in chronic, outpatient studies of this nature is rarely, if ever, obtained. It therefore seems impractical to expect that very many patients could achieve a mean daily dose equal to their prescribed dose across a 6 week period.

RECEIVED
NATIONAL CENTER
AUG 12 1986
HFN-130
FOR DRUGS & BIOLOGICS

For the above reasons, we believe it necessary to allow for some flexibility in compliance and to structure the cohort for analysis accordingly. We propose the cohort to be composed of patients who have a minimum mean daily dose of 300 mg (excluding dose ascension) which represents at least 80% compliance with the lower bound of a dosing regimen of 375-450 mg/day. At least 1500 patients in this cohort will have met the minimum mean daily dose requirement for a period of six weeks or more. Patients who meet the minimum daily dose requirement for a period less than six weeks will be included in the cohort through the use of a survival analysis as described in Item #2 below.

Analysis of seizures for patients who do not meet this criteria of at least 80% compliance with the dosing range of 375-450 mg will be discussed under Item #5 below.

Documentation of patient medication intake in this study will be based on pill counts and patient take-home diaries. With this rigorous monitoring, we expect a level of compliance which will be comparable to that attainable in other outpatient studies in psychiatric patients, and certainly better than that expected in general clinical practice. Thus, the mean daily dose for patients who qualify for the cohort described above should be at least as high, if not higher, than mean daily doses attained under conditions of marketing. If any bias were to be introduced from this approach, it should be toward detecting a higher seizure rate in this study, since mean daily doses encountered in general clinical practice would likely be lower.

2. Estimation of Seizure Risk in the Identified Cohort

An estimate of the cumulative seizure risk for six weeks of exposure will be calculated using appropriate survival methodology for patients who qualify for inclusion in the cohort as described in Item #1 above.

We agree to revise the product labeling prior to marketing to reflect the results of Study 86 and the bulimia seizure incidence, and to clearly state the treatment period over which the risk estimate from Study 86 is based (i.e., six weeks) and that the risk for a longer treatment period could be higher. It is our understanding that no numerical extrapolation about the risk of seizure over a longer treatment period will be made.

3. Adjustments for Cases Lost from the Cohort Where Status is Unascertained

You have proposed that the study be declared failed if more than 2% of the patients who have entered the study have an unascertained status regarding seizure. We are unaware of prior experience with studies of similar design to Study 86 (large outpatient studies in psychiatric private practice) that would suggest reasonable rates of patients lost to follow-up, thus making the selection of a

criterion somewhat arbitrary. Our concern is that the study will be declared invalid on the basis of the 2% criterion, when 98% follow-up may not be obtainable in studies of this nature under the best of circumstances. Since there is no prior experience on which to base the selection of a reasonable criterion, we consider this requirement to declare the study failed on the basis of an arbitrary number of patients lost to follow-up to be unacceptable.

We do, however, understand your concern that some proportion of patients whose outcome is unascertained will have experienced a seizure which is not detected. We believe it unlikely though that patients enrolled in an investigational drug study designed to detect seizures, having signed informed consent agreements to this effect, will fail to report a seizure to their physician. As a result, we expect that patients lost to follow-up would likely have lower incidences of serious adverse events than patients for whom outcome is determined. Nevertheless, we will be willing to adjust the seizure risk calculation in this cohort by adding 1% of the number of patients lost to follow-up to the numerator. (We will likewise add the total number of patients lost to follow-up to the denominator.) This 1% penalty is approximately 2.5 times the estimated seizure incidence based on the original 2400 patients in our NDA and should provide assurance that reasonable losses to follow-up will not bias the outcome toward an artificially low seizure rate. The 8% level recommended in your letter of July 9 is unacceptable, as it is 20 times the original seizure rate and is based on an extremely small sample size of 55 patients with an illness different than that for which the product is indicated.

4. Patient Monitoring

As indicated in Item #1 above, we will utilize pill counts as well as patient take-home diaries to monitor compliance and determine actual medication use.

All serious adverse events will be detected through evaluations conducted at every treatment visit and at the end of eight weeks of therapy, or sooner if treatment is terminated before eight weeks. Patients will be seen by the investigator according to their clinical judgment, but will be contacted at least every two weeks as specified in the protocol. All serious adverse events will be recorded when they are reported to the investigator.

5. Decision Rule for Marketing of Wellbutrin®

We agree with your recommendation to market Wellbutrin if the seizure incidence is calculated to be within the upper bound of 7/1000 for the one-sided 95% confidence interval for the 6 week cumulative risk of seizure.

You also recommended an upper limit of seizure incidence of 4/1000 for the patients who do not qualify for inclusion in the cohort. Based on the expectation that only a small number of patients will

be excluded from the 375-450 mg/day cohort, we expect the estimate of seizure risk in this group to have wide confidence intervals and to be, therefore, relatively unreliable. We are reluctant to base the marketing decision on a potentially unreliable estimate of seizure incidence, but agree that seizures in this group cannot be ignored. We propose, alternatively, to base the marketing decision on obtaining no statistically significant increased seizure risk in this group compared to the 375-450 mg cohort, provided, of course, that the 7/1000 criteria is met for the 375-450 mg cohort. This hypothesis test comparing the seizure risks in the two groups would be one-sided, conducted at the .05 level of significance, and would use a survival analysis.

The design of this study has evolved with ongoing interaction between your office and Burroughs Wellcome Co. over the past several months. Your constructive criticism has been appreciated and your comments have been incorporated into the final protocol wherever possible. Since this is our final draft, any further changes will result in a scientific impass requiring resolutions at the office level. We are confident that this study will provide the information necessary to satisfy our mutual goals in determining the best attainable seizure incidence rate under clinical trial conditions. We believe that both Burroughs Wellcome Co. and the FDA have acted responsibly and in the public interest, and will continue to do so in the future.

Sincerely,

Donald A. Knight
Associate Director
Drug Regulatory Affairs

MADE IN JAPAN

- Per Subj R. Bastal ORIGINAL

REPORTS

Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, N. C. 27709

Wellcome

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

August 4, 1986

Noted
This case is confounded by poly-drug therapy
RM Leber 8-6-86

Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 18-644
WELLBUTRIN• Tablets

Dear Dr. Leber:

We are submitting herewith an adverse experience report on a patient who had three seizures while being treated with WELLBUTRIN under Clinical Study 39, "A WELLBUTRIN Treatment Protocol."

The patient, #015, was a 44-year-old male being treated by , M.D. Summary information is attached.

A revised protocol for this study was submitted to FDA on June 18, 1984 and amended on February 6, 1985 and September 3, 1985. Dr was registered for this study on October 18, 1982.

We will forward any additional data we receive on this patient.

Sincerely,

B. Randall Verbit for

J. Greg Perkins, Ph.D.
Associate Director
Drug Regulatory Affairs

RECEIVED
NATIONAL
AUG 4 1986
HFN-120
FOR DRUGS & BIOLOGICS

NDA 18-644

Burroughs Wellcome Co.
Attention: Donald A. Knight
3030 Cornwallis Road
Research Triangle Park, North Carolina 27709

JUL -9 1986

Dear Mr. Knight:

We have received and carefully reviewed your submission of June 19, 1986 to your New Drug Application for Wellbutrin® (bupropion hydrochloride) which presents, in brief outline, a proposal for a study intended to estimate the risk of seizure associated with the use of bupropion under conditions that you believe simulate those that would be expected under general clinical use if bupropion were marketed.

Although this proposal makes some attempt to remedy the deficiencies in design and evaluation criteria that we identified and discussed during our June 4, 1986 meeting, it remains, in our view, critically flawed. Knowledge of an estimate of risk obtained using your proposed design and analytic methods cannot provide the information we require to make a prudent judgment about the future status of Wellbutrin.

The proposed study, as we understand it from the outline presented, is incapable of providing a reasonably precise estimate of the risk of seizure for any meaningful interval of exposure to a dose of 450 mg of bupropion a day, a dose recommended in the current labeling and the only dose at which we know with certainty bupropion is effective. In our view, it would be imprudent to contemplate the marketing of Wellbutrin without first determining a reasonably reliable estimate of the upper bound of this risk.

In the worst case, if a reliable estimate of the six week cumulative risk of seizure at doses of bupropion of 375 to 450 mg a day is high in absolute terms (i.e., over 0.007), we would have to give serious consideration to withdrawing approval of the NDA. A risk of this magnitude means that as many as 6 in a 100 depressed patients treated with Wellbutrin for six months (the minimum duration of treatment commonly recommended for an episode of major depression) might suffer a seizure. In our view, a rate of this magnitude is simply too high; indeed, it may be an order of magnitude or more greater than that associated with the use of most currently marketed antidepressants.

Furthermore, even if the cumulative risk proves to have a lower upper bound, it is still critical to know, before marketing is begun, what the actual risk is likely to be. Remember, the currently approved labeling of Wellbutrin is clearly 'false and misleading' in regard to the incidence of seizure at recommended doses. Indeed, beyond the legal requirements for accurate labeling, both the prescriber and patient each need to have this information prominently displayed so that they can choose, weighing risk and benefit, among the many marketed antidepressant drug products.

Consequently, we must again ask you to revise your planned study in a manner that will permit us to rely upon its results. The remainder of this letter provides a point by point discussion of the elements in the design or analytic methodology that must be modified.

Before turning to the specific items and elements, one general point is worth making. Because your proposal is presented with little detail, it's subject to misinterpretation and misunderstanding. In sections, for example, the language used is ambiguous (i.e., you indicate that the study will be done under "IND conditions," rather than simply and clearly stating that it will be done under an IND). We ask, therefore, should you elect to submit a revised protocol, that it be presented in greater detail than the current one.

Our major concerns are the following:

1. Identification of Cohort at Risk

   The general problem involves the matter of the representativeness of the cohort that might be assembled under your protocol. We are concerned that the proposed rules may lead to the formation of a cohort of patients that, on average, is exposed to bupropion for a period of time less, and at a dose far lower, than the time and dose that are of concern. 'Safe passage' over short intervals of time (e.g., less than 6 weeks) of large numbers of patients at subtherapeutic doses (e.g., less than 7 mg/kg or so) provides virtually no reassurance about the risks of bupropion use at the only dose we know with certainty is effective, 450 mg/day (from 6.4 to 9 mg/kg for the 70 to 50 kg patient, respectively).

   It is possible that the use of survivor function techniques may permit the construction of cumulative risk estimates that 'adjust' for the failure of all patients in a cohort to complete their planned time on drug. Adjustments, however, are never fully satisfactory because they require sanguine assumptions to be made about the nature of the data. For example, if the 'hazard' of seizure is not constant over time a problem may arise. Consider the not implausible scenario in which the risk of seizure is minimal over the period of treatment induction (i.e., titration of bupropion to the dose of interest) but then increases steadily for several weeks as metabolites of bupropion accumulate. In such circumstances, if the vast majority of patients are exposed for a total of only 3 or 4 weeks (of which 2 are at unquestionable subtherapeutic doses), the study will not be able to provide precise, let alone valid, estimates of the risks of bupropion's use.

   Consequently, while we believe that a cohort of 3000 patients is likely to be able to provide a reasonably precise estimate of a risk, we disagree with your rules for defining the cohort of completed patients. In order to form a cohort which is representative of the condition we wish to model, we ask that, at a minimum, the cohort consist of at least 3000 patients who have been continuously exposed to a dose of at least 375 mg of bupropion for a duration of at least 6 weeks. In addition, we ask that at least 1500 patients in this

cohort (i.e. half of those satisfying the 375 mg criterion) be exposed to a dose of 450 mg of bupropion for a minimum duration of 6 weeks. If a life table approach to cumulative risk estimation is used, the population at risk will at some time points obviously be larger than 3000 (i.e., it will contain patients exposed to a minimum dose of 375 mg of bupropion for periods less than 6 weeks). It is important to note, however, that patients on doses of less than 375 mg a day will not be considered at risk for purposes of a rate estimate that we would rely on for making a regulatory decision.

Of course, patients exposed to doses less than 375 mg/day must also be followed, but any seizures occurring in this group will be utilized in a separate calculation of seizure risk (see No. 5 to follow).

2. Estimation of Seizure Risk in the Identified Cohort

Your proposed rules for calculating seizure incidence are improper. You have proposed to calculate a crude estimate of seizure incidence based upon the assumption that any patient for whom a completed study report is available, regardless of the duration or dose of exposure, is 'at risk' for seizure.

A rate calculated in this manner is potentially misleading. First, it is unclear to what interval of time the risk applies. Second, it is virtually certain that such a calculation will underestimate the seizure incidence of clinical importance; that is, the incidence of seizure among patients treated with an effective dose of bupropion for a 'treatment episode' of appropriate duration (6 months to a year).

Clearly, for practical reasons, we would not expect you to be able to estimate directly the incidence per treatment episode in a premarketing trial. However, we do expect you to calculate a fair and representative estimate of the seizure incidence for a shorter interval. With such an incidence estimate in hand, and making a sanguine assumption that the 'hazard' is uniform with time, a meaningful statement about the estimated risk for a treatment episode can be inserted in the product's labeling.

Consequently, we ask that you use the rules that we will now specify for calculating a risk estimate. You may, if you wish, simply calculate the seizure incidence for a six week interval for the cohort of 3000 patients defined under No. 1 above. However, since you will have data on patients taking a minimum of 375 mg/day for periods of time less than six weeks as well, you may alternatively calculate a cumulative risk using appropriate survivor methodology, providing again that all patients included in the cohort meet the minimum dosage requirement of 375 mg/day. In addition, whatever method you use for calculating risk, patients to be considered in the calculation must have been adequately monitored for compliance with treatment and for ascertainment of seizures (see No. 4 to follow).

3. Adjustments for Cases Lost from the Cohort Where Status is Unascertained

We propose that if more than 2% of the patients who have entered your study have an unascertained status (regarding seizure), the study should be declared invalid.

The reason for this requirement should be evident. If the rate of loss to follow-up (i.e., unascertained cases) is substantial, and if the adverse event of interest can itself account for loss to follow-up, doubt about the validity of any estimated incidence increases as the incidence of unascertained cases increases. In our view, if 2% or more of entered patients are unascertained, the study must be considered a failed study.

Furthermore, we believe that some conservative rule must be used to adjust the risk calculation for unascertained losses up to the 2% limit. We acknowledge that virtually any penalty level is arbitrary. All or some fraction of cases going unascertained could be declared seizures. We believe that the worst incidence rate observed to date, however, is about 8% for a period of 4 - 6 weeks or so. Thus, we propose that any calculated risk estimate include as seizures, in addition to those actually detected, a number equal to the number of unascertained cases multiplied by 0.08, truncated to the lowest full integer. For example, if 30 patients were not accounted for, the product of 0.08 X 30 rounded down would be 2 penalty events.

If a life table is used for the calculation of the estimate of seizure, the assigned time of seizure for the penalty events would also have to be chosen arbitrarily. We propose to equate the interval of loss to the average interval of loss of all the patients who go unascertained.

4. Patient Monitoring

In order to rely on the estimate of seizure risk derived from the cohort as defined above, we must be assured that patients take their bupropion and that any seizures that occur are detected. Therefore, we ask that you utilize pill counts or some other systematic approach to monitoring compliance in order to estimate actual medication use. In addition, patients must be interviewed at least weekly (even if by telephone) to determine whether or not seizures have occurred. This is essential if life table methods are to be used, in order to correct for time at risk.

5. Decision Rule for Marketing of Wellbutrin

If you meet our requirements for forming an appropriate cohort, estimating seizure incidence, making an adjustment for unascertained cases and carefully monitoring patients, we will make our decision regarding the marketability of bupropion on the basis of the upper 95% confidence limit for the cumulative risk of seizure at six weeks in the cohort as defined above. Specifically, we will not object to

the marketing of bupropion if the upper bound of the one-sided 95% confidence interval for cumulative risk of seizure at the end of six weeks is no greater than 7/1000 for this cohort.

In addition, seizure risk must be monitored on an ongoing basis and the study must be terminated if an interim incidence of seizure exceeds some critical value. We ask that you propose a rule for such termination, explain how it was derived and discuss how the rule protects patients from unreasonable risk. It will also be necessary to evaluate the risk of seizure among patients not qualifying for inclusion in the cohort as described under No. 1. Specifically, patients on bupropion at doses lower than 375 mg must be monitored for seizures. The cumulative incidence of seizure among these patients cannot exceed 4/1000 if Wellbutrin is to be marketed.

Finally, it must be understood that should marketing occur, the labeling of bupropion must be revised to reflect the experience with the patients in the Bulimia study and the new estimated risk of seizure.

Should you have any questions please contact Mr. Tony DeCicco, Consumer Safety Officer at (301) 443-4020.

Sincerely,

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

MADE IN JAPAN

Review and Evaluation of Clinical Data
NDA 18-644

JUL -9 1986

Sponsor: Burroughs Wellcome Co.

Drug: Wellbutrin (bupropion)

Drug Category: Antidepressant

Material Submitted: Proposal for an open, uncontrolled trial to estimate the seizure rate assosiated with Wellbutrin use.

Correspondence Date: June 19, 1986

Date Received: June 19, 1986

Background:

Subsequent to the approval of Wellbutrin in December, 1985, the reporting of four seizures early in 1986 in a study involving approximately 50 bulimic patients taking Wellbutrin at doses less than 450 mg per day raised concern that the risk of seizure associated with Wellbutrin use might be higher than the estimate derived from data in the NDA. Since those reports, we have had ongoing discussions with the sponsor regarding how best to resolve this concern. Although the sponsor has agreed not to proceed with the marketing of Wellbutrin until this issue is resolved, there has not yet been agreement on the design of a study for resolving this question. Several earlier proposals by the sponsor have been rejected. The current submission contains the most recent proposal by the sponsor for a study designed to estimate the risk of seizures associated with Wellbutrin use.

Summary of Proposal:

This proposal is for an open, uncontrolled, multicenter trial to be done under the IND with written informed consent. The sponsor plans to obtain data from N=3000 completed patients, where a completed patient is defined as one who either completes eight weeks of treatment or is terminated earlier and for whom a treatment evaluation form has been completed. The plan is to enter patients with a diagnosis of "depression" who are 18 years of age or older and who have none of the following exclusionary conditions: history of bulimia or anorexia nervosa; no unpredisposition to seizures; pregnant or nursing women.

The recommendation for dosing is essentially the guideline provided in the current labeling for Wellbutrin, i.e., up to 450 mg/day by day 10. However, patients who do not tolerate dose escalation or who improved at doses lower than 450 would not be increased to 450. An eight week course of treatment will be encouraged, and patients may be treated beyond eight weeks if this is clinically indicated.

The sponsor has made no requirements regarding the scheduling of patient visits and/or phone contacts, other than to indicate that patients should be treated "in accordance with good clinical practice." The only absolute requirements for assessment are the following: a history and demographics form at study entry; a concomitant medication and dosing record during the study; an adverse experience probe for seizures at eight weeks or at termination, whichever comes first.

Upon completion of the 3000 patient, the sponsor plans to calculate the seizure incidence as the number of patients experiencing a seizure divided by the number of completed patients. The sponsor does not plan to include patients lost to follow-up in any way in the calculation. The sponsor proposes that, if the calculated seizure rate is 0.45% or less, they be allowed to proceed with the marketing of Wellbutrin.

Comments:

In my view, the sponsor has not addressed most of the critical issues raised at the June 4, 1986 meeting between sponsor and FDA staff. These issues included the following:

1. Duration

   Nominally, this is an eight week study. However, the sponsor's plan to include as completed patients those patients who terminate prior to eight weeks would allow for many patients treated for far less than eight weeks to be included in the calculation of seizure rate. In my view, this is unacceptable unless duration of exposure is taken into consideration in calculating the rate.

2. Dose

   By design, many of the "completed" patients may receive far less than 450 mg/day. Again, this diminishes the usefulness of any estimate of risk based upon these data since risk is very likely dose related and our interest is in assesing seizure risk at the higher end of the dose range recommended for Wellbutrin.

3. Ascertainment

   Despite our discussion of the need for adequate ascertainment at our June 4 meeting, the sponsor has still made no requirement for any contact with patients other than at entry and at termination.

4. Compliance

   In a study of this type it is clearly important to verify that patients actually took medication. Again, the sponsor has included no requirement for pill counts or any other approach to monitoring compliance.

5. Patients Lost to Follow-up

   The sponsor has also failed to deal with patients who are lost to follow-up.

Conclusions and Recommendations:

In my view, this latest proposal by the sponsor for a study to provide an estimate of seizure risk associated with Wellbutrin use is unacceptable as it stands. I believe the decision to define completed patients as the sponsor has done would be acceptable only if the sponsor were willing to calculate seizure risk using a life table method that would take into consideration duration of treatment. I also believe that dose is critical, and that the calculation of seizure risk should include only patients exposed to a dose of at least 375 mg/day.

Regarding ascertainment, I believe it is not unreasonable to ask for some contact with patients at least every two weeks, even if by phone. In addition, I think it is important that there be some approach to monitoring compliance.

With regard to patients lost to follow-up, I believe that there needs to be a rule to deal with such patients. I propose that we agree to accept up to 2% of patients being lost to follow-up, as long as those patients are considered to have seizures at the same rate as the observed rate in the remaining entered patients. Should more than 2% of patients be lost to follow-up, I believe that the study should be considered a failure.

Finally, the sponsors rule for accepting an observed seizure rate of 0.45% on a sample of 3000 patients would yeild an upper bound on the 95% confidence interval of approximately 7/1000. I would consider this to be an acceptable upper bound only if the calculation was based on patients actually treated at doses of 375 mg/day (or more) for eight weeks.

I recommend that the following comments be conveyed to the sponsor:

We have reviewed your most recent proposal for a study to estimate seizure rate associated with Wellbutrin use. We disagree with this proposal in regard to the following issues:

1. Duration of Treatment

   Your defenition of "completed patients" would allow for many patients exposed to Wellbutrin less than eight weeks to be included in the calculation of seizure risk. Thus, while nominally an eight week study, in actuality the extent of exposure to Wellbutrin would be less than eight weeks for many patients. We would permit the inclusion of patients exposed for less than eight weeks only if the risk calculation would take into account the duration of exposure, i.e., a life table method.

2. Dose

   By design, many of the "completed" patients may receive far less than 450 mg/day. Again, this diminishes the usefulness of any estimated risk since this is likely dose related and our interest is in assessing risk at the higher end of the dose range recommended for Wellbutrin. Therefore, we do not feel it would be appropriate to include patients exposed to less than 375 mg/day in the calculation. For patients exposed to 375 mg/day or more, we would consider there treatment duration to be only that time spent on 375 mg/day or more, and would not include time utilized in titrating them to that dose.

3. Ascertainment

   Your proposal makes no requirement for physician contact with patients other than at entry and termination. We consider this unacceptable, and we would require that patients be contacted at least every two weeks during the study, even if by phone, to ascertain whether or not seizures had occurred.

MADE IN JAPAN

4. Compliance

Your proposal makes no requirement for monitoring of compliance. In a study of this type, it is clearly important to ensure that patients actually take medication. Therefore, we would require that you obtain pill counts or utilize some other systematic approach to monitoring compliance.

5. Patients Lost to Follow-up

As discussed at our June 4, 1986 meeting, we believe that patients lost to follow-up must be taken into consideration in calculating seizure rate. We also believe that the overall number of patients lost to follow-up is a measure of the adequacy of a study of this type. Therefore, we propose that no more than 2% of entered patients may be lost to follow-up in order for the study to be considered successful. For any patients lost to follow-up (up to this limit of 2%), they must be considered to have had seizures at the same rate as the observed rate in the remainder of the patient sample (where duration of exposure for each patient would be estimated on the basis of the time of last contact).

6. Upper Bound of 95% Confidence Interval for Seizure Risk

The observed rate of 0.45% which you propose as an acceptable seizure rate (in a sample of 3000 patients) yields an upper bound for the 95% confidence interval of approximately 7/1000. We consider this to be an acceptable upper bound, but only if the seizure rate is calculated for patients receiving 375 mg/day or more. In addition, the calculation would need to be based on actual duration of exposure at 375 mg/day (or more), and the upper bound for patients exposed eight weeks could be no greater than 7/1000.

Thomas P. Laughren 6-26-86

Thomas P. Laughren, M.D., HFN-120

MADE IN JAPAN

REPORT

Burroughs Wellcome Co.

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

Wellcome

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

June 19, 1986

RECEIVED
CENTER FOR DRUGS & BIOLOGICS
JUN 23 1986
CENTRAL DOCUMENTS ROOM

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Dear Sir or Madam:

Pursuant to 21 CFR 314.80, this is to advise that WELLBUTRIN• Tablets were not marketed during this quarter and no adverse experience reports were received through our spontaneous reporting system for the time period March 1, 1986 through May 31, 1986. Two adverse experience reports which occurred in our clinical trial program were submitted during the quarter under our IND and NDA 18-644. Since these reports do not meet the "15-Day reporting criteria," they were not forwarded to Division of Epidemiology and Surveillance.

NDA 18-644

Sincerely,

Donald A. Knight
Associate Director
Drug Regulatory Affairs

DAK/pg/X2-19

X/DRA/1/29
TRZO/86/0400

RECEIVED
NATIONAL CENTER
JUN 26 1986
HFN-120
FOR DRUGS & BIOLOGICS

130

MADE IN JAPAN

PERSONALLY SUBMITTED BY
Loren Miller

SUPPL NEW CORRES

Burroughs Wellcome Co.

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

Wellcome

cables & telegrams
Tabloid Raleigh, N.C.
TWX5109270915
tel. 919 248-3000

CENTER

HFN-130

June 19, 1986

Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 18-644
Wellbutrin® (Bupropion) Tablets

Dear Dr. Leber:

In prior correspondence and meetings, we have indicated that there has been no significant change in the overall incidence of seizures associated with Wellbutrin. This is based on examination of data for 3,981 patients/volunteers in IND trials which includes 1,583 patients added since the NDA approval. Hence, as previously stated, the primary unresolved issue remaining for Wellbutrin is the incidence of seizures under conditions of general clinical use. Based on this, three proposals have been made previously, each having the major objective of obtaining an estimate of the seizure incidence in clinical practice.

The first proposal (March 25, 1986) was a clinical experience program for psychiatrists which would allow for the evaluation of seizure occurrence in over 3,000 patients. This proposal was withdrawn because FDA restrictions placed on the conduct and analysis of this program would have made it impractical to conduct. Furthermore, an accurate estimate of seizure incidence for current antidepressants was not available to help in determining the relative risk of seizures.

A second proposal (May 19, 1986) consisted of two separate methods for obtaining estimates on the incidence of seizures with Wellbutrin. One estimate was to be obtained through a monitored release to psychiatrists (3,000 patients); the other estimate was to be obtained through a tricyclic controlled study (2,800 Wellbutrin patients, 2,800 tricyclic patients) conducted under IND conditions. This proposal would have provided 1) an estimate of the seizure incidence with Wellbutrin under expected marketing conditions, 2) further IND data on the seizure incidence with Wellbutrin, and 3) data on the relative incidence of seizures compared to a standard antidepressant. This proposal was withdrawn since FDA would not allow the monitored release until further seizure data were obtained under IND conditions. Since the above IND study would take approximately two years to complete and the results still would

not necessarily be representative of the seizure incidence expected under general clinical use, this approach was no longer considered appropriate.

At an FDA meeting (June 4, 1986), a third proposal was presented which involved an IND study allowing investigators to use Wellbutrin® under conditions simulating expected general clinical use. IND conditions would be met as requested by FDA but investigators would use Wellbutrin in a method simulating clinical practice. Following is a description of this proposed IND study. Significant changes based on our June 4, 1986 discussion have been incorporated into the study design.

Multicenter Open Uncontrolled Wellbutrin Trial
To Evaluate the Observed Seizure Rate

Objective:

To obtain an estimate of the Wellbutrin seizure incidence when used under conditions simulating clinical use upon marketing.

Design:

- IND conditions (central IRB, written informed consent, form 1573, etc.)
- Multicenter (80-100 sites), open, uncontrolled, prospective
- N = 3,000 completed Wellbutrin patients (a patient who completes eight weeks of treatment or is terminated earlier and for whom a treatment evaluation form has been completed).

Inclusion Criteria:

- Diagnosis of depression
- Eighteen years of age or older

Exclusion Criteria:

- Known contraindications to Wellbutrin
- History of bulimia or anorexia nervosa
- Known predisposition to seizures (history of head trauma, brain tumor, seizures, concomitant medications which lower seizure threshold, etc.)
- Pregnant or nursing women

Dosing:

- Patients will be dosed according to the following schedule:

Treatment Day	Dosing Schedule 75 mg Tablets Morning	Midday	Evening	Total Daily Dose
1-3	1	1	1	225 mg
4-6	2	1	1	300 mg
7-9	2	2	1	375 mg
10-56	2	2	2	450 mg

Dosing must follow the above schedule unless the patient cannot tolerate dose ascension or the patient responds clinically prior to dose ascension. In these cases, the patient should be maintained at the highest dose tolerated or at the dose at which the response occurred. All other patients should be maintained at 450 mg unless intolerance develops. Patients extending beyond eight weeks of treatment may be maintained at any dose up to 450 mg following the eighth week of treatment.

Treatment Duration:

- Eight weeks for purposes of data analysis. Further treatment will be permitted if clinically indicated.

Assessments:

- Investigators will be asked to treat patients in accordance with good clinical practice. Scheduling of patient visits and/or phone contacts will be determined by the treating physician and all contacts should be documented in the patient record. For the purpose of this study, a history and demographics form will be completed at study entry, a concomitant medication and dosing record will be maintained throughout the study, and an adverse experience probe for seizures will be completed at eight weeks of treatment or termination from Wellbutrin®, whichever comes first. For patients receiving treatment beyond eight weeks, a concomitant medication and dosing record will be maintained and an adverse experience probe for seizures will be completed at termination of Wellbutrin or termination of the study. Investigators will be asked to report all seizures or possible seizures immediately by phone to B.W. Co. Any report of a seizure or a possible seizure will have an indepth assessment completed by the investigator and Burroughs Wellcome medical personnel.

Data Analysis:

Seizure incidence will be calculated using the observed rate (# of patients experiencing a seizure/# of completed patients). All efforts will be made to locate and complete a treatment evaluation for patients thought to be lost to follow-up. Patients lost to follow-up will not be included in the calculation of seizure incidence. There will be an ongoing calculation of seizure incidence. To facilitate timely review of the study results, the FDA will be provided with periodic reports.

Marketing:

- Upon completion of the 3,000th patient, the seizure incidence will be calculated. If the observed rate is 0.45% or less, marketing of Wellbutrin® will ensue.

As indicated above, this proposal has evolved with ongoing interaction between the FDA and B.W. Co. We would now like to proceed with its implementation as soon as possible. Your prompt written response will be appreciated.

Sincerely,

for Don Knight

Donald A. Knight
Associate Director
Drug Regulatory Affairs

MAY 23 1986

Review and Evaluation of Clinical Data
NDA 18-644

Sponsor: Burroughs Wellcome

Drug: Wellbutrin (bupropion)

Drug Category: Antidepressant

Material Submitted: Proposal for the limited market of Wellbutrin and the simultaneous conduct of a post-marketing study comparing the seizure rate for Wellbutrin and imipramine.

Correspondence Date: May 22, 1986

Date Received: May 22, 1986

Summary of Plan:

The sponsor proposes to supply trial kits to psychiatrists who wish to participate in this limited marketing. This plan is similar to a previously proposed plan, in that psychiatrists must agree to report ADRs, must fill out an initial registration card and must agree to submit followup cards that are completed either at termination or at the end of six weeks of treatment. However, there is no provision for informing patients about the purpose of this limited exposure (i.e., assessing seizure risk) and no provision for adequate followup of patients. There is also an important difference, in that the drug will now be distributed to retail pharmacies, so that patients requiring continued treatment will obtain prescriptions from pharmacies. The firm further states that they would reassess their marketing of Wellbutrin after receiving 3000 followup cards. If they determine that the seizure rate is less than 0.6%, they would proceed with a full promotion of Wellbutrin.

The post-marketing study described is essentially the same study comparing Wellbutrin and imipramine as was previously proposed.

Conclusions and Recommendations:

I disagree with the sponsor's plan for a limited marketing of Wellbutrin for several reasons:

1. The purpose of this limited exposure is primarily to assess the seizure risk associated with Wellbutrin, and I believe that patients should be informed of this.

2. There is no guarantee about adequate ascertainment of seizures in this quasi-study. Therefore, a rule would be needed for handling missing data, and this is not addressed in this submission.

3. If Wellbutrin were to be distributed to retail pharmacies, there would be no control over its use. In fact, I believe that introducing the drug in this manner may actually increase its appeal to practitioners.

4. Finally, and most important, we took this issue to the Psychopharmacologic Drugs Advisory Committee and the consensus of our Advisors was that marketing should be delayed until the risk of seizures in association with Wellbutrin use can be determined in an unselected population of depressed patients with greater certainty. I am in agreement with this position.

Therefore, I recommend that the following comments be conveyed to the sponsor:

> We have reviewed your proposal for the limited marketing of Wellbutrin, and we wish to state our strong disagreement with this plan. Our primary reason for taking Wellbutrin to the Psychopharmacologic Drugs Advisory Committee on April 25, 1986 was our concern about the reliability of the original estimate of seizure risk associated with Wellbutrin (based on data in the NDA), given the new information about four seizures occurring in a study population of 55 patients. There is no readily apparent explanation for this finding, a d you also acknowledge in your letter that you haven't been able to adequately explain this higher seizure risk estimate. It is our view that, until the original estimate of seizure risk can be confirmed in a prospective study (conducted under an IND) of Wellbutrin in an unselected population of depressed patients, Wellbutrin should not be marketed. A majority of our Advisors in the Psychopharmacologic Drugs Advisory Committee agreed with this position.
>
> We would be willing to meet with you to further discuss your plans for a prospective study. However, we ask that you not proceed with your plan to market Wellbutrin until the original, lower estimate of seizure risk associated with Wellbutrin is confirmed.

Thomas P. Laughren 5-23-86

Thomas P. Laughren, M.D.

Pers. sub. by
L. Miller.

SUPPL NEW CORRES

Burroughs Wellcome Co.

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

Wellcome

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

As a result of this submission a memo proposing issuance of Notice of Opportunity for Hearing was prepared and submitted to P/Cats on 5-28-86
RMMcIntyre
5/29-86

May 22, 1986

Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products
Office of Drug Research and Review
Centers for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 18-644
Wellbutrin® (Bupropion) Tablets

Dear Dr. Leber:

As requested during your May 5, 1986 conversation with , the following is a statement of the Burroughs Wellcome Co. position on Wellbutrin and a description of the strategy we wish to pursue regarding marketing. We propose a three point plan as outlined below.

- The initial marketing of Wellbutrin will limit patient exposure and provide an early evaluation of the Wellbutrin seizure profile under conditions of clinical practice. Broader marketing will be contingent upon this evaluation.

- A randomized, open, controlled trial to evaluate the incidence of seizures with Wellbutrin versus a tricyclic antidepressant will be initiated. This study will be conducted to place the seizure rate for Wellbutrin in proper perspective and may provide a basis for future changes in labeling.

- The labeling will be revised to contraindicate the use of Wellbutrin in patients with a diagnosis of bulimia or anorexia nervosa.

The rationale supporting this proposal, and a detailed description of the strategy are provided in the sections that follow.

RECEIVED
NATIONAL CENTER
MAY 22 1986
HFN-120
FOR DRUGS & BIOLOGICS

Rationale Supporting Marketing of Wellbutrin:

As you are aware, in January and February, 1986, four bulimic patients out of a study population of 55 patients receiving Wellbutrin experienced seizures within our recommended dosage range. In March, 1986, we voluntarily interrupted, on a temporary basis, the planned commercial distribution of Wellbutrin pending a full evaluation of these seizures. The results of a thorough review of the bulimia seizures, as well as all other seizures which had been reported to us during the conduct of our clinical trial program are as follows:

- Each of the four bulimia seizures was thoroughly investigated, and reviewed by a panel of consultants with recognized expertise in eating disorders, epilepsy, or general psychopharmacology. Based on this evaluation, the reason for the apparent higher incidence of seizures in the bulimia study cannot be identified.

- Various physical and chemical characteristics of the drug were rechecked. Dissolution rate, percent label strength, and purity were all found to be within acceptable standards.

- Seizure incidence rates were recalculated to include all seizures (including the bulimia seizures) that have occurred with Wellbutrin. This recalculated rate is based on an updated denominator of patient exposures (3981) which includes 1583 new patients (including the bulimia patients). The revised incidence for dosing below 450 mg/day is 0.3%, compared to the previous incidence of 0.2%; the revised incidence at 450 mg/day is unchanged from the previous rate of 0.3%.

- All seizures were reviewed for history of eating disorder, relationship to time on drug and dose, correlation with plasma levels, predisposing factors (e.g., concomitant medications, history of seizures, head trauma, tumors, etc.), clustering of seizures, and relationship to drug batch. In addition, other potential causative factors were sought. This review produced no new leads and the updated seizure profile for Wellbutrin remains consistent with the profile upon which the December, 1985 approval was based.

- The literature was carefully reviewed to determine the reported incidence of seizures associated with tricyclic therapy. The seizure incidence rates varied widely, ranging from 0.06% to 15%. Methodological flaws in these studies, however, raise serious questions about the validity of the incidence estimates.

From the above information, we conclude that:

- The seizure profile for Wellbutrin is essentially the same as it was at the time of NDA approval in December, 1985, and the labeling, as approved at that time, continues to provide an accurate description of the seizure experience in clinical trials.

- The true relative seizure incidence rate for Wellbutrin compared to other marketed antidepressants is not known.

- No specific explanation for the apparent higher incidence of seizures in bulimic patients has been established. It is conceivable, however, that these patients may be predisposed to seizures with Wellbutrin by some unknown mechanism.

Based on these conclusions, we propose to resume the marketing of Wellbutrin with labeling revised to contraindicate use in patients with a diagnosis of bulimia or anorexia nervosa. During the initial period of marketing, commercial release will be limited as described below, until the results of a post-marketing evaluation of seizure incidence are available. This post-marketing evaluation will provide an estimate of the seizure incidence for Wellbutrin under conditions of general clinical practice. Such an estimate is one that cannot be obtained through further IND studies, since conditions approximating clinical use cannot totally be achieved through studies conducted under the controls required by an IND. This evaluation, therefore, will provide an estimate of the seizure incidence for Wellbutrin under conditions of general clinical use which is the primary issue that remains for this drug. A related issue, the relative incidence of seizures for Wellbutrin compared to other antidepressants, will be addressed by the results of a controlled clinical trial designed to determine the relative seizure rate for Wellbutrin versus a tricyclic antidepressant (under the conditions of an IND controlled trial). This controlled trial will be conducted in order to place the seizure rate for Wellbutrin in proper perspective, and may provide a basis for future changes in labeling if warranted by the study results and other post-marketing experience.

MARKETING PROPOSAL:

We propose to initiate the marketing of Wellbutrin through a limited release to psychiatrists designed to limit patient exposure and to provide an early evaluation of the Wellbutrin seizure profile under conditions of clinical practice.

Psychiatrists will be notified by mail that Wellbutrin can be made available to them, upon request, in the form of free trial kits which consist of 6 bottles of 21 and 6 bottles of 100 75 mg tablets. Physicians will be able to request a kit by calling a toll-free telephone number. Each request will result in a visit by a Burroughs Wellcome representative, who will deliver a trial kit and inform the physician as to his responsibilities for participating in this program and for reporting adverse experiences. Physicians will be required to sign a statement acknowledging requests for the trial kit, and willingness to report major adverse experiences in patients who receive the Wellbutrin. Upon enrolling each patient, the physician will be instructed to fill out a patient registration card which will include demographic information, a statement of the indication for which Wellbutrin was prescribed, and the prescribed dose. Each registration card should be mailed to Burroughs Wellcome at the time the patient is enrolled. The physician will be instructed to evaluate each patient and complete a second card (follow-up) when the patient

is terminated from treatment or completes six weeks of treatment, whichever occurs first. This follow-up card will contain information describing any major adverse experiences reported, and the doses of Wellbutrin taken.

Each trial kit will provide enough medication for approximately 20-30 days of treatment for each of 6 patients. When the patient has taken his trial kit supply, additional medication may be provided through prescriptions filled at retail pharmacies. Retail pharmacists will be asked to order Wellbutrin from their wholesalers on a prescription-by-prescription basis, rather than ordering quantities for stocking. The initial distribution will involve approximately 360 wholesalers, each of whom will receive 12 bottles of 100 75 mg tablets. Letters announcing this program will be sent to wholesalers, pharmacists and psychiatrists. No promotional activity will be undertaken during this period.

Once 3000 follow-up cards are received, an analysis of the seizure incidence will be conducted. If the observed incidence of seizures among the registered patients is 0.6% or less, promotional activities will begin.

This limited release will make drug available in a highly restricted fashion. Initial stocking in wholesalers will be limited to 4,320 bottles of 100 75 mg tablets, which is a 93% reduction from the approximately 64,000 bottles originally planned for distribution during the launch of the product. The size of restocking shipments will be contingent on retail demand. This, together with lack of stocking in retail pharmacies, will force a close correspondence between the quantities of drug shipped from Burroughs Wellcome and the amounts distributed to patients, thereby precluding the possibility that large numbers of patients could receive Wellbutrin without our knowledge during the initial period of marketing. Also, the restricted audience (psychiatrists only), the highly restrictive labeling for Wellbutrin, the lack of promotional activities, and the linkage of prescriptions to prior users of the trial kits will assure a slow rate of increase in use during the initial marketing period.

While the trial kit and the post-marketing evaluation associated with it are the key elements in the introduction of Wellbutrin, it is possible that some physicians will prescribe Wellbutrin directly without using the trial kits and thus will not provide data on patient exposure. This should be relatively infrequent, however, since no promotional activities will be conducted during this period. It should also be noted that the labeling for Wellbutrin is highly restrictive, limiting the recommended use of the drug to patients who have failed to respond adequately to or who have been unable to tolerate alternative antidepressant treatments. Thus, Wellbutrin is categorized as a drug of second choice because of seizures and this in itself should severely restrict the use of the drug. Any patient exposures that occur from physician prescriptions that are not associated with the trial kits will be monitored for adverse experiences using the standard post-marketing surveillance method of spontaneous reporting.

Finally, a randomized, open, controlled trial to evaluate the incidence of seizures with Wellbutrin versus a tricyclic antidepressant will be initiated. This trial will be conducted under IND regulations, and will involve 2800 patients in each group. We welcome your input into the final design of this trial, and, in any case, would await your approval before initiating this study.

We would like an opportunity to meet with you as soon as possible to discuss this proposal of a limited release for Wellbutrin.

Sincerely,

Donald A. Knight
Associate Director
Drug Regulatory Affairs

M. Dalla

REPORTS

Burroughs Wellcome Co.

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

Wellcome

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

May 9, 1986

Noted
KWK
5-13-86

Paul D. Leber, M.D., Director
Division of Neuropharmacological
Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 18-644
WELLBUTRIN® Tablets

Dear Dr. Leber:

We are submitting herewith an adverse reaction report on a patient who died from a massive myocardial infarction while being treated with WELLBUTRIN in clinical study 39, "Protocol for Long-Term Treatment of Depression with WELLBUTRIN."

The patient, #86, was a 38-year-old male being treated by , M.D.

A revised protocol for this study was submitted to the FDA on June 18, 1984 and amended on January 31, 1985, February 6, 1985, April 18, 1985, and September 3, 1985. Dr was registered for this study on July 8, 1982.

We will submit any additional information we receive on this patient.

Sincerely,

Donald A. Knight
Associate Director
Drug Regulatory Affairs

RECEIVED
NATIONAL CENTER
MAY 9 1986
HFN-120
FOR DRUGS & BIOLOGICS

Department of Health and Human Services
Public Health Service
Food and Drug Administration

Memorandum

To: Director
Center for Drugs and Biologics

April 28, 1986

Through: Paul D. Leber, M.D.
Director, Division of Neuropharmacological Drug Products

Noted
5-13-86

From: Frederick J. Abramek, MS
Executive Secretary, Psychopharmacologic Drugs Advisory Committee
Division of Neuropharmacological Drug Products, HFN-120

Subject: Psychopharmacologic Drugs Advisory Committee Meeting #29
April 25, 1986 (An Open Session):
INFORMATION ALERT MEMORANDUM

I. NDA 18-644 - Wellbutrin^{R} (bupropion hydrochloride): Significance of Reports of Seizures in Bulimic Patients

[Wellbutrin^{R} (bupropion hydrochloride) is an antidepressant of the aminoketone class, chemically unrelated to tricyclic, tetracyclic, or other known antidepressant agents. It was approved for marketing in December, 1985.

Based on data gathered during its development, the estimated risk of seizure among patients treated with 450 mg or less of Wellbutrin^{R} a day (the recommended dose and below) is approximately 0.3 to 0.4 percent. However, at doses only slightly greater than those recommended, the risk climbs to clearly unacceptable levels (i.e., circa 1-3% of those exposed). Consequently, Wellbutrin's labeling restricts its recommended use to patients "who cannot tolerate or do not respond to alternative antidepressants."

During the first two months following its approval, however, reports were received that raised concerns that the incidence of seizure at recommended doses might actually be higher than estimated. Specifically, four seizures were reported in an ongoing clinical trial of 50 nondepressed patients treated for bulimia at doses well within the recommended range (e.g. 300 to 375 mg per day).

The sponsor, after consulting with the Agency, agreed to delay its planned commercial marketing of the product until the new information could be fully evaluated. As part of the evaluation, it was also agreed that some prospective effort should be made to determine whether the rate estimated by the NDA was reliable. Clearly, the rate of 0.3 to 0.4 percent based upon the NDA experience is inconsistant with the 8.0 percent rate observed in the bulimia study.

The firm made two proposals to the Agency for a study of the problem. However, before the Advisory Committee meeting took place, the firm withdrew the first proposal (i.e. one for an open, uncontrolled, limited distribution study) in favor of a second (i.e., one for a prospectively randonized comparsion of Wellbutrin^{R} and imipramine, a standard antidepressant, in a multicenter trial involving 5600 patients).]

The problem of the best approach to evaluating the risk of seizure at this time was discussed with the Committee. In the course of the discussion, the Committee was asked the following questions: 1) whether they endorsed the concept of a controlled clinical trial with full informed consent to assess the comparative risk of seizure for bupropion and a standard antidepressant; 2) if they endorsed the concept, what patient population ought to be enrolled in the trial; 3) if a controlled trial is not possible under the conditions recommended by the Committee, what alternative course of action would they suggest; and 4) would the Committee recommend that Wellbutrin^{R} not be marketed at all?

Committee recommendations were as follows:

1.) The Committee recommended [8 for, 0 against, 1 abstention] to endorse the concept of a controlled clinical trial with full informed consent as an appropriate means to reassess (i.e., confirm or reject) the current estimated risk of seizure associated with the use of Wellbutrin^{R} within the approved dosage range.

2.) The Committee recommended [8 for, 0 against, 1 abstention] that the sponsor employ a comparative study design of bupropion and a standard drug. In further discussion, a consensus emerged that imipramine was the best choice for the comparative agent.

3.) The Committee was asked to state, in quantitative terms, how it would interpret the outcome of the study. It declined to answer the question prospectively.

4) A consensus emerged among Committee members that the proposed study could enroll any depressed patient who was an appropriate candidate for antidepressant treatment. Specifically, there was no need to restrict entry to patients who satisfy the criteria described in Wellbutrin's approved indication.

While not proposed as a formal question, the Committee did discuss the propriety of marketing Wellbutrin^{R} at this time. The sense of the majority of the Committee was that it was not unreasonable to delay marketing until the results of the proposed study became available.

The Committee also made several suggestions to the sponsor about the design of the proposed study.

UCN 501 MADE IN JAPAN

Wellcome

Burroughs Wellcome Co. 3030 Cornwallis Road
Research Triangle Park, N.C. 27709

cables & telegrams
Tabloid Raleigh, N.C.
TWX5109270915
tel. 919 248-3000

April 4, 1986

Listed Previously seen in other submissions RWMayer 4-30-86

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Dear Sir or Madam:

Pursuant to 21 CFR 314.80, enclosed are Initial 15-Day FDA 1639 Reports for WELLBUTRIN® Tablets. These reports have previously been submitted to the Division of Neuropharmacological Drug Products for both IND and NDA 18-644, since they occurred during clinical trials of WELLBUTRIN.

Burroughs Wellcome Co. #	Adverse Experience	Date Previously Submitted
	Cerebral ischemic attack	3/18/86
	Seizure	1/31/86 and 3/3/86
	Seizure	3/3/86
	Seizure	1/31/86 and 3/3/86
	Seizure	3/3/86

NDA 18-644

Sincerely,

Donald A. Knight
Associate Director
Drug Regulatory Affairs

RECEIVED
APR 9 1986
HFN-120 FOR DRUGS & BIOLOGICS
NATIONAL CENTER

RECEIVED
CENTER FOR DRUGS & BIOLOGICS
APR 4 1986
CENTRAL DOCUMENTS ROOM

REPORTS

Burroughs Wellcome Co.

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

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

April 8, 1986

Noted
No spontaneous
ADRs occurred
as drug is not
yet marketed
- RM Kapit
4-16-86

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Dear Sir or Madam:

Pursuant to 21 CFR 314.80, enclosed is the Periodic ADR Report for Wellbutrin® Tablets.

NDA 18-644

The time period covered by this report is December 31, 1985 - February 28, 1986.

Sincerely,

Donald A. Knight
Associate Director
Drug Regulatory Affiars

120

RECEIVED
NATIONAL CENTER
APR 16 1986
HFN-120
FOR DRUGS & BIOLOGICS

RECEIVED
CENTER FOR DRUGS & BIOLOGICS
APR 09 1986
CENTRAL DOCUMENT ROOM

ADR PERIODIC REPORT

MADE IN JAPAN

MAY - 8 1986

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUGS AND BIOLOGICS

DATE: May 1, 1986

FROM: Richard Kapit, M.D.

SUBJECT: Wellbutrin

TO: File, NDA 18-644

1.0 Summary:

On April 15, 1985, the Burroughs Wellcome Company submitted a report on seizures occurring on Wellbutrin. The report consists of:

1) Final report on seizures in 4 bulimic patients.
2) A table of overall seizure incidence.
3) Graphs showing the occurrence of seizures as a function of time and dose.

In general these report tables and graph are sufficently informative and succint so that there will be no advantage to summarizing this information in this memorandum. It will be simpler and better to review the submission itself. However, a few points will be highlighted.

2.0 Bulimic Patients:

Seizure occurred in 4 women in the bulimia study in January and February 1986.

Age Range:	23 to 42
Weight Range:	39.9 to 71.2 kg
Dose Range:	300 to 375 mg/day
	5.27 to 9.4 mg/kg
Time on Wellbutrin	7 to 23 days
Time on dose:	1 to 20 days

Other than being bulimic women, no factor save one was common to all the seizure patients: the only other common factor was that all had elevated amylase at screening or at time of seizure, or both. Other factors were common to some subset of the women: 3 were on BCPs; two had been very active prior to seizure, etc.

3.0 Overall Seizure Rate:

The Company's table shows that seizure rate increases rapidly with dose above 450 mg/day. However, it should be noted that prior to the July 1985 safety update, 3 of 27 seizures occurred at doses of less than 400 mg while subsequent to the safety update 5 of 8 seizures decreased at doses of less than 400 mg. (This possibly might be attributed to the fact that patients did not receive Wellbutrin in doses over 450 mg/day after July 1985).

4.0 These graphs show that 27 of 32 (84%) seizures occurred in less than 43 days on Wellbutrin and that 15 of 32 seizures occurred in the first week on drug. At doses less than 450 mg/day, slightly fewer patients (proportionally) seized in less than 43 days (10 of 14 or 71%).

Richard Kapit, M.D.

NDA-18-644
hFN-120
HFN-120/TLaughren
HFN-120/RKapit/5/1/86 5-7-86

5-8-86
The issue of seizure occurring in association with Wellbutrin use was discussed at a meeting of the PDAC 4-25-85.
T. Laughren

P. Sub. by
R. Vestal.

ORIGINAL

SUPPL NEW CORRES

Burroughs Wellcome Co.

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

Wellcome

cables & telegrams
Tabloid Raleigh, N. C.
TWX5109270915
tel. 919 248-3000

April 15, 1986

Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products
Office of Drug Research and Review
Centers for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 18-644
Wellbutrin® (Bupropion) Tablets

Dear Dr. Leber:

As discussed in our meeting of April 8, 1986, we enclose, herewith, the following information for your review and subsequent distribution to the Psychopharmacologic Drugs Advisory Committee prior to the Advisory Committee meeting scheduled on April 25, 1986:

Attachment 1. Final updated reports on the 4 bulimic patients who experienced seizures and summary charts of these 4 events

Attachment 2. A revised table of the overall seizure incidence with Wellbutrin based on a revised data base that includes 1583 additional patients added since the August 9, 1985 submission of the safety update (total data base includes 3981 patients)

Attachment 3. Figures illustrating the following:

a. The distribution of all seizures as a function of total time on Wellbutrin

b. The distribution of all seizures as a function of time on the dose at which the seizure occurred

c. The distribution of seizures occurring at 450 mg/day and below as a function of total time on Wellbutrin

RECEIVED
NATIONAL CE
APR 15 1986
HFN-120
FOR DRUGS & BIOLOGICS

d. The distribution of seizures occurring at 450 mg/day and below as a function of time on the dose at which the seizure occurred

We are preparing documents in support of our revised data base of 3981 patients, which will include summary tables of patient demographics, dosing information, adverse experiences, and individual patient listings. This submission is planned for early May, 1986. We are also preparing proposed confidence limits of seizure incidence for use in decisions regarding possible termination of the clinical experience program. In addition, we will propose an upper confidence limit for the seizure incidence observed in the clinical experience program. These limits will be submitted later this week.

Finally, Attachment 4 describes presentations which we would like scheduled for the Advisory Committee meeting. We may elect not to present one or more of these topics if we determine they are not necessary.

Sincerely,

J. Greg Parham, Ph.D.

Donald A. Knight
Associate Director
Drug Regulatory Affairs

Rec'd Sept. by Mr. Knight

SUPPL NEW CORRES

Wellcome

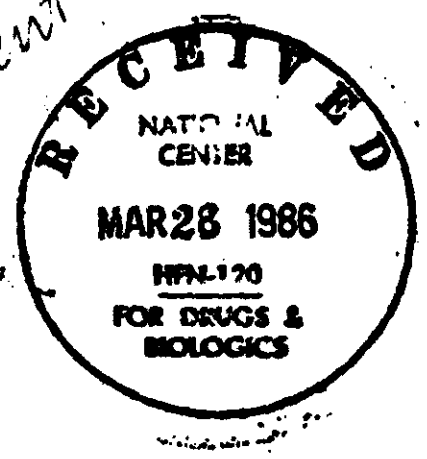
Burroughs Wellcome Co.

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

cables & telegrams
Tabloid Raleigh, N.C.
TWX:510 928 0915
tel. 919 248-3000

March 25, 1986

Noted
This proposal discussed at recent meeting - BW
3/26-16



Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products
Office of Drug Research and Review
Centers for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 18-644
Wellbutrin® (Bupropion) Tablets

Dear Dr. Leber:

Pursuant to our recent conversation of March 14, 1986 regarding Wellbutrin, we wish to propose a strategy for obtaining additional safety data on Wellbutrin prior to the formal launch of the product. The objective of this program is to provide rapid entry of a relatively large number of patients while capturing significant adverse events. Patients will be recruited through practitioners specializing in psychiatry, who will be instructed to complete a case report form for each patient receiving the drug. These data will be used to further evaluate the safety profile of Wellbutrin with emphasis on seizure potential. Details of the program are described below.

Psychiatrists will be notified by letter that Wellbutrin will be made available to them, upon request, in the form of trial kits which consist of six bottles of 21 and six bottles of 100 75 mg tablets. Each trial kit will provide enough medication for approximately 20 days of treatment for six patients. Burroughs Wellcome will continue to supply free product to physicians for patients enrolled until launch of Wellbutrin or until termination of this program. The current Wellbutrin package insert will be revised to include a contraindication in patients with bulimia or anorexia nervosa. Informational material would also be modified to reflect this change.

Physicians will be able to request these kits by calling a toll-free telephone number. Each request will result in a visit by a Burroughs Wellcome representative, who will deliver a trial kit and instruct the physician as to his responsibilities for participating in this program and for reporting adverse experiences. The physician will be required to sign a statement acknowledging his request for the trial kit, and his willingness to report on the experiences of the patients who receive the medication. Upon enrolling each patient, the physician will be instructed

MADE IN JAPAN

to fill out a patient registration card which will include demographic information, a statement of the indication for which Wellbutrin® was prescribed, and the prescribed dose. Each registration card should be mailed to Burroughs Wellcome at the time the patient is enrolled. The physician will be instructed to evaluate each patient and complete a second card (follow-up) after six weeks of treatment or after discontinuation of Wellbutrin therapy, which ever comes first. This follow-up card will contain information describing the therapeutic response of the patient, any adverse experiences reported, and the doses of Wellbutrin taken.

The goal of the project will be to accumulate a series of at least 3000 patients who have completed 6 weeks of treatment. A data cut-off will be established at this point, and all patients for whom follow-up cards have been received (3000 patients completing six weeks of therapy and all patients discontinued prior to six weeks) will form the data base upon which the safety profile of Wellbutrin will be evaluated. It is estimated that a sample size of 3000 Wellbutrin patients will be adequate to provide at least a 95% chance to estimate the true seizure incidence within $\pm$ 0.25%.

In order to facilitate the earliest completion of this program, we propose to initiate it as soon as possible. We anticipate that the initial letters to psychiatrists could be mailed as early as the week of April 7, 1986. We would be pleased to discuss any questions you may have regarding this proposal.

Sincerely,

Donald A. Knight
Associate Director
Drug Regulatory Affairs

MADE IN JAPAN

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 3-20-86
FROM: R. M. Kapit M.D.		OFFICE HFN-120
TO: File & NDA 18644		DIVISION DANDP
SUBJECT: Correspondance re Wellbutrin.		

SUMMARY

The company has submitted (3-13-86) copies of its correspondance re Wellbutrin with physicians, pharmacists, pharmaceutical distributors, medical writers, and clinical investigators.

Almost all of these communications suggest an association between the occurrence of seizures and the concurrent use of bulimia and anorexia nervosa. For example the company uses the comment that "there is an unacceptably high incidence of seizures in bulimic patients receiving Wellbutrin." A more neutral association would have been: An unacceptably high rate of seizures occured in one study of bulemic patients receiving Wellbutrin.

Rec. No recommendation at this time. Continue to monitor this situation

Dist. T. Laughren
P. Leber
R. Kapit

4-1-86

SIGNATURE R M Kapit MD

DOCUMENT NUMBER

FORM FDH-2034 (11/66)

MADE IN JAPAN

REPORTS

Burroughs Wellcome Co.

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

cables & telegrams
Tabloid Raleigh, N.C.
TWX5109270915
tel. 919 248-3000

March 18, 1986

Noted
R M Lyon
3-28-86

Paul D. Leber, M.D., Directo
Division of Neuropharmacological
Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 18-644
WELLBUTRIN• Tablets

Dear Dr. Leber:

We are submitting herewith an adverse experience report on Patient #196, entered in Dr. John P. Feighner's clinical study 39, "A WELLBUTRIN Treatment Protocol." Summary information on the patient is attached.

A revised protocol for this study was submitted to FDA on June 18, 1984 and amended on January 31, 1985, February 6, 1985, September 3, 1985, and December 17, 1985. Dr. Feighner was registered to conduct this study on March 17, 1981 and his completed Form FD 1572/1573 was submitted November 8, 1979.

We will submit any additional data we receive on this patient.

Sincerely,

George M. Lyon, Jr., M.D.
Director
Drug Regulatory Affairs

RECEIVED
NATIONAL CENTER
MAR 20 1986
HFN-120
FOR DRUGS & BIOLOGICS

RECEIVED
MAR 20 1986

LION 301 MADE IN JAPAN

MEMORANDUM OF TELEPHONE CONVERSATION

March 24, 1986

Between: Mr. Dan Seigelman - Weiss Sub-committee

and: Paul Leber, M.D. - FDA

Subject: Wellbutrin

Mr. Seigelman called to inquire whether the review of the Wellbutrin NDA included the calculation of a cumulative risk for seizure for the 450 mg dose. I replied that if such a calculation had been done, there should be a record of it in the file. If no record existed, I could not help him further.

Paul Leber, M.D.

cc: HFW-12/Hugh C. Cannon
Orig. NDA 18-644
HFN-120
HFN-120/PLeber/3/24/86
Doc. # 3799p

PLEASE HAND DELIVERED BY

ORIGINAL

SUPPL NEW CORRES

Wellcome

Burroughs Wellcome Co.

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

cables & telegrams
Tabloid Raleigh, N.C.
TWX5109270915
tel. 919 248-3000

March 13, 1986

Mailed
FAX Sept
3-20 &c

Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products
Office of Drug Research and Review
Centers for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RECEIVED
NATIONAL CENTER
MAR 14 1986
HFN-130
FOR DRUGS & BIOLOGICS

RE: NDA 18-644
Wellbutrin® (Bupropion) Tablets

Dear Dr. Leber:

On Thursday, February 27, 1986, Burroughs Wellcome Co. received notification of a seizure occurring in a patient receiving Wellbutrin while enrolled in a clinical trial to assess the efficacy of Wellbutrin in bulimia. This seizure represented the fourth such event in a population of 50 nondepressed bulimics; all four seizures occurred within the recommended dosing range for Wellbutrin. IND Safety Reports on the first two seizures were submitted on January 31, 1986. The third seizure occurred on February 10, 1986, and an IND Safety Report was in preparation for submission to FDA. Also, in preparation was a letter detailing the actions taken in response to the third event. These actions included suspending patient enrollment at all 3 centers and reducing the maximum dose for ongoing patients from 450 mg/day to 300 mg/day. Upon notification of the fourth seizure, Burroughs Wellcome terminated dosing of all patients in this multicenter trial. On February 28, 1986, FDA was notified by telephone of the four seizures and the actions taken by Burroughs Wellcome in response to these events. FDA was also informed that drug distribution for market launch had begun. After internal Burroughs Wellcome discussions and further discussions with FDA, Burroughs Wellcome decided to delay launch and voluntarily withdraw all Wellbutrin from the marketplace. As of close of business on February 28, 1986, 60,832 bottles of 100 tablets had been shipped to 375 different wholesale accounts.

The following is a summary of the actions taken in association with the withdrawal:

1. All wholesalers who had received Wellbutrin were directed by mailgram (Attachment A) on February 28, 1986, to cease distribution of the product and return all material to Burroughs Wellcome.

2. On March 3, 1986, all wholesale accounts were called to assure that they had not only received the mailgram but to inquire as to whether distribution had occurred from their warehouses. It was determined that only 130 bottles had been shipped to retail pharmacies.

3. On March 4 and 5, 1986, Fisher-Stevens sent info-grams (Attachment B) to all retail pharmacies in the U.S. informing them that the product should not be dispensed. The second phase of the Fisher-Stevens industry procedure (follow-up letter with special return label and shipping instructions) was deemed unnecessary because of the small number of bottles distributed to the retail pharmacies; it was decided that direct telephone contact was more rapid. Thus, on March 4, 1986, Burroughs Wellcome office staff began calling the retail pharmacies who had received Wellbutrin to request return of goods to their wholesaler.

4. As of March 12, 1986, all but 2 of the 60,832 bottles that had been shipped to wholesalers had been either returned to wholesalers or to Burroughs Wellcome. Attempts are continuing to contact two pharmacies with requests to each to return the single bottle they had received.

5. Two-hundred and three (203) trial kits, each containing 6 bottles of 21 tablets and 6 bottles of 100 tablets, had been shipped to 69 different physicians. Fifty-nine of these physicians had been investigators in a Wellbutrin clinical trial and 10 were physicians who had requested drug for their patients (nonresponders or nontolerators) but who had not previously been Wellbutrin investigators. On February 28, 1986, each of these 69 physicians was notified by Telex (Attachments C and D) to terminate dosing in any patient who had a diagnosis of bulimia or anorexia nervosa and to not dispense any further samples. A follow-up letter (Attachments E and F) was sent to instruct them on the procedure for returning the samples.

Burroughs Wellcome took additional action with regard to a press conference for medical writers held in on February 24, 1986. Attendees of this meeting were notified by mail of the seizure incidence in bulimic patients and requested to hold their stories on Wellbutrin until the matter was resolved (Attachment G).

Finally, all Wellbutrin investigators were notified by Telex (Attachment H) of the seizure incidence in bulimic patients, and informed not to enroll any patients with a diagnosis of bulimia or anorexia nervosa and to discontinue Wellbutrin treatment in any ongoing patients that had either of these diagnoses. Follow-up letters (Attachment I) were sent to these physicians to confirm the earlier notification. All other activities in ongoing clinical trials were permitted to continue.

It is our understanding that FDA intends to refer this issue to the Neuropharmacology Advisory Committee for discussion at a meeting tentatively planned for late April, 1986. In preparation for FDA and Advisory Committee review, we are updating our reports on the bulimia seizures with information that was not available at the time of our prior submissions. We are also compiling relevant information from the literature and seeking the opinions of investigators and other experts in this area regarding the incidence of seizures and other neurological problems in patients with eating disorders. Finally,

LION 301 MADE IN JAPAN

we are updating our tabulation of patient exposures to Wellbutrin by dose and by duration of treatment for use in assessing the overall seizure incidence with Wellbutrin.

We would appreciate an opportunity to meet with you as soon as possible prior to the Advisory Committee meeting to discuss the strategy for the further evaluation of the bulimia seizures and possible implications for revisions in the product labeling.

Sincerely,

MADE IN JAPAN

Burroughs Wellcome Co.

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

Wellcome

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

March 3, 1986

Noted
Rm Report
3-19-86
As of this time, marketing of Wellbutrin has been delayed

Paul D. Leber, M.D., Director
Division of Neuropharmacological
Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 18-644
WELLBUTRIN® Tablets

Dear Dr. Leber:

We are submitting herewith two additional adverse reaction reports on patients who experienced seizures while being treated with WELLBUTRIN in clinical study 83, "Multicenter Evaluation of Bupropion Hydrochloride (Wellbutrin) and Placebo in Female Patients with Chronic Bulimia". We have also included a copy of our January 31, 1986 submission which provides information on the first two patients who experienced seizures while being treated for Bulimia. Study 83 has been discontinued and all patients have been taken off drug.

As discussed during our telephone conversations on February 28, 1986, we have instituted a voluntary withdrawal of marketed product to the retail level. Since distribution to wholesalers commenced just a few days ago, it is likely that relatively few patients will be exposed to WELLBUTRIN.

We feel that these seizures, in selected, nondepressed bulimic patients, represent a unique subset of patients who exhibit a propensity for seizures. The addition of these four seizures to our database does not appreciably affect the overall incidence of seizures within the recommended dosage range. We feel this can be adequately described in labeling and allow for safe use of the drug product, and we would hope for rapid agreement on these points.

Sincerely,

Donald A. Knight
Associate Director
Drug Regulatory Affairs

MADE IN JAPAN

REPORTS

Burroughs Wellcome Co.

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

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

No date
Appears to be
a new case of Seizure
Note that this woman
was on 225 mg / day
Rx Kapra
5-7-86

Paul D. Leber, M.D., Director
Division of Neuropharmacological
Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 18-644
WELLBUTRIN® Tablets

Note also
patient took
Halcion on
night before
event

Dear Dr. Leber:

We are submitting herewith an adverse reaction report on a patient who experienced a seizure while being treated with WELLBUTRIN in clinical study 39, "Protocol for Long-Term Treatment of Depression with WELLBUTRIN."

KCMK

The patient, #2, is a 37-year-old female being treated by M.D.

5-2-86

A revised protocol for this study was submitted to the FDA on June 18, 1984 and amended on January 31, 1985, February 6, 1985 and September 3, 1985. Dr. was registered for this study on May 23, 1985.

We will submit any additional data we receive on this patient.

Sincerely,

Donald A. Knight
Associate Director
Drug Regulatory Affairs

RECEIVED
NATIONAL CENTER
MAY 2 1986
HFN-120
FOR DRUGS & BIOLOGICS

MADE IN JAPAN

Review and Evaluation of Clinical Data
NDA 18-644

Sponsor: Burroughs Wellcome Co. - 7 1986

Drug: Wellbutrin

Drug Category: Antidepressant

Dosage Form: Oral Tablets

Material Submitted: Re-analysis of safety data

1.0 Summary:

On February 17, 1986 the company responded to a request made in the approval correspondence for Wellbutrin. In this submission the company submitted cross-tabulation plots and tables for clinical laboratory parameters of patients who participated in nine studies submitted to the NDA. All patients who received treatment (either placebo, amitriptyline or Wellbutrin) and who had a baseline and one or more treatment period clinical laboratory evaluations were included in this analysis. The studies include five pivotal placebo-controlled studies, two amitriptyline-controlled studies, and two long-term studies. In addition to presenting cross-tabulations, the analysis provided identification of patients with potentially significant abnormalities, values of the abnormal parameters and values of any related parameters.

2.0 Hematology:

In the opinion of this reviewer, there were seven patients who exhibited an abnormal hematologic parameters which possibly resulted from Wellbutrin administration. In these subjects an abnormality occurred on treatment which was not present during periods when the drug was not administered. Four of these had low white counts, and three had high white counts. The lowest was 3.3 and the highest was 17.5. None of these seven subjects made a convincing case for the occurrence of a serious abnormality due to Wellbutrin.

3.0 SGOT, SGPT, Alkaline Phosphatase, Bilirubin:

There were ten subjects who had an abnormality of one of these parameters judged to be potentially significant by this reviewer and who showed such abnormality on Wellbutrin but not on no drug treatment. Three of these patients had abnormal LDHs; five had abnormal alkaline phosphatases; one had an abnormal SGPT. The only parameter which exceeded twice the upper limit of normal was a single bilirubin of 9.4 mg/dl; however, this appears to be an erroneous value since the same subject had normal values for SGOT, SGPT, and alkaline phophatase at the same time that the bilirubin was reported to be 9.4.

MADE IN JAPAN

4.0 BUN and Creatine:

Only one subject showed a very mild elevation of BUN on Wellbutrin, with a normal value occurring while on no drug treatment. There were no abnormalities of serum creatinine that could be attributable to drug treatment.

5.0 Glucose:

Six patients exhibited elevated blood glucose levels while on Wellbutrin but had normal levels while on no drug treatment. However, 8 patients in the same group of glucose abnormalities had elevated glucose levels on no drug treatment, but normal levels while on Wellbutrin. Of the abnormalities occurring on Wellbutrin, the highest glucose was 244 mg/dl. The other 5 Wellbutrin abnormalities were all below 200.

6.0 Other Clinical Lab:

Only one abnormality of calcium could possibly be attributed to Wellbutrin; this was a very mild elevation 11.3 mg/dl (10.5 upper limit of normal).

Two abnormalities of serum cholesterol might possibly be attributed to Wellbutrin; one is a lowering to 74 mg/dl (lower limit 120); the other is an elevation to 362 (upper limit 330).

There were no abnormalities of phosphorous level that could be attributed to Wellbutrin.

7.0 Conclusions:

In this submission the company presented all potentially significant abnormalities of clinical hematology and clincial chemistry which occurred in 9 of the studies submitted to NDA 18-644. There was no instance of a seriously abnormal clinical lab parameter which might be attributable to Wellbutrin.

However, there were several instances of mild abnormalities of serum enzyme levels which might possibly be due to the drug.

Richard Kapit, M.D.

NDA 18-644
HFN-120
HFN-120/TLaughren
HFN-120/P/Leber
HFN-120/RKapit/3/5/86
FT:ees/3/5/86
Doc. #0355h

4-4-86

MADE IN JAPAN

SUPPL

Wellcome

Burroughs Wellcome Co.

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

cables & telegrams
Tabloid Raleigh, N.C.
TWX5109270915
tel. 919 248-3000

February 17, 1986

Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 18-644
WELLBUTRIN® Tablets

Dear Dr. Leber:

Reference is made to your letter of December 30, 1985, approving our original NDA for WELLBUTRIN Tablets.

As indicated therein, we are submitting herewith analyses of the clinical laboratory data from nine clinical studies included in our NDA.

Sincerely,

Donald A. Knight
Associate Director
Drug Regulatory Affairs

RECEIVED
FEB 18 1986

MADE IN JAPAN

Burroughs Wellcome Co.

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

cables & telegrams
Tabloid Raleigh, N.C.
TWX5109270915
tel. 919 248-3000

February 12, 1986

Noted
Nat
Annleyer
2-21-86

Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

SUPPL NEW CORRES
2-21-86
We should check to make sure that Burroughs has this information

Re: NDA 18-644
WELLBUTRIN® Tablets

T. Laughren

Dear Dr. Leber:

Reference is made to WELLBUTRIN (bupropion hydrochloride) Tablet NDA approvable letter dated December 31, 1984.

As requested in the above referenced letter, we have scheduled a meeting with Dr. Paul Hepp of the FDA's Division of Biopharmaceutics to discuss additional investigations regarding dose proportionality and the pharmacokinetic parameters of bupropion in the elderly. In preparation for the meeting scheduled for February 18, 1986, at 1:30 p.m., I have enclosed the following:

(1) A brief summary of a recently completed study entitled "The Disposition of Bupropion and its Basic Metabolites in Young and Elderly Healthy Volunteers".

(2) An outline of a proposed study entitled "Steady-State Pharmacokinetics of WELLBUTRIN and Two Basic Metabolites Following Subchronic Dosing of the Parent Drug".

Burroughs Wellcome Co. will be represented at the meeting by Allen Lai, Ph.D., Dave Schroeder, Ph.D., and Don Knight.

Sincerely,

Donald A. Knight
Associate Director
Drug Regulatory Affairs

RECEIVED
FEB 12 1986
FOR BIOLOGICS

LION 501 MADE IN JAPAN

REPORTS

Wellcome

Burroughs Wellcome Co.

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

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

January 31, 1986

Noted
Ellen Koput
2-21-86

Paul D. Leber, M.D. Director
Division of Neuropharmacological
Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 18-644
WELLBUTRIN® TABLETS

Dear Dr. Leber:

We are submitting herewith two adverse reaction reports on patients who experienced seizures while being treated with WELLBUTRIN.

The first patient, #324, is a 26 year-old female who was being treated by in clinical study 83, "Multicenter Evaluation of Bupropion Hydrochloride (WELLBUTRIN) and Placebo in Female Patients with Chronic Bulimia." was registered for this study on October 2, 1985.

The second patient, #218, is a 25 year-old female who was being treated by in clinical study 39, "Protocol for Long-Term Treatment of Depression with WELLBUTRIN." A revised protocol for this study was submitted to the FDA on June 18, 1984 and amended on February 6, 1985, September 3, 1985 and December 17, 1985. was registered to conduct this study on August 18, 1982.

We will forward any additional information we receive on these patients.

Sincerely,

Donald A. Knight
Associate Director
Drug Regulatory Affairs

RECEIVED
NATIONAL CENTER
FEB 3 1986
HFN-120
FOR DRUGS & BIOLOGICS

SUPPL NEW CORRES

Wellcome

Burroughs Wellcome Co.

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

cables & telegrams
Tablo'd Raleigh, N.C.
TWX 5109270915
tel. 919 248-3000

January 27, 1986

2-5-86
Natl. NAT.
T. Laughren

Paul Leber, M.D., Director
Division of Neuropharmacological
Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 18-644
WELLBUTRIN® Tablets

Dear Dr. Leber:

Reference is made to Dr. Temple's letter of December 30, 1985, granting approval of our NDA for WELLBUTRIN Tablets, and to the approvable letter of December 31 1984. We are submitting herewith a copy of our proposed initial advertising and promotional material, as well as a copy of our approved package insert.

A copy of this material is also being submitted to the Division of Drug Advertising.

Sincerely,

Donald A. Knight
Associate Director
Drug Regulatory Affairs

RECEIVED
NATIONAL CENTER
JAN 27 1986
HFN-120
FOR DRUGS & BIOLOGICS

NDA 18644

BEST POSSIBLE COPY

Bupropion HCl
Wellbutrin
75, 100 mg Tablets
NDA 18-644
Wang [redacted]
1-D

Burroughs Wellcome Co.
Research Triangle Park, NC
Submission Dated:
September 26, 1985

DEC 1 2 1985

Review of Dissolution Data

The firm has submitted dissolution data (attached) pursuant to Dr. Karin Kook's review of the firm's May 21, 1985 submission where she requested the raw dissolution data used in the firm's basket vs. paddle method comparison. Dr. Kook's request that interim (i.e. prior to 45 minutes) dissolution data be submitted if available could not be complied with due to such data's lack of availablility.

Recommendation:

Dr. Kook's provisions for setting a dissolution specification of Q=80% at 45 minutes using the paddle method (50 rpm) in 900 ml water at 37°C have been met. This recommendation should be forwarded to the firm.

Paul L. Hepp, Pharm.D.
Pharmacokinetics Evaluation Branch

RD Initialed by C.T. Viswanathan, Ph.D.
FT Initialed by C.T. Viswanathan, Ph.D. 12/12/85

cc: NDA 18-644 orig., HFN-120, HFN-226(Hepp), Chron, Drug, and FOI files.

PLH:smj:kek [redacted] (12-06-85)

MADE IN JAPAN

DISSOLUTION OF WELLBUTRIN® Tablets

% l.s. Bupropion Hydrochloride Dissolved

Batch	Basket Method 45 min.	Paddle Method 45 min.
2E2791 (75 mg)		
Mean	96.9	96.5
Std. Dev.	1.1	1.9

Batch	Basket Method 45 min.	Paddle Method 45 min.
216030 (75 mg)		
Mean	94.0	91.2
Std. Dev.	0.3	4.0

Batch	Basket Method 45 min.	Paddle Method 45 min.
216031 (75 mg)		
Mean	93.2	90.5
Std. Dev.	1.6	1.8

DAK/mg/1D
TRZO/85/0629-3

DISSOLUTION OF WELLBUTRIN® Tablets

% l.s. Bupropion Hydrochloride Dissolved

Batch	Basket Method	Paddle Method
	45 min.	45 min.
2I6032 (100 mg)		
Mean	93.7	87.8
Std. Dev.	1.8	4.1

Batch	Basket Method	Paddle Method
	45 min.	45 min.
2I6033 (100 mg)		
Mean	94.1	90.9
Std. Dev.	1.4	4.3

Batch	Basket Method	Paddle Method
	45 min.	45 min.
2D6011 (100 mg)		
Mean	96.7	84.3
Std. Dev.	1.1	3.8

DAR/mg/1D
TRZO/85/0629-4

Rx

Bupropion HCl
75, 100 mg Tablets
NDA 18-644
Reviewer: Karin A. Kook, Pharm.D.
1-D
Wat.g [redacted]

Burroughs Wellcome Co.
Research Triangle Park, NC 27709
Date of Submission:
May 21, 1985

SEP 25 1985

Review of In Vitro Dissolution Data

In the early development of bupropion, a non-standard basket method (100rpm, 500ml of 0.6% HCl at 37°C) was used; the sampling times were twenty minutes or, more often, thirty minutes. As a result of an FDA Review Chemist suggestion, the procedure was changed on June 10, 1982 to a paddle method (50 rpm, 900ml water at 37°C) with a 45 minute sampling time. During the review of the NDA submission, one lot of 100mg Tablets [redacted] was found to have poor in vivo absorption relative to another lot (7J2700). These lots were tested in vitro with the basket method and poorer dissolution was also noted (60% at 20 minutes versus 104%); lot 8A2704 was 102.5% dissolved after 30 minutes. Thus, the Division of Biopharmaceutics recommended the basket method with a specification of not less than [redacted] percent (Q) drug dissolution in 20 minutes.

The firm has responded to the proposed specification. They indicate that the baskets will ultimately be corroded by the acidic medium and, thus, could give erratic results. They furthermore state that the paddle method is easier to automate. They claim limited experience with a 20 minute sampling time using a basket method. They propose the dissolution specifications to be not less than [redacted] dissolved in 45 minutes using the paddle method at 50 rpm in 900 ml water at 37°C. In support, they provide summary comparative dissolution on three batches of their 75 mg and 100mg tablets (Table 1). Further comparative data was provided in the previously reviewed NDA submission and is summarized on Table 2. Finally, they indicate that they "will further evaluate the possibility of reducing the time specification below 45 minutes if warrented, as data and experience is accumulated with production batches."

Table 1

Batch	Basket Data, 45 Minutes Mean	Basket Data, 45 Minutes Std. Dev.	Paddle Data, 45 Minutes Mean	Paddle Data, 45 Minutes Std. Dev.
75 mg				
2E2791	96.9	1.1	96.5	1.9
216030	94.0	0.3	91.2	4.0
216031	93.2	1.6	90.5	1.8
100 mg				
206011	96.7	1.0	84.3	3.8
216032	93.7	1.8	87.8	4.1
216033	94.1	1.4	90.9	4.3

Table 2

Batch	$\bar{X}$ Paddle @ 45 Min[1]	S.D	$\bar{X}$ Basket @ 20 min[2]	S.D.
2J3145	103.8	1.7	96.0	3.87
3A2716	100.7	1.0	81.0	21.76
3A2717	100.7	1.0	99.3	2.38
3A2718	100.2	3.5	98.3	2.20
3A2719	101.6	3.7	95.9	14.62
3A2720	102.6	3.4	100.5	2.92

[1] n=6
[2] n=12

Recommendation

The Division of Biopharmaceutics agrees to dissolution testing with the paddle method. However, the firm is requested to supply the raw dissolution data used in making the basket versus paddle methods comparisons. This has been communicated by telephone. They were also asked to provide interim (i.e. 30 minute) results, if available. Provided the data are in support, a dissolution specification of Q=[redacted] at 45 minutes using the paddle method in 900 ml water at 37°C could be set.

Karin A. Kook, Pharm.D.
Pharmacokinetic Evaluation Branch

RD Initialed by Paul L. Hepp, Pharm.D.
FT Initialed by C.T. Viswanathan, Ph.D. CTV 9/25/85

cc: NDA 18-644 orig., HFN-120, HFN-226(Kook), Chron, Drug, and FOI Files

KAK:tw:kek:smj:(5004x) 9/16/85

BEST POSSIBLE COPY

おおきな木

BEST
COPY
AVAILABLE

LION 301 MADE IN

Ester copy

NDA 18-644

DEC 30 1985

Burroughs Wellcome Company
Attention: Donald A. Knight
3030 Cornwallis Road
Research Triangle Park, North Carolina 27709

Dear Mr. Knight:

Please refer to your new drug application dated December 28, 1981, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation Wellbutrin (bupropion hydrochloride) Tablets, NDA 18-644.

We also acknowledge receipt of your additional communications dated:

March 14, 1985
March 19, 1985
March 21, 1985
April 9, 1985
May 1, 1985
May 21, 1985
June 11, 1985
June 21, 1985
August 9, 1985
September 20, 1985
September 25, 1985
September 30, 1985
November 20, 1985
November 26, 1985

We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that bupropion is safe and effective for use as recommended in the revised labeling that was developed at our meeting on December 20, 1985. Accordingly, the application is approved, effective on the date of this letter, provided that the precise text of the labeling to be employed is that incorporated in the body of this letter.

Twelve copies of the final printed version of the revised labeling (including container and package labeling) must be submitted to FDA prior to marketing. Marketing of the drug before the changes specified above are made and submitted to FDA renders the product misbranded under 21 U.S.C. 352.

In addition to the submission of revised labeling, the approval of the application is conditioned upon your commitment, made earlier, to undertake the program of post-marketing studies enumerated in our December 31, 1984 approvable letter. Also, as agreed at our December 20, 1985 meeting, you will modify your plans for the post-marketing chronic, repeated dose, dose proportionality 'bio' study to evaluate not only bupropion but its major, active metabolites. As agreed December 30, 1985, by telephone conversation between Richard Kiernan and Dr. Stanley Blum, the Dissolution Specification will be: Q=80% at 45 minutes, using the paddle method (50 rpm) in 900 mL water at 37°C. Finally, you must also submit, within a reasonable interval, the laboratory test results and cross-tabulations requested earlier.

The approved labeling of Wellbutrin follows:

Final labeling:
December 20, 1965

WELLBUTRIN® Tablets (bupropion hydrochloride)

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 $C_{13}H_{18}ClNO.HCl$. 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 50 mg (white), 75 mg (yellow-gold), and 100 mg (red) film-coated tablets.

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 ten fold 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 (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 five-fold) 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 200 micromolar (200 ug/ml).

INDICATIONS AND USAGE:

WELLBUTRIN® is indicated for the treatment of depression in patients who fail to respond adequately to or who cannot tolerate alternative antidepressant treatments. Wellbutrin is not recommended as an antidepressant of first choice for most patients because its use at doses approximately one and one third times greater than the usually required daily dose (450mg) is associated with a high risk of seizure (see Warnings).

The efficacy of WELLBUTRIN was demonstrated in placebo controlled clinical trials which enrolled principally hospitalized patients with diagnoses of depressive neurosis or manic-depressive (depressed type) disorder. The depressive illness of the patients studied most closely corresponds 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 fatiyability, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and suicidal ideation or attempts.

Evidence to demonstrate the sustained effectiveness of WELLBUTRIN after three weeks of use in placebo controlled investigations is not presently available.

CONTRAINDICATONS:

Because of its potential to induce seizures, Wellbutrin should not be used in patients with a convulsive disorder.

The concurrent administration of WELLBUTRIN and a monoamine oxicase (MAO) inhibitor is contraindicated; at least 14 days should elapse between discontinuation of a MAO inhibitor and initiation of treatment with WELLBUTRIN.

WELLBUTRIN is contraindicated in patients who have shown an allergic response to it.

WARNINGS:

Convulsions: (This title will appear in bold, emphasized capitals)

(The following two paragraphs will be printed in bold, dark type.)

Wellbutrin appears to possess a greater epileptogenic potential than other marketed antidepressants. While the estimated risk of seizure at doses of 450mg and below does not appear excessive in comparison to the risk reported for other antidepressant drug products, the estimated risk increases almost 10 fold between a dose of 450 and 600 mg a day. Given the wide variability among individuals in their capacity to metabolize and eliminate drugs, this disproportionate increase in seizure incidence with dose incrementation is a cause for concern.

During the period of premarketing evaluation, 25 among approximately 2400 patients treated with Wellbutrin experienced seizures. At the time of seizure, seven (7) patients were receiving daily doses of Wellbutrin at or below the lowest documented effective daily dose of 450mg. Twelve (12) patients experienced seizures at daily doses of 600mg; six (6) additional patients had seizures at daily doses between 600 and 900 mg. The risk of seizure appears to be strongly associated with dose and may be increased by predisposing factors (e.g. head trauma, CNS tumor, etc.) or a history of prior seizure. In addition, sudden and large increments in dose may contribute to an increased risk. While many seizures occurred early in the course of treatment, some seizures did occur after several weeks of use at fixed dose.

(end bold, dark type)

N.B. A new column will be added to the following table. The column, placed at the very left side of the table will identify the first two rows (less than 450mg and 450 mg as being "within the recommended dose" and the last two rows (600mg and 600 to 900mg) as being "above the recommended dose"

INCIDENCE OF SEIZURES IN PATIENTS RECEIVING WELLBUTRIN

WELLBUTRIN Dose mg/day	Total Seizure Incidence (%)	Seizure Incidence in Patients Without Seizure Predisposition (%)
less than 450	0.2%	0.0%
450	0.3%	0.2%
600	2.3%	1.3%
600-900	2.8%	1.9%

N.B. The next sentence will appear in bold, dark capitals:

Dosage and administration recommendations should be strictly followed to minimize the risk of seizure (see DOSAGE and ADMINISTRATION).

(end bold caps; resume bold, dark type.)

Extreme caution should be used when combining WELLBUTRIN with other agents which lower seizure threshold, or when administering WELLBUTRIN to patients with a history of seizure disorder or cranial trauma.

N. B. (End all emphasized type.)

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 an 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 [illegible] 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 20% 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 minimzed, and, if possible, avoided completely.

Patients should be advised to inform their physician 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 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 (2-3x 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.

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:

It is not known whether WELLBUTRIN is excreted in the milk of lactating women. Because many drugs are excreted in human milk, caution should be exercised when WELLBUTRIN is administered to women who are nursing.

Pediatric Use:

The safety and effectiveness of WELLBUTRIN in individuals under 18 years old has 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 the product's premarketing clinical trials. 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, primarily rashes (1.4%). 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

events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of WELLBUTRIN under relatively similar conditions of daily dosage (300-600mg), 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 section.

> M.D. NOTE TO THE FIRM: At this point insert, using the same tabular format as in our 12/18/85 draft labeling, the new incidence figures provided in your 12/20/85 table of Emergent or Exacerbated ADRs from studies 05, 00, 09, 14 and 25.
>
> As agreed, all events occurring at an incidence below 1.0% among Wellbutrin treated subjects will be eliminated. These events, however will be added, if missing, to the narrative enumeration of ADRs in the section, titled "Other events observed during the premarketing evaluation of Wellbutrin." It will also be necessary to delete from the same narrative section any item now appearing in the 12/20 tabular enumeration that did not appear in the 12/18 FDA draft.
>
> A copy of an edited version of the 12/20 table is attached.

TABLE IS INSERTED AT THIS POINT M.D. FOOTNOTE IS NOW REQUIRED INDICATING THAT TABULATION IS LIMITED TO EVENTS AT OR ABOVE 1 percent:

*Events reported by 1% of patients are included.

Other events observed during the entire premarketing evaluation of Wellbutrin.

During its premarketing assessment, Wellbutrin was evaluated in almost 2400 subjects. 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 at incidences below 1/1000.

N.B. NOTE THAT THE NEW DEFINITIONS EMPLOYED FOR THIS SECTION REQUIRE ITS REVISION TO REMOVE UNNECESSARY REFERENCES TO EVENTS THAT DID NOT OCCUR AT A "frequent" LEVEL OF INCIDENCE. Again, appropriate additions and deletions as required by the insertion of the 12/20 ADR tabulation should be made. The text below remains without these changes inserted; Burroughs-Wellcome staff will make these changes. Corrections in the text made at our 12/20 joint meeting, however, have been inserted in CAPITALS to draw attention to the change-- in FPL capitalization should not be used.

Cardiovascular: The most frequent were palpitations, edema and syncope; less frequent were chest pain, EKG abnormalities (PREMATURE BEATS AND NON-SPECIFIC ST-T changes), and shortness of breath/dyspnea; and rare were pallor and phlebitis.

Dermatologic: Pruritis, non-specific rashes were frequent; less frequent were alopecia and dry skin; change in hair color and hirsutism were rare.

Endocrine: No event occurred at an incidence of 1.0%; gynecomastia was a less frequent event [illegible] and [illegible] were reported at a rare incidence level.

Gastrointestinal: No events occurred at a frequency exceeding one percent; less frequent events were dysphagia, thirst disturbance and liver damage/jaundice; rare events were rectal complaints, colitis, G.I. bleeding and intestinal perforation.

Genitourinary: Urinary frequency was reported at a level considered frequent; less frequent events were testicular swelling, urinary tract infection, painful erection and retarded ejaculation; rare events included dysuria, enuresis, urinary incontinence, menopause, ovarian disorder, pelvic infection, cystitis, dyspareunia and painful ejaculation.

Hematologic/Oncologic: Lymphadenopathy was reported rarely.

Neurological: (see Warnings) Frequent events were impaired sleep quality, ataxia/ incoordination, seizure, cutaneous temperature disturbance, myoclonus and dyskinesia; less frequent were mydriasis, vertigo and dysarthria; and rare events included EEG abnormality, abnormal neurological exam, impaired attention and sciatica.

Neuropsychiatric: (see Precautions) The most frequent events were disturbed concentration, increased libido, hallucinations, depression and delusions; less frequent were memory impairment, depersonalization, psychosis, dysphoria, mood instability, paranoia, formal thought disorder and frigidity; suicidal ideation was reported as a rare event.

Oral Complaints: Stomatitis occurred at a frequent incidence rate. Less frequent events were toothache, bruxism, gum irritation and oral edema; glossitis was reported rarely.

Respiratory: No events were reported at a frequency exceeding one percent. Less frequent events were bronchitis and shortness of breath/dyspnea; epistaxis and rate or rhythm disorder was reported rarely.

Special Senses: No events were reported at an incidence greater than one percent. Visual disturbances were reported less frequently and reports of diplopia were rare.

Nonspecific: Frequent events were fever/chills and flu-like symptoms; less frequent was nonspecific pain; body odor, surgically related pain, infection, medication reaction and overdose were reported rarely.

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 LD50 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,

ION NOT MADE IN JAPAN

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.

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:

At doses that are one and one-third times the usually required dose (450mg/day), (See Warnings), the observed incidence of seizure increases by as much as ten fold. This predicts a relatively narrow therapeutic ratio for the safe use of bupropion, especially as there is considerable inter-individual variability in the capacity of patients to metabolize drugs.

Consequently, it is particularly important to administer bupropion in a manner that is most likely to minimize the risk of seizure. Retrospective analysis of clinical experience gained during its premarketing development suggests that the risk of seizure may be minimized if 1) the total daily dose of WELLBUTRIN does not exceed 450mg, 2) the daily dose is administered in divided doses to avoid high peak concentrations of bupropion and/or its metabolites, and 3) the rate of incrementation of dose is very gradual.

WELLBUTRIN should, therefore, be given t.i.d., preferably with intervals of at least 6 hours between successive doses. Besides its apparent value in lowering the risk of seizure, gradual dose escalation is important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these side effects may be managed by temporary reduction of dose or the transitory administration of a sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment.

The following suggested dosing regimen incorporates the principles described above.

Usual Adult Dosage:

A starting dose of 225 mg/day given as 75 mg t.i.d. is recommended. Based on clinical response this dose may be increased by 75 mg/day no sooner than every three days according to the following schedule up to a total maximum daily dose of 450 mg/day. Of course, if distressing untoward effects supervene, dose escalation should be stopped.

Dosing Schedule

Treatment Day	75 mg Tablets Morning	Midday	Evening	Total Daily Dose
1	1	1	1	225 mg
4	2	1	1	300 mg
7	2	2	1	375 mg
10	2	2	2	450 mg

In patients who do not demonstrate an adequate response after an appropriate period of treatment at 450 mg/day, drug should be discontinued. While no systematic study of withdrawal has been conducted, it seems prudent to recommend gradual tapering of drug over a period of a week.

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. The maximum recommended maintenance dose is 450 mg/day. While it is generally recommended that a course of antidepressant drug treatment should continue for several months and many patients have been treated with WELLBUTRIN in long-term clinical trials of up to 2 years duration, there has been no systematic

placebo-controlled evaluation of the efficacy of WELLBUTRIN for a period beyond three to four weeks.

HOW SUPPLIED:

WELLBUTRIN (bupropion hydrochloride) tablets are supplied as follows:

50 mg (white) round biconvex tablets printed "WELLBUTRIN" and "50"
-bottles of 100 (NDC 0081-0176-55)

75 mg (yellow-gold) round biconvex tablets printed "WELLBUTRIN" and "75"
-bottles of 100 (NDC 0081-0177-55)

100 mg (red) round biconvex tablets printed "WELLBUTRIN" and "100"
-bottles of 100 (NDC 0081-0178-55)

Store at 15°-30°C (59°-86°F)

END OF TEXT

Twelve copies of the final printed version of the revised labeling must be submitted to the FDA prior to marketing. (21 CFR 314.60(c)).

RT

Should additional information relating to the safety and effectiveness of these drug products become available prior to our receipt of the final-printed labeling, revision of that labeling may be required.

Please submit one market package of the drug when it is available.

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

Sincerely yours,

RTemple 12/30/85

Robert Temple, M.D.
Acting Director
Office of Drug Research and Review
Center for Drugs and Biologics

cc:
Orig. NDA 18-644
ATL-DO
HFN-100
HFN-120
HFN-120/Leber/revisions/
HFN-226/Hepp
HFN-713/Marticello/Stein
HFN-120/Zinsitz/Shultz
HFN-120/Rosloff/Contrera
HFN-120/Laughren/Lee
HFN-120/Vocci
HFN-120/TDeCicco/10/28/85/12/23/85
DOC 1053x

12/26/85

DMB jr FZ RCS 12/26/85
JMR 12/26/85 VKW 12/26/85
JC Stein 12-27-85

ION 301 MADE IN JA

Summary for Basis of Approval

NDA 18-644

Applicant:
Burroughs Wellcome Company
Research Triangle Park, NC 27709

Drug Generic Name:
bupropion hydrochloride

Brand Name:
Wellbutrin

I. Indications for Use:

WELLBUTRIN® is indicated for the treatment of depression in patients who fail to respond adequately to or who cannot tolerate alternative antidepressant treatments. Wellbutrin is not recommended as an antidepressant of first choice for most patients because its use at doses approximately one and one third times greater than the usually required daily dose (450 mg) is associated with a high risk of seizure (see Warnings).

The efficacy of WELLBUTRIN was demonstrated in placebo controlled clinical trials which enrolled principally hospitalized patients with diagnoses of depressive neurosis or manic-depressive (depressed type) disorder. The depressive illness of the patients studied most closely corresponds 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.

Evidence to demonstrate the sustained effectiveness of WELLBUTRIN after three weeks of use in placebo controlled investigations is not presently available.

II. Dosage form, route of administration and recommended dosage:

At doses that are one and one-third times the usually required dose (450 mg/day), (See Warnings), the observed incidence of seizure increases by as much as ten fold. This predicts a relatively narrow therapeutic ratio for the safe use of bupropion, especially as there is considerable inter-individual variability in the capacity of patients to metabolize drugs.

Consequently, it is particularly important to administer bupropion in a manner that is most likely to minimize the risk of seizure. Retrospective analysis of clinical experience gained during its premarketing development 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 in divided doses to avoid high peak concentrations of bupropion and/or its metabolites, and 3) the rate of incrementation of dose is very gradual.

WELLBUTRIN should therefore be given t.i.d., preferably with intervals of at least 6 hours between successive doses. Besides its apparent value in lowering the risk of seizure, gradual dose escalation is important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these side effects may be managed by temporary reduction of dose or the transitory administration of a sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment.

The following suggested dosing regimen incorporates the principles described above.

Usual Adult Dosage:

A starting dose of 225 mg/day given as 75 mg t.i.d. is recommended. Based on clinical response this dose may be increased by 75 mg/day no sooner than every three days according to the following schedule up to a total maximum daily dose of 450 mg/day. Of course, if distressing untoward effects supervene, dose escalation should be stopped.

Dosing Schedule

Treatment Day	75 mg Tablets			Total Daily Dose
	Morning	Midday	Evening	
1	1	1	1	225 mg
4	2	1	1	300 mg
7	2	2	1	375 mg
10	2	2	2	450 mg

In patients who do not demonstrate an adequate response after an appropriate period of treatment at 450 mg/day, drug should be discontinued.

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. The maximum recommended maintenance dose is 450 mg/day. While it is generally recommended that a course of antidepressant drug treatment should continue for several months and many patients have been treated with WELLBUTRIN in long-term clinical trials of up to 2 years duration, there has been no systematic placebo-controlled evaluation of the efficacy of WELLBUTRIN for a period beyond three to four weeks.

LION 301 MADE IN JAPAN

III. Chemistry:

A. Manufacturing and Controls: The description of the synthesis included in the application provides additional details not completely covered by the referenced U.S. Patent 3,819,706 which permits evaluation of the specifications and tests including those limits on impurities detected by the use of TLC and HPLC.

B. Stability Studies: Stability data has been included for all proposed marketed dosage strengths which support the recommended 18 month expiration dating for the drug product stored within the label stated limits.

C. Methods Validation: The analytical methods were validated by both the New York District and the Division of Drug Chemistry Laboratories and found satisfactory for regulatory purposes.

D. Labeling: The draft labels for 50 mg, 75 mg and 100 mg strengths include the required statements; however, those labels used for containers of 100's of the tablet strengths require repositioning of the Caution statement from the vertical side panel to the horizontal center panel.

E. Establishment Inspection: Evaluation of establishment inspection reports on January 18, 1983 by HFN-320 indicate the referenced fac ities are in conformance with CGMP's.

F. Environmental Impact Analysis Report: A statement on EIAR has been provided in accordance with 21 CFR, Part 25(g). This statement has been reviewed and found to be acceptable.

IV. Biopharmaceutics:

Using normal healthy volunteers, five full-scale bupropion HCl bioavailability/pharmacokinetic type studies were conducted along with several in-vitro dissolution studies.

1. In study No. 27, seven fasting male volunteers received 200 mg of an aqueous solution of ^{14}C-bupropion HCl orally. Blood, urine and fecal samples were collected for 96 hours.

   Study results indicated that over 96 hours, approximately 87% of the administered radiolabeled dose was excreted in urine, and approximately 10% was excreted in the feces. For those two routes of elimination, only a negligible amount of the parent drug, i.e., less than 1%, was recovered by each route. From the results of this study and from animal data, it appears that bupropion undergoes significant first-pass metabolism.

Nine metabolites were identified in urine; four were shown to have some pharmacologic activity in mice. For this study, the mean elimination (beta phase) half-lives were about 21 and 32 hours for bupropion and total plasma radioactivity, respectively.

2. In study No. 30, eighteen fasting male volunteers received single oral doses of 2 x 50 mg WELLBUTRIN tablets, and 100 mg and 250 mg of bupropion in an aqueous solution of bupropion HCl in a three period crossover study. Plasma samples were collected for 60 hours following administration. The 50 mg tablet lot tested was used in four clinical trials, including one that was positive; it was made on production-size equipment using the same procedures as those for the marketed drug.

   This study demonstrated that a single dose of two 50 mg tablets is equivalent in its absorption to the 100 mg aqueous solution, and that bupropion plasma concentrations are dose proportional following the 100 and 250 mg doses which are the lowest and highest (t.i.d.) doses recommended in the labeling.

3. Study No. 07A was a crossover bioequivalence study in which 16 fasting male volunteers received single doses of 4 x 50 mg capsules, 2 x 100 mg capsules, 4 x 50 mg tablets and 2 x 100 mg tablets. Plasma samples were collected for 24 hours following each dose. Calculated area under the plasma level vs. time curves (AUC) for this interval (0-24 hours) accounted for about 88% of AUC, calculated from time zero to time infinity.

   The tested batches of capsules were used in early clinical trials and it was necessary to compare them to the final marketed product. The batches of tablets in this study, however, were made by procedures different from those used for making the final marketed product. Although this study demonstrated that the different treatments are bioequivalent in absorption, other data are needed to conclude that capsules are equivalent to the marketed product (see study 07D).

4. Study No. 07B was a crossover in which 12 females and 12 males received 1 x 50 mg tablet, 1 x 100 mg tablet, and 2 x 100 mg tablets while fasting. Plasma samples were collected over 24 hours, and calculated AUC_{0-24} values accounted for about 88% of $AUC_{0-infinity}$ values. The tablet batches in this study were the same batches tested in Study No. 07A.

   This study demonstrated bupropion to be dose proportional over a dosing range of 50 to 200 mg.

5. Study No. 07D was an additional study period (fourth) added to Study No. 07B. Eleven male volunteers received 1 x 50 mg modified tablet and 11 female volunteers received 1 x 100 mg modified tablet. The modified tablets were from pilot batches that were made by the same procedures used for the final marketed tablets and were used in clinical trials.

LION 30 MADE IN JA

This study demonstrated the 50 mg modified tablet to be similar in its extent of drug absorption to the 50 mg reference tablet. The 100 mg modified tablet, which had poorer in vitro dissolution, was shown to be marginally equivalent in its extent of drug absorption to the 100 mg reference tablet.

Using an in vitro dissolution test method (USP XX, Apparatus 1, 500 ml of 0.6% HCl, 100 rpm, 37°C) that tended to reflect in vivo drug absorption, three production size batches each of the 75 mg and 100 mg tablets, formulations proportionally similar in their active and inactive ingredients to the 50 mg tablet, were shown to have in vitro dissolution characteristics similar to the 50 mg tablet batch tested in Study No. 30.

Other general pharmacokinetic information from bio-studies included the following:

1. Bupropion plasma concentration-time data following single oral doses are described by a two-compartment open model with first-order absorption.

2. The half-life for the initial disposition phase (alpha phase) for the drug's biexponential decay curve is approximately 1-2 hours. The decay curve's second phase half-life (beta phase) is approximately 14 hours, with a range of about 8 to 24 hours.

3. Peak bupropion plasma concentrations occur within two hours following oral administration.

4. Bupropion is approximately 80% bound to human serum albumin.

As a condition of approval the Applicant is required to conduct as Phase IV studies 1) a multiple-dose dose proportionality study that covers the drug's recommended dosing range and 2) a multiple-dose study in geriatric patients.

The basis for requiring the Phase IV studies are the following:

1. The Applicant has conducted only single dose bioavailability/pharmacokinetic studies. From animal studies in the mouse, rat, and dog, bupropion has been shown to induce its own metabolism. For example, mouse whole body bupropion levels were reduced 58% following subchronic treatment for 10 days; dog plasma levels declined by 76% and 90% for two different dose levels following chronic treatment for 366 days).

2. Bupropion is extensively metabolized. Only a small fraction of the absorbed dose reaches the systemic circulation intact. Bupropion has at least two metabolites with significant pharmacologic activity. Because of their longer elimination half-lives, these metabolites, are likely to accumulate when bupropion is administered repeatedly.

For both reasons, well-controlled multiple dose bioavailability/pharmacokinetic studies are needed. In addition all bioavailability/pharmacokinetic studies have been carried out in normal healthy young volunteers. Although no differences in the drug's clinical behavior have yet been seen in different age groups, there should be a specific evaluation of metabolism and kinetics in the elderly who may have altered hepatic metabolism of drugs.

IV. Pharmacology:

A. Survey of Effects: Bupropion (BUP) is structurally similar to amphetamine, fenfluramine, diethylpropion, and other phenethylamine derivatives. Its pharmacological profile is that of a CNS stimulant with several similarities to amphetamine.

BUP was active in three types of tests predictive of antidepressant activity: prevention or reversal of tetrabenazine/reserpine effects in mouse, decreased immobility in the Porsolt behavioral despair test in rats, and potentiation of the behavioral effects of pargyline plus DOPA in mice.

BUP was shown to be a relatively weak blocker of the uptake of NE (norepinephrine) and 5-hydroxytryptamine (5-HT) into brain and peripheral nerve compared with classical tricyclics. It was somewhat more potent in blocking dopamine (DA) uptake, although the dose in rat (40 mg/kg i.p.) needed to produce serum levels high enough to cause 50% inhibition of DA (or NE) uptake into brain synaptosomes was 4x greater than the ED_{50}% in the Porsolt test. (The reverse holds true for imipramine regarding the potency ratio for "antidepressant effect" and NE uptake blockade.) The relationship between the blockade of DA (or NE) uptake and the "antidepressant" effect of BUP, therefore, is problematic. However, destruction of dopaminergic neurons with 6-hydroxydopamine + DMI blocked the effect of BUP in the Porsolt test in rats, suggesting that DA neurons are involved in some way. BUP did not inhibit MAO or elevate brain NE or DA at relatively high doses.

B. Comparison with Amphetamine and other CNS Stimulants: Many similarities between the pharmacological profiles of BUP and amphetamine (and other CNS stimulants) were noted, along with some differences, as follows:

1. BUP, amphetamine, and methylphenidate all produce dose-related antitetrabenazine effects and cause dose-related increases in locomotor activity in mice. However, the ratio of the i.p. ED_{50}% values for these two effects was approximately 1:2 for BUP, compared with 2:1 for amphetamine or methylphenidate. (In contrast, classical tricyclics cause decreased locomotor activity above "antidepressant" doses.)

2. Amphetamine and methylphenidate reversed tetrabenazine-induced sedation in mice whether given before or after the tetrabenazine; BUP was active only when given before.

3. Selective depletion of brain DA blocked the locomotor effects of both BUP and amphetamine; selective depletion of NE had no effect on either drug.

4. The locomotor effect of BUP and methylphenidate depends primarily on a storage (reserpine-sensitive) pool of catecholamines, whereas that of amphetamine depends primarily on newly synthesized (alpha-methyltyrosine sensitive) catecholamines.

5. BUP caused an increase in stereotyped behavior in rats; no direct comparison to amphetamine was made.

6. Several behavioral (operant) tests showed the profile of BUP to be more similar to amphetamine than to classical tricyclics.

7. BUP had an anorexic effect in mice. (Oral potency was at least 2x less than that of fenfluramine and diethylpropion; amphetamine was not tested.)

8. Drug discrimination studies in rats showed similarities between BUP and several CNS stimulants (e.g., amphetamine, methylphenidate, caffeine, cocaine) as well as the newer antidepressants viloxazine and nomifensine.

9. At high doses BUP caused hypothermia in mice, whereas amphetamine caused hyperthermia.

10. Grouping of mice caused an increase in the i.p. lethality of amphetamine but had no effect on that of BUP; BUP decreased the lethality of amphetamine in grouped mice.

C. Cardiac Effects: Cardiovascular studies showed rather large but generally transient decreases in cardiac output and right ventricular contractile force, and both increases and decreases in heart rate (HR) and blood pressure (BP), at i.v. doses of 1-20 mg/kg in anesthetized dogs and cats. (It is not clear if these results were corrected for vehicle effects). In conscious dogs, 20 mg/kg p.o. caused slight increases in HR and BP lasting at least 6 hrs.; in conscious rats 50 mg/kg caused a slight increase in HR lasting 3 hrs. Comparison drugs were not used in these studies so that the relative potency of BUP in causing these changes is not known. No effect on EKG (aside from increased HR) was seen in dogs at 10 mg/kg i.v. (2 mg/kg/min). In dogs, 5-10 mg/kg i.v. caused rather large increases in respiratory rate and smaller increases in minute volume. A relatively weak depressant effect on cardiac tissue in various in vitro preparations was noted which may have been due to the local anesthetic properties of BUP (equipotent with cocaine in guinea pig cornea); the potency of BUP was generally 5-15x less than that of imipramine and amitriptyline.

D. Receptor Agonist/Antagonist Effects: Several studies were performed to assess the anticholinergic effects of BUP, and such effects were generally weak or absent. Antagonist actions at other receptors (adrenergic, serotonergic, and histaminergic) were also generally weak or absent, although reference drugs which could have validated the systems and formed a basis for estimating the relative potency of

BUP were not used. Likewise, binding studies showed little or no interaction of BUP with a variety of receptors, but no reference drugs were used.

E. ADME/Pharmacokinetics: ADME/pharmacokinetic studies were performed in rat, mouse, and dog. After oral dosing, plasma levels of BUP peaked rapidly (within 1/4-1/2 hr.) and declined rapidly with a T 1/2 in the 1-4 hr. range. Over a dosage range of 10-100 mg/kg p.o. in rats, plasma levels increased with increasing dose but slightly less than proportionately at the highest dose. Studies comparing plasma AUC after i.v. and p.o. dosing showed a bioavailability of 8-21% in rats and 4% in dogs; however, excretion studies using labeled drug showed complete absorption in dogs and a high, if not complete, degree of absorption in rats after p.o. dosing. BUP was widely distributed in rat tissues; levels were highest in liver and lung after p.o. and i.p. dosing, respectively; lowest levels were in plasma. BUP was shown to be rapidly and extensively metabolized, in agreement with the low oral bioavailability of the drug. Plasma and tissue levels of metabolites were generally substantially higher than those of unchanged drug, except in the brain. Very little unchanged BUP was found in rat or dog urine; acidic metabolites were predominant; m-chlorohippuric and m-chlorobenzoic acids, and a conjugate of the former were identified, presumably arising from side chain oxidation. In human urine, in contrast, acidic and basic metabolites were present in nearly equal amounts. Plasma and tissue levels of metabolites declined much more slowly than those of unchanged drug; in one study the plasma T 1/2 for metabolites appeared to be about 12 hours, suggesting that whereas the parent drug is unlikely to accumulate with repeated dosing due to its short T 1/2, metabolites may. In one mouse study, however, 10 days dosing did not lead to an accumulation of metabolites; such a tendency may have been counteracted by an enzyme-induction effect, since levels of unchanged BUP were decreased.

The ability of BUP to induce liver microsomal metabolic enzymes was demonstrated in rat, mouse, and dog. In rat, pre-treatment with 15-50 mg/kg/day p.o. for 13 days decreased the rise of BUP in plasma seen after an acute dose of 50 mg/kg i.p., and 50 mg/kg/day p.o. for 4 days decreased the rise of BUP in tissues seen after an acute dose of 50 mg/kg i.p. In mouse, 50 mg/kg i.p. for 8 or 10 days decreased the rise in whole body level of BUP seen after an acute dose of 50 mg/kg. In dog, plasma levels after 1 year treatment at 40 or 80 mg/kg/day p.o. were significantly less than those seen on day 1.

Studies on pentobarbital sleep time in mice showed a decrease after 5-150 mg/kg/day p.o. for 10 days; the effect at HD was slightly less than the effect of phenobarbital pretreatment at 80 mg/kg/day; in rats a slight decrease was seen at high doses (100-150 mg/kg/day) only. It is possible that part or all of these effects on pentobarbital sleep time were due to CNS stimulation by BUP. Thus, although BUP appears to induce its own metabolism, its ability to induce the metabolism of other compounds has not been clearly demonstrated.

MADE IN JAPAN

Excretion of BUP + metabolites was shown to be primarily via the kidney in rats (78%) and exclusively by this route in dogs.

Over concentration ranges that were stated to be "normally found in animals and during clinical studies in man," BUP was 75-85% bound to plasma proteins from mouse, rat, dog, and man. Binding was generally constant over the concentration ranges used, although it tended to fall off in man at the highest concentration (1000 micromolar).

There appear to be some sex differences in the disposition of BUP, at least in rats. Plasma and tissue levels of unchanged drug, plasma AUC, and oral bioavailability were several-fold greater in F; T 1/2 was greater in F in one rat study, but apparently not in another. There did not appear to be any important sex differences in metabolic pattern or excretion, although data on these points were limited. No sex differences in plasma levels in dogs were apparent, although only two dogs per sex were used. The acute toxicity of BUP in rats was slightly greater in F than M, but the reverse appeared to be true in the chronic rat toxicity studies.

F. Toxicology: The acute oral LD_{50} was 544 (M) and 636 (F) mg/kg in mouse, and 607 (M) and 482 (F) mg/kg in rat. Acute i.p. LD_{50} was 273 and 263 mg/kg in male mice and male rats, respectively. Prominent acute signs in the mouse included: ataxia, convulsions, prostration, ptosis, and compulsive gnawing by both routes, plus labored breathing, decreased respiration, and salivation after i.p. only. Signs in the rat included: ataxia, loss of righting reflex, labored breathing, prostration, salivation, ptosis, arched back, and compulsive gnawing by both routes.

Acute p.o. toxic interaction studies were performed in rats. Phenelzine (at highest no-effect and highest non-lethal doses) caused a marked decrease in the LD_{50} of BUP. (However, no pharmacodynamic interactions were seen in several tests at lower doses). Only a slight potentiation of the lethality of BUP was caused by treatment with ethanol at its highest non-lethal dose; this was seen in F only. Lethal potentiation was noted between BUP and amitriptyline (each given at 1/2 LD_{50}), in F only.

The following oral subacute/chronic toxicity/carcinogenicity studies were performed (daily dose in mg/kg in parentheses):

Rat (Long Evans)	3 month (150, 300, 450)
Rat (Charles River CD)	55 week (25, 50, 100)
Rat (Charles River CD)	2 year (100, 200, 300)
Mouse (Charles River CD-1)	21-22 month (50, 100, 150)
Dog (Beagle)	3 month (15, 35, 75 to 150)
Dog (Beagle)	1 year (40, 80, 150)

The principal findings are as follows:

1. Rat:

a. General: Increased mortality, associated with convulsions, was seen in the 2 year study at all doses (except LD M), and was marked at HD (300 mg/kg). No effect on mortality was seen in the 55 week study (HD = 100 mg/kg); in the 3 month study 2/20 died at 450 mg/kg. Observed signs included urinary incontinence/urine staining (all studies, all doses), dried blood around nose/mouth (55 wk and 2 yr studies, all doses), and convulsions (2 yr study, all doses). Slight decreases in bodyweight gain were seen in all M groups in the 2 yr study. Slight decreases in blood glucose were seen above 100-150 mg/kg.

b. Gross/Histopathology: The most prominent findings were:

(1) Liver: In the two-year study there was an increase in incidence of hyperplastic nodules and hepatocellular hypertrophy at all doses; hyperplasia was increased at LD and MD only. (In a consultant report many of the hyperplastic nodules were reclassified as "foci or areas of altered hepatocytes.") The incidence of these findings is underestimated in the drug groups in a dose-related fashion due to the increased mortality and the late appearance of the lesion. (Most hyperplastic nodules were found at the terminal sacrifice, and almost all were found after 90 weeks). There was no increase in the incidence of hepatocellular carcinoma; the observed incidence 0/147, 3/140, 1/141, and 1/123 in control, LD, MD, and HD, respectively is within the historical control range. Similar findings were not seen in the 55 week study (HD = 100); in the 3 month study a low incidence of hyperplasia and "prominent cellular organelles" was seen at all doses. Increased liver weights were seen in all studies at all doses except LD in the 3 month study. Grossly, in the 2 year study, slight increases in the incidence of masses/nodules/raised area (F only) and dark red/brown/hemorrhagic foci were seen at all doses at termination but not among deaths.

The significance of these proliferative lesions in the liver is not straight-forward. The sponsor suggests they may arise as either (1) a result of microsomal enzyme induction or (2) an adaptive response to hepatic injury. Regarding the former, BUP has been shown to induce its own metabolism (see above). Regarding the latter, no other indication of hepatic damage (including blood chemistry) was obtained in rats, although some indications of liver damage were obtained in dogs.

Nonetheless, there has been controversy concerning the possible role of hyperplastic nodules in the development of hepatocarcinomas in rodents. Several years ago some

MADE IN JAPAN

pathologists suggested that such lesions should be considered "pre-neoplastic" or "neoplastic" because it was hypothesized that they could progress to malignant tumors (Squire and Levitt, Cancer Res. 35: 3214, 1975; Williams, Biochem. et Biophys. Acta 605: 167, 1980). These pathologists th. suggested replacing the term "hyperplastic nodule" with "neoplastic nodule". (It has also been suggested that "foci of cellular alteration" are also "pre-neoplastic" in the sense that they might progress to neoplastic nodules or even directly to malignant tumors.)

The subject was discussed at a symposium (Rodent Liver Nodules - Significance to Human Cancer Risk?, International Symposium of the Society of Toxicological Pathologists, May 10-12, 1982, Reston, Va.; proceedings published in Toxicologic Pathology, Volume 10, Number 2, 1982). Data was presented to challange the view that proliferative hepatic lesions are progenitors of hepatic malignancy. The outcome of several types of experimentally induced hepatic nodules, including those induced by drugs, was reviewed. In several cases, nodules and foci of cellular alteration regressed after cessation of treatment, documenting that proliferative lesions are not inherently malignant. The fact that proliferative lesions are not necessarily transplantable was considered to add additional support to conclusion that these lesions may be entirely benign. In any event, based on these and related observations, symposium participants reached an informal consensus that the term "neoplastic nodule" was a misnomer and that such lesions do not necessarily progress irretrievably to malignancy. However, while these proliferative lesions may not be autonomous and do not necessarily progress to malignancy, it is possible that they might progress under the influence of continued drug administration or, alternatively, they may simply be "markers" for malignancy, i.e., if a drug produces such lesions it is an indication that the drug is also likely to produce malignancies. Again, based on an informal vote a majority of pathologists present at this symposium appeared to believe that the production of nodules or foci of cellular alteration in the liver by a chemical is not sufficient evidence to establish that chemical as a hepatocarcinogen. Although several potent hepatocarcinogens do produce nodules and foci of cellular alteration, there are several examples of drugs, dietary regimens, and surgical manipulations which produced nodules or foci but did not produce malignancies despite prolonged treatment. Thus, no generalization about the carcinogenicity of agents which cause nodules is possible.

Thus, bupropion's capacity to produce proliferative lesions raises questions that cannot be answered absolutely. It is reassuring, however, that despite continued administration of bupropion in a lifetime rat study, the proliferative

lecions did not progress to malignancy. In addition, the nodules were very late appearing (most seen at terminal sacrifice; almost all after 90 weeks), in contrast to the effects of established hepatocarcinogens. In summary, the evidence at this time does not support identification of BUP as a hepatocarcinogen.

(2) Hemosiderosis: In the 55 week rat study an increase in hemosiderosis (as determined either by H + E stain, iron stain, or presence of pigment-containing macrophages) was seen in spleen, kidney, lung, and liver. This was seen primarily at HD, but lung and liver were not examined at the lower doses. Likewise, in the two year study, evidence of increased hemosiderosis was seen in spleen, lung, and lymph nodes at MD and HD; these organs were not examined in LD animals. No other pathological findings were present to help explain the increased hemosiderosis. Hematology did not reveal any striking abnormalities. (2/20 HD in the 55 week study had low Hb, Hct, and RBC; no effect was seen in the two year study; slight decreases in Hb and Hct were seen in the 3 month study, but no hemosiderosis reported.)

(3) Kidney: Slight increases in the incidence of chronic nephritis were seen in the 55 week study (HD only) and in the MD and HD groups in the two-year study in which LD was not examined. (There were no consistent effects on lab tests indicative of renal function; in the 55 week study there were elevations of BUN in 3/40 rats at MD and HD.) Kidney weights were elevated in all studies at all doses.

c. Neoplasia: There were no drug-related increases.

2. Mouse:

a. General: In the 22 month study, mortality was increased in all M groups and HD F. There was no effect on weight gain. As in rats, convulsions were seen (MD and HD). Laboratory studies were not performed.

b. Gross/Histopathology: In the 22 month study most prominent postmortem findings were in the uterus, consisting of a dose-related increased incidence of extremely dilated blood vessels, with thrombus, in all F groups; this increase was seen both among mice which died and those which survived to termination, suggesting it is not associated with lethality. On gross examination, there was an increased incidence of uterine nodules/masses; according to the histopathologic report, these were extremely dilated veins with thrombosis. The antemortem urogenital staining noted was probably also related to these changes.

MADE IN JAPAN

An increased (dose-related) incidence of acute metritis and/or pyometritis in the uterus was also seen in all drug groups, along with a slight increase in the incidence of uterine hemorrhage in all drug groups (not dose-related). Splenomegaly and hematopoiesis in spleen and liver were also seen in F; the pathology report considered these to be secondary to the uterine blood loss, although an independent analysis by the sponsor did not show a good correlation between the uterine and spleen/liver changes. Changes similar to those in uterus were not clearly seen in other organs, although a low frequency of hemorrhage and ulcer in stomach and small intestine was noted, primarily at HD. The incidence of thrombus in heart was increased in HD among deaths but not at termination, and the incidence of congestion and/or hemorrhage in lung was increased in HD M. An increased incidence of atrophic tubules in testes at HD was also seen in this study, although there was no effect on the incidence of aspermatogenesis.

c. Neoplasia: There was no drug-related effect on the incidence of neoplastic changes.

3. Dog:

a. General: No significant toxic effects were seen in the 90 day study (HD = 75 to 150), a slight increase in liver weight was seen with no associated pathology. In the one year study, the HD (150 mg/kg) produced 3/16 deaths; this dose also produced convulsions in one dog and body trembling in several others. Emesis and ptyalism were seen at both MD and HD. Bodyweight gain was decreased at HD. There was a dose-related elevation of serum alkaline phosphatase in all groups at all months measured, and the magnitude increased over time; no elevations were seen in recovery dogs. Elevations of SGOT and SGPT were also seen mainly at the higher doses, starting at three months but not clearly progressive over time. Some recovery dogs still had elevated SGPT after the recovery period, but of smaller magnitude. Slight increases in BSP retention were seen at MD and HD. Liver weights were increased in all groups (dose-related) at both six and 12 months but not at recovery.

b. Gross/Histopathology: In the 1 year study microscopic exam of liver showed several drug-related changes including finely granular "ground glass" cytoplasm (MD and HD, seen at 12 months but not at six months or after recovery period), dark brown pigment in hepatocytes and phagocytic cells (MD and HD, seen at 12 but not at six months, and seen at all doses after recovery period), slight coarse vacuolation of hepatocytes (seen in HD at 12 months and in LD and MD at six months and in the one MD which died; not seen after recovery period), and bile duct proliferation (very slight to slight, seen at MD and HD at 6 months and at HD at 12 months, also seen after recovery period in 2/4 LD and 2/3 HD and in 1/4 control but absent in three at MD). Kidney weight was elevated in all groups at 6 months; at 12 months an increased relative weight only was seen at HD —

HD. Histologically, the incidence and severity of brown pigment in tubular epithelium was increased in all groups at termination. The incidence of this finding among recovery dogs was similar across groups although severity was greater at MD and HD. No clear abnormalities of renal function were noted.

C. Mutagenicity: BUP was weakly positive in some Salmonella strains in the Ames Test. (TA 100, both with and without metabolic activation, and TA 1535, with activation only.) Greatest effects were 2-3 X control revertant count; positive controls caused 6-10 X increases. In a rat bone marrow chromosome study, an increase in aberrations was seen at 300 but not 100-200 mg/kg p.o., given for 5 days; the increase was 2-3 X control compared to 6-19 X for the positive control. In a study of binding to rat liver DNA after oral administration, it was found that the binding of BUP (+ metabolites) was much lower than that of known hepatocarcinogens; it was concluded that the effect is nonspecific.

H. Reproduction: A two generation reproduction and fertility study was performed in rats. Both M and F (of the F 0 generation only) were drug treated at dosages of 100, 200, and 300 mg/kg/day. Except for wobbly gait in one MD and one HD, no drug-related signs were observed. Bodyweight gain was slightly increased in all treated groups, but was not dose-related. There was no drug-related increase in mortality. No drug effects on M or F mating performance, on F fertility or reproductive parameters, or on pup (F 1 generation) survival and body weight were seen. There were no significant effects on mating or reproductive performance of the F 1 generation. Pup survival (F 2 generation) was not affected by treatment, although F 2 pups in all drug groups had slightly increased body weight.

Segment II reproduction studies were performed in rats and rabbits. In rats (dosages = 150, 300, and 450 mg/kg/day), signs including ataxia, urinary incontinence, and gnawing were seen primarily in HD dams. Mortality was increased at HD (24/53 = 45%). Bodyweights were transiently decreased in all drug groups after the first dose. There was a slight decrease in fetal weight and length in all drug groups, not dose-related. There were no drug-related effects on gross or visceral fetal abnormalities. A slightly increased incidence of reduced or absent ossification of some bones was seen at MD and HD and to a smaller extent at LD; this was reflected in a slight increase in total skeletal findings in all drug groups.

Two segment II reproduction studies were performed in rabbits, one within the sponsor's lab and the other by International Research and Development Corporation. Dosages were 25 (latter study only), 50, 100, and 150 mg/kg/day. Does displayed slight hypoactivity at 100 and 150 mg/kg, and convulsions, ataxia, tremors, and hyperpnea were seen in some does at 150; convulsions were also seen in one doe at 100 mg/kg. In one study, decreased doe food consumption on individual days was seen in all drug groups, but no overall effects on body weight were seen; however, the other study showed reduced weight gain at 100 and 150 mg/kg. There was no drug-related increase

MADE IN JAPAN

in mortality in either study. Fetal weight was slightly reduced in all drug groups at 30 mg/kg and above, and these reductions were dose-related. Fetal length (reported in one study) was slightly reduced at 150 mg/kg. There was a trend toward an increase in gross, visceral, and skeletal abnormalities in fetuses of all drug groups, which was partly dose-related. The increase in gross and visceral abnormalities does not appear to be biologically significant in that no pattern of abnormalities was seen, i.e. there was no significant increase in any particular type of abnormality, and the overall percent of fetuses affected was relatively low. Regarding skeletal abnormalities, a significant increase in supernumerary ribs occurred in all drug groups which was dose-related in one study but not in another. In addition, one study showed an increase in reduced ossification of the palate (all drug groups, not dose-related), and the other study showed an increase in delayed ossification of the fifth phalanx of the forelimb at HD only as well as a low incidence of barbell-shaped thoracic centra in all drug groups. Reduced ossification (also seen in rat study) and supernumerary ribs are considered to be normal variations, and it is concluded that the above skeletal findings, as well as the findings of decreased fetal weight and length, were secondary consequences of maternal toxicity.

V. Clinical Evidence:

This section presents 1) a brief overview, 2) a description of the adequate and well-controlled clinical trials which provided evidence of efficacy, 3) a brief review of other adequate and well controlled controlled trials which failed to support the efficacy claim, and 4) two sections listing general and special safety considerations pertinent to this drug product.

A. General: The approval decision is based on clinical studies enrolling a total of approximately 2400 patients. The original NDA provided reports on clinical trials involving 1300 patients and volunteers. Prior to final approval, however, data and information from experience with an additional 1000 or so individuals was submitted and reviewed.

The agency relied solely upon the results of placebo controlled investigations to reach its conclusion that bupropion is an effective antidepressant. The amended application provided full reports on 5 investigations that employed placebo controls: numbers 06, 08, 09, 14 and 25. The agency also evaluated the results of all active control investigations. Only one of the latter, study 13, demonstrated consistent, statistically significant differences among treatments.

Among the placebo controlled trials, only 06 and 25 provide clear support for the antidepressant efficacy of bupropion under the conditions of use recommended in its approved labeling. Study 14 is a strongly positive study, but a substantial proportion of the individuals who participated in it were treated with bupropion at

doses exceeding the maximum recommended daily dose (450 mg/day). Study 08 was equivocal in its results, showing significant treatment by investigator interactions between its two major components (08-01 and 08-02).

B. Studies demonstrating or supporting efficacy for this indication:

Two placebo controlled inpatient studies of similar parallel design provide persuasive evidence of bupropion's efficacy as an antidepressant.

1. Study 06 (K. Brodie, W. Zung, L. Fabre, and D. Garver)

a. Design: The study was planned as a 28-day trial comparing titrated doses of bupropion with placebo. Because of its design, which allowed withdrawals at day 21, many patients failed to complete the full 28 days and 21 days is a more accurate description of the study's duration.

The inclusion criteria in this and other inpatient studies required that patients be non-psychotic and exhibit a depressed mood (characterized as sad, blue, low, despondent, hopeless, or gloomy) plus at least four of these symptoms:

anhedonia
poor appetite
sleep difficulty (insomnia or hypersomnia)
loss of energy, fatigue, lethargy
agitation
retardation
decrease in libido
loss of interest in work or usual activities
feelings of self-reproach or guilt
diminished ability to think or concentrate
thoughts of death and/or suicide attempts
feelings of helplessness and hopelessness
anxiety or tension
bodily complaints

Exclusion criteria for this and other studies were as follows:

actively suicidal ideation
schizophrenia
organic CNS disease
severe dementia
incapable of spontaneous conversation or behavior
seizure disorders
alcoholism
glaucoma
prostatic hypertrophy
abnormal laboratory or ECG values

women of childbearing potential who were not willing to sign an intent to avoid pregnancy form
lactating women, if breastfeeding

Patients were randomly assigned to either BUP or PBO. Drug was administered according to a titration schedule that allowed for individual dose adjustment. In the first week, patients received BUP in a dose of 300 to 400 mg (divided t.i.d.). From day 8 to the end of the study, the dosage could be increased to 600 mg/day. Psychoactive drugs were interdicted, except chloral hydrate for sleep.

Weekly assessments included the Hamilton Depression (HAM-D), Hamilton Anxiety (HAM-A), Self-Rating Depression (Zung-D), Self-Rating Anxiety Scale (Zung-A), Clinical Global Impressions (CGI), Dosage Records and Treatment Emergent Symptoms (DOTES) Scales and the Patient Termination Record. The protocol permitted replacement of any subject who dropped from the study before 21 days and interdicted use of psychoactive drugs.

b. Conduct and Execution: A total of 85 adult inpatients were enrolled. The principal diagnoses (DSM-II classification) were:

manic-depressive (depressed)	55%
depressive neurosis	35%
involutional melancholia	8%
manic-depressive (circular)	2%

Over the evaluable course of the study (days 1-21), the dose of BUP for the vast majority of patients was 450 mg or less. At day 7, all participants were on 450 mg or less. At day 14, 42 of 50 participants were receiving 450 mg or less. At day 21, 38/49 patients were receiving 450 mg or less. Ten patients (BUP x 7, PBO x 3) received hypnotic drugs at some time during the study, usually flurazepam. Dropouts occurred for:

ineffectiveness or deterioration	2 PBO
adverse reactions	1 BUP, 1 PBO
intercurrent illness	1 BUP
did not return or refused treatment	4 BUP
administrative or uncooperative	1 BUP, 2 PBO

The number of patients participating after day 21 was markedly reduced from the original number.

c. Results: Because a substantial number of patients dropped out before the day 28 ratings, analyses were performed on the combined data from all three sites using the day 21 ratings or the last observation carried forward (LOCF) for those who dropped out earlier. Four combined study analyses were performed by weighting centers equally as well as proportionally to sample size and by subtracting as well as not subtracting baseline scores. These analyses all provided consistent statistical evidence of effectiveness which is provided in the following table:

Protocol 06

**LOCF (21) Analyses of Wellbutrin Minus Placebo
Change from Baseline Score for
All Patients Randomized
Investigators Weighted Proportionally to Sample Size**

Scale	# of Patients	Wellb. Minus Pbo Change from Baseline	2-tail p-value
HAMD Total	81	3.82	.05
CGI-SI	81	.631	.04
Depr. Item* of HAMD	79**	NA*	.01

* Based on Blocked Wilcoxon Rank Sum test of LOCF(21) value blocked on baseline value

** Two obse: tions fell into blocks with no other data.

2. Study 25: (Investigators: G. Chouinard, A. Halaris, O. Karabanow and M. Mandel/C.Welch).

a. Design: The study was planned as a four site, multicenter parallel comparison of two levels of bupropion (300 mg and 450 mg a day) with placebo. The original goal of the study was to evaluate the "efficacy and chronic dose tolerance of low doses of [bupropion] in ...hospitialized depressed patients." The study called for each site to contribute 30 patients, 10 assigned to each of the three treatment arms.

Inclusion and exclusion criteria were essentially identical to those employed in study 6 described above. Patients recruited were overtly depressed, non-psychotic, without evidence of severe dementia or a recent history of alcohol or substance abuse. The current depressive episode had to have been present at least 4 weeks and not longer than 2 years. A minimum total score of 18 on the 21 item version of the Hamilton Depression Scale and at least a moderate rating on the Global Severity Scale were required for admission.

Schizoaffective and schizophrenic patients were to be excluded. Patients could also be excluded for medical reasons if it was thought necessary by investigators or monitors.

Concomitant medications: Washout of active psychotropic medications was required before the start of active medication: one month for fluphenazine esters, two weeks for MAOIs and

MADE IN JAPAN

phenothiazines, and one week for benzodiazepines. During the trial, the protocol disallowed the use of all psychotropic medications save chloral hydrate for sleep.

Rating instruments for assessment of outcome included the Hamilton Depression and Anxiety Scales, the patient rated Zung Depression and Anxiety Scales, Clinical Global Impressions, and the SCL 90. Laboratory tests and side effect assessment was carried out predrug and throughout the trial.

The protocol allowed replacement of patients who terminated prior to day 21.

b. Conduct and Execution:

One hundred and twenty eight patients were randomized to treatment. Eighteen patients did not have a rating obtained on drug treatment. Because of the protocol design which allowed withdrawals at day 21, many patients did not complete the full 28 days of the study. Indeed, 24/43 placebo, 22/45 bupropion 300 mg and 24/40 bupropion 450 mg patients did not complete the study. The causes of premature termination, however varied with treatment assignment. Among the 43 placebo patients, 16 discontinued because of deterioration or lack of efficacy. Among the 85 treated with bupropion only 14 terminated for similar reasons. In contrast, no placebo patient was terminated because of an adverse effect, but 4/45 bupropion 300 mg and 7/40 bupropion 450 mg patients were.

c. Analysis of Results:

The study was analysed by 1) an intent to treat analysis employing a last observation carried forward (LOCF) methodology and 2) an observed cases (i.e., those patients actually observed at a particular time) analysis. 109 patients were evaluated in the LOCF analysis; 19 patients who had been randomized to treatment were excluded due to the absence of efficacy assessments during double-blind treatment.

The results of the LOCF analysis at day 21 are generally more favorable than those obtained with the observed cases method. The differences between the results of the two analyses are related to the fact that both the timing of withdrawals and the scores of the patients at the time of their withdrawal differ as a function of treatment assignment. In particular, there are more dropouts before day 21 among placebo patients (6) than among bupropion 300 mg (4) and bupropion 450 mg (4). Furthermore, as the causes for dropout would predict (see above), the status of bupropion assigned patients at the time of their withdrawal was generally better those assigned to placebo. For dropouts on bupropion 300 mg, the average improvement in the Ham D total score was 16 points. For dropouts from the bupropion

450 mg group, the average improvement was 20 points. In contrast, the average improvement among placebo dropouts was only 6.5 points.

In summary, the missing data brought forward in the LOCF is generally more favorable to drug and less favorable to placebo. In contrast, the observed cases analysis is strongly biased against bupropion because prematurely terminating bupropion patients who were doing comparatively well and prematurely terminating placebo patients who were doing comparatively poorly were excluded from it.

In its assessment of study 25, the agency relied primarily upon the results of the LOCF analysis evaluated at day 21. Day 21 was selected because of the large number of dropouts that occurred in all groups following that study day. The results of the LOCF analysis are presented below for the HAM D total score.

Hamilton Depression Total Score: Study 25
LOCF data: Mean decrease from baseline

Day	Placebo	Bupropion 300mg	Bupropion 450mg	PBO vs. 300mg*	PBO vs. 450mg*
7	9.6	8.8	10.4	.64	.65
14	13.1	13.2	17.0	.95	.06
21	13.3	16.1	17.7	.21	.06

*(2-tail 'p' values)

By day 21 (LOCF analysis) patients assigned to 450 mg of bupropion improved to a statistically significant greater extent (or nearly so) than those on placebo on other standard measures of efficacy (i.e., Ham-D retardation factor (p=0.03), Clincal Global improvement rating (p=0.06) and Clinical Global Severity of Illness (p=0.014)). The LOCF analysis, however, failed to detect statistically significant differences between bupropion and placebo on the HAM-D depression item (i.e., at day 21, p=0.26 and p=0.87 respectively for the 300 mg and 450 mg groups). This failing may reflect the early timepoint employed for trial assessment. If the depression item reflects primarily verbal reports of patients, it is likely to lag behind other measures of improvement, much as improvement judged by self-report scales lags behind improvement judged by observer scales in depressed patients.

d. Conclusion:

Despite the relatively high drop-out rate, analysis of the drop-out pattern and use of scores at the time patients left the study show a clear improvement in the treated group on the Hamilton Total Score and the Clinical Global Items providing evidence of bupropion's antidepressant efficacy. The study does <u>not</u>, however, demonstrate the efficacy of a 300 mg dose.

The following study supports the efficacy of bupropion at doses between 450 and 600 mg. Because a substantial proportion of patient were treated at doses outside the recommended dose range, the study cannot be considered a persuasive source of evidence of efficacy for the drug's approval under the proposed labeling. However, given the wide variability in the capacity of individuals to metabolize drugs, and the variability of the pharmacodynamic response, the study does lend additional support to the conclusion that bupropion is effective as an antidepressant.

3. .Study 14 (J. Feighner and J. Cohn)

a. Design: This was a five week (four weeks of treatment, one week of follow-up) randomized comparison of titrated bupropion and placebo at two centers.

b. Conduct and Execution: There were 117 patients enrolled and 86 included in the efficacy analysis (60 BUP, mean age = 45.9 yr; 26 PBO, mean age = 48.2 yr; 50 M, 36 F). The sponsor's analyses excluded five patients (BUP x 2, PBO x 3) who received psychoactive concomitant medications for eight or more days for anxiety or agitation, 25 who were treated (BUP x 14, PBO x 11) for less than 14 days, and one who received less than the minimum dose of BUP for 27 days. Principal diagnoses were:

depressive neurosis	50%
manic depressive (depressed)	40%

Dosage of BUP was 300 mg for days 1-4, 400 mg for days 5-7, and 600 mg up to day 28. Mean dose at days 22-28 was about 470 mg (546 at center 02 vs 392 at center 01); 13 patients (BUP x 8, PBO x 5) received flurazepam or diphenhydramine concurrently for sleep. Patients who failed to complete the study included:

ineffective or deterioration	(22)	10 BUP, 12 PBO
adverse effects	(8)	6 BUP, 2 PBO
intercurrent illness	(4)	3 BUP, 1 PBO
did not return or refused treatment	(12)	7 BUP, 5 PBO
administrative reasons		1 BUP

Medication was discontinued in 16 BUP and five PBO patients for clinically significant adverse experiences. Adverse reactions to BUP included seizure (1), agitation/excitement (3), increased insomnia and anxiety (1), and total body rash (1).

c. Results: There were quantitative but no qualitative center by treatment interactions, with marked BUP/PBO differences at center 01 with 49 patients (34 BUP, 15 PBO), and minimal differences at center 02. Additional analyses, with techniques similar to those described above for study 06, disclosed the following two-tailed p-values:

Protocol 14

LOCF (21) Differences in Change from Baseline between Wellbutrin and Placebo Groups

All Patients Randomized
Investigators Weighted Proportionally to Sample Size

Scale	# of Patients	Differences for Change from Baseline Scores	2-tail p-value
HAMD Total	114	6.94	.01
CGI	114	.594	.01
Depr. Item* of HAMD	113**	NA*	.01

* Based on Blocked Wilcoxon Rank Sum test of LOCF(21) value blocked on baseline value.
** One Wellbrutrin observation fell into a block with no other data.

C. Studies of adequate design that failed to provide support for the indication:

1. Study 08 (A. Halaris and W. Fann)

a. Design: This was a five week (four weeks of treatment, one week of followup) study. Data from three centers following a single protocol were submitted. Inclusion criteria were identical to those for Study 06, above.

b. Conduct and Execution: Sixty-eight patients were enrolled and 59 were included in the analysis (34 with mean age of 42.8 yr on BUP, 25 with mean age of 40.8 yr on PBO; 40 M, 26 F, and two unlisted). Principal diagnoses were:

depressive neurosis	60%
manic-depressive (depressed)	30%
other diagnoses	10%

Dosage started at 300 mg/day and was increased to 750 mg/day by day 11 if lower doses were well-tolerated. Mean daily dose of BUP for weeks 2-4 was about 725 mg. Thirty patients received either chloral hydrate or flurazepam for sleep at some time during the study. In addition to measures listed above, this study employed the BPRS, and the POMS at center 01. Dropouts were attributed to:

ineffectiveness	1 BUP
adverse reactions	3 BUP
intercurrent illness	1 BUP

After inspections disclosed that one investigator had violated regulations pertaining to the conduct of clinical studies, the investigator was disqualified from handling investigational drugs, and results from all 16 patients at that site were excluded from subsequent consideration for efficacy.

a. Results: A strong qualitative treatment by center interaction was found; center 02 was essentially negative while the results at center 01 supported the efficacy of bupropion. Because it had been designed as a multicenter trial, the agency examined only the combined results of these two centers; a subset analysis of each subcenter was conducted but was not relied upon.

Because of the strong qualitative treatment by investigator interaction, no combined data analysis of Study 08 could be considered reliable.

2. Study 09 (L. Fabre and J. Mendels)

a. Design: This was an eight week study with one week of PBO washout, six weeks of treatment, and one week of followup comparing two dose ranges of BUP to PBO at two centers. The low dose (LD) group started at 150 mg and was increased to 400 mg/day at day 15; the high dose (HD) group received double these amounts. Inclusion and exclusion criteria were similar to those listed above. After approximately one-fourth of the patients were completed, the study was amended to delete the HD group because one patient had a seizure at 900 mg/day.

b. Conduct and Execution: A total of 160 outpatients were entered; 29 were removed during the initial PBO week, and 131 were admitted to the randomized treatment period. Mean daily doses ranged from 137 to 331 mg in the LD and from 287 to 687 mg in the HD group. Patients were excluded from the sponsor's efficacy analysis if they either failed to complete two weeks of randomized treatment or required unacceptably large doses of anxiolytic drugs; 97 were included on this basis; 66 F & 31 M, 40 LD, 42 PBO, and 15 HD. Principal diagnoses were:

manic depressive (depressed)	60%
depressive neurosis	35%

Dropouts were attributed to:	LD	HD	PBO	Total
did not return or refused treatment	9	4	6	19
did not meed study criteria	1			1
ineffectiveness/deterioration		1		1
adverse reactions	6	4	1	11
Totals	16	9	7	32

c. Results: With data combined across centers, neither dose range was significantly more effective than PBO at any period on the rating scales employed. Patients rated much or very much improved at termination included 62% on LD, 60% on HD, and 43% on PBO.

D. Active control studies bearing on the relative efficacy of bupropion:

Active control trials are generally poor sources of information about the efficacy of antidepressant drugs. In the typical case, the study results in a finding of no difference between the treatments compared. However, even if there is adequate statistical power, such a result cannot be accepted uncritically as evidence of drug effect. A finding of no difference may occur for many reasons other than that both drugs were effective; for example, neither drug may have worked in the population studied. Consequently, the finding that six of the seven active control studies submitted in the NDA failed to distinguish between bupropion and an active control was not considered evidence of bupropion's antidepressant efficacy.

However, when one active treatment betters another in an adequate and well controlled investigation, the difference can generally be attributed to a drug effect of the superior drug, unless the inferior drug had been used in a manner that actually made patients worse than they would have been had they received no drug at all. Of course, such a finding does not speak to the question of whether the poorer performing drug is effective, a point that should be born in mind when considering the results of study 15 described below. The study suggests that in some settings, bupropion may not be as effective as traditional antidepressant drugs.

1. Study 15 (R. Remick, A. Cooper, J. Mendels, A. Singh, M. Amin, and G. Chouinard)

a. Design: This was a 92 day comparison to amitriptyline (AMI), with an initial week of PBO washout, at six centers. After the first week, patients received either 300 mg BUP or 75 mg AMI for one week; BUP could then be increased to 450 mg and AMI dosage doubled.

b. Conduct and Execution: A total of 196 outpatients were enrolled, and 190 continued after the PBO week. Five patients randomized but treated for one day or less were excluded from efficacy analyses as well as two who had no evaluations after treatment was instituted. Prescription of concomitant drugs was more frequent in BUP patients; twenty such patients and six randomized to AMI were excluded at FDA request because they received antihistamines or psychoactive drugs concomitantly. After four weeks on active drugs, at least 70% of randomized

patients remained under treatment at all six centers; at center 02, 70% were retained through six weeks.

c. Results: For the combined centers, results favored AMI numerically on the Ham-D total score and change from baseline, Ham-D retardation factor, Ham-D depression item score and change from baseline, CGI Severity and change from baseline, and CGI Improvement. These differences achieved statistical significance for AMI over BUP on all except the retardation factor change item at most observation points in both weighted and unweighted analyses.

E. Limits on Evidence of Efficacy and Duration of Effect: On the basis of the evidence available it is not known whether bupropion maintains its therapeutic effect for more than three weeks. The number of patients remaining in placebo controlled trials after that point does not permit any conclusions for a longer duration. BUP failed to do better than the control treatment in both outpatient studies, in one compared to PBO and, in the other, to amitriptyline.

F. Safety Data from Clinical Studies: More than 2400 patients participated in clinical studies of bupropion during its premarketing testing and evaluation. The original NDA reported on data involving approximately 1300 individuals. In subsequent amendments, including the 'safety update,' the sponsor provided additional reports and summaries of experience with an additional thousand or so patients.

The safety review focused primarily upon events that led to the discontinuation or death of patients. The safety review also considered the pattern and relative incidence of abnormalities in vital signs, laboratory and special tests, and reports of adverse events. Of particular importance for comparative and relative event incidence assessment are data submitted to the original NDA from four double-blind, PBO-controlled studies involving over 300 patients; two double-blind studies controlled with amitriptyline (AMI) in which over 100 patients received BUP, including about 25 who received the drug for up to three months. All information concerning more chronic experience with bupropion, however, is derived from open clinical trials.

1. Effects on Vital Signs and Physical Measurements:

a. Heart Rate: Doses of BUP up to 800 mg in volunteers did not cause significant changes in heart rate. In Study 08, mean supine heart rates on BUP rose gradually from 80.9 to 87.6/minute; rates on PBO varied from 84.1 at baseline to 82.4 at 21 days and declined to 77.7 at 28 days, a statistically significant difference at that point. In other studies, there was no consistent pattern of BUP effect on heart rate.

b. Blood Pressure: In Study 06, statistically significant differences were found in within-treatment comparisons to baseline on BUP in standing blood pressure, with decreases of 4-9 mm Hg for systolic readings, compared with 1-3 mm on PBO; supine readings were not consistently affected, and diastolic measurements indicated no trend. No consistent changes in supine or erect blood pressure were seen in other studies. Long-term treatment with BUP was associated with either small decreases or no change.

Among patients with a history of clinically significant orthostatic hypotension on tricyclic antidepressants (TCA) who were enrolled and showed no blood pressure effects on PBO, none of 12 who had received ascending doses of BUP (at the time of data cutoff) showed significant changes between PBO and BUP periods. In 86 hypertensive patients, vital signs did not differ significantly from baseline during BUP treatment. Among 156 patients with cardiac disease, symptoms and complaints did not increase during BUP treatment.

c. Respiration: No clinically important increases or decreases in respiratory rate were seen.

d. Temperature: In those instances in which body temperature was measured, no consistent changes were found on BUP.

e. Body Weight: Weight loss of five or more pounds was noted in more BUP patients than PBO patients (23% vs 11%). Weight gain of five or more pounds was only about one-third as likely on BUP as on AMI and only 40% as likely on placebo. Patients whose weights were measured and who gained or lost at least five pounds were as follows:

	BUP			PBO			TCA		
Studies	n	+5	-5	n	+5	-5	n	+5	-5
06, 09, 14	130	6%	23%	81	14%	11%			
15, 21	91	13%	34%				67	39%	9%
35	298	3%	15%						
Total	519	5.7%	20.2%	81	14%	11%	67	39%	9%

2. Adverse Effects on Laboratory Evaluations:

a. EKGs and Cardiac Conduction: 4/304 patients developed abnormalities during BUP treatment. One was noted to have a single premature ventricular contraction (PVC) during BUP; another had abnormal ST-T wave recordings at baseline that

worsened during treatment; the third was a woman aged 61 who had APC and PVC at 5, 12, and 21 days which were still present two weeks after discontinuance; the fourth, a woman aged 58, had newly observed junctional or nodal premature beats.

The overall effect of treatments on ECG recordings is as follows:

	BUP	PBO	TCA
n =	304	123	72

Baseline - Treatment	Percent of Patients		
Normal - Normal	69.7	79.7	65.2
Normal - Abnormal	8.6	3.2	15.3
Abnormal - Normal	5.6	3.2	6.9
Abnormal - Abnormal	16.1	13.8	12.5

One study center provided lead II rhythm strips of 15 seconds taken at double paper speed and voltage for 62 patients; these were to be scored on a blinded basis by the sponsor for the duration of the QRS; P-R, R-R, and the corrected QT intervals (QTc) and the amplitude of the QRS complex; tracings taken on days 14, 21, and 42 were found scorable for 23 BUP and 23 TCA patients. For BUP, there was no statistically significant difference in the length of QRS or P-R intervals developing during treatment; for TCA, these were significantly longer, but the between-treatment comparisons did not show significance.

Overall, there appeared to be no consistent or clearly drug-related on ECG effects of bupropion.

b. Clinical Hematology Evaluations: Decreased hematocrit following a normal baseline value occurred more frequently with BUP than with PBO or TCA treatment. One BUP patient was recorded as having a WBC value of 2300 one day post-treatment in a 42 day study; the result was within the normal range when repeated one week later. BUP was associated with decreases in mean values for hemoglobin (in study 08 at day 14, in study 21 at termination, and in study 26 at 3-8 weeks), hematocrit (in study 21 at termination, and in study 26 at 3-8 weeks), WBC (in study 15 at day 29 and day 92, and in study 17 at 1-2 months and over 6 months), lymphocytes (in study 17 at 1-2 months, in study 08 at day 14, and in study 15 at day 92), monocytes (in study 17 at 3-6 months), and RBC (in study 15 at day 29), and with increased neutrophils (in study 08 at day 14). PBO was associated with increased WBC in one study at termination and with increased neutrophils in another at day 14. TCA was associated with decreased hemoglobin and decreased hematocrit in discrete studies at one point each, and with increased blood glucose (in study 17 at over 6 months, and in study 21 at termination), and increased monocytes (in study 17 at 3-6 months).

Overall, there were no consistent

e. Clinical Chemistry Evaluations: For liver enzyme values, the pattern of results was similar. Overall, liver enzyme values showed no consistent change during BUP treatment.

BUP was associated with altered mean values for other chemistry examinations at 14 time points during these studies, but the changes appear to occur in a random fashion. PBO was associated with sig[illegible]icantly altered mean values in three instances, and AMI in fo[illegible]

3. Observed A[illegible]se Reactions: The Standard Adverse Experience Listing or [illegible] Dosage Record and Treatment Emergent Symptoms (DOTES) Sc[illegible] was administered at baseline and at intervals during the studies. In listing the data derived from these questionnaires, neither the severity of the reported reaction nor the investigator's judgment of the probability that the event was drug-related has been taken into account.

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 incidence figures cited in the following discussion must be accepted as rather imprecise estimates. They cannot be used to predict 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 calculated incidence estimates cannot reflect the relative severity and/or clinical importance of events. Whether or not an event was severe enough to cause discontinuation of a drug's use is one guide to its importance.

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 the product's premarketing clinical trials. 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, primarily rashes (1.4%). It is important to note, however, that many of these events occurred at doses that exceed the recommended daily dose.

LION 301 MADE IN JAPAN

Because the design and duration of a study can influence both the calculated incidence of adverse events and the inferences subsequently drawn, the following discussion provides a separate assessment for each related group of clinical studies.

a. <u>During PBO-Controlled Studies</u>: Data from 222 BUP and 136 PBO patients in studies 06, 08, 09, and 14 were initially combined. Subsequently, the results of another placebo controlled study were added. These results are shown in the attached labeling. The excess of adverse effects in patients on BUP (compared to PBO) was largest for agitation, dry mouth, sweating, and tremor. Other adverse experiences reported more frequently by BUP patients than those on PBO included insomnia, constipation, syncope/dizziness/fainting, weight loss and confusion.

b. <u>During TCA-Controlled Studies</u>: Data from 120 BUP and 83 AMI patients in studies 15 and 21 were combined. There was a notable excess of complaints of increased salivation, nausea/vomiting, headache, and decreased appetite/anorexia in BUP patients, and a numerical excess for complaints of euphoria, numbness, dystonic symptoms, paresthesia, chills, diarrhea, urinary frequency, increased libido, decreased libido/impotence, edema, and dermatologic symptoms compared to AMI patients.

<u>During Long-Term Studies</u>: The percent of 60 patients receiving BUP in studies 17 and 26 who developed symptoms not present at baseline was as follows:

Dry Mouth	28%
Tremor	15%
Menstrual Disturbance	13%
Increased Appetite	13%
Nausea/Vomiting	13%
Syncope/Dizzy/Fainting	13%
Headache	12%
Blurred Vision	12%
Pruritis	11%
Skin Lesion	10%
Agitation/Excitement	10%
Decr Libido/Impotence	8%
Ataxia	6%
Swelling (Testis/Breast)	6%
Peculiar Taste in Mouth	6%

In comparison with the 19 AMI patients in study 17, there was a notable excess of complaints of agitation/excitement, insomnia, and tiredness/fatigue on BUP. (AMI patients had notably more complaints of dry mouth, drowsiness or sleepiness, and constipation than those treated with BUP.)

d. <u>Associated with Discontinuance</u>: Adverse reactions caused discontinuation of BUP treatment in 177 instances. Three patients were receiving both BUP and a neuroleptic under

LION 301 MADE IN

circumstances in which attribution of the event to either drug is problematic; 6/40 patients in one protocol received doses of more than 750 mg/day, a dose larger than that recommended in the originally proposed labeling, and 2/157 normal volunteers were discontinued after receiving doses larger than those anticipated in the t.i.d. schedule adopted. Excluding these 11 cases, the rates are:

Drug	# Treated	# Discontinued	Percent
BUP	1153	166	14.4
PBO	177	10	5.6
AMI	196	33	16.8

Among subjective, behavioral, or psychological adverse reactions, the one most frequently associated with discontinuance of BUP was excitement/agitation in 9.1%, compared with 6.8% on PBO and 9.2% on AMI. In the nonsubjective, nonbehavioral, or nonpsychological category, the reaction most frequently associated with discontinuance of BUP was dermatologic (usually urticarial or pruritic skin rashes).

e. Post-NDA Exposures: As noted earlier, experience with approximately 1000 additional patients and volunteers was included in the sponsor's final cumulative safety review. In general, no new events or findings that might affect either the approval decision or product labeling were identified that had not been detected in the data submitted with the original NDA.

However, the added experience did affect the precise incidence figures calculated for adverse events and for discontinuations. The revised estimates of incidence are not tabulated herein, but may be found in the attached final product labeling. The safety update, however, did provide greater detail about certain events, especially those that had been described ambiguously. In general, however, the safety update did not substantively alter any conclusion about the safety or relative risk and benefit of bupropion as an antidepressant.

F. Special Safety Considerations:

1. Seizures:

Seizures were first seen in volunteers participating in Phase I studies and the relatively high risk of seizure associated with the use of bupropion is an important determinant of dosing recommendations. The data suggest that high daily dose dose and/or rapid escalation of dose are strong predictors of seizure risk. Prior history of seizures and primary structural brain disease also appear to increase the risk of seizure.

The table below illustrates the relationship between dose, predisposing factors and seizure risk:

INCIDENCE OF SEIZURES IN PATIENTS RECEIVING BUPROPION

BUPROPION Dose mg/day	Total Seizure Incidence (%)	Seizure Incidence in Patients Without Seizure Predisposition (%)
Less than 450mg	0.2%	0.0%
450mg	0.3%	0.2%
600mg*	2.3%	1.3%
600mg-900mg*	2.8%	1.9%

*: symbol indicates a dosage exceeding the maximum recommended daily dose.

2. Overdoses, Suicides and Deaths:

In the original NDA, reports described five outpatients who ingested single overdoses in amounts of 900 to 3000 mg BUP during clinical trials. Several vomited, and all recovered without sequellae following hospital admission. (OD-5 ingested an overdose of diphenhydramine 11 days after being restarted on BUP and was terminated from the study at that point.) Three other patients receiving BUP in clinical trials ingested overdoses of other drugs, and one attempted suicide by cutting his wrists.

The safety update included 8 more overdoses, for a total of 13. None had proven fatal, although seizures occurred definitely in one and probably in another. All these patients recovered without "residual impairments."

Fatalities in temporal association with the use of bupropion were reported in 14 patients prior to approval. None are known or believed to be a consequence of treatment with bupropion. Nine deaths were self-inflicted. Three deaths occurred in elderly and/or seriously ill patients.

3. Evaluation of Abuse Potential:

Preclinical studies in rodents suggest weak amphetamine-like effects with respect to locomotor activity and effects on schedule controlled behavior; in animals trained to discriminate amphetamine from PBO, BUP was identified as amphetamine-like.

Data obtained from clinical efficacy studies suggest mild amphetamine-like effects, with increased motor activity. Neither notable anorectic effect nor peripheral sympathomimetic activity was consistently observed with BUP; although, in regard to the former, weight loss in patients was more common than in TCA treated patients.. A dose of 400 mg produced a modest elevation over PBO responses on the morphine benzedrine group subscale of the Addiction Research Center Index (ARCI), and a score intermediate between amphetamine and PBO on the Liking Scale of the ARCI.

VI. Advisory Committee and Foreign Regulatory Agency Actions:

Psychopharmacologic Drugs Advisory Committee (PDAC):

Wellbutrin was presented to the Committee on June 10, 1982, prior to the assessment of the data and reports bearing on its safety. The application was presented to the Committee in an attempt to gain their views about the adequacy of the three week long efficacy trials. The Committee, however, elected to consider the issue of approval.

The Committee reviewer noted that all four PBO-controlled studies showed the common problem of an inordinate drop-out rate at day 21, due to a feature which allowed patients to be removed from the study at that point if favorable therapeutic effects were not apparent.

It was noted that results in study 15 favored AMI over BUP, significantly in some instances. The reviewer concluded that BUP was associated with greater improvement than PBO in the three inpatient studies, based on Ham-D and Clinical Global Severity of Illness scores at day 21.

The Committee recommended approval of bupropion for the treatment of depression, but conditioned their recommendation upon acceptable findings in the then incomplete safety review. The Committee was not aware of the inordinately high risk of seizure at the time its recommendation was made.

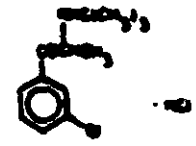
VII. Conditions for Approval:

Performance of (1) a multiple-dose dose proportionality study covering the drug's recommended dosage range which is to evaluate bupropion and its active metabolites, (2) a multiple-dose pharmacokinetic study in geriatric patients, (3) clinical studies to determine whether or not the antidepressant effect persists beyond three weeks, (4) a program to determine the potential of bupropion to cause seizures, (5) an investigation for an extended period to determine the extent of abuse and diversion of the drug in comparison to other antidepressants will be required after marketing is approved, and (6) the submission of laboratory data collected in the period following the submission of the original NDA.

VIII. Approved Package Insert:

The approved package insert is attached.

WELLBUTRIN® (bupropion hydrochloride) Tablets



CLINICAL PHARMACOLOGY

INDICATIONS AND USAGE

CONTRAINDICATIONS

WARNINGS

[illegible] 301 MADE IN JA[illegible]

[illegible] (phenobarbital) [illegible]

[illegible] and [illegible]

[illegible] (phenobarbital) sodium combines a mixed barbiturate, a sedative with a variety of antiepileptic drug effects, and a hormonal growth stimulant which results in better activity and [illegible] development.

In populations of [illegible]-supervised with [illegible] of [illegible], a single dose of [illegible] produces [illegible] and [illegible] in a comparable [illegible] as the [illegible] [illegible] of the [illegible] [illegible] dose. [illegible] and [illegible] [illegible] [illegible] and [illegible] at the [illegible] [illegible] of the [illegible]. [illegible] [illegible] [illegible]

LON 301 MADE IN

811

NDA 18-644

12/31/84

Burroughs Wellcome Company
Attention: Donald A. Knight
3030 Cornwallis Road
Research Triangle Park, North Carolina 27709

Gentlemen:

Please refer to your new drug application dated December 28, 1981 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation Wellbutrin (bupropion hydrochloride) Tablets, NDA 18-644.

We also refer to your additional communications dated:

June 10, 1982 (submitted to IND)
July 1, 1982
July 22, 1982
October 7, 1982
November 8, 1982
November 10, 1982
December 1, 1982
December 8, 1982
January 25, 1983
February 17, 1983
March 18, 1983
March 31, 1983
April 25, 1983
April 27, 1983
April 28, 1983
June 6, 1983
June 23, 1983
July 13, 1983
August 3, 1983
August 15, 1983
September 9, 1983
September 19, 1983
October 26, 1983
November 3, 1983
February 3, 1984
March 20, 1984
April 13, 1984
May 3, 1984
May 8, 1984
May 16, 1984
May 22, 1984
June 6, 1984
July 25, 1984
September 18, 1984
November 27, 1984

We have completed our review of this application as submitted with draft labeling.

The application is approvable provided that:

1) You agree to (a) perform the modifications of your analytical methods for the product described in the section entitled Analytical Methods; (b) reposition the Caution statement from the side panel of the 100 mg strength, 100 tablet container to the front; and (c) replace the proposed quality control in vitro dissolution test method (paddle) with the basket method which was used throughout the development of Wellbutrin (i.e., USP XX Apparatus 1, 100 rpm, 500 ml of 0.6% HCl 37°C.) The recommended dissolution specification for the basket method should be not less than 75 percent (Q) drug dissolved in 20 minutes.

2) You make a commitment to conduct additional clinical investigations, to be initiated within the first year of marketing, that will provide evidence to demonstrate that the antidepressant effect of Wellbutrin persists beyond three weeks. This information is essential if the labeling of Wellbutrin is to provide adequate directions for its use. Our reasoning about this matter is described in detail, including a suggestion for design of the study, in the section entitled Clinical Studies.

3) You make a commitment to conduct a clinical investigation to elucidate the relationship between bupropion's dose, the timing of the administration of this dose, the clinical response and the untoward event incidence. Understanding this relationship is especially important in view of the apparent high incidence of seizures to date, particularly among individuals receiving higher doses of bupropion.

4) You initiate a comprehensive post-marketing program to evaluate the potential of bupropion to cause seizures in actual medical use. As you are aware the power of controlled trials to detect rare events is limited; consequently, the important issue of epileptogenic risk should also be assessed using epidemiological-styled strategies. Acceptable approaches might include following prospectively cohorts of users (e.g., in the style of the Puget Sound Health Cooperative program) or retrospective analyses of third party data bases. An alternative to be explored is a large cohort involving randomized assignment of patients to bupropion and a standard drug followed forward under not especially close surveillance, but nonetheless, surveillance sufficient to detect seizures.

5) You conduct a long term, post-marketing, epidemiologically styled investigation, with yearly interim analyses, to determine the extent of abuse and diversion of buproprion in comparison to other antidepressant drug products.

6) You conduct the following biopharmaceutic investigations within 180 days of final approval of the application:

   a) A multiple-dose, dose proportionality study that covers the dosing recommended in the product's labeling.

   b) One or more investigations suitable for determining the pharmacokinetic parameters of bupropion in the elderly, that is, those over the age of 65.

7) You submit a comprehensive Safety Update covering all clinical experience with bupropion, regardless of the use investigated. This

LION 391 MADE IN JAPAN

update should provide an enumeration of all patients who suffered a mortal or morbid event and any who were forced to withdraw from treatment because of an adverse experience regardless of assumptions or judgments about the relationship of drug treatment to the observed or reported reaction.

8) You make substantive changes in the draft labeling regarding the description of the product's clinical and pharmacological effects, the claimed indication and the population for which its use should be considered, and the warnings and directions for its use. The labeling we would tentatively agree to accept, if all other conditions are met, is described in detail in the section entitled Labeling.

Analytical Methods

The results of our laboratory investigations show that with some relatively minor modifications the proposed methods will be suitable for regulatory and control purposes. Our comments and suggestions are the following:

a) IR Identification

Our initial curves of the New Drug Substance (NDS) and the reference standard, as KBr pellets, did not match in the regions around 100 and 700 cm^{-1}. When the bupropion KBr mixture was prepared by use of a "Wigglebug," the spectra were similar. We feel that the initial problem was due to a difference in particle size of the standard and NDS. Visual inspection of the two indicated a different appearance as well. A Wigglebug, or other similar mechanical vibrating ball mill, should be specified in the method as one means of preparation of the KBr mixture.

b) NDS Assay

As further evidence of a particle size problem, our initial attempt with the HPLC assay for the NDS yielded results which were below the NDA specifications. Use of a sonic bath corrected this problem. Aliquots were chromatographed every 5 minutes until reproducible areas were obtained. A total of 15 minutes in the bath was required.

c) Melting Range

The NDA specifications include the melting range; however, the certificates of analysis do not include the results of this procedure. The Atlanta District reported difficulties with the melting point determination; their results were low. We found the melting range for the standard to be 217-220° and for the NDS to be 215-218°. Determination by Differential Scanning Calorimetry (DSC) gave somewhat variable results,

MADE IN JAPAN

generally at the high end of the allowed 218-226° range or above it. Since there are already two identification tests, IR and HPLC, and since both FDA laboratories obtained unsatisfactory results, it might be appropriate to eliminate this test. In further support of this deletion is the fact that testing for the related substances by TLC provides another built-in identification test.

d) We recommend inclusion of an upper limit in the specifications for the chloride assay.

e) We also recommend that specification limits on impurities be reduced to reflect those found in the drug substance used in clinical studies and reported in your March 18, 1983 amendment.

Clinical Studies

The application provides evidence that bupropion is effective when used for periods up to three weeks in inpatients. We are unable to determine, however, whether its antidepressant effect persists beyond three weeks, and we find the data on its efficacy in an outpatient setting equivocal. We are also concerned about the relative paucity of systematically obtained information on the relationship between the dose of bupropion administered, the incidence of adverse events and the therapeutic effect.

In regard to bupropion's efficacy in outpatients, the only placebo controlled study in this population, 09, provides inconclusive evidence. As you pointed out in your submission of September 18, 1984, in one analysis some measures in the 09-01 substudy are supportive of efficacy; however, the 09-02 substudy fails totally to confirm this finding.

In regard to the question of sustained efficacy, there is virtually no useful evidence. While some of the active standard drug controlled investigations evaluated patients for a period beyond three weeks, their outcome (i.e., standard drug superior to bupropion [#15], or a failure to detect a difference between bupropion and standard drug) does not provide convincing support for the sustained efficacy of bupropion. Active control studies may fail to detect a difference between treatments for reasons unrelated to drug effect. Only clinical investigations that demonstrate that an experimental drug is superior to a control treatment can provide unequivocal evidence that drug rather than spontaneous remission (or other factors) accounts for clinical improvement seen over the course of a study.

In some situations, admittedly, active control studies that fail to distinguish among treatments may provide useful information about efficacy. However, such situations are limited to those wherein the course of untreated patients is known with great certainty from historical evidence.

To be sure, general clinical experience suggests that patients recovered or recovering from a recent episode of depression are more likely to suffer a relapse if antidepressant treatment is withdrawn rather than maintained. However, a single, reliable estimate of relapse rate in untreated remitted

depressed patients, the sine qua non for the valid interpretation of antidepressant trials controlled only with an active drug, is simply not knowable.

Furthermore, even advocates of active control designs for the determination of drug efficacy admit that their use is questionable when their power to detect a difference is weak. Unfortunately, because of sample attrition (dropouts), statistical power to detect clinically substantial differences is especially poor in the later stages of the bupropion trials.

We acknowledge that similar questions might be raised about the sustained efficacy of currently marketed antidepressants. However, extensive clinical experience with the "older" antidepressants provides some measure of reassurance regarding their sustained efficacy. Unfortunately, that reassurance cannot be extrapolated readily to bupropion.

As you have indicated, bupropion is a novel drug, at least in regard to its mechanism of action which presumably differs from that of other antidepressants. Furthermore, bupropion shares some features in common with amphetamine or amphetamine-like drug substances, drugs which are known to produce only transient improvements in mood in some depressed subjects. Typically, tolerance occurs to the euphoriant effect of amphetamine, accounting for the general view that amphetamine and similar drugs cannot be considered true antidepressants. Therefore, we wish to be certain that the effects of bupropion do not rapidly dissipate with the passage of time.

Also, the only dible evidence supporting the efficacy of bupropion is derived from trials that are atypical by usual standards of antidepressant drug development. As noted above, they are of comparatively short duration, effectively three weeks, rather than the usual four to six weeks. Second, they were conducted in an inpatient setting which is not representative of the conditions under which the drug will be used most frequently, i.e., in an outpatient setting. As mentioned earlier, the only placebo controlled outpatient trial failed to demonstrate consistent support for the efficacy of bupropion.

Finally, the matter of the relationship between bupropion's dose and its adverse event profile and efficacy is especially important because bupropion's potential to cause seizures is apparently dose related. This is of particular concern because doses that cause seizures in a substantial proportion of the population (i.e., 800mg) are not far removed from the recommeded daily total dose of 750mg.

Consequently, we believe that additional clinical data on the proper use of bupropion is needed. The data should be obtained in controlled trials that can provide (1) evidence of bupropion's sustained efficacy, and (2) information about the relationship between the dose of bupropion administered, the extent of therapeutic response, and the incidence of adverse events.

We intend that information obtained in these studies will be used to revise and expand the information provided in labeling as directions for use.

It is essential that information bearing on these matters be collected in studies designed to demonstrate a difference between treatments. Thus, bupropion, administered at some dose within the range recommended in its labeling, may be compared with any number of control treatments, (e.g. placebo, a lower dose of bupropion, and/or a standard antidepressant) with the goal of showing its superiority to the control.

You are, of course, free to develop any specific designs that satisfy these requirements. The following "discontinuation" design study is offered as one possible approach to assess the duration of effectiveness question.

> Recently recovered depressed patients who were treated for their acute episode of depression with bupropion and are being "maintained" on bupropion during the early phase of their remission would be considered candidates for participation in the study. (As you are aware, recently "recovered" patients are usually maintained on antidepressant treatment for several months after their "recovery", that is, return to euthymia.) After one or two months of "euthymia" on bupropion, patients would be randomly assigned to 1) continued treatment with bupropion or 2) placebo. The sustained efficacy of bupropion would be demonstrated by a superior outcome of patients assigned to bupropion. Of course, the variable(s) used to assess outcome would need to be declared prior to the study and defined in operational terms (e.g. lower relapse rate, significant difference in clinical global depression score, etc.)
>
> We recognize that a procedure which provides for the withdrawal of treatment from recently recovered patients may be open to criticism or objection because of the belief, mentioned earlier, that continued treatment for six months or more reduces the risk for relapse. We are not aware of any persuasive body of evidence derived from adequately controlled experiments which directly addresses the question of how long antidepressant treatment should be continued. Not only can the case be made that such a study is ethically justified, but it can provide critically important information on the question of the need for extended drug treatment. Furthermore, the trial can be carried out with provision for subject rescue (i.e., reinstitution of treatment with known antidepressant). If this is done blindly, the difference in rates of rescue between the treatment groups can itself be used as an outcome assessment measure.

As you will recognize, other designs are possible, and we would welcome the opportunity to work with you to develop a specific experimental approach that would be mutually acceptable.

We are also prepared to discuss the details and to work cooperatively with your staff on the design of studies to further evaluate bupropion's potential to cause seizures or drug abuse problems and the biopharmaceutic study listed above.

Labeling

The draft labeling submitted is unsatisfactory as it is promotional in tone and contains claims and statements that either lack evidential support or are inadequately documented, and extensive revision is necessary. As noted earlier, labeling we would be prepared to accept follows. This labeling is intended to bring the form and tone of Wellbutrin's labeling into conformity with the labeling of other recently marketed antidepressant drug products.

The labeling follows the outline of 21 CFR 201.57. When text is provided by the agency, please use it without modification. In other sections, instructions or suggestions are provided. (The suggestions are indented and appear within brackets, [sic].) It is important, however, when providing new text, to supply appropriate documentation and annotations for any statement. The annotations will not appear in the final labeling, but are essential for our review.

The labeling should be printed and submitted in the format in which it will appear. But it will still be considered draft labeling. Therefore, the number of total copies printed should be limited, as further revision may be necessary.

Labeling text:

Wellbutrin® Tablets (bupropion hydrochloride)

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 similar to those of fenfluramine and amphetamine. It is designated as 2-tert-butylamino-3'-chloropropiophenone hydrochloride. The molecular weight is 276.2. The empirical formula is $C_{13}H_{18}ClNO \cdot HCl$. Wellbutrin 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:

[insert chemical structure]

Bupropion is supplied for oral administration as 50 mg (white), 75 mg (yellow-gold), and 100 mg (red) film-coated tablets.

MADE IN JAPAN

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, but it does inhibit the neuronal re-uptake of dopamine to some extent, and animal studies suggest that it may act through dopaminergic mechanisms.

[To Firm: Please use this section to describe, if known, the results of studies on the binding of bupropion to dopaminergic, serotoninergic, adrenergic, cholinergic and other CNS receptors.]

In animals, bupropion exerts dose-related CNS stimulant effects.

[To Firm: Please describe these CNS behavioral effects in greater detail.]

In animals, bupropion is epileptogenic at multiples of the human therapeutic dose (HTD).

[To Firm: In the next section, describe the epileptogenic action of bupropion observed in animal studies. In your description describe any differences between acute and chronic threshhold and the actual dose, in mg/kg, for each condition and species. You may compare these doses directly with the recommended maximum human dose.]

Absorption, Distribution, Pharmacokinetics, Metabolism and Elimination:

In man, following oral administration of Wellbutrin (bupropion), peak plasma concentrations are usually achieved within 2 hours, followed by a biphasic decline.

[To Firm: Please provide an indication of just what fraction of the oral dose is bioavailable; that is, how extensive is first pass or presystemic metabolism. Also, at this point, indicate which metabolites of bupropion have pharmacologic activity. It is important to provide ADME information on active metabolites, especially if they are likely, by virtue of either accumulation or intrinsic activity, to contribute to the beneficial or untoward effects of bupropion.]

The average half-life of the parent drug in its initial phase is 1-2 hours, and the half-life of the second phase is approximately 14 hours, with a range of eight to 24 hours in individual values. Plasma concentrations are dose-proportional following a single dose of 100 to 250 mg. Six hours after dosing, plasma levels are approximately 30% of peak levels. Considerable variation among individuals in serum "trough" concentration (i.e., C_{min}) has

been observed. In one study of patients 50 years and older, three of the 11 individuals demonstrated C_{max} values three to five times higher than those observed in the other eight patients who participated in the study.

Bupropion induces its own metabolism in three animal species.

> [To Firm: If you have any specific information about which enzyme system(s) is (are) induced, you may add it here. Please, however, do not characterize the extent of activation or induction with qualitative modifiers. Identify the metabolites and their routes of excretion. Discuss, in quantitative terms, how much and over what time course the parent compound accumulates. Provide, if available, similar data on all active metabolites. Provide, too, basic information on other parameters such as the volume of distribution, and describe the sites of principal metabolism -- gut, liver, kidney, etc. -- and the major routes of elimination. Describe how disease states or altered organ function may influence metabolism and/or elimination.]

In-vitro tests show that bupropion is 80% or more bound to human albumin at plasma concentrations up to 800 micromoles.

INDICATIONS AND USAGE:

Bupropion is indicated for the treatment of depression. However, because experience in clinical studies suggests that Wellbutrin (bupropion) may pose a greater risk of seizure than other antidepressant drug products (see Warnings), Wellbutrin should not generally be considered as the antidepressant of first choice for most depressed patients.

The efficacy of bupropion was demonstrated in clinical trials of three weeks duration which enrolled principally hospitalized patients with diagnoses of depressive neurosis and manic-depressive (depressed phase) disorder. The depressive illness of the hospitalized patients studied meets the Major Depressive Episode criteria of the APA Diagnostic and Statistical Manual III.

Major Depressive Episode 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.

The only placebo controlled trial of bupropion in depressed outpatients failed to provide unequivocal evidence of its efficacy.

Evidence to demonstrate the sustained effectiveness of bupropion after three weeks of use is not available from adequate and well controlled investigations, leaving unanswered the question of what constitutes the appropriate duration of treatment of patients who show a positive clinical response.

CONTRAINDICATIONS:

The concurrent administration of bupropion and a monoamine oxidase (MAO) inhibitor is contraindicated; at least 14 days should occur after discontinuation of an MAO inhibitor before beginning treatment with bupropion. Bupropion is contraindicated in patients who have shown an allergic response to it and in those taking medications which lower the seizure threshold.

WARNINGS:

[Note to Firm: The following statement should appear in bold type, within a box.]

Convulsions:

During the period of its clinical investigation, there were 20 reports of major motor seizures among approximately 2000 patients treated with bupropion at doses within and above the recommended dosing range. In 14 of 20 the dose at the time seizures occurred was 600mg per day or more, and in five subjects, the daily dose exceeded 11mg/kg (5mg/lb). Of particular importance, only one of these patients had a history of seizure disorder. Consequently, attention should be paid to the relative risks and benefits of bupropion in all patients, particularly at doses approaching the limits recommended (see DOSAGE AND ADMINISTRATION). Use of bupropion should be avoided in patients with a history of seizure disorder or cranial trauma.

[The box may close here.]

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 suggestive of impaired liver function were noted. Although scattered abnormalities in liver function tests were detected in patients participating in clinical trials, there is no direct evidence that bupropion acts as an hepatotoxin in humans. Nonetheless, the possibility of hepatotoxicity should be kept in mind, particularly in patients treated for protracted periods and those with preexisting impairment of hepatic function.

PRECAUTIONS:

General:

Suicidal patients:

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

Weight loss:

Bupropion appears to exert an anorexigenic effect. Weight gain of five or more pounds was only about one-third as likely among patients treated with bupropion as among patients receiving tricyclic antidepressants. Weight loss of five or more pounds was noted in about ten percent more bupropion patients than those on placebo in clinical trials. This effect should be considered when prescribing for patients who have lost weight in association with their depressive episode.

Agitation:

Many patients treated with bupropion, especially shortly after the initiation of treatment, experience increased restlessness, agitation, anxiety and insomnia. In controlled trials, these symptoms were often of sufficient magnitude to require treatment with sedative/hypnotic drugs and, in some instances, symptoms were sufficiently severe to require that affected patients be withdrawn from treatment with bupropion.

Use in patients with systemic illness:

There is no clinical experience establishing the safety of bupropion 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.

Because bupropion and its metabolites are almost completely excreted through the kidney, treatment of patients with renal impairment should be initiated at reduced dosage. 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 instructed to take bupropion on a t.i.d. basis and not as a single daily dose.

Patients should notify their physician if they become pregnant or intend to become pregnant during therapy.

Drug Interactions:

No information is available concerning the consequences of the concomitant administration of bupropion and other antidepressants. However, bupropion does induce hepatic enzyme systems, and this may influence the metabolism of other drugs. The effect of concurrent administration of other drugs on the metabolism and/or blood level of bupropion has not been studied. Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine (see CONTRAINDICATIONS).

Animal studies also suggest that bupropion potentiates the effects of L-dopa. Administration of bupropion to patients receiving L-dopa concurrently should be undertaken with caution, using small initial doses and small increments of bupropion.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

In a two year 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. In the bupropion studies, no increase in malignant tumors was seen in liver or other organs in either rats or mice.

Bupropion produced a borderline positive response 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.

Pregnancy:

Teratogenic Effects:

Pregnancy Category B. Reproduction studies have been performed in rabbits and rats at doses up to 30-60 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 bupropion on labor and delivery in humans is unknown.

MADE IN JAPAN

Nursing Mothers:

It is not known whether bupropion is excreted in the milk of lactating women. Because many drugs are excreted in human milk, caution should be exercised when bupropion is administered to lactating women who are nursing.

Pediatric Use:

The safety and effectiveness of bupropion in individuals under 18 years old has not been established.

ADVERSE REACTIONS:

[To Firm: This section should consist of the following:

A. An introductory part which states in narrative style the more common reactions encountered with use of the drug, listing the effects which represent pharmacological extensions of drug action, i.e., what the physician and the patient may expect in routine use;

B. A table showing the incidence of adverse effects encountered during the controlled trials; and, finally,

A list of all adverse reactions, organized by body system or symptom class in the manner traditionally found in this section of the package insert.

In regard to the enumeration of events for item B, we request that the incidence rates for adverse reactions be based upon data obtained from controlled clinical trials that allow valid comparisons of incidence between treatments. We are especially interested in the incidence rates of events in all the controlled trials which included placebo, whether they were of two- or three-way design. Events enumerated for incidence calculations should include all events reported regardless of their significance or alleged cause. Incidence rates used should not be adjusted in any way (e.g., placebo incidence should not be subtracted from the drug incidence rate, adjustments for "baseline" should not be made, etc.). Incidence rates should be calculated separately for studies 06, 08-01, 14-01, and 15.

We define the treatment specific incidence for each event as the proportion of patients in the study experiencing, reporting, or being reported to experience the event while on treatment among the total randomized to the treatment and receiving at least one dose of the treatment.

Events occuring prior to treatment assignment should not be considered as adverse drug reactions unless the severity of the sign or symptom present at baseline worsened after treatment began. We make this point explicitly because your submission does not make clear how you constructed incidence figures. We suspect that you may have included phenomena in your tabulations of adverse events that occurred before patients were assigned to treatment. In our view, inclusion of events or phenomena present at baseline that subsequently abated, or remained unchanged merely adds background "noise" to the adverse reaction data base. For example, inclusion of depression, the basis for patient selection for treatment, as an adverse reaction is pointless. The inclusion and tabulation of less clearly defined phenomena, especially if most individuals experiencing the phenomena did so before they were assigned to treatment, causes even greater confusion. For example, your tabulation of adverse reactions includes the term "toxic confusion" and records that 15 to 20 percent of patients experienced this event. It is not clear to us what this means. Did patients entering the studies present with the clincal features of an organic brain syndrome or did they develop an organic delirium while on treatment? This distinction cannot be made when the adverse reaction tabulation contains baseline data.

In any event, while you have made it clear that you employed a systematic checklist to collect adverse event data, you have failed to explain how data obtained using this technique was combined with treatment emergent events that were reported spontaneously. Obviously, the two types of data are not easily combined. An event elicited using a checklist at baseline may not correspond qualitatively to a treatment emergent event that is actively brought to the investigator's attention, either by the patient or the staff.

Thus, we ask that the data on adverse reactions be retabulated to include only those events that were treatment emergent. We are most interested in the treatment emergent events that were spontaneously reported or observed. However, you may present the tabulations using both approaches, one with events reported spontaneously and the second with events elicited using the checklist. The latter should distinguish between patients whose symptoms or signs became more severe and those whose symptoms or signs arose <u>de novo</u>.

The problem of retrospective classification of untoward events using commonly understood terminology remains, and we ask that you follow a procedure we have successfully employed with other sponsors in the past.

> Because terminology for adverse events is often idiosyncratic, it will be necessary to construct a glossary so that related events may be enumerated under a single term. For example, motor restlessness, hyperactivity, wandering, and pacing may all be subsumed under the term agitation. Clustering of related events is intended to produce

a list of untoward events of reasonable length. After you have constructed such a glossary, we suggest that you provide us an opportunity to review it with you. Once we have agreed on the terms, the comparative incidence of each glossary term within each study for each treatment should be enumerated in tabular form. Generally, pooling across all studies is inappropriate because patients were studied at different doses, for various lengths of time, under variable conditions. It is advisable, however, to pool data from groups of studies planned and conducted according to common protocols. For example, the studies providing evidence of efficacy in this application may serve as the source of adverse reaction data for display in this section of the labeling.

Please use the text which follows exactly.]

There was no significant difference in the incidence of abnormalities in laboratory values in patients receiving either bupropion or placebo during the clinical trials except for elevations of blood glucose and LDH to abnormal levels, both of which occurred in approximately five percent of patients treated with bupropion.

DRUG ABUSE AND DEPENDENCE:

Studies in rodents have shown that bupropion exhibits some pharmacologic actions common to psychostimulants, including increases in locomotor activity and the production of stereotyped behavior and anorexia. Bupropion showed effects similar to amphetamine in several animal models of schedule-controlled behavior, and a drug discrimination study in rats showed stimulus generalization between bupropion and amphetamine and other psychostimulants. Monkeys were shown to self-administer bupropion intravenously. In contrast, 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 but provided no appreciable evidence of a psychostimulant effect. Tolerance to the antidepressant action of bupropion did not develop, and phenomena thought to constitute an amphetamine withdrawal syndrome were not seen during the post-treatment period. In a population of individuals experienced with drugs of abuse, a dose of 400 mg produced a modest elevation over placebo responses 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.

OVERDOSAGE:

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.

There has been very limited clinical experience with overdosage of bupropion. Three patients ingested 2000-3000 mg and recovered without incident.

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. 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 at present there is no clinical experience with lavage following an overdose of bupropion, it is likely to be of benefit within the first 12 hours post-dose 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 as to their effects in the management of Wellbutrin overdose. Because diffusion of bupropion 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:

Dosage should be initiated at a low level and increased gradually, noting the clinical response and any evidence of intolerance. Bupropion should be given on a t.i.d. basis, preferably with intervals of at least 6 hours between successive doses. Once and twice a day dosing has not been evaluated. It is likely that many patients will experience increased agitation and signs of motor restlessness and insomnia during the first several days of treatment. These untoward consequences may be managed by a more gradual escalation of dose or by the transitory administration of a sedative hypnotic. The latter adjunctive treatment need not be continued beyond the first week as tolerance to these activating effects of bupropion appears to develop in a few days.

[To Firm: Please develop the evidence and logic behind the dosage recommendations given in your draft labeling. We find no basis for your recommendation that mild to moderate depression be treated with lower doses of bupropion than severe depression. There may be little need to make such a distinction if dose escalation is titrated.

Because several of the patients who convulsed at 600 or 750 mg daily doses weighed less than 120 lb, we recommend that the upper limit of dose be stated "not to exceed 5 mg/lb (11 mg/kg)."

In any case, please provide a full explanation of the basis of your dosing recommendations.]

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. In clinical trials, older adults tolerated bupropion at the doses listed above. Usage of an initial dose of 300 mg/day is recommended, with adjustments according to effect.

Maintenance:

The lowest dose which maintains remission is recommended. This is likely to be within the range of 300-450 mg/day for most patients. While it is generally recommended that a course of antidepressant drug treatment should continue for several months, there has been no systematic evaluation of the efficacy of bupropion for a period beyond four weeks.

HOW SUPPLIED:

Wellbutrin (bupropion hydrochloride) tablets are supplied as follows:

50 mg (white) round biconvex tablets coded "WELLBUTRIN" and "50" - bottles of 100 (NDC 0081-0176-55)

75 mg (yellow-gold) round biconvex tablets coded "WELLBUTRIN" and "75" - bottles of 100 (NDC 0081-0177-55)

100 mg (red) round biconvex tablets coded "WELLBUTRIN" and "100" - bottles of 100 (NDC 0081-0178-55)

Store at 15°-30°C (59°-86°F).

End of Labeling Commentary

Our announced intention to approve your application is based upon your acceptance of the conditions enumerated in this letter. In particular, the development of satisfactory labeling and the submission of a fully documented and comprehensive Safety Update remain as major projects.

The Safety Update should contain any new data bearing on the safe use of Wellbutrin. Given the need for an extensive revision of the ADR section of the labeling, it would make sense to include the basis for ADR tabulations (e.g., glossary of terms, data enumeration, etc.) as part of the Safety Update.

If additional information relating to the safety or effectiveness of this drug becomes available before we receive the revised labeling, further revision of the labeling may be required.

We would appreciate your submitting copies of the introductory promotional material which is proposed for this product. Copies should be submitted with a cover letter to both the Division of Neuropharmacological Drug Products and the Division of Drug Advertising and Labeling. Please submit all proposed materials in draft or mock-up form, not final printed form. Also, please do not use Form FD-2253 for this submission; this form is for routine use, not proposed materials.

Please submit twelve copies of the printed labels and other labeling.

In addition, it is required that information and case reports of adverse reactions not previously submitted to your IND or NDA be provided.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Sincerely yours,

R Temple 12/31/84

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics

cc:
Orig. NDA 18-644
ATL-DO
HFN-100
HFN-120
HFN-120/Leber working copy October 23, 1984; revised 11/27/84
Hayes (revised 11/28/84)/Davis A Hayes 11-29-84
Shultz/Zinsitz
Contrera/Rosloff
DeCicco
HFN-713/Stein
rd/mlm/10/17/84/10/23/84
ft/mlm/10/26/84
ft/mb/11/29/84
DOC 1513C

REVIEW AND EVALUATION OF CLINICAL DATA
NDA 18-644

Sponsor: Burroughs Wellcome

Drug: Wellbutrin (bupropion)

Category: antidepressant

Date of Submission: May 1, 1985

Date of Review: May 16, 1985

This is five volume submission. The first volume is a response to our approvable letter and includes revised labeling. The major difference between the revised labeling and the FDA proposed labeling is in the Indications section and Dosage section. A complete review of the labeling follows the safety update below. The remaining volumes contain the safety update.

Safety Update.

The following areas will be discussed. The material is taken from volumes 9.2 though 9.5.

1. Data Base
2. Serious Events
   a. Deaths (primarily suicides) and bupropion overdoses
   b. Seizures
   c. Terminations (adverse effects and other reasons)
   d. Other (pregnancies)]
3. Lab tests, vital signs, weight, EKG
4. Adverse Events
5. Conclusions

1. Data Base

The data base now includes 2,398 subjects who were given bupropion (1482 females and 1157 males.) In the original NDA submission, there were 1315 subjects exposed to bupropion (735 females and 580 males). Occasionally, the number of exposures (2642) and not the number of patients form the basis for tables.

A number of tables were provided to describe the data base. A listing of each study, the type of study and the number of patients enrolled is provided by the sponsor. There is also a listing of all the investigators by study. In addition, there is a breakdown of the number of patients by dosage (less than or equal 600 mg and greater than 600 mg) for patients and volunteers separately for the NDA and for the total data base (NDA and post NDA). A total of 2182 unique individuals received bupropion up to 600 mg/day and 213 received doses greater than 600 mg/day. Case records for the approximately 1100 new patients have not been submitted. It is noteworthy that study 39, a multicenter humanitarian treatment protocol, contributed 23% of the total patient exposures.

The submission also contains a table of the number of patients in each age category by study for males and females separately and a table of age and sex for the NDA and for the total data base. Fifty-eight percent of patients were females and the median age for all subjects was between 40 and 50 years of age. Nineteen percent (428 patients) were 60 years of age or older.

There is a table of the number of patients for each dosage and duration for the total data base and for the NDA. The highest number of patients received bupropion for 1-4 weeks followed by 5-8 weeks, 13-26 weeks (286 patients), 9-12 weeks (169 patients), 27-52 weeks (147 patients), 53-78 weeks (101 patients) and out to 104 weeks (26 patients).

There are some studies ongoing. The sponsor has included in this submission all adverse experiences "of substantial clinical significance" reported to them through April, 1985.

2. Serious Events

a. Deaths (primarily suicides) & Bupropion Overdoses

Three tables with information on bupropion overdoses, deaths, and suicide attempts were provided by the sponsor and these are included in the following pages (Tables 1, 2, & 3). Table 1 describes 14 deaths which occurred in patients while on bupropion. (Nine of the deaths occurred on the "humanitarian" protocol.) Nine were suicides. None of the deaths involved bupropion directly. Table 2 describes 13 suicide attempts with bupropion (overdoses from 850-9000 mg) none of which had sequellae. The patient who took 9000 mg had a seizure and sinus tachycardia but she had also ingested tranylcypromine. Table 3 details suicides and suicide attempts by means other than bupropion. (This table overlaps partially with Table 1.) There were 14 suicide attempts and 9 deaths. Again, 13 of the 23 cases were from the humantarian protocol.

TABLE 1 (sponsor . 17)

Patient Deaths Which Occurred While Taking Bupropion

Study	Investigator	Pt #	Sex	Age	Wt (kg)	Race	Daily dose (mg) at time of event	Duration on Bupropion		Related to Bupropion?	Cause of Death/Comments
								Total Days	Days on Dose at which Event Occurred		
16-001		69	M	23	87	C	0	7	5 days post-dose	No	Suicide by asphyxiation. Patient had history of prior suicide attempt
17-005		6C	M	80	66	C	250	149	60	No	Septic shock following development of a perforated ulcer and peritonitis
29-001		1	F	40	59	C	0	28	4 days post-dose	No	Suicide by overdose of desmopressine, amount unknown
39-001		1026	M	53	81	C	600	14	9	No	Suicide by gunshot
39-002		03	M	52	83	C	600	19	13	No	Suicide by gunshot. Prior suicide attempts though not suicidal at study entry
39-022		103H	F	68	59	C	600	656	57	No	Suicide from overdose of Tomal. Patient had made previous suicide attempt with overdose of Tomal and Halmane
39-027		1	F	34	54	C	300	195	156	No	Patient went into cardiac arrest the evening following her first chemotherapy treatment for Hodgkin's Disease
39-047		1304-A	F	49	54	C	400	44	13	No	Suicide from overdose of barbiturate, benzodiazepines, Quaaludes, and alcohol, amount unknown
39-047		2529	M	55	95	C	500	343	239	No	Death from metastatic cancer, patient had terminal pre-existing medical condition prior to administration of WELLBUTRIN
39-048		9	F	72	62	C	400	27	20	No	Patient had a brain stem cerebrovascular accident with respiratory arrest and subsequent death
39-048		85	M	53	77	C	0	120	6-21 days post dose	No	Suicide by gunshot. Unknown how long patient off bupropion. Estimated 1-3 weeks post-treatment
39-086		5	M	46	82	C	0	75	2 days post-dose	No	Overdose with propranolol. Patient stopped bupropion (300 mg/day) two days prior to overdose. Medical examiner's final anatomic diagnoses: 1) acute propranolol poisoning, 2) pulmonary congestion and edema
40-001		32	M	34	83	C	Tapering off 300	73	4	No	Suicide by hanging. Patient was schizophrenic with depression. Had made suicide attempt prior to study entry (was not suicidal when enrolled)
Treat-ment France		---	F	[illegible]	..	..	300	...	---		Details unavailable at time of this submission

P85/1126

LION 401 MADE IN U.S.A.

TABLE 2 (Sponsor's Table 18)

Suicide Attempts by Bupropion Overdose

ody	Investigator	Pt #	Sex	Age	Wt (kg)	Race	Dosage of Bupropion Ingested		Other Chemicals Ingested (Rx = prescribed)	Side Effects	Recovery	Comments
							mg	mg/kg				
001		70	F	35	65	C	900	14	None	None	No sequelae	Self treated by emesis
001		17	F	27	53	C	3000	57	75 300 mg Dalmane	Nausea, vomiting, headache, drowsiness	No sequelae	Drowsiness possibly related to Dalmane
009		07	F	22	52	C	2200	42	None	Dry mouth, lethargy, possible visual hallucinations, serum K⁺ = 3 5, nonspecific T wave changes	No sequelae	History of multiple drug overdose
001		36	F	44	53	C	1700	32	Unknown	Unknown	Unknown	None
011		01	F	53	79	C	2400	30	140 mg Tranxene	Hostility, slurred speech, dizziness, grogginess, mild sinus tachycardia, serum K⁺ = 2 7	No sequelae	None
002		18	M	39	66	C	850 2000	13	400 ml 12 5% ethanol	Questionable seizure, exhaustible horizontal nystagmus	No sequelae	None
002		222	M	43	74	C	2000	27	None	Mild sinus tachycardia, mild coarse tremor, drowsiness, nonspecific T-wave changes	No sequelae, returned treatment	None
032		01	[illegible]	...	81	C	1250	15	None	Nausea, vomiting, drowsiness	No sequelae, returned treatment	None
036		10	F	57	98	C	9000	92	300 mg tranylcypromine, unknown quantity acetylsalicylic acid	Sinus tachycardia, tonic-clonic seizure, serum K⁺ = 3 3, vomiting	Initially semi-comatose (due to Valium), recovered subsequently and returned treatment	Treatment for overdose-10 mg Valium, I V , 200 mg Dilantin, I V
054		02	F	27	50	C	4200	84	--50-100 tablets acetaminophen	None	No sequelae	None
071		18	F	29	53	C	2250	42	Rx 10 mg/1 days Prolixin Decanoate	Dry mouth, vomiting, feeling cold	No sequelae	None
079		08	F	39	82	C	1050	13	ethanol Rx 6 mg/day Xanax, 5 10 mg/day Provera	None	No sequelae	None
123		01-957	F	26	61	C	3000	49	None	Experienced a high feeling temporary amnesia	No sequelae	History of phenelzine overdose

LION 361 MADE IN

...e 3 (Sponsor's Table 19)

Suicides/Attempted Suicides by Means Other Than Bupropion Overdose

Study	Investigator	Pt #	Sex	Age	Wt (kg)	Race	Daily dose (mg) at time of event	Duration on Bupropion		Event	Outcome
								Total Days	Days on Dose at which Event Occurred		
[illegible] 001		33	F	24	50	C	[illegible]	21	21	Overdose of approximately 6 Mandrax and 10 Anadin tablets	Survival
15 001		40	F	33	59	C	450	17	10	Overdose of 20 grams/day of hydrate	Survival
16 001		35	F	50	54	C	[illegible]	3	2	Overdose of Bupropion, amount unknown	Survival
16 001		69	M	23	87	C	0	7	5 days post dose	Suicide by asphyxiation. Patient had history of a prior suicide attempt	Death
17 001		8	M	25	68	C	400	8	2	Slashed wrists	Survival
26 01A		43	M	39	87	C	500	426	9	Overdose involving an unknown quantity of alcohol and up to 700 mg of diazepam, ingested during recreational abuse	Survival
26 018		21	M	52	92	C	550	88	28	Patient began drinking heavily and attempted to slit his wrists. Lacerations superficial	Survival
29 001		1	F	40	59	C	0	28	4 days post-dose	Overdose of desmopressome, amount unknown	Death
29 006		56	F	51	45	M	150	11	11	Patient slipped from ward and stabbed herself in the stomach	Survival
39 001		1026	M	53	81	C	600	14	9	Suicide by gunshot	Death
39 001		42	F	51	54	C	300	213	20	Overdose with kerosene	Survival
39 001		167	F	26	...	C	225	16	6	Overdose with Xanax, Mellaril and Restoril, amounts unknown	Survival
39 002		03	M	52	83	C	600	19	13	Suicide by gunshot. Prior suicide attempts though not suicidal at study entry	Death
39 022		103H	F	68	59	C	600	656	57	Overdose of Tuinal, amount unknown, prior overdose of Tuinal and Dalmane	Death
39 029		...	F	...	...	...	450	...	5	Overdose of 100 mg Valium (additional demographic/history unavailable at time of this submission)	Survival
39 043		38003	M	21	101	C	600	36	1	Slashed wrists	Survival
39 047		1304 A	F	49	54	C	400	44	13	Overdose of barbiturates, benzodiazepines, Quaaludes and alcohol, amounts unknown	Death
39 048		85	M	53	77	C	0	120	6 21 days post dose	Suicide by gunshot. Unknown how long patient off bupropion, estimated 1-2 weeks post-treatment	Death
39 052		17	F	38	78	C	600	480	129	Slashed wrists	Survival
39 063		45	F	36	87	C	400	71	71	Overdose of diazepam, amount unknown, cut wrists superficially	Survival
39 086		5	M	46	82	C	0	75	2 days post-dose	Overdose of propranolol, amount unknown	Death
39 120		07	F	27	45	C	450	109	6	Overdose of Halcion, Ativan, Macrodantin and Axsym, amounts unknown	Survival
40 001		32	M	38	83	C	Tapering off 300	73	4	Suicide by hanging. Patient was in hospital with depression and made suicide attempt prior to study entry (was not suicidal when enrolled)	Death

[illegible]1.'6

Comment. A rather nigh number of deaths and overdoses have occurred during the premarketing program. However, these did not occur in the controlled trials but during the humanitarian protocol, an open and possibly less well supervised situation.

In summary, bupropion overdoses (850 - 9000 mg) did not result in death. In addition, bupropion did not appear to be directly implicated in the deaths which occurred in patients while on the trials.

b. Seizures

Extensive information was provided on the 26 cases of seizure from the total data base. Table 4 (taken from the sponsor's submission) gives the details on each case. Table 5 (taken from the sponsor's submission) shows the breakdown by dosages and the presence or absence of predisposing factors. The risk is dose dependent in patients without predisposing factors with an escalating incidence above 450 mg daily.

The sponsor has also provided graphs for each individual subject showing the dose, duration of treatment and time of seizure. The sponsor examined the relationship between seizures and duration of treatment. In this analysis, they excluded four patients (brain cancer, overdose, cerebral palsy, and alcohol withdrawal) and found that 9/22 seizures occurred within the initial 1-2 days following a dosage increase, and 18/22 occurred within the first three weeks of a dosage escalation. Seizures also occurred, occasionally, with drug initiation).

Comment. Table 5 is misleading. It combines the one seizure at 9000 mg with the six which occurred at doses from 600 - 900 mg. Since this table also appears in the labeling, I would suggest that the category be changed by moving the one patient at 9000 mg to a separate line. In addition, there is no statement in the labeling indicating the seizures generally follow dosage increases.

c. Terminations

All raw data forms (? case report forms) were reviewed by the sponsor to identify terminations. In the introduction (page 8), a termination was defined as occurring whenever a patient discontinued more than one day prior to study completion. However, this would not apply to the open ended studies (long-term continuation and humantarian protocols). On page 15, it states that subjects from these protocols were included as a termination only if toxicity occurred.

TABLE 4 (Sponsor's Table 20)

Seizures Which Occurred During Bupropion Treatment

Study	Investigator	Vol./Pt. #	Sex	Age	Wt. (kg)	Dose at which seizure occurred	Days on dose at which seizure occurred
01A		1	M	36	66	800	4
01A		8	M	24	67	800	2
09-002		35	M	30	73	900	6
14-001		76	F	38	66	600	1
19-001		3	F	25	50	600	2
21-001		48	M	48	70	450	8
21-001		51	M	31	67	600	2
22-003		2	M	37	97	600	2
23-002		1	F	51	50	600	1
28-001		151	M	35	74	700	40
28-002		203	F	26	66	600	1
34-001		11	M	26	52	750	2
39-001		14H	F	56	53	100	55
39-001		117H	F	37	51	600	20
39-001		161	F	46	46	450	1
39-028		30	F	45	50	700	63
39-036		10	F	57	99	9000	---
39-048		56	F	38	75	600	28
39-052		43	F	31	71	300	18
39-063		45	F	36	87	400	---
39-098		174	F	32	78	600	14
39-098		115810	F	24	63	550	67
39-105		30034	F	45	56	600	14
54-001		4	M	59	66	200	1
55-001		90	F	38	59	600	20
UK-SA*		7	F	29	78	450	7

* US-SA is a study conducted in South Africa by the Wellcome Research Laboratories in England (clinical trial material manufactured in U K.)

Table 5 (Sponsor's Table 21)

Incidence of Seizures During Bupropion Treatment by Dose

Bupropion Dose Mg/Day	# Total Seizures[a]/ # Patients (%)	Seizures in Patients Without Predisposing Factors (%)	PREDISPOSING FACTORS	
			# Seizure Patients with History of Head Trauma or Seizure[b]	# Seizure Patients with Concomitant Agents Which Lower Seizure Threshold[c]
<450	4/2398 (0 17)	0/2398 (0.00)	3/4	2/4
450	3/1281 (0 23)	2/1281 (0.16)	1/3	0/3
>450-600	12/527 (2 28)	7/527 (1.33)	2/12	3/12
>600-9000[d]	7/213 (3 29)	4/213 (1 88)	0/7	3/7

[a] Patient 39-002/18 experienced a questionable seizure subsequent to an overdose of bupropion and is excluded from all seizure analyses.

[b] Patients 21-001/48, 22-003/2, 28-002/203, 39-001/14H, 39-052/43, 39-063/45

[c] Patients 28-001/151, 34-001/11, 39-001/117H, 39-036/10, 39-048/56, 39-052/43, 54-001/4, 55-001/390

[d] >600-9000 mg is outside recommended dosing range

The number and percent of patients dropped from "all clinical trials" and the reasons were as follows:

		Number Dropped				
	Number Treated	Toxicity	*Therapy Failure	*Clin. Events	*Other	Total Dropped
Bupropion	1734	262 (10.5)	231 (31.3)	23 (3)	298 (40)	737 (43)
Imipramine	48	3 (6.3)	11 (29.7)	3 (8)	20 (54)	37 (77)
Amitriptyline	181	24 (13.3)	15 (16.7)	2 (2)	49 (54)	90 (50)
Doxepin	48	12 (25)	10 (29.4)	2 (6)	10 (29)	34 (71)
Placebo	282	12 (4.3)	83 (55.7)	4 (3)	55 (37)	149 (53)

* Numbers and percent for bupropion in these columns do not include the long-term continuation protocol and the humantarian protocol.

The number of dropouts for toxicity and therapeutic failure in the controlled trials are given in Table 6 taken from the sponsor's submission.

A listing of the specific adverse effects resulting in discontinuation are given in Table 7 (taken from the sponsor's submission. It is not clear why the table does not include the 12 new seizures. What else is excluded? (The total number of patients dropped agrees with the table on page 6.)

Comment. The number of patients dropped from the studies is high. There are some discrepancies in the numbers of patients examined which I am unable to clarify.

TABLE 6 (Sponsor's Table 15)

Patient Discontinuation in Controlled Clinical Trials

Placebo-Controlled Clinical Trials

Number of Patients Treated			Number of Patient Discontinuations (%)			
			Ther. Failure		Toxicity	
Study	PBO	BUP	PBO	BUP	PBO	BUP
06	27	55	8 (29.6)	8 (14.5)	0 (0.0)	2 (9.1)
08	24	42	12 (50.0)	9 (21.4)	0 (0.0)	5 (11.9)
14	40	77	18 (45.0)	17 (22.1)	2 (5.0)	8 (10.4)
09	52	77	17 (32.7)	12 (15.6)	1 (1.9)	14 (18.2)
TOTAL	143	251	55 (38.5)	46 (18.3)	3 (2.1)	29 (11.6)

Amitriptyline-Controlled Clinical Trials

Number of Patients Treated			Number of Patient Discontinuations (%)			
			Ther. Failure		Toxicity	
Study	AMI	BUP	AMI	BUP	AMI	BUP
15	62	150	7 (11.3)	17 (11.3)	5 (8.1)	13 (8.7)
21	82	92	7 (8.5)	12 (13.0)	16 (19.5)	14 (15.2)
TOTAL	144	242	14 (9.7)	29 (12.0)	21 (14.6)	27 (11.2)

Table 7 (Sponsor's Table 16)

Number and Percent of Patients/Volunteers Discontinued Due to Adverse Experiences

NON-COSTART TERMS

BODY SYSTEM	PREFERRED TERM	N	% TOTAL BUPROPION PATIENTS
Cardiovascular	Cardiac Arrhythmias	3	0.11
	Chest Pain	2	0.07
	Dizziness	7	0.26
	EKG Abnormality	2	0.07
	Hypertension	3	0.11
	Hypotension	3	0.11
CV SUBTOTAL		20	0.75
Dermatologic	Pruritus	7	0.26
	Rash/Lesion	31	1.16
DERM SUBTOTAL		38	1.42
Gastrointestinal	Anorexia	5	0.19
	Appetite Increase	1	0.04
	Colitis	1	0.04
	Constipation	1	0.04
	Diarrhea	1	0.04
	Liver Damage/Jaundice	1	0 04
	Nausea/Vomiting	38	1.42
	Upset Stomach	6	0.22
	Upset Stomach/Gas	2	0.07
	Weight Gain	1	0.04
GI SUBTOTAL		57	2.13
Genitourinary	Impotence	1	0.04
	Painful Ejaculation	1	0.04
	Urinary Retention	5	0.19
GU SUBTOTAL		7	0.26
Musculoskeletal	Arthritis	1	0.04

Table 7 (Cont.)

BODY SYSTEM	PREFERRED TERM	N	% TOTAL BUPROPION PATIENTS
Neurological	Ataxia/Incoordination	2	0.07
	Autonomic Disturbance (Salivary Flow)	2	0.07
	Extrapyramidal Abnormalities	3	0.11
	Headache/Migraine	9	0.34
	Myoclonus	3	0.11
	Seizure*	14	0.52
	Sleep Disturbance (Impaired Quality)	1	0 04
	Sleep Disturbance (Insomnia)	8	0 30
	Tremor	4	0.15
NEUROLOG SUBTOTAL		46	1.72
Neuropsychiatric	Abnormal Mental Status	12	0.45
	Cognitive Impairment	1	0.04
	Cognitive Impairment (Attention)	1	0.04
	Delirium	11	0.41
	Mood Disturbance (Agitation)	44	1.65
	Mood Disturbance (Anxiety)	4	0.15
	Mood Disturbance (Hostility)	3	0.11
	Mood Disturbance (Mania)	3	0.11
NEUROPSYCH SUBTOTAL		79	2.96
Nonspecific	Fatigue	3	0.11
Oral Complaints	Glossitis	1	0.04
	Stomatitis	3	0.11
ORAL SUBTOTAL		4	0.15
Respiratory	Upper Respiratory Complaint	1	0.04
Special Senses	Auditory Disturbances	5	0.19
	Visual Disturbances	3	0.11
SS SUBTOTAL		8	0.30
TOTAL		264	9.88†

*Does not include 12 seizures for whom data was not available at the time of the data base cut-off. Details of all seizures reported through April, 1985 are discussed in Section II F

†[illegible] based on combined patient and volunteer discontinuations

3. Vital Signs, Weights, Laboratory Tests

a. Vital Signs

A summary table of vital sign changes (systolic and diastolic blood pressure, supine and standing; pulse rate, supine and standing; and respiratory rate) and a table of changes as a function of baseline measures separately for each drug were provided by the sponsor. Inspection of the tables indicated that there was an overall tendency for blood pressure to decrease (systolic more frequently than diastolic) and it was slightly more marked in patients with higher initial measures. At the same time, there was a slight increase in pulse rate overall, with greater increases in patients with lower baseline pulse rates. There were also decreases in pulse rates in patients with higher initial rates. There did not appear to be any consistent changes in respiration rate.

b Weight

Bupropion produced weight loss in more patients than weight gains. The weight losses tended to occur more frequently in patients with higher initial weights. The greatest number of losses were in the 1-5 pound category (114/341 patients) followed by the 6-10 pound category (77/341 patients). Amitriptyline produced more weight gains in the same two categories.

c. Laboratory Data

No information was provided in the submission.

d. ECG Data

No information was provided in the submission.

4. Adverse Events

The sponsor provided a table of adverse events using COSTART terms giving the percent of patients reporting each event for the NDA and for the NDA-plus-post-NDA patients. Its appears that this table was developed to demonstrate whether there have been new serious effects or increases in frequency of effects since the NDA was submitted. There did not appear to be significant differences between the NDA and NDA-plus-post-NDA percent occurrences. However, it is difficult to evaluate, by inspection, changes in percent of occurrence. This table (Table 8) is included on the following pages. For some reason, the numbers of subjects in the total group is less than the sponsor indicated were used as the data base.

TABLE 8 (Sponsor's Table 10)

OBSERVED ADVERSE EXPERIENCES - PERCENT OF PATIENTS/VOLUNTEERS REPORTING AND NUMBER REPORTED PER PATIENT

	NDA PLUS POST-NDA (N = 2313; 1296 F, 1017 M)		NDA (N = 1315; 735 F, 580 M)	
Adverse Experience	% Subjects	# Reports Per Subject	% Subjects	# Reports Per Subject
ABSCESS	0.17	1.3	0.30	1.3
ACNE	0.35	3.0	0.00	0.0
AGITATION	28.92	2.0	27.45	2.0
AKATHISIA	3.03	1.7	2.59	1.8
AKINESIA	0.22	1.2	0.38	1.2
ALLERG REACT	0.04	2.0	0.00	0.0
ALOPECIA	0.32	2.2	0.15	1.0
ALTERED HORMON LEVEL	0.04	2.0	0.00	0.0
AMBLYOPIA	10.68	2.2	11.63	2.0
AMNESIA	0.69	1.8	0.84	1.3
ANOREXIA	18.50	1.9	18.40	1.9
ANXIETY	1.90	1.7	2.05	1.7
APPETITE INC	5.62	1.8	5.40	1.4
ARRHYTHMIA	0.09	1.0	0.08	1.0
ARTHRALGIA	4.02	1.7	3.50	1.6
ARTHRITIS	0.04	7.0	0.08	7.0
ASTHENIA	12.62	1.9	9.89	2.0
ATAXIA	0.91	1.3	0.61	1.0
BRONCHOSPASM	0.13	1.3	0.15	1.0
CHILLS	1.38	1.4	0.68	1.0
CNS DEPRESS	0.04	3.0	0.08	3.0
CNS STIMULAT	0.04	1.0	0.08	1.0
CONFUS	5.19	1.8	3.73	1.8
CONJUNCTIVITIS	0.09	1.0	0.08	1.0
CONSTIP	12.36	2.1	12.24	1.9
CONVULS	0.52	1.0	0.53	1.0
COORDINAT ABNORM	1.69	1.4	0.91	1.3
COUGH INC	0.30	1.1	0.15	1.0
CYSTITIS	0.09	1.0	0.00	0.0
DEAF TRANS PART	0.09	1.0	0.00	0.0
DELUSIONS	0.86	1.2	0.15	3.0
DEPERSONAL	0.26	1.2	0.46	1.2
DEPRESSION	1.73	1.6	2.81	1.6
DIARRHEA	3.11	1.4	1.90	1.2
DIZZINESS	8.99	1.6	9.66	1.6
DREAM ABNORM	3.72	1.9	1.75	1.6
DRY MOUTH	17.03	2.0	16.65	2.0
DYSARTHRIA	0.09	1.5	0.00	0.0
DYSKINESIA	0.73	2.1	0.76	2.1
DYSMENORRHEA	0.08	1.0	0.00	0.0
DYSPEPSIA	3.33	1.4	1.83	1.1
DYSPHAGIA	0.17	1.3	0.23	1.0
DYSPNEA	0.17	1.0	0.08	1.0
DYSTONIA	0.48	1.5	0.38	1.2
ECCHYMOSIS	0.17	1.0	0.15	1.0
ECG ABNORM	0.09	3.5	0.15	3.5
ECZEMA	0.04	1.0	0.00	0.0
EDEMA	0.78	1.5	0.30	1.0

TABLE 8. (CONT'D.)

OBSERVED ADVERSE EXPERIENCES - PERCENT OF PATIENTS/VOLUNTEERS REPORTING AND NUMBER REPORTED PER PATIENT

	NDA PLUS POST-NDA (N = 2313; 1296 F, 1017 M)		NDA (N = 1315; 735 F, 580 M)	
Adverse Experience	% Subjects	# Reports Per Subject	% Subjects	# Reports Per Subject
EDEMA TONGUE	0.04	1.0	0.00	0.0
EEG ABNORM	0.04	1.0	0.00	0.0
EJACULAT ABNORM	0.10	2.0	0.00	0.0
EMOTION LABIL	3.20	1.7	2.59	1.5
EPISTAXIS	0.04	1.0	0.08	1.0
ERUCTAT	0.09	1.0	0.00	0.0
EUPHORIA	1.73	1.7	1.22	1.8
EYE DISORDER	0.17	1.0	0.23	1.0
FACIES MASK	0.17	2.8	0.30	2.6
FECES DISCOLOR	0.04	1.0	0.08	1.0
FEVER	0.13	1.7	0.00	0.0
FEVER CHILLS	0.13	2.7	0.23	2.7
FLATUL	0.65	1.5	0.61	1.0
GALT ABNORM	0.09	1.0	0.15	1.0
GI DISORDER	0.04	1.0	0.00	0.0
GINGIVITIS	0.04	2.0	0.08	2.0
GLOSSITIS	0.04	1.0	0.00	0.0
GLYCOSURIA	0.04	1.0	0.08	1.0
GYNECOMASTIA	0.86	1.9	0.38	1.8
HALLUCIN	1.56	1.7	1.52	1.7
HEADACHE	16.99	1.9	16.50	1.7
HEMORR GUM	0.04	1.0	0.08	1.0
HOSTILITY	0.13	1.0	0.15	1.0
HYPERKINESIA	0.82	1.8	1.44	1.8
HYPERTENS	0.61	1.6	0.76	1.8
HYPERTONIA	1.04	2.3	1.14	2.6
HYPERVENTIL	0.13	1.0	0.15	1.0
HYPOKINESIA	0.61	1.1	0.99	1.2
HYPOTENS	0.26	1.0	0.15	1.0
HYPOTENS POST	0.13	2.0	0.00	0.0
IMPOTENCE	5.06	2.7	5.70	2.7
INFECT	0.04	2.0	0.00	0.0
INFECT URIN TRACT	0.09	1.0	0.00	0.0
INSOMNIA	21.79	2.0	18.48	2.0
JAUNDICE	0.04	1.0	0.00	0.0
LARYNGITIS	0.17	1.5	0.15	1.5
LEUKEMIA CHRON LYMPHO	0.04	1.0	0.00	0.0
LEUKORRHEA	0.08	1.0	0.00	0.0
LIBIDO DECREASE	2.59	2.2	0.00	0.0
LIBIDO INCREASE	1.30	1.8	0.84	1.5
LIVER FUNC ABNORM	0.04	1.0	0.00	0.0
LYMPHADENO	0.04	1.0	0.00	0.0
MALAISE	0.13	1.0	0.00	0.0
MANIC REACT	0.22	1.0	0.23	1.0
MENOPAUSE	0.08	7.0	0.00	0.0
MENS DISORDER	3.32	1.8	2.59	1.4
MONILIA VAGINA	0.08	1.0	0.00	0.0
MS/MUS	0.04	1.0	0.00	0.0
MYALGIA	0.35	1.0	0.30	1.0

TABLE 8 (CONT'D.)

OBSERVED ADVERSE EXPERIENCES - PERCENT OF PATIENTS/VOLUNTEERS

REPORTING AND NUMBER REPORTED PER PATIENT

	NDA PLUS POST-NDA (N = 2313; 1296 F, 1017 M)		NDA (N = 1315; 735 F, 580 M)	
Adverse Experience	% Subjects	# Reports Per Subject	% Subjects	# Reports Per Subject
MYDRIASIS	0.04	1.0	0.08	1.0
MYOCLONUS	0.99	1.3	0.91	1.1
NAUSEA VOMIT	10.55	1.6	9.51	1.7
NERVOUSNESS	0.73	1.2	0.68	1.0
NEUROPATHY	0.04	1.0	0.08	1.0
NEUROSIS	0.17	2.0	0.15	2.0
NOCTURIA	1.34	2.0	1.52	2.0
OTITIS MED	0.04	1.0	0.08	1.0
OVAR DISORDER	0.04	1.0	0.00	0.0
OVERDOSE INTENT	0.04	1.0	0.00	0.0
PAIN	2.72	1.5	1.83	1.3
PAIN ABDO	0.82	1.3	0.61	1.1
PAIN BACK	0.26	1.5	0.23	1.7
PAIN BREAST	0.09	1.0	0.08	1.0
PAIN CHEST	0.61	1.2	0.53	1.3
PAIN EAR	0.09	1.0	0.1	1.0
PAIN EYE	0.04	1.0	0.00	0.0
PAIN NECK	0.13	1.3	0.15	1.0
PAIN TOOTH	0.22	1.2	0.15	1.0
PALLOR	0.04	1.0	0.08	1.0
PALPITAT	4.50	1.6	4.18	1.5
PARANOID REACT	0.04	1.0	0.08	1.0
PARESTHESIA	3.24	2.0	2.59	1.5
PENIS DISORDER	0.10	1.0	0.17	1.0
PERSON DISORDER	2.03	1.6	1.44	1.4
PETECHIA	0.43	1.1	0.00	0.0
PHARYNGITIS	0.22	1.2	0.30	1.0
PHLEBITIS	0.04	1.0	0.00	0.0
PHOTOPHOBIA	0.04	2.0	0.08	2.0
PROCTITIS	0.04	1.0	0.00	0.0
PRURITUS	2.38	1.5	1.52	1.4
PSYCHOSIS	0.30	2.7	0.53	2.7
RASH	2.72	1.4	2.74	1.4
RASH MAC PAP	0.04	1.0	0.00	0.0
RASH PHOTO	0.35	2.4	0.15	3.0
RESPIRAT DISORDER	0.17	1.0	0.08	1.0
RHINITIS	0.69	1.1	0.99	1.1
SALIVA INCREASE	0.78	1.4	0.76	1.5
SINUSITIS	0.13	1.0	0.08	1.0
SKIN DRY	0.09	1.0	0.00	0.0
SOMNOLENCE	10.51	1.6	11.18	1.6
SPEECH DISORDER	0.22	1.0	0.23	1.0
STOMATITIS	0.78	1.2	0.30	1.0
SWEAT	7.26	1.8	6.69	1.8
SYNCOPE	0.61	1.2	0.15	1.0
TACHYCARDIA	0.73	1.4	1.22	1.4
TASTE PERVERS	3.03	1.6	2.36	1.4
THINKING ABNORM	6.79	1.9	4.03	1.6
THIRST	0.13	1.0	0.15	1.0

LION 301 MADE IN

TABLE 8 (CONT'D.)

OBSERVED ADVERSE EXPERIENCES - PERCENT OF PATIENTS/VOLUNTEERS REPORTING AND NUMBER REPORTED PER PATIENT

	NDA PLUS POST-NDA (N = 2313; 1296 F, 1017 M)		NDA (N = 1315; 735 F, 580 M)	
Adverse Experience	% Subjects	# Reports Per Subject	% Subjects	# Reports Per Subject
TINNITUS	2.98	1.6	2.21	1.5
TREMOR	8.73	2.0	7.83	1.9
TRISMUS	0.09	1.5	0.15	1.5
TWITCH	0.17	1.0	0.23	1.0
URIN FREQUENCY	2.85	1.6	1.67	1.7
URIN INCONTIN	0.04	1.0	0.00	0.0
URIN RETENT	1.73	1.9	0.91	1.5
URTICARIA	1.30	1.3	0.91	1.3
VAGINITIS	0.23	1.0	0.41	1.0
VASODILAT	1.77	1.7	1.29	1.6
VERTIGO	0.04	1.0	0.00	0.0
VISION ABNORM	0.04	1.0	0.00	0.0
VOMIT	0.04	1.0	0.00	0.0
VULVOVAGINITIS	0.08	1.0	0.00	0.0
WEIGHT DECREASE	0.04	1.0	0.00	0.0
WEIGHT INCREASE	0.69	1.3	0.76	1.2

NOTE: For the following adverse experiences, the % subjects was calculated using the # females, rather than the # subjects: DYSMENORRHEA, LEUKORRHEA, MENOPAUSE, MENS DISORDER, MONILIA VAGINA, VAGINITIS, and VULVOVAGINITIS. For the following adverse experiences, the % subjects was calculated using the # males: PENIS DISORDER, EJACULAT ABNORM.

Also note that the % subjects was calculated using only the subjects who had at least one treatment period evaluation. Therefore, the number of patients/volunteers used in this analysis (2313) is less than the number of unique patient/volunteer entries (2398). The # reports per subject was calculated as follows: # reports of an event / total # subjects reporting that event.

The incidence of convulsions reflects only those instances in which a seizure was recorded on adverse experience forms and entered into the computerized data base (through August 1, 1984). Details of all seizures reported through April, 1985 are presented in this update (see Section II.F.).

Table 9 gives the most frequent events (greater than one percent). This table was developed by the sponsor from the previous exhaustive list. Table 10 (developed by the sponsor) uses non-COSTART categories (which are not those used in Table 7) to show the incidence for bupropion and placebo in controlled trials. The sponsor also developed a table (by study) where each adverse event that occurred was classified as trivial (requiring no action), of some concern (requiring some action exclusive of discontinuation) and serious (requiring study discontinuation). This table gives head counts but does not give a listing of the actual events. Finally, life table analyses by dosage category of the three most frequent events (agitation, insomnia, anorexia) are provided.

Number and Percent* of Patients Reporting Adverse Experiences

	Number Treated	No Adverse Effects	Trivial	Some Concern	Serious**
Bupropion	2486	404 (16)	1185 (47.7)	635 (25.5)	262 (10.5)
Imipramine	48	3 (6.3)	25 (52.1)	17 (35.4)	3 (6.3)
Amitriptyline	181	4 (2.2)	93 (51.4)	60 (33.1)	24 (13.3)
Doxepin	48	4 (8.3)	15 (31.3)	17 (35.4)	12 (25)
Placebo	282	35 (12.4)	174 (61.7)	61 (21.6)	12 (4.3)

* ( ) = percent
** Serious - dropped from the study.

5. Conclusions.

The sponsor has provided an update of serious events, seizures, terminations, adverse events and vital signs. There do not appear to have been any new events or increases in the frequency of known events. The discussion of the seizures identifies the risk factors (dosage changes, higher dosages and, for some, predisposing factors).

The sponsor should submit a cross tabulation of all laboratory results in the tests where there were abnormalities. This should be done for bupropion, placebo and any relevant standard. In addition, a listing of all ECG abnormalities for each treatment should be provided.

Table 9 (Sponsor's Table 11)

Adverse Experiences Which Occurred at Frequencies Greater Than One Percent*

Frequency	Adverse Experience	% Patients
> 20%	Agitation	28 9
	Insomnia	21 8
>10% ≤20%	Amblyopia	10 7
	Anorexia	18 5
	Asthenia	12 6
	Constipation	12 4
	Dry Mouth	17.0
	Headache	17 0
	Nausea/Vomiting	10.5
	Somnolence	10.5
>5% ≤10%	Appetite Increase	5 6
	Confusion	5.2
	Dizziness	9.0
	Impotence	5.1
	Sweating	7.3
	Thinking Abnormalities	6.8
	Tremor	8.7
>1% ≤5%	Akathisia	3 0
	Anxiety	1.9
	Arthralgia	4.0
	Chills	1 4
	Coordination Abnormalities	1 7
	Depression	1 7
	Diarrhea	3.1
	Dream Abnormalities	3 7
	Dyspepsia	3 3
	Emotional Lability	3.2
	Euphoria	1 7
	Hallucinations	1 6
	Libido Decrease	2.6
	Libido Increase	1 3
	Menstrual Disorder	3 3
	Nocturia	1.3
	Pain	2 7
	Palpitations	4.5
	Paresthesia	3 2
	Personality Disorder	2.0
	Pruritus	2.4
	Rash	2.7
	Taste Perversion	3.0
	Tinnitus	3.0
	Urinary Frequency	2.9
	Urinary Retention	1.7
	Urticaria	1.3
	Vasodilation	1 8

*Data derived from Table 10.

THZZ/85/1132
RB:dlm(doh)*

TABLE 10 (Sponsor's Table 12)

ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS*

(Percent of Patients Reporting)

Adverse Experience[1]	Bupropion (n = 218)	Placebo (n = 140)
AUTONOMIC		
Dry Mouth	34.9	27.1
Saliva Increase	3.2	4.3
Constipation	31.2	26.4
Diarrhea	7.8	11.4
Sweat	22.0	19.3
CARDIOVASCULAR		
Tachycardia	12.8	11.4
Palpitation	18.3	15.7
Hypertension	4.6	2.1
Hypotension	3.2	2.9
CNS		
Agitation	28.4	21.4
Anxiety	1.4	0.0
Confusion	6.4	1.4
Emotion Lability	4.6	2.9
Euphoria	1.8	0.0
Insomnia	12.4	12.1
Personality Disorder	4.1	3.6
Somnolence	20.2	20.0
DERMATOLOGIC		
Rash	8.3	7.1
GASTROINTESTINAL		
Anorexia	35.8	44.3
Appetite Increase	2.8	2.1
Dyspepsia	1.8	1.4
Nausea/Vomiting	28.4	23.6
Weight Increase	17.4	30.0
GENITOURINARY		
Urinary Retention	1.8	2.9
Nocturia	5.0	5.7
Menstrual Disorder	11.4	7.8
MUSCULOSKELETAL		
Arthralgia	6.0	5.7

*Studies 06, 08-001, 08-002, 09, 14

TABLE 10 (Cont.)

ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

Adverse Experience	Bupropion (n = 218)	Placebo (n = 140)
NEUROLOGICAL		
Asthenia	3.7	7.1
Dizziness	31.2	25.7
Dystonia	1.4	0.7
Headache	29.4	20.7
Hyperkinesia	13.8	5.7
Hypertonia	2.3	1.4
Hypokinesia	9.2	10.0
Tremor	17.9	7.1
Paresthesia	2.3	0.7
OCULAR		
Amblyopia	16.1	12.9
RESPIRATORY		
Rhinitis	5.0	12.9
SEXUAL FUNCTION		
Impotence	29.8	23.6
OTHER		
Tinnitus	4.1	1.4
Taste Perversion	2.8	1.4

[1]Events reported by $\geq$1% of bupropion patients are included.

Labeling Changes.

Indications Section. We had suggested that the following statement be included: "However, because experience in clinical studies suggest that Wellbutrin may pose a greater risk of seizure than other antidepressant drug products, Wellbutrin should not generally be considered as the antidepressant of first choice for most depressed patients." Burroughs Wellcome rejected this proposal. Their indications read, "Wellbutrin is indicated for the treatment of depression. The efficacy of Wellbutrin was demonstrated in placebo control clinical trials which enrolled primarily hospitalized patients with diagnoses of depressive neuroses or manic depressive disorder." Our equivalent was, "The efficacy of bupropion was demonstrated in clinical trials of three weeks duration which enrolled, etc." We also had recommended the following, "The only placebo controlled trial of bupropion in depressed outpatients failed to provide unequivalent evidence of its efficacy." The sponsor's equivalent was, "As with other antidepressants, the appropriate treatment duration for patients who have shown a positive clinical response to Wellbutrin is not known. Although many patients have been treated with Wellbutrin in long term clinical trials of up to two years in duration, these studies were not placebo controlled and evidence to demonstrate the sustained effectiveness of Wellbutrin after three weeks of use in placebo controlled investigations is not presently available."

Dosage Section. This section was changed to recommend a lower dosage range. The sponsor is now recommending as the usual adult dosage, a starting dose of 225 mg/day g[illegible]as 75 mg t.i.d. "Based on clinical response this dose may be increased by [illegible] mg/day no sooner than every three days according to the following schedule up to a total daily dose of 450 mg/day. Most patients who respond do so at a total daily dose of 450 mg/day or less." There then is a dosing schedule to tell how many tablets of 75 mg to give in the morning, midday and evening. They go on to say that in patients who do not respond at 450 mg., dose escalation may continue in 75 mg/day increments no sooner than every five days to a maximum of 600 mg/day or 4 mg/pd/day which ever is smaller. Similarly a table is given showing how many tablets should be administered at each time of the day.

The sponsor had been requested to show that patients did respond at a dose of 450 mg/day. That is, because the dosage range was changed to a lower range, we requested that an efficacy analysis be carried out for the revised dosage schedule. The sponsor did not provide this. They referred us to studies 06, 08, and 14-01. Dr. Leber has talked to them about this. (See Dr. Leber's memo of May 16, 1985.)

Specific Changes.

The sponsor has made the following possibly significant changes:

1. Under Warnings, the potential for hepatotoxicity was characterized as mild. Since we do not have a laboratory test update, it is not possible to verify this.

2. Under Use in patients with systemic illness, the sponsor added a sentence suggesting that Wellbutrin "was well tolerated in patients who developed orthostatic hypotension on tricyclic antidepressants."

3. Under Adverse Reactions, the sponsor deleted the final paragrapn concerning glucose and LDH changes. They state that the original expanded summary suggests that the percentage of patients who had normal or near normal baseline blood glucose and LDH levels and subsequently experienced significant elevations was approximately the same in the bupropion and placebo groups (2-3%).

Conclusions.

1. Safety Update. The sponsor should submit a cross tabulation of all laboratory results for tests where there were abnormalities. This should be done for bupropion, placebo and any relevant standard. In addition, a listing of all ECG abnormalities for each treatment should be provided.

2. Labeling. A decision should be made about the indications and dosage section. The seizure discussion should be changed by removing the 9000 mg case from the normal dosing group and by including a statement to the effect that they occurred more frequently following dosage increases. Finally, the above "specific changes" must be supported by data.

J. Hillary Lee, Ph.D. (HFN-120)

cc:
Orig:NDA 18-644
HFN 120
HFN-120/Thayes/Pleber
HFN-120/HLee
rd/mb/5/23/95
DOC 0108n

Review and Evaluation of Clinical Data
Proposed Labeling

NDA: 18-644
Sponsor: Burrough s Wellcome Co.
Drug: Wellbutrin
Date of Submission: 1985, Nov. 26, 1985
Date of Review: December 12, 1985

Material Reviewed: Indications, Warnings, Precautions, Drug interactions, and Adverse Reactions. Some sections from earlier submissions in 1985 have also been reviewed again to amplify some issues in the labeling.

1. Indications.

2. Warnings . The table of seizures should be revised as it is misleading. That is, the bottom line (number of seizures occurring between 600 and 9000 mg) should be divided into two lines with one line for dosages between 600 and 900 and the second line for dosages above 900mg. That is, the overdose at 9000 mg should be separated from those seizures occurring within the former prescribed range.

   In addition, the text on the page immediately preceeding the table of seizures should include a statement to the effect that BLANK percent of seizures occurred within two days of a dosage increase.

3. Precautions. Since weight loss is more unusual and potentially more serious than weight gain, I would recommend that the weight loss effect be discussed before the weight gain.

   Under Drug Interactions, reference is made to an interaction with phenylzine in animals. Do we know anything about other MAOI's in animals?

   Should the Information for patients section contain a caution about abrupt withdrawal? I am not aware of problems on withdrawal except for one case of a second seizure during gradual withdrawal from Wellbutrin following the original seizure.

4. Adverse Reactions. In the table of adverse experiences in the placebo controlled trials, I noted that approximately 12 percent of the subjects had akinesia/bradykinesia. When I went to see where this side effect came from, I found that there were four or five cases of akinesia from study 38, a study evaluating the effect of Wellbutrin vs. placebo in schizophrenic patients receiving fluphenazine who showed pseudoparkinsonism. Bradykinesia was not listed as a side effect in any of the earlier submissions. I did, however, find hypokinesis which was listed as an effect occurring in depression studies. I assume this was combined with the akinesia to form the new category. I have two comments. First, I think the table of adverse effects in controlled trials should be limited to trials in depression and this could be stated in the table heading. Second, I wonder if hypokinesis is a BW classification for psychomotor retardation? Perhaps we could ask for clarification on this.

In keeping with my review of the psychiatric side effects, namely, confusion and psychosis(hallucinations), I would recommend these categories be combined and read as confusion/psychosis (hallucinations).

I still find the section following the table confusing. That is, an effect is classified as most frequent yet it does not include effects occurring in the table. Although the section is prefaced with a phrase ("In addition to the events described above"), this could be missed when the reader jumps into the listing. Also, the distinction between most frequent and less frequent is artificial. Perhaps the distinction could be dropped.

Under 'Gastrointestinal',the items for changes in weight are confusing. That is, 33 percent of Wellbutrin and 30 percent of placebo patients have weight loss as an adverse effect while 20 of Wellbutrin and 30 percent of placebo have weight gain as an adverse effect. Could this possibly mean weight change and not an adverse effect? It would be understandable that 60 percent of patients had a weight change. Perhaps we should ask the sponsor to set a minimum change before it would be reported as an adverse effect? It is possible that by reporting all weight changes, they are obscuring large weight losses on Wellbutrin, for example.

Conclusions. The above items are for discussion concerning the final labeling.

J. Hillary Lee

J. Hillary Lee, Ph.D.
Psychologist

18.444
NDA
120/Hlee

KON 301 MADE IN JAPAN

Clinical Review of Submission

NDA 18-644

Drug: Wellbutrin (bupropion)

Sponsor: BW

Submission date: 9/18/84

Introduction:

The submission contains a response to our request for evidence supporting the sustained antidepressant efficacy of bupropion beyond three weeks.

To be acceptable as a source of evidence for a given duration of antidepressant effect, we required that any study selected for presentation retain at least 70% of the subjects at the time point of the analysis (vide infra). This rule was used to preclude the presentation of data from trials that were of longer than three weeks duration in name only.

Specifically, we asked the sponsor to conduct an "intent to treat" analysis of 1) all patients and 2) the same cohort excluding those who violated the protocol because of sedative/hypnotic use. Each analysis was to be an "end point" analysis (last observation carried forward or LOCF). The endpoint chosen was to be selected as the latest time for which observations were available at which at least 70% of the subjects randomized to treatment were retained in each treatment group. Importantly, the firm was told explicitly that the time should not be selected as the time when the study, overall, retained 70% of its subjects. This qualification was made to preserve the quality and validity of between groups comparisons when the rate and timing of dropouts varied between treatments.

Using these rules, the sponsor was to analyze the raw data and the change from baseline scores for all treatments on the following items: the Ham-D total, the Ham-D depression item, the Ham-D retardation factor and the two globals (severity and improvement). Power calculations and/or confidence limits for each calculation were to be presented for the between treatment contrasts.

Results of the sponsors presentation:

After examining the trials available, the sponsor concluded that only one study, # 15, an active control trial employing amitriptyline as the standard treatement, satisfied the retention criterion sufficiently far beyond three weeks to deserve analysis.

The salient points of the sponsor's presentation are summarized below:

Point 1: The study 15 Analysis:

Study 15 consists of 6 subcenters or sites. While nominally following the same protocol, the results varied from center to center.

LION 301 MADE IN

While the sponsor did not present the analysis for the items requested at the single time point requested, he did provide tables and graphical displays which permitted this reviewer to reconstruct the information requested. Using a graphical technique (i.e., dropping a vertical line from the point of 70% retention for the first treatment crossing this retention boundry to the time (X) axis), I estimated the time at which each center and the combined centers met our analysis criteria, that is, the time at which the regular scheduled LOCF analysis could be performed.

For all sub-studies but one, including the combined study, 29 days was the appropriate 'endpoint' analysis point. For study 1502, 43 days was used.

The Hamilton depression scale score change from baseline difference for each center for bupropion and amitriptyline are presented below:

Hamilton total change from baseline score:

Study	Bupropion	Amitriptyline	better	Number bup:ami
1501	- 7.7	-13.6	ami	25:13
1502*	-11.5	- 9.7	bup	11:7
1503	-15.4	-18.9	ami	32:16
1504	-17.2	-17.4	?ami	13:7
1505	-10.6	- 9.2	bup	19:10
1506	- 7.1	-12.9	ami	21:9
all (#)	-11.3	-14.2	ami	121:62

Hamilton Depression item change from baseline scores:

Study	Bupropion	Amitriptyline	better	Number bup:ami
1501	- 1.04	- 1.62	ami	25:13
1502*	- 1.64	- 1.29	bup	11:7
1503	- 1.56	- 1.94	ami	32:16
1504	- 1.85	- 1.71	none	13:7
1505	- 1.32	- 1.2	bup	19:10
1506	- 1.00	- 1.78	ami	21:9
all (#)	- 1.33	- 1.66	ami	121:62

NB: *=day 43, all others day 29; #=weighted analysis.

Although not tabulated here, the global severity and global improvement results generally confirm the findings on the Hamilton Depession Scale.

Several statistically significant differences favoring amitriptyline were found; none favoring bupropion were detected. The times and conditions in the 'all patients analysis' at which statistically significant differences were detected are enumerated. As noted, all favored amitriptyline.

For the Ham-D Total:

on observed data: combined unweighted analysis and 15-01, 15-06 barely missed (p-0.073).

on change from baseline data: study 1501, 15-06 was close(p=0.084)

For Hamilton Depression Item:

observed data: combined centers, both equal and weighted, 15-01

change score: combined centers, both equal and weighted, and 15-06

For CGI Severity:

observed: combined centers only, 15-06 was close (p=0.064)

change score: combined centers, only

For CGI Improvements:

observed: combined, both analyses, 15-01
there is no change score for this item

On the Ham-D retardation factor, the combined center results also achieved significance, ut no single cen[illegible] did.

Conclusion regar[illegible]ing study 15 and the sponsor's discussion:

Commenting upon th[illegible].e results without benefit of formal statistical consultation, I find little that is of immediate use to us. The results suggest that in some settings, patients assigned to amitriptyline fare better than those on bupropion. Of some interest is the fact that the three largest studies by rank, 03.01 and 06, all favor amitriptyline, the standard drug, a point reflected, I believe, in the larger differences found using the weighted analysis.

Whether or not the results may be explained by agitation caused by bupropion, or the sedation caused by amitriptyline, is irrevelant. Without placebo, there is simply no way to know if the poorer showing of bupropion is meaningful.

In any event, whatever the explanation, I do not find in this data proof that bupropion is effective for twenty-nine days.

Indeed, rather than focusing on the issue of sustained efficacy, the issue that motivated our request for the analysis, the sponsor's discussion of study 15 appears to have an apology for the "poorer" showing of bupropion as its major thrust. For example, the analysis and discussion is not limited to the duration question but attempts to review the entire study including results at

MADE IN JAPAN

much later time points, times when the differences favoring amitriptyline are less apparent (and when few patients remain in the study). The sponsor also attempts a refutation of the significance of the statistically significant differences found that favored amitriptyline at the 70% retention endpoint for 15-01 and 15-06 and at virtually all points in the combined study result.

We read the old argument that the size of the mean treatment differences are not clinically significant. I will not get into the issue here, but I would point out that this interpretation of mean differences is a bit specious; indeed, it is the very argument that we refuse to accept as a reason to discard small treatment differences between an experimental drug and placebo when we accept such differences as proof of efficacy.

In any event, I am not prepared to explain why amitriptyline beat bupropion, or what this finding means about the true efficacy of bupropion as an antidepressant. Without placebo as a marker of location, this trial cannot be interpreted in regard to bupropion's absolute efficacy; nevertheless, I must admit, based upon current policy, that the data in study 15 might be used as evidence to support the efficacy of amitriptyline. More to the regulatory point, however, not every drug is good for every patient and bupropion may have advantages not identified in the efficacy relative to amitriptyline (e.g., less anticholinergic properties, less cardiotoxicity, etc.).

Point II: Earlier Evidence on Outpatient Efficacy:

In the course of their reply, the sponsor, anticipating our concern about the lack of evidence on bupropion as an antidepressant in outpatient settings, mentions that a revised analysis of 90-01, one of the two centers of the single placebo controlled outpatient trial, provides evidence that at day 21 Wellbutrin (at a so-called low dose of 150-450 per day) is superior to placebo.

The sponsor correctly notes that the re-analysis was one requested by the agency (we did not like their original analysis of covariance) and the "reanalysis does show that the Ham-D total and CGIs for the 21 day LOCF between groups contrast to be statistically significant (p= 0.053, 0.03 and 0.02 respectively). Unfortunately, in the original analysis of covariance presented by the sponsor, the p values for these very same items at the very same times are quite far from statistical significance (p=0.87, 0.84, 0.81).

Thus, the outcome appears clearly to be dependent upon the type of analysis carried out. A bit surprising, but, without the individual study results on the observed data, there is no intelligent way to respond. Dr. Stein's Novemeber 18, 1982 statistical review had reviewed the reanalysis; in fact, his review tabulates the same data as the sponsor. However, Dr. Stein concludes that that 09 is a study lacking statistical evidence of efficacy. (Incidentally, I do not think the sponsor ever submitted the individual study data for 09-01 or 02; in any event, given the organization of the submission, we can't find it and given the type of information supplied in earlier submissions it is likely that the data will not follow analysis rules we would now use in regard to exclusions, etc.) In any event, the second site, 9-02 fails to confirm the findings in 9-01, even in the "reanalysis."

Conclusion:

The sponsor's submission fails to establish that bupropion is effective for more than three weeks in inpatients, or effective at all in outpatients.

The labeling must, therefore, state these limitations on our judgment and/or our basis for that judgment. Full information is critical to the intelligent use of antidepressant drugs.

Paul Leber, M.D.
October 17, 1984

cc: NDA 18-644
HFN-120/Haye indelar/Davis
HFN-713/Stein, Pledger
HFN-120/PLeber/1018/84
Doc. 2495C

LION 361 MADE

41.3

Clinical Review

of

NDA 18644

I. Sponsor: Burroughs-Wellcome
3030 Cornwallis Road
Research Triangle Park, North Carolina

II. Drug name (Action): bupropion (antidepressant)

III. Trade name: Wellbutrin

IV. Summary:

Sponsor has responded to our letter of September 8, 1983 in which labeling revisions were recommended. The format of this reviewer's comments will be to first address the changes which we proposed in the Sept. 8 letter and then to suggest some additional revisions.

Item 1. We suggested the deletion of the phrase which stated that bupropion is effective [illegible]TCA non-responders. Sponsor in its answer has cited a retrospective study of 30 patients which were judged by clinicans to be TCA non-responders. Sponsor has slightly-modified its claim to include the fact that the effectiveness of Wellbutrin was seen in a retrospective study.

RECOMENDATION: Delete the claim altogether since a sample of 30 patients is hardly sufficient to establish the claim.

Item 2. We suggested a contraindication of concurrent administration of bupropion with MAOI's. This has been done.

Item 3a. Sponsor was requested to delete the word "small" from the second sentence of the "Carcinogenesis" section. This has been done.

Item 3b. Sponsor was requested to add a statement regarding the weakly positive effects on the Ames Test in the Mutagenesis section. This has been done.

Item 3c. Sponsor was requested to use a Category C pregnancy Listing instead of "B". This has not been done. Sponsor has submitted a letter from Dr. James Wilson, a Burroughs consultant (Page 31 of Sponsor's submission).

RECOMMENDATION: A determination should be made by Dr. Leber and the reviewing pharmacologist. Category C is appropriate if the existing data is insufficient to make a clear determination.

Package insert, page 5. (This is Sponsor's change, not our request). The paragraph now reads:

Nursing Mothers: It is not known whether Wellbutrin is excreted in the milk of lactating women. Because many drugs are excreted in human milk, caution should be exercised when Wellbutrin is administered to a nursing women.

RECOMMENDATION: The proposed labeling is inappropriate. Change as follows:

It is not known whether Wellbutrin is excreted in human milk. Because many drugs are excreted in human milk the possibility of fetal risk from the maternal ingestion of Wellbutrin cannot be excluded. Therefore, Wellbutrin should be used in women who are or might become pregnant only if the clinical condition clearly justifies potential risk to the fetus.

Item 4a. We objected to the first of the "Adverse Reaction" section as overtly promotional. Sponsor revised the statement by deleting the phrase "was very well tolerated". The statemnent now reads "Wellbutrin produced few significant adverse reactions in clinical trials involving 1153 patients.".

RECOMMENDATION: Delete not only the revised first sentence, but the entire first paragraph as being promotional.

Item 4b. We noted that limiting the presentation of data to patients who received no more than 750 mg per day had the effect of reducing the number of patients reported from 1153 to 361. Sponsor states that this is incorrect and that only 45 patients would fall into this category.

RECOMMENDATION: Sponsor' point seems to be correct and should stand.

Item 4c. We noted that reporting only those reactions which the investigator felt to have at least a 50% probability of relation to drug resulted in underreporting and that raw figures should be presented. Sponsor has added a table showing raw figures.

RECOMMENDATION: Two sets of data are somewhat confusing and the results between the two are disparate. A single set would be better if we and Sponsor can agree on what to use.

Item 5. We questioned the use of a "Comparative Differences" section in which Wellbutrin was compared to other products. Sponsor has removed the heading but not the content (page 9 of package insert).

RECOMMENDATION: It is not appropriate in labeling to list adverse effects which a drug may not produce. This is true whether it is in comparison with another agent or not. The entire paragraph is promotional and should be deleted. If such is allowed, one is opening a "Pandora's Box" for promotion and advertising. I have no doubt that Wellbutrin does not cause hang nail, athletes foot, dandruff, etc. This is true even in cases where other drugs of a class are known to cause a certain reaction and the compound in question does not.

Item 6. A "Drug Abuse and Dependence" section has been added as we requested.

RECOMMENDATION: Drs. Leber and Vocci should decide on the adequacy of this section.

Item 7. In the "Overdosage" section we requested deletion of the sentence dealing with phenytoin and barbiturates. Sponsor has done this.

Package insert, page 10. (This is Sponsor's change, not one that we requested.). Under "Dosage and Administration" a new second sentence has been inserted. This reads "A dose of 300 mg per day (100 mg T.I.D.) can be given from the outset since the side effects characteristic of other antidepressants are usually minimal with Wellbutrin.".

RECOMMENDATION: Delete the sentence. It is both promotional and redundant. The 300 mg. per day dose is already given in the two paragraphs below. For clarity insert "(100 mg. T.I.D.)" after "300 mg/day" in both of these paragraphs.

Other Suggested Revisions:

These are the reviewer's comments.

1. Under "Indications and Usage" delete all the symptoms listed in parentheses on page 2 of the package insert. Also, Sponsor has apparently used both DSM II and DSM III nomenclature. Probably only DSM III should be used.

2. In the third paragraph of this section Sponsor states that "There is no clinical experience with Wellbutrin in patients with a recent history of myocrdial infarction or unstable heart disease, however." Add to this sentence "and is not recommended in these groups."

3. In the "Overdosage" section Sponsor has given preclinical data (first paragraph). This shold be deleted or placed in a "Preclinical Pharmacology" section on the first page of the package insert.

Summary of current state of NDA:

The statistical enclosure has been reviewed and found satisfactory by the Division of Statistics. The SBA is about 75 % complete and should be finished soon. The chemistry is still incomplete but the problems seem to be minor and relate to validation methods. The biopharmaceutics seem to be satisfactory.

David M. Davis
Psychologist, HFN-120

Dist:
Orig: NDA
HFN-120
HFN-120/DDAVIS
Doc# 5189B

T.A. Hayes 04-30-83

LION

JUL 2 3 1982

25

Clinical Review of NDA 18-644

I. Sponsor: Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park
North Carolina 27709

Telephone (919) 541-9090
Project Officer: Warren Stern, Ph.D.
Head, Psychiatry Section

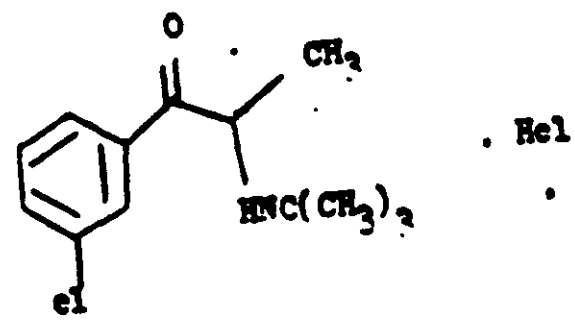
II. Drug Name (Action): bupropion (Presumed Antidepressant)

III Trade Name: Wellbutrin

IV. Summary:

A. Introduction:

Wel rin (bupropion HCl) is a new antidepressant compound having the mical formular C13H18CLNO. Its molecular weight (for the hydrochloride) is 276.21 and has the following chemical structure:



Wellbutrin is chemically but not pharmacologically (in Sponsor's view) related to a marketed anorectic, diethylpropion (Tenuate). The compound appears as a white powder with a slight characteristic odor. The marketed formulation would be as a tablet in 3 potencies. These are 50 mg (white), 75 mg (yellow) and 100 mg (read).

Bupropion is an Aminoketone which is chemically distinct from all marketed antidepressants. It is neither a tricyclic nor MAOI. Moreover, it is dissimilar to the newer antidepressants such as

LION 301 MADE IN JA

Trazodone and Merital. The compound is not currently marketed anywhere in the world although a New Drug Application has been filed in Canada concurrently with this one. There is, therefore, no significant body of clinical literature either domestic or foreign.

In preclinical studies the absorption and disposition of Wellbutrin were determined in rats, mice and dogs. Toxicological effects were also investigated.

In an acute toxicity study in mice TTEP/78/0028 (Sponsor's protocol designation) bupropion was administered orally to 2 groups (20 male and 20 female) mice at doses of 400, 500, 600, and 700 mg/ kg. The observed LD/50's were 544 ± 29 mg/kg (males) and 636 ± 23 mg/kg (females).

In a second study, a group of 20 male mice were given IP doses of 200, 225, 250, 275 and 300 mg/kg. The observed LD_{50} in the group was 273 ± 4 mg/kg. All deaths occurred within 17 minutes after dosing.

In a acute toxicity study in rats (TTGP/78/0036) the observed oral LD[illegible]s 606 .9 ± 51 mg/kg (males) and 481.7 ± 91 mg/kg (females). The IP LD_{50} was 263 ± mg/kg (makes only).

Sponsor also conducted a 90 day oral toxicity study in rats (TTGP/70/0009). Twenty rats, 10 per sex, were treated orally for 90 days with doses of 150,300 and 450 mg/kg of bupropion. In the low dose group, one rat died spontaneously, 2 were killed accidentally in the mid dose group. One rat was sacrificed in a moribund condition and one died spontaneously in the high dose group. No specific toxicity was noted although there was a dose related increase in liver growth and an increase in the total serum protein. These findings are regarded as being related to enzyme induction.

There were also 55 week (TTGP/78/0070) and 104 week (TTGP/76/0031) oral toxicity studies in rats. Again, the major findings were dose related increase in liver weights.

Finally, in a 90 day oral toxicity study in dogs (TTGP/70/0001), 4 groups, 2 per sex were treated with doses of lactose (control group), 15, 35, and 75 (increased to 150 after 45 days) mg/kg/day of Wellbutrin. No toxicity was observed in the dogs at any dose level.

Sponsor's proposed maximum human dose of 750 mg/day is approximately 11 mg/kg in a 150 lb (68 kilogram) person.

LION 301 MADE IN JAPAN

Absorption and disposition of bupropion in animals:

1. Male and female rats were dosed at 50 mg/kg IP and plasma concentrations were measured over 4 hours. The elimination in male rats was much more rapid than in females. the respective plasma half lives were .95 and 2.3 hours. In a second study, rats were dosed orally or intravenously and plasma and brain concentrations were determined. The dose was 10 mg/kg. A sex difference in bioavailability of the compound was found with the drug being 8% bioavailable in male rats and 21% in females. Also, the brain concentrations over the 4 hours post dose was 10-15 time the serum concentration.

2. In the mouse metabolism studies it appeared that the drug and its metabolites undergo rapid elimination from the entire animal and that the rate of metabolism increases over time.

3. In beagle dogs, bupropion was administered both I.V. and orally at doses of 10 mg/kg. The plasma half-life of I.V. Wellbutrin was 1.7 hours and no sex differences were observed.

Tissue distribution:

1. In the rat, following I.P. administration the greatest concentrations were found in the lung, but following oral administration the greatest accumulation was in the liver. The drug was widely distributed in tissue in both cases. In another study of adult female rats various dose levels produced the greatest concentrations in the liver and kidney followed by the brain and spleen. The tissue concentrations declined significantly after the 6th hour post dose. The tissue plasma ratios were 45 for the liver, 20-30 for the kidney, brain and spleen, 15 in the lung and 10 in the heart. The ratios were similar at 1 and 6 hours after dosing.

2. In a study of pregnant rats bupropion was found in placenta, amniotic fluid as well as the fetus. The fetal levels were lower than levels found in maternal organs.

Teratology:

1. In two teratology studies in rabbits (TTGP/77/0003 and TTGP/77/0004). The key findings were dose related maternal toxicity including clonic convulsions at doses of 100 and 150 mg/kg/day. there was an increased number of offsprings who had extra rib formation — a condition reported to occur spontaneously in the rabbit strains used. There were no drug related teratogenic effects.

LION 501 MADE IN

2. In a rat study, no teratogenic effects were seen.

Carcinogenicity:

Hyperplastic nodules appeared in a 104 week rat study. The animals were given 0, 100, 200 or 300 mg/kg/day. The nodule incidence was dose related. Also dose related were increases in liver weight and hepatocellular hypertrophy associated with hepatic enzyme induction. the incidence of hepatocellular carcinomas did not exceed that which occurs by chance.

Dose MG/KG/Day	N		Nodular Hyperplasia		Hepatocellular Carcinoma	
	M	F	M	F	M	F
0	73	74	2	1	0	0
100	72	68	7	10	1	2
200	70	71	9	10	0	1
300	64	59	0	5	1	0

Bupropion does not elevate prolactin levels in humans and did not cause an increase in the incidence of mammary tumors in rats.

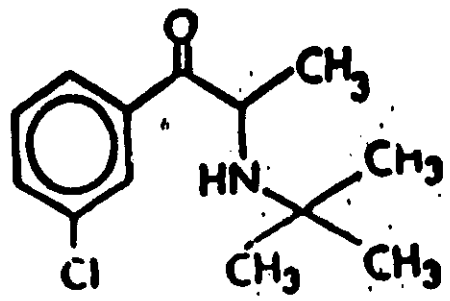
Additional information on preclinical pharmacology is found in the Sponsor's pharmacology Summary (Item L).

B. Clinical Pharmacology

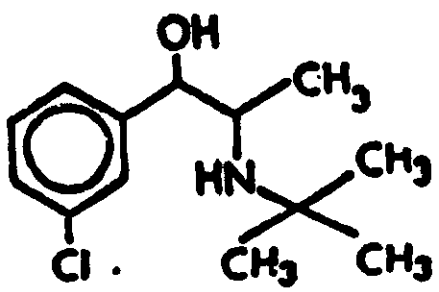
The neurochemical mechanism of Willbutrin is unknown. It has a very slight effect on the inhibition of dopamine and norephinephrine re-uptake.

There is no effect on serotonin or monoamine oxidase. The compound is rapidly absorbed following oral administration. with peak plasma levels typically occurring within 2 hours after dosing. This is followed by a biphasic decline with a half-life of 14 hours (range 9.6-20.9). After 6 hours bupropion plasma levels are almost 30% of peak. The drug is metabolized almost completely and there is no evidence of accumulation. Even so, the metabolic pathway of Wellbutrin in man is not well understood. As in animals, the drug is likely to distribute extensively in tissues. No gender differences were found in the pharmacokinetics of Wellbutrin.

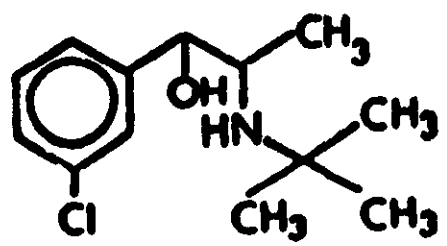
Following the administration of a carbon fourteen labeled dose of Wellbutrin 89% of the radioactivity was recovered in the urine, 10% more was recovered in the feces within 96 hours after dosing. Unchanged bupropion in the urine was .5%. Six urinary metabolites have been identified. These are shown in Figure 1.



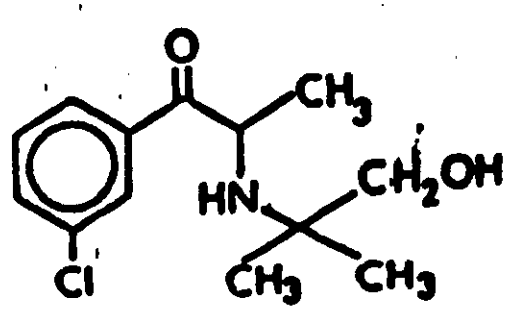
323U66
Bupropion



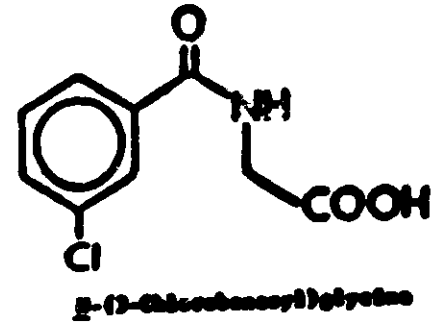
494U73
(±,-)(R*,R*)-2-tert-Butylamino-1-(3-chlorophenyl)propanol



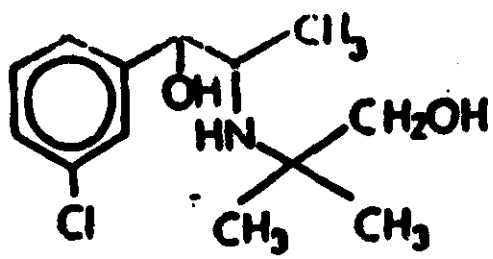
17U67
(±,-)(R*,R*)-2-tert-Butylamino-1-(3-chlorophenyl)propanol



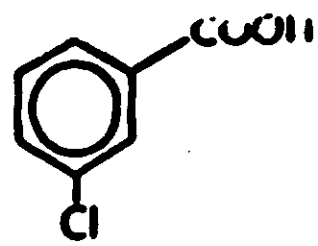
306U77
(±,-)-3'-Chloro-2-(2-hydroxy-1,1-dimethylethylamino)propiophenone



N-(3-Chlorobenzoyl)glycine



287U73
(±,-)(R*,R*)-1-(3-Chlorophenyl)-2-(2-hydroxy-1,1-dimethylethylamino)propanol



3-Chlorobenzoic acid

Figure 1: Wellbutrin and its metabolites.

C. Early Clinical Studies (01A, 02, 03, 04, 05)

A series of 5 exploratory studies were conducted to determine safety and tolerance. Study 01A employed normal volunteers. The remaining 4 employed depressed patients.

1. Study 01A

This was a parallel treatment, double blind, randomized design with placebo control. The dosage was fixed, ascending over a 44 day period. The range was 15-1200 mg/day. the major finding of study 01 were that doses up to 500 mg/day were well tolerated and that the dose was rapidly absorbed.

2. Studies 02, 03, and 04 were open uncontrolled trials of bupropion in hospitalized depressed patients. In study 02 patients had to be adults, free of cardiovascular, renal, hepatic and neurologic disease with no recent history of alcohol or drug abuse. Laboratory exams were given periodically during the 3-4 weeks of treatment. Four subjects participated with a mean daily dose in the range of 600-700 mg. The results showed a moderate effect (HAM-D total change of 20-39% from baseline) on depression. Patient 4 who was started at 900 mg per day was tearminated on 5 due to tremors, excitation, restlessness, agitation and confusion. At termination the dose had been decreased to 800 mg/day. Sponsor concluded that 900 mg/day was poorly tolerated.

3. Study 03 patients initially started at 600 mg/day and were rapidly titrated to 900 mg/day. These doses produced agitation, tremulousness, and anxiety. later patients were started at 300 mg/day and increased more gradually to 900 mg/day. This regimen was better tolerated. The HAM-D total and CGI in this study (N=11) showed significant improvement in change from baseline. one patient was discontinued due to urticarial rash and one became overtly psychotic. This patient had a history of paranoid personality.

4. Study 04 was an open 28 day evaluation of bupropion with initial doses of 30 mg/day titrated to 900. Patients were 14 hospitalized depressives of moderate severity. A significant improvement occured within one week on the HAM-D total. No further improvement was noted after the first week (mean change from 28.3 to 20.3 after 3 days). The Zung Depression Scale showed little change, however.

LION 301 MADE IN JA

deterioration - 2 (placebo), adverse reactions - 2 (1 each group), intercurrent illness - 1 (Wellbutrin), did not return/eloped/refused treatment - 4 (Wellbutrin), administrative/uncooperative - 3 (2 placebo, 1 Wellbutrin).

The inclusion criteria here and in the other inpatient studies required that patients be non-psychotic and exhibit a depressed mood plus have at least 4 additional symptoms as follows:

a. depressed mood characterized by any of the following: sad, blue, low, despondent, hopeless, gloomy
b. anhedonia
c. poor appetite
d. sleep difficulty (insomnia or hypersomnia)
e. loss of energy, fatigue, lethargy
f. agitation
g. retardation
h. decrease in libido
i. loss of interest in work or usual activities
j. feelings of self-reproach or guilt
k. diminished ability to think or concentrate
l. thoughts of death and/or suicide attempts
m. feelings of helplessness and hopelessness
n. anxiety or tension
o. bodily complaints

Patients were randomly assigned to either bupropion or placebo using a fixed, changing, individualized schedule. In the first week, patients received from 300-400 mg of Wellbutrin (divided t.i.d.). From day 8 to end of study, the dosage could be increased to 600 mg/day.

Assessments were done weekly and included the Hamilton Depression Scale, Hamilton Anxiety Scale, Self-Rating Depression Scale (Zung), Self-Rating Anxiety Scale (Zung), Clinical Global Impressions, Dosage Records and Treatment Emergent Symptoms Scale, and Patient Termination Record.

Results:

The mean dose of Wellbutrin was 450 mg for weeks 2-4. Three placebo and seven bupropion patients received sedative/hypnotic medication at some time during the study. Dalmane (30 mg) was the most commonly used sedative. Analysis of covariance was employed using both age and baseline scores as covariates. There were significant interactions for age by treatment and baseline by treatment (p less than .10). The HAM-D Scale Factors analyzed were 1.

LION 301 MADE IN

5. Study 05 was a double blind placebo controlled 3 week comparison with a maximum dose of 450 mg/day. the patients were hospitalized depressives. Of the 24 patients starting this study, only 13 were included in the analysis (8 bupropion, 5 placebo). Again, the HAM-D showed improvement, but not the Zung. When comparisons from baseline to termination were made there was no significance in comparison to placebo. This was due, in sponsor's view to low power, and a large placebo response.

Overall conclusions from these studies were that bupropion had minimal anticholinergic and cardiovascular effects. The occurrence of rash was an occasional problem. Agitation and anxiety were the most significant adverse behavioral effect. At the high dose 800 mg (not divided) grand mal seizures occurred in 2 of the subjects. Of course, it was not the point of these studies to establish efficacy.

D. Major Studies to Evaluate Efficacy

Altogether 40 studies at 112 investigational centers have been conducted. Ninety-one of these centers are in the U.S. remaining centers are located in Canada and the United Kingdom. A total of 1153 patients had been started at the data cutoff date of June 1981. Of these, 359 patients participated in the placebo controlled studies (Sponsor's protocol number 06, 08, 09, 14) and 186 participated in the active drug controlled trial (10c, 15, 21). The total patients then in the major efficacy trials are 545. Three of the placebo controlled trials were inpatient and had a similar design. These were 06, 08, 14. The remaining study, 09, utilized outpatients. Finally, there are 3 supportive studies (17, 26, and 35). The study summaries will follow the ordering above.

1. Study 06, placebo controlled (K. Brodie, W. Zung, L. Fabre, D. Garver).

This was a 28-day, double-blind, placebo-controlled trial which was conducted at 3 centers. A total of 85 inpatients were enrolled and 75 patients were included in the analysis (27 placebo, 48 bupropion). The patients consisted of 16 females and 59 males with an age range of of 21-62 (M=40.7) (placebo) and 18-70 (M=42) (bupropion). The main diagnoses (DSM-II classification) were: manic-depressive (depressed) 55%, depressive neurosis 35%, involutional melancholia 8%, and manic-depressive (circular) 2%. The dropouts occurred for the following reasons: ineffectiveness or clinical course

anxiety/somatization, 2. weight loss, 3. cognitive disturbance, 4. diurnal variation, 5. psychomotor retardation, 6. sleep disturbance. For these factors, only the termination scores were analyzed. There was significance favoring bupropion on anxiety/somatization (p = 0.17), cognitive disturbance (p = .001), psychomotor retardation (p = .033). There was a trend toward less sleep disturbance (p = .09). Also, significant were the Hamilton Total Score at day 21 (p = .004) and day 28 (p = .009). At day 28 the bupropion mean was 14.9 compared to 19.6 for placebo. The CGI ratings also showed Wellbutrin to be superior on the "Severity of Illness" item at day 21 (P = .009) and day 28 (p = .006). At day 28 the means were 3.20 (Wellbutrin) and 4.06 (placebo). The HAM-A showed a similar superiority for bupropion. On the SDS (Zung) and SAS, trends favored bupropion but were not statistically significant. More detailed summaries are shown in the Study 06 Summary Tables which include Sponsor's Tables #19, 20, 21, 24, 25, 26, 29, and 31.

2. Study 08, placebo-controlled (A. Halaris, W. Fann, D. Dressler):

This was a 5-week (4-week treatment, 1-week followup) study of bupropion versus placebo at 3 centers. 68 patients enrolled, 59 were included in the efficacy analyses (34 bupropion, 25 placebo). There were a total of 40 males and 26 females (sponsor's summary table shows 2 less than listed in his description above). The age ranges were 21-61 with a mean of 40.8 (placebo) and 22-75 with a mean of 42.8 (Wellbutrin). Major diagnoses were depressive neurosis about 60%, manic-depressive (depressed) about 30%, other diagnoses 10%. Dropouts occurred for the following reasons: ineffectiveness - 1 (bupropion), adverse reactions - 3 (bupropion), intercurrent illness - 2 (bupropion), did not return/elapsed/refused treatment - 4 (2 placebo, 2 bupropion).

Inclusion criteria were the same for Study 06, above.

Exclusion criteria for this and other studies were:

a. patients who were actively suicidal
b. schizophrenic
c. organic CNS disease
d. severe dementia
e. incapable of spontaneous conversation or behavior
f. hypersensitivity to drugs
g. abnormal lab or ECG values
h. glaucoma
i. seizure disorders
j. prostatic hypertrophy
k. lactating females who are breastfeeding
l. women of childbearing potential who refused to sign an intent to avoid pregnancy form
m. alcoholism

ION 301 MADE IN JAPAN

Results: Doses were started at 300 mg/day and titrated to 750 mg/day by day 11 if the lower dose was well-tolerated.

The mean daily dose of bupropion for weeks 2-4 was about 725 mg. Again, the most commonly used coadministered drug was a sedative, chloral hydrate or flurazepam, which was administered to 30 patients at some time during the study. In addition to the psychiatric rating scales used above, this study also employed the BPRS, the Beck Scale (mainly at center 03), and the POMS at center 01.

The sample sizes at individual centers are rather small and not all scales are included in the major efficacy analyses. Age X treatment interactions were not significant in this study. A treatment by center interaction was found with center 02 (which had enrolled male patients only) showing fewer differences than the other two centers. Baseline X treatment interactions occurred in about half the analyses with more severely ill patients doing relatively better on bupropion than on placebo. On the HAM-D factors, bupropion was significantly better than placebo on anxiety/somatization (p=.002), cognitive disturbance (p=.030), psychomotor retardation (p=.012), and sleep disturbance (p=.035). The HAM-D total was also significant at day 28 (p=.001). Other findings in favor of Wellbutrin at day 28 were CGI Severity (p=.01), HAM-A total (p=.02), SDS (p less than .05), SAS (p=.009), BPRS (p=.001). More detailed summaries are shown in the Study 08 Summary Tables which include sponsor's Tables 20, 21, 22, 25, 26, 27, 30, and 32.

3. Study 14, placebo-controlled (J. Feighner, J. Cohn):

This was a two-center study which lasted for 5 weeks (4 weeks treatment, 1 week followup. The followup was to test for withdrawal effects.) There were 117 patients enrolled with 86 being included in the efficacy analysis (26 placebo, 60 bupropion). There were 50 males and 36 females. Center 02 had 1 female and 36 males. Age range was from 23-74 (M=48.2) for placebo and 20-83 (M=45.9) for Wellbutrin. Major diagnoses were depressive neurosis about 50%, and manic depressive (depressed) about 40%. Dropouts were: Ineffective or deterioration - 19 (10 placebo, 9 Wellbutrin), adverse effects - 15 (5 placebo, 10 Wellbutrin), intercurrent illness - 3 (1 placebo, 2 Wellbutrin), did no return/elapsed/refused treatment - 11 (5 placebo, 6 Wellbutrin), administrative - 1 (Wellbutrin).

Results: The initial dosing of bupropion was 300 mg for days 1-4, 400 mg for days 5-7, and 600 mg for days 8-28. All doses were divided and given t.i.d. Adjustment within the limits could be made

by the investigator. The mean dose at days 22-28 was 466.9 mg. The doses at center 02 averaged 546.2 mg compared to 392.1 mg at center 01. The most commonly prescribed concurrent medications were Dalmane and Benadryl which were administered to 10 and 9 patients respectively. Again, the HAM-D and HAM-A, SDS, SAS, and CGI were the rating scales employed.

There were significant baseline by treatment interactions such that bupropion-placebo differences were greater in more severely ill patients. Moreover, while there were no significant age X treatment interactions, there were center by treatment interactions such that there were minimal bupropion-placebo differences in center 02, but marked differences favoring Wellbutrin at center 01. It was therefore decided to analyze the studies separately and accept them as the key analyses for this study.

Briefly, in the combined analysis, sponsor found significance for the HAM-D total, CGI-S and CGI-I at day 28 and in some instances earlier. The HAM-A and SAS showed no significant differences.

Efficacy results for center 14-01: Center 14-01 studied 49 patients, 15 on placebo and 34 on bupropion. There was a significant age X treatment interaction with younger ptients doing relatively better on Wellbutrin compared to placebo than older patients. The baseline by treatment interactions were significant at the 2-week rating only and were dropped from the analysis. On the HAM-D factors, bupropion was significantly better than placebo on anxiety/somatization, cognitive disturbance, psychomotor retardation, and sleep disturbance (p less than .01).

The CGIs were significant in favor of Wellbutrin. The HAM-A total was also significant at day 28. The SDS and SAS showed no significance.

Efficacy results for center 14-02: Center 14-02 included 37 patients in its study (11 placebo, 26 Wellbutrin). There were no significant differences at any time period on any scale. There was a large placebo response in this study. See study 14 Summary Tables which include sponsor's tables 24, 25, 27, 30, 31, 32, 33, 34, 35, 36, 38, 41, 42, 43, 44, and 45.

4. Study 09, placebo-controlled (L. Fabre, J. Mendels): This was the only placebo-controlled outpatient study. In several previous studies subjects who began as inpatients could be released and continue as an outpatient after 14 days.

LION 301 MADE IN JAPAN

This was also longer than the previous studies with a one-week placebo treated washout period, six weeks of treatment and a one-week followup. In the prior studies, it does not appear that any washout period was included. In this study, two dose ranges of Wellbutrin were compared with placebo. Each of the 3 groups shared equally in the total sample of 160 patients. Results from 97 patients were included in the efficacy analyses with 40 patients having received the low dose of bupropion, 42 placebo, and 15 the high dose of bupropion. The smaller number in the high dose group reflects sponsor's decision to delete the high dose group during the course of the study. There were 66 females and 31 males included in the efficacy analyses. Age range was 21 to 67 with an average age in the mid to upper thirties. The main diagnoses were manic depressive (depressed) - about 60%, depressive neurosis - about 35%. Dropouts occurred for the following reasons: did not return/refused treatment - 19 (6 placebo 9 low dose bupropion, 4 high dose bupropion), did not meet study criteria - 1 (LD bupropion), ineffectiveness/deterioration - 1 (HD bupropion), adverse reactions - 11 (1 placebo, 6 LD bupropion, 4 HD bupropion).

Inclusion and exclusion criteria are the same as described above.

Results: The dosage schedule was fixed/ascending with the low dose/high dose groups starting at 150/300 mg per day and increasing twice-weekly as follows 200/400, 300/600 and at day 15 400/800 mg daily. All doses were divided t.i.d. The doses could be adjusted if needed by the investigator. The mean doses ranged from 137-331 and 287-687 my per day.

The usual battery of psychiatric rating scales was included and the Hopkins Symptom Checklist (58 item) was used in addition. The most widely prescribed concomitant medications were antifertility drugs and sedative/hypnotics. The use of sedatives were somewhat lower in this study.

The usual analysis of covariance model was used. There were a number of significant interactions between age and treatment such that low dose Wellbutrin was better in younger patients and the high dose bupropion and placebo was better in older patients.

This was a negative study. The only significant differences on any of the scales were (1) LD bupropion was significantly better than PBO on HAM-D anxiety/somatization factor at day 42 ($p = .027$) and (2) the HSCL total at day 42 showed bupropion to be better than placebo ($p = .028$). The study 09 Summary Tables contain additional information. These include Sponsor's Tables # 18, 19, 20, 21, 24, 25, 26, 30, 32, 34, 35.

LION 301 MADE IN

E. Major Active Drug Controlled Clinical Trials

1. Study 10 C, imipramine controlled (B. Shopsin)

Fifty-five patients were enrolled in this outpatient single blind study. Twelve were dropped during the first week (placebo treatment period). Forty patients were included in the efficacy evaluations. Patients were divided into 4 groups, 3 dose ranges of Wellbution and imipramine. The groups were divided as follows: 9 received bupropion - 150 mg/day, 10 received 300-450 mg/day, 10 received 300-900 mg/day and 11 received imipramine 75-300 mg/day. There were 21 females and 19 males - age range was from 23-72 with a mean of 45.4. The diagnoses were: manic-depressive psychosis (depressed) - 70%, manic-depressive psychosis (circular) - 25%. Concomitant medication was not systematically employed. Sedatives were used in 10% of the patients.

Study duration was 7 weeks which included the one week placebo treated washout period. Again, assessments were made at baseline and weekly, thereafter. The same efficacy measures were employed. Dropouts occurred for the following reasons: (a) placebo responder - 6 (2 each bupropion 150 and 300-450 mg/day, 1 each bupropion 300-900 mg/day and imipramine, (b) ineffectiveness - 3 (1 bupropion 300-450 ,g/day 2 imipramine) (c) adverse experience - 1 (bupropion 300-900 mg/day), (d) intercurrent illness - 1 (bupropion 300-450 mg/day), did not return/noncompliance - 5 (2 bupropion 150 mg, 1 each in the other 3 treatments).

Results:

The observed average doses received were low dose Wellbutrin - 150 mg/day, medium dose - 360 mg/day, high dose - 785 mg/day, imipramine - 271 mg/day. There were no significant differences between treatments using pair wise comparisons with each of the 3 Wellbutrin doses and imipramine. Sponsor concludes that bupropion was as good as imipramine in reducing depression. Patients on all treatments showed similar improvement with HAM-D total scores being reduced by 1/3 to 1/2 with typical changes from 26 down to 18. See Study 10C Summary of Table #17. Additional information is shown in other tables which includes Sponsor's numbers 17, 18, 19, 20, 21, and 22. Also included are Sponsor's figures # 1-6 inclusive.

2. Study 15, amitriptyline controlled (R. Remick, A. Cooper, J. Mendels, A. Singh, M. Amin, G. Chouinard).

This was a 15 week double-blind six-center comparison of Wellbutrin and amitriptyline. One hundred twenty-four patients were enrolled and 101 patients were included in the efficacy analysis. The dosage schedule was fixed/ascending with placebo being given from days six to 0 (placebo responders were replaced if they showed improvement of 10 or more points on the HAM-D total or had a HAM-D total of 18 or less at day 0. Following the placebo treatment period, patients were given 75 mg of amitriptyline or 300 mg of bupropion for drugs 1-7. After this, the amitriptyline dose was increased to 150 mg and bupropion to 450 mg. Within these limits dosage adjustments were permitted.

The patients in the efficacy analysis included 39 on amitriptyline and 62 on Wellbutrin. The age range was 19-62 (M-about 37). Main diagnoses were; manic-depressive illness (depressed) about 70% and depressive neurosis about 20%. The most commonly prescribed medications that were coadministered were analgesics and sedatives, the latter being given to 17% of the amitriptyline patients and 30% of bupropion patients.

Results:

The observed average doses from days 8-91 were 126 mg of amitriptyline and 392 mg of bupropion.

There were no significant differences between the 2 groups at termination with both groups showing substantial improvement during the course of the study. The average decline in HAM-D total was 15.7 in both groups. See Sponsor's Summary Tables # 21, 22, 23, 25, 26, 27, 29, 30, and 31.

3. Study 21, Amitriptyline Controlled (J. Cohn, R. Miller, J. Ananth, S. Preskorn)

This was an inpatient amitriptyline controlled trial at 4 centers. The plan was to include 160 patients (40 per center, 20 per treatment at each center). The results presented here are from an interim analysis for 92 who had completed the study by October 1, 1980. Results from 65 of these patients are included in the efficacy analysis. The dosing schedule was ascending, individualized with and initial dose of 75 mg of amitriptyline or 300 mg of bupropion. After day 4, doses could be increased to 100 mg of amitriptyline or 450 mg of bupropion.

LIC'N 301 MADE IN

On day 8 the next increase to 150 mg and 600 mg was permitted. Finally, on day 11 and thereafter, respective doses of 225 and 750 mg were allowed. Study duration was six weeks. There was no washout period. The same efficacy measures were employed with the SCL-90 also being included. Dropouts were as follows: ineffectiveness or deterioration - 7 (6 bupropion, 1 amitriptyline), adverse experiences 7 (3 bupropion, 4 amitriptyline), did not return/refused treatment - 5 (2 bupropion, 3 Endep), administrative - 2 (1 each treatment). The primary diagnoses were - depressive neurosis about 53%, manic depressive psychosis (depressed) - about 25%, psychotic depressive reaction - 12%.

Results:

The observed average doses were 520-620 mg/day of Wellbutrin and 150-170 mg/day of Endep. There were no baseline or age by treatment interactions. The only significant center by treatment interactions occurred on the SCL-90. There were no significant differences between treatments. The average HAM-D total scores declined from 28.3 at baseline to 10.9 at termination for Wellbutrin patients. For Endep patients, the change was from 27.6 to 9.5. See Sponsor's Summary Tables # 22-28 and Figures 1-14 inclusive.

F. Other Efficacy Studies

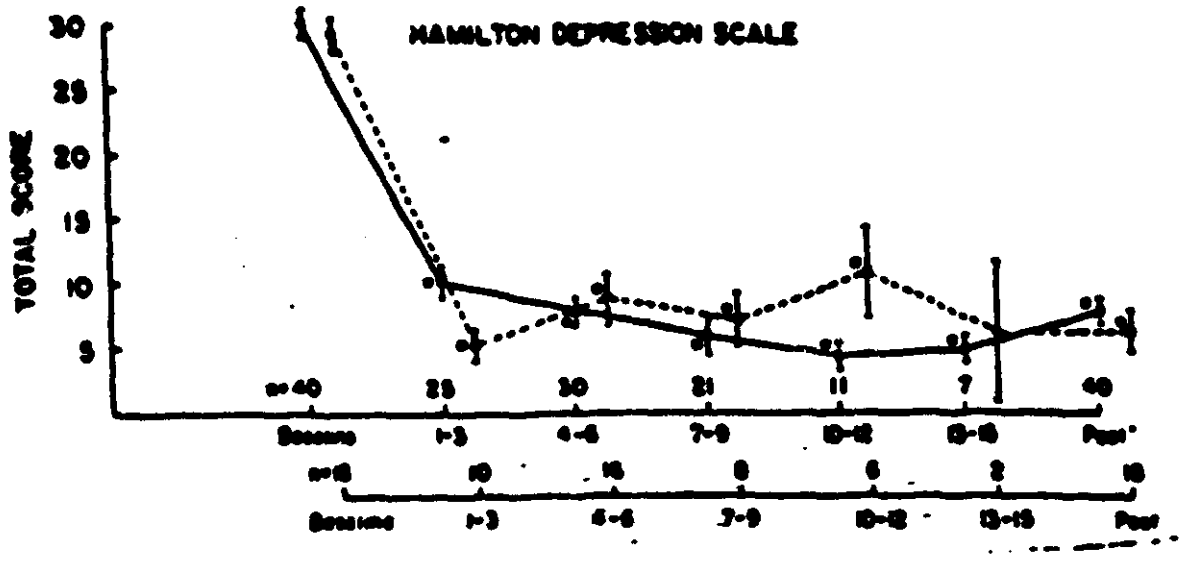
There are three other studies of efficacy which are intended to be supportive rather than primary. Two of these are uncontrolled. The third included an amitriptyline control group.

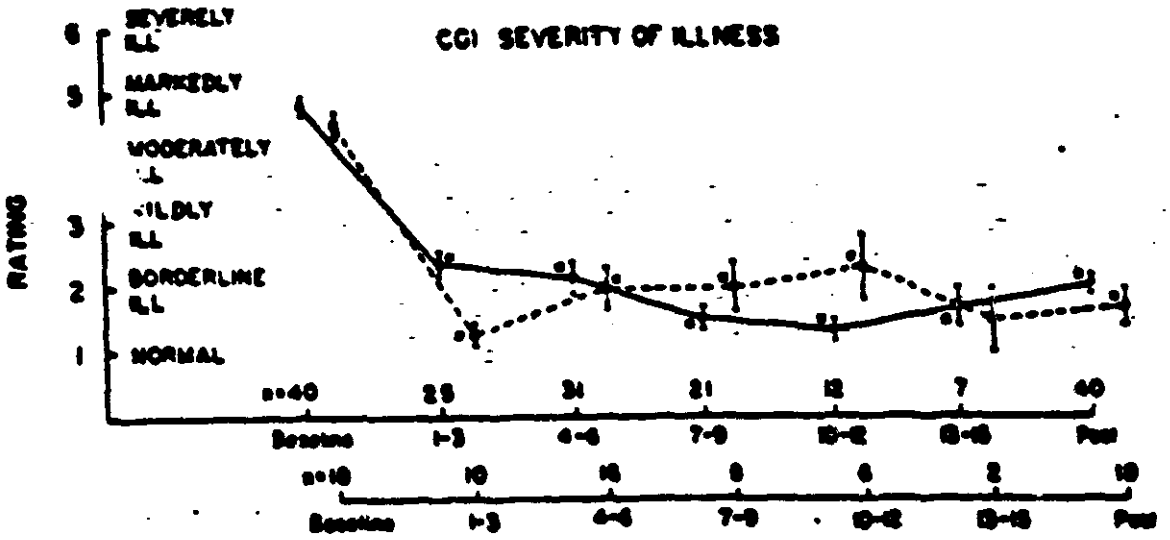
1. Study 17, amitriptyline controlled (J. Fgighner , J. Cohn, E. Othmer, M. Mandel, R. Remick, G. Chouinard, F Abuzzahab, A. Halaris).

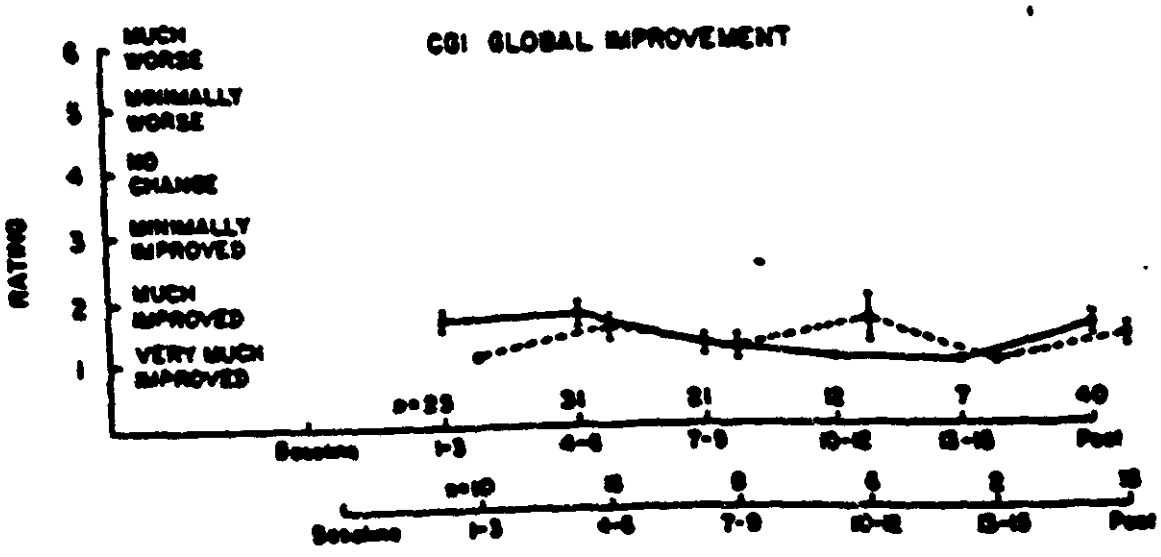
A total of 74 patients participated in this study which allowed continued treatment with study medication for up to 2 years. Forty-one patients received bupropion, 19 received amitriptyline. Total duration of bupropion therapy ranged from 2 weeks to 1 year. The average duration was 7 months. The "Continued" patients were those that received at least a 35% decrease from baseline on the Hamilton Depression Scale total score during the initial short-term study. In addition, 12 hospitalized patients who had received placebo or bupropion (less than 450 mg/day) were eligible for inclusion in the study and receive bupropion at a higher dose in an open manner. Only the HAM-D total scores and CGIs were included in this interim analysis (see Figure 2). The time periods shown in Figure 2 are

FIGURE 2

SUMMARY OF HAMILTON DEPRESSION SCALE AND CLINICAL GLOBAL IMPROVEMENT (CGI) SCORES







Observed data for each Time Period are expressed as mean values with the standard error bars and number of patients (n) indicated for baseline (start of the initial study), during drug therapy, and after (Post) drug therapy. Solid symbols joined by solid lines signify bupropion data, while open symbols joined by dashed lines signify [illegible] an asterisk (*) indicates a statistically significant

months. The solid line is bupropion data. The broken line is data for amitriptyline. The HAM-D total shows significant improvement over time (p less than .05). The CGIs also showed improvement.

2. Study 26, Uncontrolled (E. Gardner)

This was a study to assess the tolerance and effectiveness of Wellbutrin in outpatients who exhibit serious side effects with tricyclics. A total of 40 patients were to have entered the study. Twenty-one patients had entered the study by the data cutoff point. One dropped out prior to receiving drug and 2 received drug for one week or less. Eighteen patients, primarily females (average age 47.7) were included in the analysis. The average HAM-D Total Score dropped from about 11 to 7 during the course of treatment. The CGIs also improved slightly over the course of 30 weeks of treatment. The usual dose range was from 261-477 mg/day.

3. Study 35, Uncontrolled (37 centers)

A total of 380 entered the study. Of these, 359 were included in the efficacy analysis. Study duration was 29 days. The d· ing schedule was flexible with a range of 150-450 mg/day. ects were outpatients in many private practice settings.

ne results showed a significant improvement on the HAM-D total, CGI, and SDS over time. (p less than .001)

6. Discussion

This appears to be a mildly positive NDA with a number of flaws - although perhaps not fatal ones. There are statistical and safety issues which will be discussed briefly here. The full safety and statistical reviews should be consulted for more detail.

There were no comparisons with both active drug and placebo. Such comparisons while not absolutely necessary are useful. A number of studies included no washout period. In general patient rating scales showed little effect. This is a common finding. It is an "interrater reliability problem" of sorts since each patient comes into the study with different attitudes and sets and the physician drings the same sets to bear on each rating. Even so, more support on the patient rating scales would be helpful. After all the scale has presumably been sensitive to drug effects in other studies or it would presumably not be in common use.

Figure 3

POSITION

A factor structure based on a 1975 analysis of the pretreatment ratings of subjects with diagnoses of neurotic depression. (Table 10).

Factor I - Anxiety/Somatization

10. Anxiety, Psychic
11. Anxiety, Somatic
12. Somatic Symptoms, Gastro-Intestinal
13. Somatic Symptoms, General
17. Hypochondriasis
19. Insight

Factor II - Weight

16A. Loss of Weight (History)
16B. Loss of Weight (Actual

Factor III - Cognitive Disturbance

2. Feelings of Guilt
3. Suicide
9. Agitation
15. Depersonalization and Derealization
20. Paranoid Symptoms
21. Obsessional and Compulsive Symptoms

Factor IV - Diurnal Variation

18A. Diurnal Variation (Time)
B. Diurnal Variation (Severity)

Factor V - Retardation

1. Depressed Mood
7. Work and Activities
8. Retardation
14. Genital Symptoms

Factor VI - Sleep Disturbance

4. Insomnia, Early
5. Insomnia, Middle
6. Insomnia, Late

INSTRUCTIONS

7. Work and Activities - Rater may seek information from relatives or ward personnel.

9. Agitation - This item - printed in the packet as a 3-point scale - should be rated on a 5-point scale as follows:

0 = None
1 = Fidgetiness
2 = Playing with hands, hair, etc.
3 = Moving about, can't sit still
4 = Hand wringing, nail biting, hair pulling, biting of lips

16. Loss of Weight - This is an "either/or" item requiring a response to only part of the item, i.e., 16A or 16B. Actual Weight Changes (16B) is the preferred choice - particularly during the course of a study. It is suggested that Weight by History (16A) be used only at the pretreatment rating.

There is a more difficult statistical problem. Sponsor seems to have conducted covariance analyses on all studies with both baseline severity and age as covariates. Age is not typically used as a covariate and adequate justification for its use here is not presented. In the raw score analyses it appears that most patients disappear at the last rating period. This is a systematic problem that occurs in both placebo and active drug groups.

Individual item analyses for the HAM-D and SDS are not presented. The items making up the HAM-D factors are shown in figure 3. Separate analyses of some individual items such as "depressed mood", "retardation", and "agitation" would also be useful.

In conclusion this appears to be a positive submission, but its ultimate approvability will depend upon the resolution of statistical questions and the determination of whether or not the studies conducted up to this point constitute substantial evidence of efficacy.

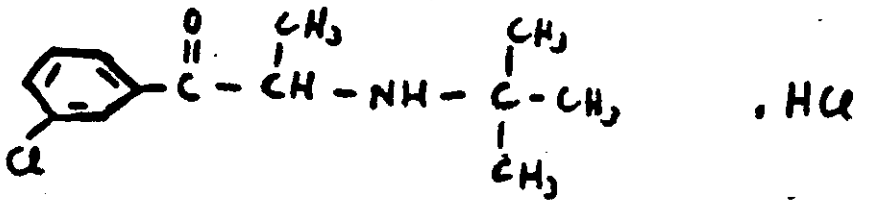
David Davis
Psychologist

Pharmacologist Review of NDA 18-644
Original Summary

SPONSOR: Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, N.C. 27709

DRUG: Wellbutrin Tablets

generic name: bupropion HCl
Code name: BW 323 U (+ others)
chemical name: 2(-tert-Butylamino)-3'-chloropropiophenone HCl (racemic mixture)



CATEGORY: antidepressant

SPONSOR's INDs For BUPROPION:

PRECLINICAL STUDIES REVIEWED:

		PAGE
1)	Pharmacodynamics	2
2)	ADME; pharmacokinetics	12
3)	Acute toxicity	16
4)	Acute toxic interactions	17
5)	12 wk. p.o. tox. in rat	17
6)	55 wk. p.o. tox. in rat	19
7)	2 yr. carcinogenesis in rat	23
8)	21/22 month carcinogenesis in mouse	29
9)	90 day p.o. tox. in dog	33
10)	1 year p.o. tox. in dog	35
11)	Mutagenicity studies	41
12)	2 generation reprod./fertility in rat	43
13)	Segment II reprod. in rat	46
14)	Segment II reprod. in rabbit (2 studies)	46, 51

All studies were performed by sponsor except the following:

6, 7, 8, 10, and 1 of the 2 segment II studies in rabbits:

Ames Test:

Bone Marrow Chromosome Study:

	PAGE
Summary	54
Evaluation	63
Recommendations	67

PHARMACODYNAMICS

All doses in mg/kg unless otherwise specified. Abbreviations used:

B	bupropion
AMI	amitriptyline
IMI	imipramine
DMI	desmethylimipramine
A	amphetamine
M	methylphenidate
DA	dopamine
NE	norepinephrine
5-HT	serotonin

A. CNS ACTIVITY

SPECIES	TEST	RESULTS
MOUSE	Prevention of tetrabenazine-induced sedation	ED 50%: B: 12.5 (i.p.) (lowest active dose = 6.5) and 32 (p.o.) AMI: 3.9 (i.p.) A: 1 (i.p.) M: 12 (i.p.)
RAT	Prevention of tetrabenazine-induced sedation	No consistent D-R effect up to 50 i.p.
MOUSE	Reversal of reserpine-induced hypothermia	B active at 12.5 + i.p. AMI - effect at 5 similar to 25-50 of B
RAT	Porsolt behavioral despair model	Approx. ED 50% (3 doses over 24 hr B: 10 i.p. (inactive at 5) AMI: 12 i.p. IMI: 10 i.p. Effect of B blocked by pre-treatm which depleted brain DA but not by that which depleted brain NE
MOUSE	Potentiation of behavioral effects of pargyline + DOPA	B active at 6.25 + i.p.; IMI equipotent
MOUSE	Locomotor activity	Approx. ED 50%: B: 25 i.p. (increased) (inacti at 6.25) A: 0.5-1 i.p. (increased) M: 6 i.p. (increased) AMI: 12.5 i.p. (decreased)

RAT	Locomotor activity	B: D-R increase at 5-50 i.p.; ED 50% about 5 A: D-R increase at 0.5-4 i.p.; ED 50% about 0.5 IMI: D-R decrease at 10-20; ED 50% about 10 Effects of B and A blocked by pre-treatment which depleted brain DA but not by that which depleted brai NE Effect of B blocked by reserpine (R and slightly by alpha-methylparatyrosine (AMT); effect of A blocked by AMT only; effect of M blocked by R only
RAT	Operant responding on a FI 60/FI 30 schedule	B increased responding during FI (10-50 i.p.); overall pattern of responding more similar to A than t IMI
RAT	Operant responding on a DLR-20 schedule	B and A decreased rewards at 25-50 and 0.5 - 2 i.p., resp. (B inactive at 5-10). IMI increase rewards at 5-30. Effect of B and A due to increase in early responses.
RAT	Geller conflict test	No antianxiety effects up to 50 i.p
RAT	Conditioned avoidance responding	Slight non-dose-related increase in avoidance at 10 and 50 (but not at 5 or 25) i.p. for B and at 0.5 - 4 i.p. for A. (IMI - no effect up to 20)
		Number of intertrial crosses (i.e. locomotor activity) increased by B at 10-50 i.p. (No effect at 5) and by A at 0.5 - 2. (IMI - slight decrease at 5 - 20).
RAT	Intracranial self-stimulation	B: dose-related increase at 25-50 i.p. (inactive at 5; slight increase at 10) A: increased at 0.5-4 i.p.; effect similar magnitude to that of B IMI: slight decrease at 10-30 i.p.

RAT	Drug discrimination (Generalization of cues produced by B at 20 i.p.)	Drugs showing generalization: A, cocaine, M, caffeine, phentermine, mazindol, tranylcypromine, viloxazine, nomifensine No generalization: DMI, AMI, TRH, fenfluramine, phenethylamine, scopolamine, diazepam, morphine, pentobarbital, haloperidol, mianserin, trazodone
MONKEY	Self-administration	B produced high rates of self-administration at 1 and 3 per i.v. injection (but not at higher or low doses); codeine at 0.32 produced lower rates.
RAT	Stereotyped behavior	Increased at 25-100 i.p. (not D-R; effect at 12.5). Degree considered mild.
MOUSE	Anorexic effect	Active at 50 and 100 (but not at 25) p.o.; fenfluramine at 30 and diethylpropion at 50 had about twice as great effect; also active at 25-50 i.p.
RAT, MOUSE	Brain NE and DA level	No effect up to 100 i.p.
RAT	Brain mitochrondial MAO	No effect up to 10^{-5}M
MOUSE	Brain and liver MAO	No effect in brain up to 100 i.p.; at this dose liver MAO (type A only) inhibited by 25%
RAT	Inhibition of amine uptake into brain slices	IC 50 (μM): NE (hypothalamus) / 5HT (midbrain) / DA (caudate) B: 32 / 90 / 7 AMI: 0.3 / 6.4 / 5.4

RAT	Inhibition of amine uptake into brain synaptosomes	IC 50 (μM): NE (hypothal.) / 5HT (hypothal.) / DA (striatum) B: 6.5 / * / 3.4 AMI: 0.1 / 0.35 / 65 IMI: 0.1 / 0.31 / 19 *10% inhib. at 10 μM
RAT	NE/DA uptake in vivo (block of AMMT -induced depletion of brain NE/DA)	DA (but not NE) depletion blocked a 50 i.p.; DMI at 30 i.p. sli[illegible]tly blocked NE (but not DA) depletion
RAT	NE/DA uptake in vivo (block of 6-hydroxy-DA-induced depletion of brain NE/DA)	DA depletion blocked at 25-100 i.p. D-R (no effect at 12.5); slight effect on NE at 100. DMI blocked NE (but not DA) depletion at 5-30 i.p.
RAT	ATP - Mg++ - stimulated uptake of NE/DA into brain synaptic vesicles	IC 50 (μM): NE: 33 (5 x less potent than in synaptosomes) DA: 60 (20 x less potent than in synaptosomes)
RAT	Spontaneous release of amines from synaptosomes	No effect on NE, DA, or 5 HT at 10^{-4}M
RAT	DA turnover in striatum (AMT method)	Increased at 50 and 75 (but not 25) i.p.
RAT	Binding assays (brain membrane fragments)	Weak inhibition of binding of [illegible]-41 (IC 50 = 51 μM vs 0.08 for IMI) and clonidine (60% inhibition at 10 μM). Little or no inhibition of the following ligands at 8 concentrations of 100-1000 μM: dihydroalprenolol, dopamine, spiroperidol, GABA, diazepam, 5-HT
RAT	NE-stimulated adenylate cyclase in cortical slices	No effect at 3000 μM
RAT/MOUSE	Beta receptor desensitization (DHA binding to brain membrane fragments)	Seen with B at 50 i.p. (3x/day for 4 days) in 1/2 of studies; DMI at 10 i.p. (2x/day for 4 days) showed a more consistent effect.

MOUSE	Anticonvulsant	ED 50 = 17 i.p. vs ECS seizures (ED 50 for AMI and DPH = 7 and 9 resp.) ; No effect vs metrazol up to 75 i.p.
RAT	Antagonism of B-induced seizures	Pretreatment with phenobarbital, trimethadione, and chlordiazepoxide (CDP), but not DPH, prevented seizures due to B at 200 i.p.; CDP was most potent (partial protection at 2.5, complete at 5 i.p.) When above drugs given after start of seizures, all (but DPH) shortened the seizure; CDP most potent (active at 5-10 i.p.)

B. CARDIOVASCULAR/AUTONOMIC

SPECIES	TEST	RESULTS
DOG	Various CV parameters	1) Anesthetized, open chested: at 10-20 i.v., decreases in MAP (20-64%), HR (10-20%), CO (15-54%), and right ventricular contractile force (60-70%); effects mostly transient; no effects on above at 5 i.v. 2)-Anesthetized, close-chested: at 5-10 i.v., transient decrease in MAP (40-75%) and transient increase in HR (15-34%). When given as a slower infusion (2 mg/kg/min), effects were of smaller magnitude, and in 1 study a slight increase in MAP (5-10%) was seen with 5 mg/kg. No effect on EKG (arrhythmias, PR, QTc) after 5-10 i.v. (2 mg/kg/min). 3) Conscious dogs: After 20 p.o., 10% and 10-20% increased MAP and HR resp., up to 6 hr.; returned to baseline at next measurement (24 hr.)

CAT	B.P. and H.R. in anesthetized cats; vagi sectioned	1, 2.5, 5, and 10 i.v. (4 min. infusions) given sequentially over 2 hr.; non D-R increases in BP (20%) up to 5 but 31% decrease at 10 (all transient); cumulative increase in HR (23%) with some increase after each dose.
RAT	BP and HR in conscious rats	No effect at 25 p.o.; at 50, HR increased (25%) with gradual return to control by 3 hr., no effect on BP
DOG	Respiratory rats (RR) and minute volume (MV) in anesthetized dogs	At 5 i.v., transient increase in RR (68%) and MV (22%); at 10, transient decrease (39%) followed by longer lasting increase (peak 26%) in MV with large increase in RR (100-150%) which was still elevated (60%) at 1 hr.
RAT/GUINEA PIG	Spontaneously beating right atria (<u>in vitro</u>)	1) RAT: D-R decrease in rate and force of contraction at 10^{-6}M +; ED 50% = 1.4×10^{-4}; complete blockade at 3×10^{-4}. AMI and IMI 5-10 x more potent. 2) GUINEA PIG: D-R decrease in rate of contraction at 10^{-5} M +; ED 50% = 1.5×10^{-4}; complete blockade at 3×10^{-4}.
GUINEA PIG	Isolated left atria (stimulated) (<u>in vitro</u>)	No significant effect up to 10^{-4} M
GUINEA PIG	Evoked action potential (AP) in atria (<u>in vitro</u>)	Decreased amplitude of AP and decreased dv/dt, and increased effective refractory period and AP duration at 10^{-5}M + D-R. Excitation totally inhibited at 5×10^{-4}M; IMI and AMI 10 x more potent.
DOG	Isolated Purkinje fibers (<u>in vitro</u>)	Decreased frequency of spontaneous depolarization at 10^{-6} M + ; complete block at $2\text{-}3 \times 10^{-4}$ (AMI, IMI 10 x more potent). At high doses (10^{-4}M +) decreased amplitude of evoked AP, decreased dv/dt, and increased effective refractory period.

DOG	Isolated papillary muscle (in vitro)	At 10^{-4}M +, decreased amplitude of evoked AP and decreased dv/dt an increased effective refractory period. Blocked excitation at 10^{-3}M (AMI and IMI 12-13 x more potent)
CAT	Isolated papillary muscle (in vitro)	No effect on electrically-stimulate contraction up to 3 x 10^{-5}M.
CAT (anesthetized)	1) Contraction of nictitating membrane by preganglionic stim. of cervical sympathetic nerve. (Measure of sympathetic function)	1, 2.5, 5, and 10 i.v. (4 min. infusions) given sequentially over hrs.: 1) No effect on response to stimul tion; direct contraction occurred 2 of 5 cats (slight).
	2) Heart rate after vagal stim. (Measure of para-sympathetic function)	2) D-R inhibition; after 10 mg/kg. 50% inhibition with return to baseline after 30-40 min. (In another study, no effect after a single dose of 10).
DOG (anesthetized, vagotomized)	Effect on pressor response to NE and tyramine	D-R potentiation of NE at 0.3 + i.v (no effect at 0.1); IMI and DMI 10 more potent and DMI shown to have much longer lasting effect. No consistent effect on tyramine (possible slight inhibition at 9 i.v.) whereas DMI caused 95% inhib tion at 1 i.v.
RABBIT	NE uptake into isolated aorta	Weak inhibition; IC 50 = 10 μM (AMI and IMI 50 x more potent)
RAT	Effect on chromodacryorrhea due to methacholine	No effect up to 50 i.p. AMI cause 84% inhibition at 25 i.p. and atro pine caused complete block at 1 i.
MOUSE	Pupil diameter	D-R dilation at 25-200 i.p. ; AMI and Atropine about 5 and 400 x mor potent, resp. B did not impair accomodation as did AMI and atropi
GUINEA PIG	Acetylcholine-induced contraction of ileum	2 x shift-to-right of acetylcholin D-R curve at 10^{-4} M; no effect at 10^{-5}. (IMI caused shift-to-right of 10 x and 490 x at 10^{-6}M and 10^{-5}M, resp., and complete block of acetylcholine at 10^{-4}.)

RAT	Acetylcholine-induced contraction of anococcygeus muscle	No effect at 10^{-5}M
GUINEA PIG	Field-stimulated contraction of ileum (under conditions said to be a measure of acetylcholine release)	Dose-related inhibition at 10^{-5} M +; EC 50% = 3.1×10^{-5}M.
RAT	NE* release from anococcygeus muscle	No effect at 10^{-4}M. Tyramine increased release 150 and 350% at 10^{-5} and 10^{-4}M, resp.
GUINEA PIG	Chronotropic response of atria to NE and isoproterenol	At 10^{-5}M, NE D-R curve shifted 3 x to left; no effect on response to isoproterenol. At 10^{-4}M, no effect on response to NE in electrically driven atria.
CAT	Response of papillary muscle to isoproterenol	No effect at 3×10^{-5}M
GUINEA PIG	NE-induced relaxation of trachea	No effect on NE response (or spontaneous tone) up to 10^{-4}M
RABBIT	NE-induced contraction of aortic strips	50% inhibition at 10^{-5}M; no effect at 10^{-7}M. No direct agonist action at these concentrations
RAT	NE-induced contraction anococcygeus muscle	Potentiation at 10^{-5}M. (Less than 10 x shift of NE D-R curve to the left.)
RAT	5-HT induced contraction of rat fundus and anococcygeus muscle	No effect on fundus response to 5HT at 10^{-5}M (slight direct contraction by B seen at this concentration); slight (about 10x) shift to right of D-R curve for 5HT on anococcygeus muscle at 10^{-4}M.
GUINEA PIG	5-HT induced contraction of ileum	D-R curve for 5-HT shifted to right at 10^{-5} and 10^{-4}M, dose-related. (approx. 10 x and 100 x shift, resp.)
GUINEA PIG	Histamine-induced contraction of ileum	D-R curve for histamine slightly shifted to the right (less than 10 x) at 10^{-4}M.

C. MISCELLANEOUS

SPECIES	TEST	RESULTS
GUINEA PIG	Local anesthetic activity (cornea)	Active at 2.5-10 mg/ml; equipotent with cocaine.
MOUSE	Effect of grouping on lethality	No effect on i.p. LD 50 for B; LD 5 for A was decreased. B at 25 i.p. decreased the lethality of A at 20 i.p. in grouped mice; AMI at 5 and 10 i.p. did not have this effect.
VARIOUS	Interactions with phenelzine	No significant potentiation of B effects by doses of P causing significant MAO inhibition were seen in several tests (mice-tetrabenazine-induced sedation; rats - Porsolt test, BP, HR; anesthetized dogs - BP; HR; and spontaneously beating or electrically driven rat atria.)
MOUSE	Body temperature (rectal)	1°(c) decrease at 30 i.p. 4° decrease at 100 i.p. (AMI caused 2° decrease at 12.5, A caused 3° increase at 10).

ADME; PHARMACOKINETICS

A. Plasma levels

1. Rat

After 50 mg/kg i.p., plasma levels of unchanged B (method:HPLC) peaked within 30 minutes and declined with a T 1/2 of 2.3 and 0.95 hr in M and F, respectively. In another study in F, after 30 mg/kg p.o., plasma level of unchanged B (method = RIA) peaked within 30 minutes and declined biphasically, with an initial (within 1 hr.) sharp decline followed by a terminal T 1/2 of 4 hr.; however plasma levels of metabolites were many times higher than those of unchanged drug (5-30 x up to 8 hr.; 100 x at 12 hr.) and declined much more slowly (T 1/2 about 12 hr.). In another study 10 mg/kg was given p.o. and i.v. Serum (and brain) levels of unchanged B (method:RIA) were several fold higher in F than M up to 24 hr. post-dose, although sex differences in T 1/2 were not apparent in this study. Comparison of serum AUC for p.o. and i.v. routes gave a bioavailability of 8 and 21% in M and F, respectively; similar values were found using brain AUC.

In another study, F rats were given 10, 30, or 100 mg/kg orally; plasma levels of unchanged drug increased with increasing doses but slightly less than proportionally at the highest dose; levels of metabolites also increased with increasing dose but less than proportionally at all doses.

2. Mouse

In males, after 50 mg/kg i.p., whole body levels of unchanged drug (method:methyl orange/spectrophotometry) peaked within 15 min. and declined with a T 1/2 of 45 min.; however, metabolite levels remained relatively constant up to 2-4 hr. before declining.

3. Dog

B was given at 10 mg/kg p.c. or i.v. Plasma levels peaked at 1/2 hr. after p.o.; decline in plasma levels by both routes was biphasic with an initial sharp decline within 2 hr. followed by a terminal T 1/2 of about 2 hr. No sex differences in plasma levels were apparent, although N was only 2/sex. A comparison of plasma AUC for i.v. and p.o. gave a bioavailability of 4%.

B. Tissue distribution

Male and female rats were given 50 mg/kg i.p. and sacrificed at 1 hr. Levels of unchanged B (method:methyl orange/spectrophotometry) were highest in lung (25x plasma levels) followed by kidney, and lowest in plasma. After 50 mg/kg given p.o., highest levels were found in liver

(30-33x plasma levels), followed by lung, and lowest in plasma. (Highest level in males was actually in intestine, but it is not clear how much of this was in intestinal contents.) After both routes, brain levels were 10-12x those in plasma; another study showed that B enters brain rapidly with peak level after p.o. administration reached at the same time as peak plasma level (15 min.). After both routes, levels in all female tissues studied were 2-3x those in male tissues.

In another study, female rats were given labelled B orally at 10, 30, or 100 mg/kg and sacrificed at 1 or 6 hr. Unchanged drug was assayed by RIA and metabolites by subtraction (i.e., total label minus unchanged drug). As found above after p.o., highest levels of unchanged drug were found in liver; lowest in plasma. Tissue levels of unchanged drug increased with increasing dose but not always proportionately (sometimes more, sometimes less). At 6 hr., tissue levels of unchanged drug declined to approximately 1/2 - 1/10 those seen at 1 hr. In contrast to unchanged drug, levels of metabolites were generally highest in lung (3-6x plasma). (Levels in liver were 1.5-2x those in plasma except approximately equal to those in plasma after 100 mg/kg). Tissue levels of metabolites increased with increasing doses but generally less than proportionately. The decline of plasma and tissue levels of metabolites over the 1-6 hr. period was usually much slower than that of unchanged drug; occasionally an increase in metabolite level over this time period was seen. Thus levels of metabolites at 6 hr. were generally several fold higher than those of unchanged drug. (Exception: brain, where metabolite level at 6 hr. was ≤ that of unchanged drug). At 1 hr. post-dosing, the level of metabolites in plasma and tissues was also generally greater than that of unchanged drug, but this effect was smaller than that seen at 6 hr. (One exception was brain where levels of unchanged drug were several fold higher than those of metabolites at 1 hr.). In this study pregnant rats also received the same doses of drug on day 16 of gestation, and results were generally similar to those for non-pregnant rats. Fetal levels of unchanged drug were 4-10x those in maternal plasma, and declined in parallel with those in maternal plasma. Fetal levels of metabolites were variable (1/3-3x maternal plasma) with no apparent accumulation during the 1-6 hr. measurement period.

C. Plasma protein binding

(Method: equilibrium dialysis)

SPECIES	CONCENTRATION RANGE (μM)	% Bound
Mouse	3-357	75
Rat	3-298	77
Dog	3-357	81
Man	0.35-8	86
	50-800	82
	1000	75

D. Metabolism

B was shown to be rapidly and extensively metabolized in the species studied. One indication of this is the low oral bioavailability of the drug (above) as contrasted with the high degree of absorption of total label after oral dosing (see excretion studies, below), suggesting a large first-pass effect. In female rats receiving 30 mg/kg p.o., plasma levels of metabolites peaked at the same time (0.5 hr.) as those of unchanged drug, and were greater than those of the latter at all time points measured (5-30x up to 8 hr.; 100x at 12 hr.). Tissue levels of metabolites in rats receiving 10, 30, or 100 mg/kg p.o. were also generally greater than those of unchanged drug at 1 and 6 hr. post-dosing (exception: brain). The rate of decline of metabolites from plasma and tissues was significantly slower than that of unchanged drug in rats.

Twenty-four hour urine and fecal samples from rats were treated with 30 mg/kg p.o. showed only trace amounts of unchanged drug (less than 0.2 % of dose, except for 0.3-2.8% in female urine). Acidic metabolites accounted for 86% of the urine label (71% of dose excreted in urine); no basic metabolites were demonstrated. Twenty-four hour urine from a dog given 50 mg/kg p.o. had 88% and 3% of urine label as acidic and basic metabolites respectively (94% of dose excreted in urine). In contrast, in man, 24 hr. urine had 56% and 45% of label as acidic and basic metabolites, respectively (dose not stated for man.)

Two metabolites were identified (method:HPLC) in 24 hr. rat urines (after 30 mg/kg p.o.): m-chlorohippuric acid (about 25% of dose, or about 1/3 of urine label) and m-chlorobenzoic acid (about 2-3% of dose.) These compounds were also present in 24 hr. feces (2-3% of dose). A conjugate of m-chlorohippuric acid was identified in urine but apparently not quantitated. In 24 hr. dog urine (single dog, 50 mg/kg p.o.) m-chlorohippuric acid and m-chlorobenzoic acid represented about 42% and 4%, respectively, of the dose (45% and 4% respectively, of the urine label).

E. Excretion

1. Rats

30 mg/kg p.o. of labelled B was given; 96 hr. urinary and fecal excretion of label was 78% and 19% respectively, mostly complete by 24 hr. Less than 1% of the dose was found in the carcass at 96 hr. No sex differences were apparent. These results suggest that at least 78% of the drug is absorbed; this figure is probably higher since only trace amounts of unchanged drug was found in feces (above).

2. Dog

One dog received 50 mg/kg p.o. Seven day urinary excretion was 100% of dose (94% in 24 hr.), suggesting complete absorption.

F. Enzyme Induction

1. Plasma and tissue levels of B in rats

Male rats received 0.5, 5, 15, or 50 mg/kg/day, p.o., for 13 days; on day 14 they received 50 mg/kg i.p. and were sacrificed 1 hr later for assay of plasma B. Levels were below acute control (about 50%) at HD only. However, in another study decreases were seen at both 15 and 50 mg/kg (39 and 22% of control level respectively). No effect on liver weight, microsomal protein, or cytochrome P450 was seen. The ability of liver microsomes from these rats to metabolize B and pentobarbital *in vitro* was studied; slight but statistically insignificant increases were seen at the higher doses.

In another study, males and females received 50 mg/kg/day p.o. for 4 days; on day 5 they received 50 mg/kg i.p. and were sacrificed 1 hr. later for assay of tissue B. The levels in the various tissues were about 1/6-1/10 of rats treated acutely.

2. Whole body levels of B in mice

Mice received 50 mg/kg i.p. daily for up to 10 days; whole body B levels were decreased on days 8 and 10 to 63 and 42%, respectively of acute controls. Levels of metabolites were unchanged.

3. Plasma levels of B in dogs

Dogs received 40 or 80 mg/kg/day p.o. for 1 year; on day 366 B levels were 25% and 3-10% of those on day 1 at 40 and 80 mg/kg, respectively. (Levels measured 3 hr. after dosing.)

4. Effect of B on pentobarbital hypnosis (rats, mice)

Doses: 5, 10, 25, 50, 100 or 150 mg/kg/day p.o. for 10 days (latter 2 groups received 50 mg/kg first 5 days). Positive control: phenobarbital at 80 mg/kg. On day 11 animals received a hypnotic dose of pentobarbital.

Results: Rats — Slight decrease (20%) in sleep time at 100-150 mg/kg; 88% decrease with phenobarbital. No effects on lag time to sleep (slight non-dose-related decrease seen with B).

Mice — Dose-related decrease in sleep time; 65% decrease at 150 mg/kg (vs 75% for phenobarbital). No effects on lag time to sleep.

ACUTE TOXICITY:

A. LD 50

SPECIES	STRAIN	ROUTE	SEX	WEIGHT	LD 50 (mg/kg)
Mouse	CD-1	P.O.	M	22 g	544
		P.O.	F	19 g	636
		I.P.	M	27 g	273
Rat	Long-Evans	P.O.	M	105g	607
		P.O.	F	99 g	482
		I.P.	M	130g	263

B. Observed signs

1. Mouse, p.o.

Dosage range = 400-700 mg/kg; deaths seen at all doses and occurred from 5 min.-2 days post-dose. The following signs were seen at all doses: ataxia, prostration, clonic convulsions, ptosis, compulsive gnawing.

2. Mouse, i.p.

Dosage range = 200-300 mg/kg; no deaths occurred at 200 or 250 mg/kg (1/20 deaths at 225). Deaths occurred within 17 min. post-dose. The following signs were generally dose-related and most were seen at all doses: ataxia, clonic convulsions or opisthotonos followed by prostration, labored breathing, decreased respiration, salivation, ptosis, and compulsive gnawing.

3. Rat, p.o.

Dosage range = 400-700 mg/kg; deaths seen at all doses. Most deaths occurred 1-22 hr. post-dose but some were delayed (4-5 days). Most of the following signs were seen at all doses: ataxia, loss of righting reflex, labored breathing, prostration, salivation, ptosis, arched back, and compulsive gnawing.

4. Rat, i.p.

Dosage range = 175-275 mg/kg; no deaths occurred at 175. Deaths occurred within 10-25 min. post dose. Signs were the same as for p.o.; most were seen at all doses.

ACUTE ORAL TOXIC INTERACTION STUDIES (RATS):

A. Bupropion (B) + phenelzine (P)

P, given at highest no-effect and highest non-lethal doses, 3 hr. before B, caused marked decreases in the LD 50 of B. (Degree of decrease hard to calculate from data, but at least 2x). Time to death also decreased. Symptoms potentiated by the combination were salivation, decreased activity, and prostration.

B. Bupropion (B) + 50% ethanol (E)

E given 30 min. after B. The highest non-lethal dose of E decreased the LD 50 of B by 39% in F. The highest non-lethal dose of B caused only very slight decreases in the LD 50 of E (NS in F). No potentiation of toxic signs. (In another study, the highest non-lethal dose of amitriptyline decreased the LD 50 of E by 36% and 20% in M and F, respectively; NS in M).

C. Bupropion (B) + amitriptyline (AMI)

AMI given 3 hr. before B. At 1/2 LD 50 of B + 1/2 LD 50 of AMI, 8/10 and 5/9 deaths were seen in F and M, respectively; thus potentiation occurred in F only. No potentiation of toxic signs.

12 WEEK P.O. TOXICITY IN RATS:

A. Dosage

10 M and 10 F at 0, 150, 300, or 450 mg/kg/day by gavage. (For first 12 days, doses were 100, 200, and 300 mg/kg in LD, MD, and HD, respectively)
Strain: Long Evans

B. Results

1. Observed signs

   a. Urinary incontinence, dose-related
   b. Blood in urine, seen after 5 weeks
   c. Irritability

2. Mortality - 1 LD, 2 HD

3. Body Weight - slightly increased gain in HD F

4. Hematology (post-study)

   a. Hb

   Very slight decrease in all groups, dose-related in F. Maximum mean decrease was to less than 10% below control mean. No extremely low values.

b. Hct

Slight decrease in all M groups, not dose related. Mean values 10% below control. No extremely low values. No effect in F.

c. MCHC

Very slight dose-related decrease in all F groups; no unusually low values.

5. Blood chemistry (post-study)

a. glucose

Slightly decreased at MD and HD (about 15% below C); no unusually low values

b. total protein

Dose-related increase in all groups. Mean at HD 9 and 16% above control in M and F, respectively. Most rats were affected but none showed extremely large elevations.

c. Other parameters measured: BUN, SGOT, SGPT, AP

6. Organ weights

a. Liver

Increased absolute and relative weight at MD and HD. At HD, mean relative weight was 48 and 35% above control in M and F, respectively.

b. Kidney

Slight dose-related increase in absolute and relative weight in all groups but LD M. At HD, mean relative weight was 12 and 14% above control in M and F, respectively.

c. Other organs weighed: heart, spleen, testes, brain

7. Gross pathology - no drug effect

8. Histopathology - (H+E stain)

Hyperplasia and/or prominent cellular organelles seen in liver of 0/20 controls, 3/20 LD, 4/20 MD, and 4/20 HD.

25 WEEK P.O. TOXICITY IN RAT:

A. Dosage

60 M + 60 F at 0 (untreated), 0 (vehicle), 25, 50, or 100 mg/kg/day, by intubation. Charles River CD rats used.

B. Results

1. Observed signs

a. Most prevalent: dose-related increase in yellow staining of hair around anogenital region

b. Also seen mainly in treated rats: dry brown material around nose or mouth and moisture around mouth.

2. Mortality

No drug effect. Overall mortality 50-60% in M and 20-25% in F. Most deaths said to be due to intercurrent respiratory disease. Untreated controls had lower mortality than other groups.

3. Bodyweight gain

Very slight decrease in HD M; final weight 5% below vehicle control.

4. Food consumption - no drug effect

5. Ophthalmoscopy

(pre-study and at 12 months in all rats, binocular indirect ophthalmoscope)

No clear drug effect. Cataracts in 2 LD and 2 MD; retinal detachment in 1 LD; neither of these findings at HD

6. Laboratory tests - (10/sex/group at 12 months)

a. Hematology

1. 1 HD M and and 1 HD F had low RBC, Hb, and Hct, and (in F only) high WBC. Group means showed no effect.

2. Other parameters measured: WBC differential.

b. Blood chemistry

1. Glucose

Slight decrease seen in most MD rats (mean 15% below control); slight increases seen in most MD F (mean 18% above control). Values stated to be WNL.

2. BUN

Elevated in 1 MD and 2 MD F (2x control). One MD F had marked focal chronic nephritis; no unusual kidney histopathology in the MD; not examined in the other MD.

3. SGOT/SGPT

Elevations of both seen in 1 LD F and 1 MD M. The M also had slightly decreased albumin (no change in total protein, slightly increased RBC, Hb, and Hct, decreased MBC, slightly increased % neutrophils, and slightly decreased % lymphocytes. No unusual histopathology in the M (kidney and spleen only); not performed in the F.

4. Total protein

Very slight increase in 1 MD F and 1 HD F; moderate increase (50% above control) in 1 HD F (the same rat with elevated BUN and nephritis, above).

5. Other parameters: AP, albumin

c. Urinalysis

1. Color mostly "straw" in control M and F and LD M, and mostly "light straw" in all other groups

2. Other parameters: volume, pH, SG, albumin, glucose, bilirubin, occult blood, ketone, sediment.

7. Organ weight

a. Liver

Absolute weight increased in all groups; dose-related increase in relative weight in all groups (15-18% above control at MD)

b. Kidney

Absolute and relative weight increased in all groups except LD M; effect on relative weight generally dose related, 16 and 7% above C in MD M and MD F, respectively.

c. Thyroid/parathyroid

Increased absolute and relative weight in HD M and HD F (relative weight 57 and 22% above C, respectively)

d. Adrenal

Increased absolute and relative weight in HD M (relative weight 29% above C)

e. Pituitary

Increased absolute and relative weight in HD M when compared to untreated control (relative weight 36% above untreated control); vehicle control value elevated due to one extremely high value.

f. Other organs weighed: testes, brain

8. Gross pathology

No clear drug effect. Enlarged liver seen in 1/29 HD M, 1/24 HD M, and 1/18 HD F which died before termination (vs 0/30 control M and 0/14 control F)

9. Histopathology

(Routine H and E exam in 15/sex in C and HD; spleen and kidney only in 15/sex in LD and MD. Iron stained sections of liver, kidney and spleen in 15/sex/group and bone marrow in 15/sex in C and HD were examined. All rats examined in C and HD were sacrificed at termination, as were 18/30 LD and 23/30 MD, the remainder having died after week 30 except 2 MD M (weeks 20 and 25).

a. Spleen

By H & E stain, increased amount of hemosiderin pigment in red pulp seen in all M groups regarding both incidence and severity and in all F groups regarding severity only (incidence in control F nearly 100%):

		M	F
Incidence:	C	7/15	14/15
	LD	10/15	15/15
	MD	12/15	14/15
	HD	15/15	13/15
Severity: (Sum of severity scores/# of rats affected	C	2.7	3.5
	LD	2.8	3.8
	MD	2.9	3.9
	HD	3.4	4.2

However, by iron staining, hemosiderosis was present in all rats examined with the only pronounced effect on severity seen in HD M with smaller equivocal effects in LD and MD M and HD F:

	M	F
C	3.5	4.6
LD	3.9	4.4
MD	3.8	4.5
HD	4.3	4.8

b. Kidney

1. Increased incidence of yellowish-brown pigment in cytoplasm of proximal convoluted tubule at HD (24/30 vs 9/30 in control); severity also greater.

2. Slightly increased incidence of focal chronic nephritis at HD (14/30 vs 9/30 control); severity slightly increased.

3. Slightly increased severity of hemosiderosis (iron stain) at HD; no effect on incidence (seen in nearly all rats.)

c. Lung

Focal aggregates of alveolar macrophages with hemosiderin pigment seen in all C and HD, but severity slightly greater at HD

d. Liver

Increased incidence of hemosiderosis (iron stain) in HD M (11/15 vs 5/15 control) but no effect on severity.

23-24 MONTH RAT CARCINOGENESIS STUDY

A. Dosage

75 M and 75 F at 0, 100, 200, or 300 mg/kg/day, by gavage. (HD received 500 mg/kg on days 1-15 and 400 mg/kg days 16-74)

Interim sacrifice (5/sex/group) at 6 months; terminal sacrifice at 23 and 24 months in M and F, respectively

Strain: Charles River CD

B. Results

1. Observed signs

   a. Intermittent convulsions, dose-related (10-20% incidence at HD for the selected weeks shown)

   b. Moisture and red/brown material around mouth, dose-related.

   c. Yellow material on anogenital region, dose-related.

2. Mortality

Dose-related increase in all groups except LD M. One-hundred week survival:

	M	(Week of 50% Survival)	F	(Week of 50% Survival)
C	27/70	(81)	49/70	(> 104)
LD	32/70	(95)	40/70	(> 104)
MD	20/70	(81)	25/70	(90)
HD	3/70	(42)	14/70	(51)

3. Bodyweight

   a. M - decreased gain in all groups (final weight 10, 17, and 16% below control in LD, MD, and HD, respectively.)

   b. F - slight dose-related increased weights seen during most of study (10% above C at HD), although final weights 2-4% below C.

4. Food consumption - very slight increase at HD

5. Ophthalmoscopic exam

(All rats, pre-drug and months 6, 12, 18, 24; binocular indirect ophthalmoscope)

Slight increase in incidence of cataracts and/or lens opacity at HD. (Not seen at HD; however this might have been obscured by the high mortality at HD and the fact that most of the findings occurred late in the study.)

6. Laboratory tests

(10/sex/group at months 6, 12, and 23/24 [except only 3 M left at 23 months]).

a. Hematology

No consistent drug effects (RBC, Hct, Hb, MBC, differential)

b. Blood chemistry

1. Glucose - slight decrease in all M groups at months 6 and 23 (but not 12) and in HD F at 24 months

2. Other parameters: BUN, total protein, albumin, AP, SGOT, SGPT

c. Urinalysis

1. Volume - slight dose-related increase in all M groups at 23 months

2. Other parameters: color, appearance, pH, SG, albumin, glucose,, bilirubin, occult blood, ketones, sediment.

7. Organ weight

(5/sex/group at 6 months, plus all surviving animals at termination)

a. Liver

Dose-related increase in absolute and relative weight in all groups. Relative weight at HD 32% and 51% above control at 6 months and termination, respectively.

b. Kidney

1. M - dose-related increased in absolute and relative weight in all groups. Relative weight at HD 21% and 45% above control at 6 months and termination, respectively.

2. F- increased absolute and relative weight at HD at 6 months (relative weight 13% above C) and in all groups at termination (not dose-related; relative weight 16% above C)

8. Gross pathology

(Separate incidence values were presented for deaths at 0-6 months, 6 month interim sacrifice, deaths from 6 months - termination, and terminal sacrifices.)

a. No drug effects at 6 month sacrifice; no effect among deaths 0-6 months aside from increased incidence of bloody oral or nasal discharge at MD and HD (see observed signs).

b. Urine/feces/red material on ventral surface or tail increased in all F groups (see observed signs).

c. Liver

1. Mass/nodule/raised area - slight increase in F at termination (3/43, 8/38, 2/24, 5/12 in C, LD, MD, HD, respectively) but no effect among deaths (6 months-termination) or overall combined.

2. Dark red/brown foci/hemorrhagic foci/area - increase in all groups but LD F at termination:
M: 4/27, 17/31, 11/20, 1/3 in C, LD, MD, HD
F: 7/43, 6/38, 10/24, 3/12 in C, LD,, MD, HD

3. Grey/yellow foci/area - slight increase in F at termination (1/43, 5/38, 2/24, 3/12 in C, LD, MD, HD)

d. Lung

Increased incidence of yellow/white/grey foci in all groups at termination:
M: 9/27, 12/31, 12/20, 3/3
F: 9/43, 17/38, 19/24, 11/12

9. Histopathology

(H&E stain. Complete exam in C, MD, and HD rats which died during the study [except not done in MD which died during first 6 months], in 5/sex in C and HD sacrificed at 6 months, and in all C, MD, and HD which were sacrificed at termination. Exam at LD limited to liver, tumors, and gross lesions suspected of being tumors.)

(Separate incidence values for non-neoplastic findings were presented for deaths at 0-6 months, 6 month interim sacrifice, deaths from 6 months-termination, and terminal sacrifice. One exception to this was liver findings which were presented in 1 overall table; however certain findings were tabulated separately by M.I.T. consultants and will be presented below. Neoplastic findings were also presented in one overall table.)

a. Neoplastic findings

There were no drug-related increases in either total benign or malignant tumors (corrected for increased mortality in drug groups by use of life-table analyses) or in any specific tumor type. Tumors with the highest incidence were mammary fibroadenoma/adenoma in F and pituitary adenoma; all others generally had an incidence of less than 5%. (Results for hyperplastic nodules in liver, which were increased in drug groups are given below under "non-neoplastic" findings since there is no evidence that these nodules were neoplastic. (See Evaluation.)

b. Non-neoplastic findings

1. Liver

a. Hyperplastic nodules

Increased incidence in all groups. The following incidence values are taken from an M.I.T. consultant report which breaks down the results into incidence at terminal sacrifice vs. incidence among rats which died week 28 and later:

		M	(%)	F	(%)
Terminal Sac:	C	2/27	(7%)	1/43	(2%)
	LD	7/31	(23%)	7/38	(18%)
	MD	7/20	(35%)	5/24	(15%)
	HD	1/3	(33%)	4/11	(36%)
Deaths:	C	0/37	(0)	0/25	(0)
	LD	1/29	(3%)	2/23	(9%)
	MD	0/43	(0)	3/40	(8%)
	HD	0/47	(0)	1/35	(3%)

It can be seen that the majority of nodules were not observed until the terminal sacrifice, suggesting a late appearance.

b. Hepatocellular hyperplasia

Increased at LD and MD. Described mainly as focal and slight or very slight:

M: 10/73, 26/72, 15/70, 2/64 in C, LD, MD, HD
F: 16/74, 29/68, 23/71, 5/59 in C, LD, MD, HD

c. Hepatocellular hypertrophy

Increased in all groups. Described mainly as focal or multifocal (with some diffuse in MD and HD F), and slight or very slight:

M: 1/73, 6/72, 15/70, 4/64 in C, LD, MD, HD
F: 3/74, 13/68, 31/71, 31/59 in C, LD, MD, HD

2. Lungs

a. dark brown pigment/macrophage accumulation, alveoli

Increased at MD and HD (both sexes) among deaths (6 months-termination) and at termination. Combined incidence = 32/133, 0/2, 66/129, 46/103 in C, LD, MD, HD

b. Interstitial inflammatory/lymphocytic/mononuclear infiltrate

Increased in MD and HD F among deaths (6 months-termination) and at termination. Combined incidence = 15/68, 0/2, 36/65, 18/50 in C, LD, MD, HD.

c. Congestion/edema

Increased incidence at HD among deaths (0 - 6 months) but equivocally among deaths (6 months - termination)

3. Spleen

Hemosiderosis - Increased at MD and HD among deaths (6 months-termination) and (in F only) at termination. Combined incidence:

M: 2/64, 0/2, 15/63, 5/49 in C, LD, MD, HD
F: 4/68, 0/1, 18/64, 14/57 in C, LD, MD, HD

4. Cervical lymph node

Slightly increased incidence of dark brown pigment laden macrophage accumulation at MD and HD among deaths (6 months-termination) and (in M only) at termination. Combined incidence:

M: 3/59, 0/0, 10/53, 5/46 in C, LD, MD, HD
F: 7/65, 0/0, 8/52, 6/45 (deaths only: 1/24, 0/0, 5/32, 5/34) in C, LD, MD, HD

5. Mesenteric lymph node

Increased incidence of pigment laden macrophage accumulation/hemosiderosis at MD and HD among deaths (6 months-termination):

M: 1/35, 0/0, 9/43, 7/44 in C, LD, MD, HD
F: 1/24, 0/1, 7/39, 7/33 in C, LD, MD, HD

An equivocal increase also seen at HD at termination

6. Thyroid

Increased incidence of light cell proliferation among deaths (6 months-termination) at HD:

M: 0/37, 0/0, 2/40, 9/46 in C, LD, MD, HD
F: 0/25, 0/0, 0/30, 4/34 in C, LD, MD, HD

7. Kidney

Slightly increased incidence of chronic nephritis at MD and HD among deaths (6 months-termination) and (in F only) at termination.

M (deaths only):	12/37, 0/0, 27/44, 24/48
F (deaths & termination):	17/67, 0/0, 26/64, 20/47

21-22 MONTH MOUSE CARCINOGENESIS STUDY

A. Dosage

100 M + 100 F at 0, 50, 100, or 150 mg/kg/day, by intubation.

(MD and HD received 50 mg/kg for first 2 weeks; HD received 100 mg/kg for next 4 weeks.)

Final sacrifice at 21 and 22 months in M and F, respectively.

Strain: Charles River CD-1

B. Results

1. Observed signs

   a. Clonic convulsions at MD and HD, dose-related, throughout the study. At week 92, 11% of HD had convulsions within 3 minutes after dosing.

   b. Increased incidence of moist red substance on urogenital region in all F groups. At week 56: 11, 23, 39, and 50% in C, LD, MD, and HD respectively. (Due to uterine bleeding - see pathology results.)

2. Mortality

Increased in all M groups, partly dose-related, and slightly at HD F. Survival at termination:

	M	(WEEK OF 50% SURVIVAL)	F	(WEEK OF 50% SURVIVAL)
C	46/55	(91)	28/100	(50)
LD	30/98	(81)	22/100	(89)
MD	33/100	(75)	31/99	(83)
HD	19/100	(66)	20/100	(81)

3. Bodyweight - no drug effect

4. Food consumption - no drug effect

5. Gross pathology

a. Uterus

1. Increased incidence of nodules/masses to about the same extent in all drug groups; seen both at terminal sacrifice and among deaths. Overall incidence = 13/100, 42/100, 41/100, and 41/100 in C, LD, MD, and HD, respectively. According to the text, these masses/nodules were actually extremely dilated veins with thrombosis. (See histopathology, below.)

2. Increased incidence of dark red-grey areas, "highly vascularized/hemorrhagic/red contents," and thickening of uterine wall in all drug groups. The incidence of these findings was generally under 10% and not dose-related except for dark red-grey areas.

b. Spleen

Enlarged spleen seen in all F groups, partly dose-related, both at termination and among deaths. Overall incidence: 18/100, 39/100, 37/100, and 48/100 in C, LD, MD, and HD, respectively.

c. Stomach

Slight increase in red foci/hemorrhagic/bloody contents in all F groups both at termination and among deaths. Overall incidence: 2/100, 5/100, 15/100, 13/100 in C, LD, MD, and HD, respectively.

d. Intestines

Slight increase in hemorrhages/blood/reddish contents in HD M and HD F among deaths: 1/55, 1/75, 6/81, 7/81 in CM, CF, HD M and HD F, respectively.

6. Histopathology

(H + E stain. Routine exam in all C and HD; spleen, uterus, and gross lesions considered possibly neoplastic in LD and MD.)

a. Neoplastic findings

There were no drug-related increases in either total benign or malignant tumors (corrected for increased mortality in drug groups by use of life-table analyses) or in any specific tumor type. The overall tumor rate was low, the highest being for lung adenoma (17% in control, 8% at HD); incidence of all other tumor types was less than 5%.

b. Non-neoplastic findings

1. Uterus

a. Increased incidence of extremely dilated blood vessels, with thrombosis, in all F groups, dose-related, both at termination and among deaths. Overall incidence: 15/100, 37/100, 52/97, and 62/98 in C, LD, MD, and HD, respectively.

b. Increased acute metritis/pyometritis in all F groups, dose-related: 4/100, 12/99, 17/98, and 21/98 in C, LD, MD, and HD, respectively.

c. Slight increase in hemorrhage in all F groups: 1/100, 3/100, 8/97, and 5/98 in C, LD, MD, HD.

2. Spleen

a. Increased hematopoietic activity in all F groups, partly dose-related, among deaths but not at termination. Overall incidence: 17/100, 35/100, 53/99, 52/98 in C, LD, MD, HD.

b. Slight increase in incidence of foamy macrophages in all groups: 0/200, 6/198, 6/199, 7/197 in C, LD, MD, HD.

3. Lymph nodes

Slightly increased incidence of foamy macrophages with cellular debris in HD M and HD F among deaths: 0/45, 0/71, 4/80, and 7/79 in CM, CF, HD M, and HD F, respectively.

4. Liver

a. Slightly increased extramedullary hematopoiesis in HD F, among deaths: 14/79 vs 4/75 in control.

b. Slightly increased incidence of lymphocytic infiltrate in HD F, among deaths: 19/79 vs 6/75 in control.

5. Heart

Increased incidence of thrombus in HD M, among deaths: 7/80 vs 1/55 in control.

6. Lung

Increased incidence of congestion/hemorrhage in HD M both at termination and among deaths. Overall incidence was 34/100 vs 14/99 in control.

7. Kidney

Increased incidence of brown pigment in tubule epithelium in HD F, among deaths: 11/79 vs 1/75 in control.

8. Testes

a. Increased incidence of atrophic tubules in HD M both at termination and among deaths; overall incidence = 21/99 vs 6/100 in control. No effect on incidence of aspermatogenesis.

b. Increased incidence of amyloidosis in HD M, among deaths: 31/80 vs 5/55 in control.

9. Stomach, small intestine

Increased incidence of ulcer, congestion, hemorrhage, and inflammation at HD, related to gross findings, above. Very low incidence.

90 DAY P.O. TOXICITY IN DOGS

A. Dosage

2M + 2F at 0, 15, 35, or 75 → 150 mg/kg/day, in capsules. (Dosage increase at HD occurred on day 45.)

Strain: beagle

B. Results

1. Observed signs

No effect. (Preliminary study showed convulsions and death with acute oral doses of 150-400 mg/kg.)

2. Mortality - none

3. Bodyweight - no effect (no data shown)

4. Hematology

(pre-drug and days 45 and 90)

a. Hb

Slight decrease in all groups. Not related to dose or time except greatest effect in HD at 90 days (28% below control). No extremely low values.

b. %Hct

Same as above. Mean in HD at 90 days 21% below control.

c. Other parameters measured: MCHC, platelets, WBC, differential, RBC appearance, clotting time, sedimentation rate, icterus index, osmotic fragility, prothrombin time.

5. Blood chemistry

(pre-drug and days 45 and 90)

No drug effects. One HD F had slightly elevated BUN and creatinine but no associated histopathology. Other parameters measured: glucose, cholesterol, thymol turbidity, AP, SGOT, SGPT, total protein, methemoglobin, Na, K, BSP retention, bilirubin.

6. Urinalysis

(pre-drug and days 45 and 90)

No drug effects (volume, color, appearance, SG, pH, bilirubin, urobilinogen, albumin, occult blood, sugar, acetone bodies, sediment exam).

7. Fecal exam

(pre-drug and days 45 and 90)

No drug effects (color, appearance, occult blood)

8. Organ weights

a. Liver

Slight increases in absolute and relative weight at HD (Relative weight 18% above control)

b. Other organs weighed: heart, spleen, adrenals, kidney, brain, testes, thyroid

9. Gross pathology - no drug effects

10. Histopathology (H&E stain) - no drug effects

52 WEEK ORAL TOXICITY IN BEAGLE DOGS:

A. Dosage

6M + 6F at 0, 40, 80 or 80 → 150 mg/kg/day, in gelatin capsules. Dosage escalation at HD complete by 5 weeks.

At 6 months, 2M + 2F from controls, LD, and MD, and 2M + 1F from HD were sacrificed and necropsied. At 12 months, 4M + 4F per group were sacrificed. All remaining dogs were kept for 2 month withdrawal period, then sacrificed.

B. Results

1. Observed signs

LD - none

MD - ptyalism, emesis, and dry nose and/or mouth noted occasionally

HD

a. Weakness in 4 dogs, mainly first 3 months.

b. Emesis, ptyalism, and dry nose and/or mouth noted occasionally to several times per week.

c. General body trembling noted occasionally in a few dogs.

d. Clonic convulsions in 1 F, week 35. Dosing stopped for 3 weeks; upon re-initiation of dosing, frequent emesis and evidence of convulsions were noted, and death occurred after 4 days.

e. One F died week 17 preceded by body trembling and blood in refuse pan.

2. Mortality

a. 1 HD M, week 35 (No signs prior to death)

b. 1 HD F, week 40 (Signs given above, 1 d)

c. 1 HD F, week 17 (Signs given above, 1 e)

3. Bodyweight gain

Decreased at HD (Overall weight gain = 27% (M) and 19% (F) for controls, and 6% (M) and 7% (F) for HD. During withdrawal period, HD gained more than controls.)

4. Food consumption

No treatment effect except very slight decrease in HD M.

5. Water intake/urine output (measured pre-drug, and months 3, 6, and 12, over 5 consecutive days, in controls and HD).

No treatment effects

6. Ophthalmoscopic exam (performed on all dogs pre-drug and months 3, 6, and 12, using binocular indirect ophthalmoscope)

No treatment effects

7. ECG (measured in all dogs pre-drug and months 3, 6, and 12.)

ECG tracings for all dogs were included in the appendix. There were apparently no calculations of segment lengths performed. The report states there were no treatment effects.

8. Hematology (measured pre-drug and months 3, 6, and 12; after withdrawal period, only total RBC, Hct, and Hb measured)

a. Total RBC

1. Moderate decrease in 1 LD dog, month 6

2. Slight decrease at HD, month 6

3. Slight decrease at HD, months 3, 6, and 12, but least effect month 12.

b. Hct

1. Moderate decrease in 1 LD dog, month 6

2. Slight decrease at HD, months 3, 6, and 12, but least effect month 12.

c. Hb

1. Moderate decrease in 1 LD dog, month 6

2. Very slight decrease at HD, month 6

3. Slight decrease at HD, months 3, 6, and 12, but least effect month 12.

d. The above effects on RBC, Hct, and Hb were greatest at HD, but did not appear to be progressive over time. The mean decreases at HD were less at 12 months vs 6 months. Some individual dogs with low values at early times showed normalization at 12 months. The values in treated dogs after the withdrawal period were comparable to controls.

e. Total WBC - increased in 2 HD dogs, month 12

f. Differential WBC

Slight increase in neutrophils and slight decrease in lymphocytes at LD, months 6 and 12, and MD, month 12.

g. No treatment effects on platelet count

9. Blood chemistry (measured pre-drug and months 3, 6, and 12; after withdrawal period, only cholesterol, AP, SGOT, and SGPT were measured)

a. AP (alkaline phosphatase)

Dose-related increase seen at all months. The magnitude of the increase, relative to controls, increased over time. At 12 months, group mean values were approximately 2x, 2x, and 4x that of the controls in LD, MD, and HD, respectively. Most of the treated dogs had elevations. However, none of the recovery animals had elevations after the 2-month withdrawal period.

b. SGPT

1. 3 months - slight elevation in 1 LD and 1 MD; slight to moderate elevation in most HD.

2. 6 months - slight elevation in 1 control, 1 LD, 1 MD, and most HD.

3. 12 months - slight elevations in most MD; slight to moderate elevations in all HD.

4. The magnitude of the elevation was greatest at HD but not clearly related to duration of treatment: The group mean values at HD were approximately 4x, 1.7x, and 3.6x that of controls at 3, 6, and 12 months, respectively. At MD, the largest increase (1.6x control mean) was at month 12. After the withdrawal period, slight elevations were seen in 2 of the 3 dogs at MD and HD (group mean values approximately 1.5x control mean); the elevations in the 2 HD dogs were considerably less than those seen at 12 months.

c. SGOT

1. 3 months - moderate elevation in 1 LD; slight elevations in 2 LD, 1 MD, and 6 HD.

2. 6 months - moderate elevation persisted in 1 LD; slight elevations in 1 control and 1 MD.

3. 12 months - slight elevation in 1 MD and most HD (group mean at HD approximately 2x control mean). The elevations in individual HD dogs at 12 months were not significantly different in magnitude than those seen at 3 months.

4. No treatment-related effects seen after withdrawal period.

d. BSP retention

Slight increases in approximately 1/2 HD at month 3, and in most HD at month 12 (mean value approximately 2x control mean). Very slight increase in mean value seen at MD at month 12.

e. Total protein

Slight decrease in most HD dogs at 6 and 12 months

f. Albumin

Very slight decrease in most HD dogs at 6 and 12 months

g. No consistent treatment effects on cholesterol, glucose, BUN, A/G ratio, prothrombin time, bilirubin, Na, K, or creatinine.

10. Urinalysis (measured pre-drug and months 3, 6, and 12)

a. Slight, dose-related decrease in pH in all treatment groups at all months.

b. No consistent treatment effects on urine volume, urine color and appearance, specific gravity, albumin, glucose, bilirubin, occult blood, or sediment.

11. Organ weights

a. Liver - increased absolute and relative weights in all groups at both 6 and 12 months, dose-related. No treatment effects in recovery dogs.

b. Kidney - increased absolute and relative weights in all groups, dose-related, at 6 months; at 12 months increase in relative weight only, at MD and HD only. After recovery period, no treatment effect on absolute weight; relative weight increased at LD and HD.

c. Ovary - absolute and relative weight increased at HD at 6 months, but decreased at 12 months. No effect at HD after recovery, except slightly increased relative weight due to decreased body weight.

d. Thyroid/parathyroid - increased absolute and relative weight at HD at 6 months only.

12. Gross pathology

a. 6 month interim sacrifice

1. Slightly yellowish liver in 1 LD

2. In the HD F which died: "Pulmonary edema and congestion and slight hydrothorax in this dog were probably compound related, agonal changes."

b. Terminal sacrifice

1. No treatment-related effects in dogs which were sacrificed at termination or after the withdrawal period.

2. In the MD M which died: hemorrhages in tracheal and bronchial mucosa and scattered hemorrhages in lung

3. In the HD F which died: hemorrhages in mucosa of stomach and small intestine, and congestion and/or hemorrhages in several other organs.

13. Microscopic pathology (H and E was only stain used, except for Giemsa-Wrights for bone marrow)

a. Liver

1. At the terminal sacrifice, the hepatocytic cytoplasm was described as having a finely granular "ground glass" appearance in 7/8 MD and 8/8 HD. (0/8 in controls and LD). The severity of this was described as slight to moderate, and was not related to dose. This finding was not reported among dogs sacrificed at 6 months, or after the recovery period. It was not reported for the 3 dogs which died during the study.

2. At 6 months, greenish-brown pigment in Kupffer cells seen in 0/4 controls, 2/4 LD, 1/4 MD, and 1/4 HD (severity was very slight to slight, not dose-related.) At termination, brown pigment in Kupffer cells was seen in 1/8 controls, 0/8 LD, 2/8 MD, and 1/8 HD; however, dark brown pigment (very slight to slight) located in "phagocytic cells, portal areas" was seen in 4/8 HD but not in other groups. In addition, at termination, fine dark brown pigment in hepatocytes was seen at 4/8 HD (very slight to slight) and 2/8 MD (slight), and in 0/8 in controls or LD. No findings of liver pigment were seen in the 3 dogs which died during the study. Among the recovery animals, dark brown pigment in Kupffer cells (very slight) was seen in 1/4 controls, 1/4 LD, 0/3 MD, and 1/3 HD, and fine brown pigment in hepatocytes was seen in 0/4 controls, 1/4 LD, 1/3 MD, and 3/3 HD (severity very slight to slight, not dose-related).

3. Slight coarse vacuolation of periportal hepatocytes was seen in 3/8 HD at terminal sacrifice. Hepatocytic vacuolation was also seen in the HD dog which died during the study. At the 6 month sacrifice, centrolobular hepatocytic vacuolation was found in 1/4 LD (slight) and 1/4 MD (moderate), but not found in the 4 control or HD dogs. Vacuolation was not seen in any of the recovery dogs.

4. Hyaline droplets in hepatocytes (very slight to slight) was seen in 3/8 HD at terminal sacrifice; it was not seen in other groups. In the recovery dogs, however, it was seen in 2/4 controls, as well as in 3/4 LD, 0/3 MD, and 1/3 HD. It was not reported in dogs sacrificed at 6 months or in dogs which died during the study.

5. Bile duct proliferation was seen at the 6 month sacrifice in 0/4 controls, 0/4 LD, 2/4 MD (very slight to slight), and 2/4 HD (slight). At termination, it was seen in 5/8 HD (very slight to slight), not seen in other groups. After recovery period, seen in 1/4 controls (very slight), 2/4 LD (very slight), 0/3 MD, and 2/3 HD (very slight to slight). It was not seen in the 3 dogs which died during the study.

b. Kidney - At termination, brown pigment in tubular epithelium was seen in 3/8 controls, 6/8 LD, 5/8 MD, and 7/8 HD. The severity was greater (very slight to moderate) in the treatment groups, but not dose related. It was not seen at the 6 month sacrifice, or in dogs which died during the study. Among recovery dogs, it was seen in 3/4 controls, 2/4 LD, 3/3 MD, and 3/3 HD, the severity being very slight in controls and LD, slight to moderate in MD, and ranged from very slight to marked at HD.

c. Among the 3 dogs which died during the study, congestion and/or hemorrhage was found in several organs.

MUTAGENICITY

A. Ames Test

1. Plate Incorporation Assay

Salmonella strains TA 98, 100, 1535, 1537 and 1538 were used. Drug levels were 60-6000 μg per plate, with and without metabolic activation (Arocior - induced rat liver S9 preparation). Bupropion was weakly positive in the following strains:

a. TA 100, without metabolic activation: at all doses, dose-related; largest increase about 2x control. Positive control (1, 3 propane sultone, 0.04 μl per plate) caused 6.5x increase.

b. TA 100, with metabolic activation: at all doses, roughly dose related; largest increase less than 2x control. (Similar results in 2 separate studies). Positive control (2 aminoanthracene, 1 μg per plate) caused 9x increase.

c. TA 1535, with metabolic activation: in one study, dose-related increase starting at 300 μg, greatest effect 2x control; in a second study, non-dose-related increase at all doses, greatest effect 3x control. Positive control (2 aminoanthracene, 1 μg per plate) caused 10x increase.

2. Preincubation assay

Same Salmonella strain as above. Drug levels used were 15-1800 μg per plate (25-3000 μg/ml), with and without metabolic activation. Bupropion was weakly positive in the same strains in which it was positive in the plate incorporation assay, above:

a. TA 100, without activation: dose-related increase at 300-900 μg (1800 μg apparently bacteriotoxic); largest effect less than 1.5x control. Positive control (1,3 propane sultone, 0.04 μl per plate) caused 8x increase.

b. TA 100, with activation: generally dose related increase at 150 μg and above; largest effect less than 1.5x control. (Similar results in 2 separate studies.) Positive control (2 aminoanthracene, 1 μg per plate) caused 6x increase.

c. TA 1535, with activation: non dose-related increase at 150 μg and above; largest increase about 2x control. (Similar results in 2 separate studies.) Positive control (2 aminoanthracene, 1 μg per plate) caused 6x increase.

B. Rat Bone Marrow Chromosome Study

SM + SF were given 0, 100, 200, or 300 mg/kg/day for 5 days by gavage. Positive control: SM + SF at 0.4 mg/kg i.p. triethylenemelamine.

No significant effects seen at LD and MD. At HD there was an increase in all types of chromosomal aberrations tabulated, with no sex differences noted. The % of aberrant cells was 4.6, 5.8, 5.3, and 9.3 in C, LD, MD, and HD, respectively. In contrast, the positive control produced 27.0% aberrant cells. The average number of aberrations per cell was also increased at HD: 0.050, 0.062, 0.067, and 0.140 in C, LD, MD, and HD, respectively. The value for positive control was 0.926. The mitotic index was decreased at HD (1.2 vs 2.4 in control) but this was stated to be not statistically significant.

C. DNA Binding

Rats were given either bupropion-C^{14} (100 mg/kg p.o.) or 2-AAF-C^{14} (20 mg/kg p.o.) and sacrificed 24 hr. later. The degree of covalent binding to liver DNA, RNA, and protein was then assessed. On a specific activity basis, 20x more 2-AAF equivalents were bound to DNA than that found for bupropion (despite the 5x higher dose of bupropion). A covalent binding index was calculated and compared with literature values for known hepatocarcinogens and non-hepatocarcinogens, and the value for bupropion was more similar to those in the latter category. The degree of binding to protein or RNA was not greatly different between bupropion and 2-AAF. It was concluded that the binding of bupropion to DNA, RNA, and protein was minimal and probably non-specific.

MEA 18-644

TWO GENERATION REPRODUCTION AND FERTILITY STUDY IN RATS

A. Method

1. Strain: Long-Evans

2. Dosage: 15 M and 30 F at 0 (2 groups - one vehicle treated, one untreated), 100, 200, or 300 mg/kg/day, by gavage, from day 60 pre-mating through mating (M) or from 15 days pre-mating through either day 13 of gestation (1/2 F) or day 21 postpartum (remaining F).

3. Procedure: Mating ratio was 2 F/M of the same dosage group. One of the 2 F mated to each M was sacrificed day 13 of gestation; the other F was allowed to deliver normally. Pup weights and survival were monitored to day 21 PP. At 12 weeks of age, these F1 generation pups were mated (1 F per litter mated to an intragroup M, but not a brother) and allowed to rear young (F 2 generation) to day 21 PP, during which time pup weights and survival were monitored.

B. Results

1. Observed signs

No drug effect in M; 1/30 MD F and 1/29 HD F had wobbly gait on days 1-2 of premating period only

2. Mortality

1 LD M, 1 MD M, and 1 HD F (dosing accidents), and 1 untreated control

3. Bodyweight

a. M - All drug treated groups gained more weight than vehicle controls, but not dose-related.

b. F - All drug teated groups gained slightly more weight than controls during mating period (not dose-related); this difference persisted through pregnancy and lactation periods.

4. Mating performance

a. M - No drug effect

b. F - No drug effects (pregnancy rate = 26/29, 24/30, 24/28, 22/30, and 23/29 in untreated controls, vehicle controls, LD, MD, and HD respectively).

5. Post-mortem uterine findings in F

   a. F sacrificed day 13 of pregnancy - no drug effects on number of total, live, or dead implants/dam, number of CL, or CL/implantation ratio.

   b. F which had not delivered by day 26 of gestation (4 vehicle controls, 3 LD, 3 MD, and 3 HD) - all had failed to implant (no implant scars seen).

   c. Pup - bearing F sacrificed day 21 PP - No drug effects on number of uterine scars.

6. Term deliveries

   No drug effects on number of live pups per dam. Slight increase in number of dead and live + dead pups per dam at HD.

7. Pup survival (F 1 generation)

   No drug effects through day 21 PP

8. Pup weight (F 1 generation)

   No drug effects through day 21 PP

9. Observed signs (F 1 generation)

   Results given up to 12 weeks of age - no drug effects

10 Bodyweight (F 1 generation)

   a. M - Slightly higher than vehicle controls at LD and HD (measured up to 12 weeks of age).

   b. F - No drug effect up to 12 weeks of age. During pregnancy, weight gain at HD was slightly decreased. No drug effect during lactation period.

11. Reproductive performance in M (F 1 generation)

   No drug effect on percent of M mating (100% in all groups) or siring litters (93, 64, 82, 82, and 90% in untreated controls, vehicle controls, LD, MD, and HD, respectively).

12. Gross necropsy in F 1 males at 12 weeks of age.

   No drug effects.

13. Reproductive performance in ♀ (F 1 generation)

    a. No drug effect on pregnancy rate (7/11, 9/11, 9/12, and 9/11 in vehicle controls, LD, MD, and HD, respectively)

    b. No drug effect on length of gestation

    c. Slight decrease in mean number of live pups at HD compared to vehicle but not untreated controls; no drug effect on number of dead pups.

    d. Slight decrease in number of implant scars at HD.

14. Gross necropsy findings in F (F 1 generation).

    No drug effects among F not selected for mating (sacrificed at 12 weeks of age) or among pup-bearing F (sacrificed day 21 PP). No drug effect among F which were mated but had not delivered by day 26 of gestation - all were not pregnant and had no implant scars.

15. Pup survival (F 2 generation)

    No drug effects through day 21 PP.

16. Pup weight (F 2 generation)

    Mean weights slightly higher than controls at most days measured in all drug groups, not dose-related.

17. Number of pups with both eyes open on day 14 PP (F 2 generation)

    No drug effects.

18. Gross necropsy of F 2 pups (day 21 PP) - no drug effects.

SEGMENT II REPRODUCTION STUDY IN RATS

A. Method

1. Strain: Long-Evans

2. Dosage: 22 F at 0, 20 at 150, 20 at 300, and 23 at 450 mg/kg/day, by gevage, from days 6-15 of gestation. (Group numbers refer to number of pregnant dams whose offspring were examined for abnormalities; the number which were started on the study cannot be determined from the data presented).

3. Procedure: Dams sacrificed day 20 of gestation, laparotomies performed. All fetuses examined for external malformations, approximately 1/3 for visceral defects (Wilson method), and approximately 2/3 for skeletal defects (Alizarin Red S staining)

B. Results

1. Observed signs in dams

Ataxia, urinary incontinence, and gnawing on cage and/or forepaws seen in 3/22 MD and 24/53 HD.

2. Dam mortality

24/53 HD died on or before day 17 of gestation (one due to dosing accident; 19 exhibited signs as stated above).

3. Bodyweight of dams

Weight loss in all treated groups after first dose, but then caught up and slightly surpassed mean control values.

4. Number of CL and implantations

Slight increase in CL/dam and slight decrease in implantations/dam in all treated groups, not dose related.

5. Number of live and dead fetuses per dam

No drug effects

6. Number of resorbed fetuses per dam

Slight increase in LD and HD, mainly due to 1 dam in each group.

7. Fetal weights

Slight decrease in all drug groups, not dose-related

8. Fetal lengths

Very slight decrease in all groups, not dose related.

9. Fetal abnormalities

a. Number of fetuses examined

	C	LD	MD	HD
gross	209	193	197	220
visceral	70	66	69	77
skeletal	139	127	128	143

b. Gross and visceral abnormalities - no drug effects

c. Skeletal abnormalities

The sponsor concludes that there were no significant treatment effects; however, the incidence tables show a trend toward decreased ossification of several structures at the higher doses, for example:

% with reduced ossification

	C	LD	MD	HD
interparietals	10.1	7.9	14.8	14.0
parietals	12.9	7.2	10.9	16.1
supraoccipital	14.4	11.8	27.3	21.0

The incidence of unossified second sternebrae was increased at LD and HD (5.8%, 19.7%, 8.6% and 22.4% in controls, LD, MD, and HD, respectively). However, the incidence of unossified 5th sternabrae appears to be decreased at MD and HD (about 1/2 control incidence).

The number of total skeletal findings per number of fetuses examined was increased in all treated groups: 3.6, 4.0, 4.2, and 4.3 in controls, LD, MD, and HD, respectively. The number of fetuses with skeletal findings per number of fetuses examined was not affected by drug, in that virtually all fetuses examined had at least one finding.

SEGMENT II REPRODUCTION STUDY IN RABBITS (1 OF 2 STUDIES IN RABBITS)

A. Method

1. Strain: New Zealand White

2. Dosage: 21 F at 0, 22 at 30, 21 at 100, and 24 at 150 mg/kg/day, by gavage, from days 6-18 of gestation.

3. Procedure: Does artificially inseminated. Ovulation induced naturally via mounting by bucks. Does sacrificed day 29 of gestation. All fetuses examined for external malformation, approximately 1/3 for visceral defects (Wilson method), and approximately 2/3 for skeletal defects (Alizarin Red S staining).

B. Results

1. Observed signs in does

a. Slight to severe clonic convulsions in 1/21 MD and 8/24 HD. One HD died during, and 1 MD survived, an opisthotonic convulsion.

b. Number of does failing to eat all of daily food ration (100 g) 1 or more days: 11/21, 15/22, 16/21, and 24/24 in controls, LD, MD, and HD, respectively.

2. Doe mortality

a. Deaths: 1 control and 2 LD (uncertain cause), 2 MD (dosing accidents), and 1 HD (following opisthotonic convulsion).

b. Sacrifices prior to delivery: 1 LD (broken back), and 2 MD (1 broken back, 1 aborted day 25 of gestation).

3. Bodyweight of does - no drug effect.

4. Number of does pregnant at day 29 of gestation: 17, 18, 16 and 17 in controls, LD, MD, and HD, respectively.

5. Number of abortions, live fetuses/doe, dead + resorbed fetuses, and total implants

No drug effect

6. Mean fetal weight

Slight decrease in all drug groups, dose-related

7. Mean fetal length

Very slight decrease at HD

8. Fetal abnormalities

a. Number of fetuses examined

	C	LD	MD	HD
gross	140	135	114	140
visceral	45	46	37	47
skeletal	95	89	77	93

b. Percent incidence of malformations (number of malformations X 100/number fetuses examined)

	C	LD	MD	HD
1) gross	0	0	0.9	2.1
2) visceral	0	8.7	5.4	6.4
3) skeletal	2.1	5.6	0	6.5
4) percent of does with malformed fetuses of any type	5.9	33.3	12.5	41.2

The sponsor states that although there does appear to be a drug-related increase in malformations, it is not considered biologically significant primarily because no pattern of abnormalities was seen, i.e., except in one instance not more than one fetus per group had any given abnormality, and there was little overlap of types of abnormalities among the different groups. The sponsor also states that all abnormalities seen in the drug groups that were not seen in the concurrent controls have been reported to occur spontaneously.

c. Incidence of common variants

1. Visceral - no drug effect

2. Skeletal

a. The percent of fetuses examined having unilateral or bilateral supernumerary 13th ribs was as follows:

C 26.3
LD 41.6
MD 45.5
HD 55.9

The percent of does with fetuses having this finding was:

C	58.8
LD	72.2
MD	68.8
HD	94.1

The sponsor states that supernumerary ribs are considered to be a normal skeletal variant in rabbits with incidences as high as 75-100%. The increased incidence in the drug groups was considered by the sponsor to be secondary to maternal toxicity.

b. There was a slight increase in incidence of decreased ossification of the palate in all drug groups, not dose-related (8.4, 14.6, 14.3, and 14.0% in controls, LD, MD, and HD, respectively). The incidence of decreased ossification of other bones was not increased by treatment.

SEGMENT II REPRODUCTION STUDY IN RABBITS (1 OF 2 STUDIES IN RABBITS)

(Performed by International Research and Development Corporation)

A. Method

1. Strain: New Zealand White

2. Dosage: 20 F at 0, 20 at 25, 28 at 50, 20 at 100, and 20 at 150 mg/kg/day, by gavage, from days 6-18 of gestation. (The group numbers refer to the numbers of pregnant does whose offspring were examined for abnormalities; the numbers which were started on the study cannot be determined from the data presented.) Thirteen F of the 50 mg/kg group were accidentally given 100 mg/kg on 1 day.

3. Procedure: Chorionic gonadotropin was given i.v. to stimulate ovulation after mating. Fetuses were delivered by cesarean section on day 29 of gestation. All fetuses were examined for external anomalies, dissected and examined for visceral anomalies, and cleared and stained with Alizarin Red S and examined for skeletal anomalies.

B. Results

1. Observed signs in does

   a. LD and MD - no drug effect

   b. M-HD - slight hypoactivity

   c. HD - slight hypoactivity plus (in 9 does) convulsions, ataxia, tremors, loss of righting reflex, hyperpnea, and muscle spasms.

2. Doe mortality

   Number dying or sacrificed due to injury = 0, 1, 1, 2, and 1 in controls, LD, MD, M-HD, and HD, respectively.

3. Bodyweight of does

   Weight gain at M-HD and HD less than controls (very slight effect at M-HD)

4. Mean number of CL and implantation sites, and number of live, dead, or resorbed fetuses per doe.

   No drug effects

5. Mean fetal weight

   Very slight dose-related decrease in all drug groups except LD.

6. Fetal abnormalities

a. Number of fetuses examined:

C	149
LD	146
MD	210
M-HD	142
HD	145

b. Incidence of anomalies

The table on the following page, taken from the IND, shows a trend toward increased incidence of gross, soft-tissue, and skeletal anomalies in the treated groups, which tended to be dose related in some instances.

The increase in gross and soft-tissue anomalies was not statistically different from controls ($\alpha = .05$), and was not discussed by the sponsor. From the table which gives the findings in individual fetuses, it does not appear that there was any pattern showing an increase in any specific anomaly in the treated groups.

Regarding skeletal anomalies, statistically significant drug effects were found for 2 anomalies which are considered common variants: accessory rib(s) (incidence = 29, 49, 51, 48, and 49% in controls, LD, MD, M-HD, and HD, respectively), and delayed ossification of the fifth phalanx of the forelimb (incidence increased at HD only; incidence = 3.4% in controls, and 10.1% at HD). In addition to these findings, a few fetuses in each drug group had "barbell" shaped thoracic centra (incidence = 0, 2.7, 1.0, 0.7, and 4.1% in controls, LD, MD, M-HD, and HD, respectively). The sponsor concludes that these skeletal findings are secondary effects of maternal toxicity in the drug-treated groups.

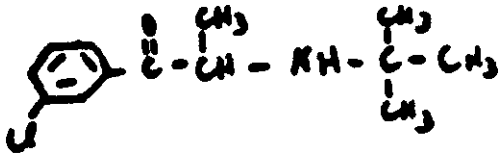
	C	LD	MD	M-HD	HD
[illegible] with Gross Anomalies (%)	1 (0.7)	5 (3.4)	5 (2.4)	4 (2.8)	9 (6.1)
[illegible] with Soft-tissue Anomalies (%)	4 (2.7)	4 (2.7)	4 (1.9)	6 (4.2)	8 (5.5)
[illegible] with Skeletal Anomalies (%)	79 (53.0)	107 (73.3)	135 (64.3)	85 (56.9)	102 (68.9)*
[illegible] Showing One or More Gross Anomalies (%)	1 (5.0)	3 (15.0)	2 (7.1)	2 (10.0)	2 (10.0)
[illegible] Showing One or More Soft-tissue Anomalies (%)	3 (15.0)	4 (20.0)	4 (14.3)	2 (10.0)	6 (30.0)
[illegible] Showing One or More Skeletal Anomalies (%)	20 (100.0)	19 (95.0)	26 (92.9)	18 (90.0)	20 (100.0)

* Significantly higher than control group ($\alpha = .05$)

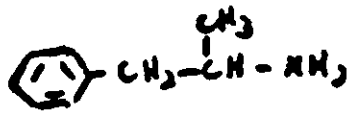
SUMMARY

A. Pharmacology

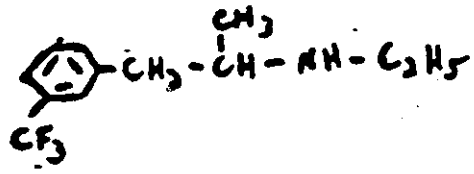
Bupropion (B) is structurally similar to amphetamine, fenfluramine, diethylpropion, and other phenethylamine derivatives.



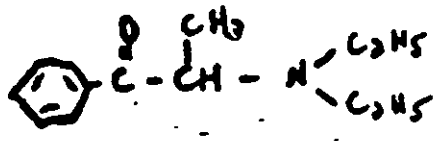
BUPROPION



AMPHETAMINE



FENFLURAMINE



DIETHYLPROPION

Its pharmacological profile is that of a CNS stimulant with several similarities to amphetamine. B was active in 3 types of tests which are predictive of antidepressant activity: prevention or reversal of tetrabenazine/reserpine effects in mouse, decreased immobility in the Porsolt behavioral despair test in rats, and potentiation of the behavioral effects of pargyline + DOPA in mice. In these studies B had an i.p. ED 50% of 10-12 mg/kg (32 mg/kg p.o. in 1 study); activity was sometimes seen at doses as low as 6.5 mg/kg i.p. The potency of B in these tests ranged from 3-5x less potent to equipotent with classical tricyclics. B produced dose-related CNS stimulation in rats and mice as evidenced by increase in locomotor activity as well as by performance in several operant behavioral tests; the potency of B was generally 10-50x less than that of amphetamine in these studies. The ED 50% for increased locomotor activity in mice was approximately 2x that for antitetrabenazine effect whereas the reverse was true for amphetamine and methylphenidate, suggesting a more specific "antidepressant" effect for B. However, some increase in locomotor activity was seen with B at all doses but the lowest which were effective in the antitetrabenazine test. Data in rats further suggested that there is little or no separation of CNS-stimulating and "antidepressant" doses.

B was shown to be a relatively weak blocker of the uptake of NE and 5 HT into brain and peripheral nerve compared with classical tricyclics. It was somewhat more potent in blocking DA uptake although the dose in rat (40 mg/kg i.p.) needed to produce serum levels high enough to cause 50% inhibition of DA (or NE) uptake into brain synaptosomes was 4x greater than the ED 50% in the Porsolt test; thus the blockade of DA (or NE) uptake is probably not involved in the "antidepressant" effect of B. (The reverse holds true for imipramine regarding the potency ratio for "antidepressant effect" and NE uptake blockade.) However, destruction of dopaminergic neurons with 6-hydroxydopamine + DMI blocked the effect of B in the Porsolt test in rats, suggesting that DA neurons are involved in some way.

B did not inhibit MAO or elevate brain NE or DA at relatively high doses.

Many similarities between the pharmacological profiles of B and amphetamine (and other CNS stimulants) were noted,, along with some differences. These may be summarized as follows:

1. B, amphetamine, and methylphenidate all had dose-related antitetrabenazine effects and caused dose-related increases in locomotor activity in mice. However, the ratio of the i.p. ED 50% values for these 2 effects was approximately 1:2 for B and 2:1 for amphetamine and methylphenidate. (In contrast, classical tricyclics cause <u>decreased</u> locomotor activity above "antidepressant" doses.)

2. Amphetamine and methylphenidate reversed tetrabenazine-induced sedation in mice whether given before or after the tetrabenazine; B was only active when given before.

3. Selective depletion of brain DA blocked the locomotor effects of both B and amphetamine; selective depletion of NE had no effect on either drug.

4. The locomotor effect of B and methylphenidate depends primarily on a storage (reserpine-sensitive) pool of catecholamines, whereas that of amphetamine depends primarily on newly synthesized (alpha-methyltyrosine sensitive) catecholamines.

5. B caused an increase in stereotyped behavior in rats; no direct comparison to amphetamine was made.

6. Several behavioral (operant) tests showed the profile of B to be more similar to amphetamine than to classical tricyclics.

7. B had an anorexic effect in mice. (Oral potency at least 2x less than that of fenfluramine and diethylpropion; amphetamine not used.)

LION 501 MADE IN JAPAN

8. Drug discrimination studies in rats showed similarities between B and several CNS stimulants (e.g., amphetamine, methylphenidate, caffeine, cocaine) as well as to the newer antidepressants viloxazine and nomifensine.

9. At high doses B caused hypothermia in mice whereas amphetamine caused hyperthermia.

10. Grouping of mice caused an increase in the i.p. lethality of amphetamine but had no effect on that of B; B decreased the lethality of amphetamine in grouped mice.

Cardiovascular studies showed rather large but generally transient decreases in CO and right ventricular contractile force, and both increases and decreases in heart rate and blood pressure, at i.v. doses of 1-20 mg/kg in anesthetized dogs and cats. (It is not clear if these results were corrected for vehicle effects). In conscious dogs, 20 mg/kg p.o. caused slight increases in HR and BP (lasting at least 6 hr.); in conscious rats 50 mg/kg caused a slight increase in HR (lasting 3 hr). Comparison drugs were not used in these studies so that the relative potency of B in causing these changes is not known. No effect on EKG (aside from increased HR) was seen in dogs at 10 mg/kg i.v. (2 mg/kg/min). In dogs, 5-10 mg/kg i.v. caused rather large increases in respiratory rate and smaller increases in minute volume. A relatively weak depressant effect on cardiac tissue in various <u>in vitro</u> preparations was noted which may have been due to the local anesthetic properties of B (equipotent with cocaine in guinea pig cornea); the potency of B was generally 5-15x less than that of imipramine and amitriptyline.

Several studies were performed to assess the anticholinergic effects of B. Effects were generally weak or absent (except for dose-related mydriasis in mice, although it is not clear if this represents an anticholinergic or sympathomimetic effect), and B was significantly less potent than amitriptyline and imipramine when compared. Antagonist actions at other receptors (adrenergic, serotonergic, histaminergic) were generally weak or absent; however reference drugs (which could have validated the systems as well as estimated the relative potency of B) were not used. Likewise, binding studies showed little or no interaction of B with a variety of receptors, but no reference drugs were used.

B. <u>ADME/Pharmacokinetics</u>

ADME/pharmacokinetic studies were performed in rat, mouse, and dog. After oral dosing, plasma levels of B peaked rapidly (within 1/4-1/2 hr) and declined rapidly with a T 1/2 in the 1-4 hr. range. Over a dosage range of 10-100 mg/kg/ p.o. in rats, plasma levels increased with increasing dose but slightly less than proportionately at the highest dose. Studies comparing plasma AUC after i.v. and p.o. dosing showed a bioavailability of 8-21% in rats and 4% in dogs; however, excretion studies using labelled drug showed complete absorption in dogs and a high if not complete degree

of absorption in rats after p.o. dosing. B was widely distributed to tissues in rats; levels were highest in liver and lung after p.o. and i.p. dosing, respectively; lowest levels were in plasma. B was shown to be rapidly and extensively metabolized, which is in agreement with the low oral bioavailability of the drug. Plasma and tissue levels of metabolites were generally substantially higher than those of unchanged drug (exception: brain). Very little unchanged B was found in rat or dog urine; acidic metabolites (m-chlorohippuric and m-chlorobenzoic acids, and a conjugate of the former, were identified), presumably arising from side chain oxidation, were predominant. This is in contrast to human urine, where acidic and basic metabolites were present in nearly equal amounts. Plasma and tissue levels of metabolites declined much more slowly than those of unchanged drug (e.g. in 1 study the plasma T 1/2 for metabolites appeared to be about 12 hours). This suggests that whereas the parent drug is unlikely to accumulate with repeated dosing due to its short T 1/2, metabolites may. However, in one mouse study, 10 days dosing did not lead to an accumulation of metabolites; such a tendency may have been counteracted by an enzyme - induction effect (levels of unchanged B were decreased).

The ability of B to induce liver microsomal metabolic enzymes was demonstrated in rat, mouse, and dog. In rat, pre-treatment with 15-50 mg/kg/day p.o for 13 days decreased the rise of B in plasma seen after an acute dose of 50 mg/kg i.p., and 50 mg/kg/day p.o. for 4 days decreased the rise of B in tissues seen after an acute dose of 50 mg/kg i.p. In mouse, 50 mg/kg i.p. for 8 or 10 days decreased the rise in whole body level of B seen after an acute dose of 50 mg/kg. In dog, plasma levels after 1 year treatment at 40 or 80 mg/kg/day p.o. were significantly less than those seen on day 1. Studies on pentobarbital sleep time in mice showed a decrease after 5-150 mg/kg/day p.o. for 10 days (effect at HD slightly less than effect of phenobarbital pretreatment at 80 mg/kg/day); in rats a slight decrease was seen at high doses (100-150 mg/kg/day) only. It is possible that part or all of these effects on pentobarbital sleep time were due to CNS stimulation by B; thus while it appears that B can induce its own metabolism, the ability to induce the metabolism of other compounds has not been clearly demonstrated.

Excretion of B + metabolites was shown to be primarily urinary in rats (78%) and dogs (100%).

Over concentration ranges that were stated to be "normally found in animals and during clinical studies in man," B was 75-85% bound to plasma proteins from mouse, rat, dog, and man. Binding was generally constant over the concentration ranges used, although it tended to fall off in man at the highest concentration (1000 μM).

There appears to be some sex differences in the disposition of B, at least in rats. Plasma and tissue levels of unchanged drug, plasma AUC, and oral bioavailability were several-fold greater in F; T 1/2 was greater in F in one rat study but apparently not in another. There did not appear to be

any important sex differences in metabolic pattern or excretion, although data on these points were limited. No sex differences in plasma levels in dogs were apparent although only 2 dogs per sex were used. The acute toxicity of B in rats was slightly greater in ♂ than ♀, but the reverse appeared to be true in the chronic rat toxicity studies.

C. Toxicology

The acute oral LD 50 was 544 (M) and 636 (F) mg/kg in mouse and 607 (M) and 482 (F) mg/kg in rat. Acute I.p. LD 50 was 273 and 263 mg/kg in male mice and male rats, respectively. Prominent acute signs included: mouse - ataxia,, convulsions, prostration, ptosis, and compulsive gnawing by both routes, plus labored breathing, decreased respiration, and salivation after I.p. only; rat - ataxia, loss of righting reflex, labored breathing, prostration, salivation, ptosis,, arched back, and compulsive gnawing by both routes.

Acute p.o. toxic interaction studies were performed in rats. Phenelzine (at highest no-effect and highest non-lethal doses) caused a marked decrease in the LD 50 of B. (However, no pharmacodynamic interactions were seen in several tests at lower doses). Only a slight potentiation of the lethality of B was caused by treatment with ethanol at its highest non-lethal dose; this was seen in F only. Lethal potentiation was noted between B and amitriptyline (each given at 1/2 LD 50), in F only.

The following oral subacute/chronic toxicity studies were performed (daily dose in mg/kg in parentheses):

1. Rat - 3 month (150, 300, 450)
2. Rat - 55 week (25, 50, 100)
3. Rat - 2 year (100, 200, 300)
4. Mouse - 21-22 month (50, 100, 150)
5. Dog - 3 month (15, 35, 75→150)
6. Dog - 1 year (40, 80, 150)

The principal findings are summarized as follows:

1. Rat

Increased mortality, associated with convulsions, was seen in the 2 year study at all doses (except LD M), and was marked at HD (300 mg/kg). No effect on mortality was seen in the 55 week study (HD = 100); in the 3 month study 2/20 died at 450. Observed signs included urinary incontinence/urine staining (all studies, all doses), dried blood around nose/mouth (55 wk and 2 yr studies, all doses), and convulsions (2 yr study, all doses). Slight decreases in bodyweight gain were seen in all M groups in the 2 yr study. Slight decreases in blood glucose were seen above 100-150 mg/kg. The most prominent post-mortem findings were as follows:

a. Liver

In the two-year study there was an increase in incidence of hyperplastic nodules and hepatocellular hypertrophy at all doses; hyperplasia was increased at LD and HD only. (In a consultant report many of the hyperplastic nodules were reclassified as "foci or areas of altered hepatocytes"). The incidence of these findings is underestimated in the drug groups in a dose-related fashion due to the increased mortality and the late appearances of the lesion. (Most hyperplastic nodules were found at the terminal sacrifice, and almost all were found after 90 weeks). There was no increase in the incidence of hepatocellular carcinoma; the observed incidence (0/147, 3/140, 1/141, and 1/123 in control, LD, MD,, and HD, respectively) is within the historical control range. Similar findings were not seen in the 55 week study (HD = 100); in the 3 month study a low incidence of hyperplasia and "prominent cellular organelles" was seen at all doses. Increased liver weights were seen in all studies at all doses except LD in the 3 month study. Grossly, in the 2 yr. study slight increases in the incidence of masses/nodules/raised area (F only) and dark red/brown/hemorrhagic foci were seen at all doses at termination but not among deaths. The sponsor suggests that these proliferative changes in liver may represent either (1) an indication of microsomal enzyme induction or (2) an adaptive response to hepatic injury. Regarding the former, B has been shown to induce its own metabolism (see above). Regarding the latter, no other indication of hepatic damage (including blood chemistry) was obtained in rats, although some indications of liver damage were obtained in dogs.

b. Hemosiderosis

In the 55 week study an increase in hemosiderosis (as determined either by H + E stain, iron stain, or presence of pigment-containing macrophages) was seen in spleen, kidney, lung, and liver. This was seen primarily at HD, although lower doses were not examined in lung and liver. Likewise, in the two year study, evidence of increased hemosiderosis was seen in spleen, lung, and lymph nodes at MD and HD. (LD not examined in these organs). No other pathological findings were present to help explain the increased hemosiderosis. Hematology did not reveal any striking abnormalities. (2/20 HD in the 55 week study had low Hb, Hct, and RBC; no effect in two year study; slight decreases in Hb and Hct seen in the 3 month study but no hemosiderosis reported).

c. Kidney

Slight increases in the incidence of chronic nephritis were seen in the 55 week study (HD only) and in the two-year study (MD and HD; LD not examined). There were no consistent effects on lab tests indicative of renal function; in the 55 week study there were elevations of BUN in 3 of 40 rats at MD and HD. Kidney weights were elevated in all studies at all doses.

d. Neoplasia

There were no drug-related increases.

2. Mouse

In the 22 month study mortality was increased in all M groups and HD F. There was no effect on weight gain. As in rats, convulsions were seen (MD and HD). Laboratory studies were not performed. The most prominent postmortem findings were seen in uterus, consisting of a dose-related increased incidence of extremely dilated blood vessels, with thrombus, in all F groups. This increase was seen both among mice which died and those which survived to termination, suggesting a lack of association with lethality. Grossly there was an increased incidence of uterine nodules/masses; according to the text these were actually extremely dilated veins with thrombosis. The red urogenital staining noticed during the in-life phase was probably also related to these changes. Also seen in uterus was increased incidence of acute metritis/pyometritis in all drug groups (dose-related) and slightly increased incidence of uterine hemorrhage in all drug groups (not dose-related). Splenomegaly and hematopoiesis in spleen and liver were also seen in F; the pathology report considered these to be secondary to the uterine blood loss although an independent analysis by the sponsor did not show a good correlation between the uterine and spleen/liver changes. Changes similar to those in uterus were not clearly seen in other organs, although a low incidence of hemorrhage and ulcer in stomach and small intestine was noted, primarily at HD, the incidence of thrombus in heart was increased in HD among deaths but not at termination, and the incidence of congestion/hemorrhage in lung was increased in HD M. An increased incidence of atrophic tubules in testes at HD was also seen in this study, although there was no effect on the incidence of aspermatogenesis. As in the rat study, there was no effect on the incidence of neoplastic changes.

3. Dog

No significant toxic effects were seen in the 90 day study (HD = 75→150); a slight increase in liver weight was seen with no associated pathology. In the 1 year study the HD (150) produced 3/16 deaths. This dose also produced convulsions in 1 dog and body trembling in

several dogs. Emesis and ptyalism were seen at both MD and HD. Bodyweight gain was decr eased at HD. Values for RBC, Hb, and Hct tended to be decreased at the higher doses but this did not progress with time and no effect was seen in recovery dogs. (Slight decreases in Hb and Hct were also seen in the 90 day study.) There was a dose-related elevation of serum alkaline phosphatase in all groups at all months measured, and the magnitude increased over time; no effect seen in recovery dogs. Elevations of SGOT and SGPT were also seen mainly at the higher doses, starting at 3 months but not clearly progressive over time. Some recovery dogs still had elevated SGPT after the recovery period, but of smaller magnitude. Slight increases in BSP retention were seen at MD and HD. Liver weights were increased in all groups (dose-related) at both 6 and 12 months but not at recovery. Microscopic exam of liver showed several drug-related changes including finely granular "ground glass" cytoplasm (MD and HD, seen at 12 months but not at 6 months or after recovery period), dark brown pigment in hepatocytes and phagocytic cells (MD and HD, seen at 12 but not at 6 months, and seen at all doses after recovery period), slight coarse vacuolation of hepatocytes (seen in HD at 12 months and in LD and MD at 6 months and in the 1 MD which died; not seen after recovery period), and bile duct proliferation (very slight to slight) (seen at MD and HD at 6 months and at HD at 12 months, also seen after recovery period in 2/4 LD and 2/3 HD but also in 1/4 control and 0/3 at MD). Kidney weight was elevated in all groups at 6 months; however at 12 months an increased relative weight only was seen (MD and HD only). Histologically, the incidence and severity of brown pigment in tubular epithelium was increased in all groups at termination. The incidence of this finding among recovery dogs was similar across groups although severity was greater at MD and HD. No clear abnormalities of renal function were seen in this study.

D. Mutagenicity

B was weakly positive in some Salmonella strains in the Ames Test. (TA 100, both with and without metabolic activation, and TA 1535, with activation only). Greatest effects were 2-3 x control revertant count; positive controls caused 6-10 x increases. In a rat bone marrow chromosome study, an increase in aberrations was seen at 300 but not 100-200 mg/kg p.o., given for 5 days; the increase was 2.5 x control compared to 6-19 x for the positive control. In a study of binding to rat liver DNA after oral administration, it was found that the binding of bupropion (+ metabolites) was much lower than that of known hepatocarcinogens and was concluded to be nonspecific.

E. Reproduction

A 2 generation reproduction and fertility study was performed in rats. Both M and F (of the F0 generation only) were drug treated, dosages = 100, 200, and 300 mg/kg/day. Except for wobbly gait in 1 MD and 1 HD, no

drug-related signs were observed. Body weight gain was slightly increased in all treated groups, but not dose-related. There was no drug-related increase in mortality. No drug effects on M or F mating performance, on F fertility or reproductive parameters, or on pup (F 1 generation) survival and body weight were seen. There were no significant effects on mating or reproductive performance of the F 1 generation. Pup survival (F 2 generation) was not affected by treatment, although F 2 pups in all drug groups had slightly increased body weight.

Segment II reproduction studies were performed in rats and rabbits. In rats (dosages = 150, 300, and 450 mg/kg/day), signs including ataxia, urinary incontinence, and gnawing were seen primarily in HD dams. Mortality was increased at HD (24/53 = 45%). Bodyweights were transiently decreased in all drug groups after the first dose. There was a slight decrease in fetal weight and length in all drug groups, not dose-related. There were no drug-related effects on gross or visceral fetal abnormalities. A slightly increased incidence of reduced or absent ossification of some bones was seen at MD and HD and to a smaller extent at LD; this was reflected in a slight increase in total skeletal findings in all drug groups.

Two segment II reproduction studies were performed in rabbits, 1 by the sponsor's lab and 1 by International Research and Development Corporation. Dosages were 25 (latter study only), 50, 100, and 150 mg/kg/day. Does displayed slight hypoactivity at 100 and 150 mg/kg, and convulsions, ataxia, tremors, and hyperpnea were seen in some does at 150 (convulsions also seen in 1 doe at 100 mg/kg). In one study, decreased dose food consumption on individual days was seen in all drug groups, but no overall effects on body weight were seen; however, the other study showed reduced weight gain at 100 and 150 mg/kg. There was no drug-related increase in mortality in either study. Fetal weight was slightly reduced in all drug groups at 50 mg/kg and above, dose-related. Fetal length (reported in 1 study) was slightly reduced at 150 mg/kg. There was a trend toward an increase in gross, visceral, and skeletal abnormalities in fetuses of all drug groups, which was partly dose-related. The increase in gross and visceral abnormalities does not appear to be biologically significant in that no pattern of abnormalities was seen, i.e. there was no significant increase in any particular type of abnormality, and the overall percent of fetuses affected was relatively low. Regarding skeletal abnormalities, a significant increase in supernumerary ribs occurred in all drug groups which was dose-related in 1 study but not in another. In addition, one study showed an increase in reduced ossification of the palate (all drug groups, not dose-related), and the other study showed an increase in delayed ossification of the 5th phalanx of the forelimb at HD only as well as a low incidence of barbell shaped thoracic centra in all drug groups. Reduced ossification (also seen in rat study) and supernumerary ribs are considered to be normal variations, and it is concluded that the above skeletal findings, as well as the findings of decreased fetal weight and length, were secondary consequences of maternal toxicity.

EVALUATION:

The preclinical data submitted for bupropion (B) adequately characterizes the pharmacological and toxicological profile of this drug.

B, unlike classical antidepressants, is a CNS stimulant in animals, with a potency of about 1/50-1/10 that of amphetamine in causing CNS stimulation in various tests in mice and rats. Although it was shown that, unlike for amphetamine, the ED 50% for increased locomotor activity in mice was greater than that for an "antidepressant" (i.e. antitetrabenazine) effect, it appeared that there was acutally little separation of doses producing "antidepressant" effects from those producing at least some CNS stimulation. Several pharmacological similarities between B and amphetamine (and other CNS stimulants) were noted, including self-administration by monkeys, raising the question of possible abuse. Studies addressing this question have been conducted in man.

The sponsor claims that B has less anticholinergic and adverse cardiovascular effects than classical antidepressants. The animal data appear to support the former: in several tests anticholinergic activity was generally weak or absent (except for dose-related mydriasis in mice, although this may represent a sympathomimetic effect) and B was significantly less potent than imipramine and amitriptyline when compared. Regarding adverse cardiovascular effects, however, the relative potency of B and classical antidepressants is difficult to determine based on the data presented. Acute i.v. doses of 1-20 mg/kg in anesthetized cats and dogs produced large but generally transient effects on blood pressure, heart rate, cardiac output, and right ventricular contractile force. In conscious dogs, 20 mg/kg p.o. caused slight increases in blood pressure and heart rate, and in conscious rats 50 mg/kg p.o. caused a slight increase in heart rate. No adverse EKG effects were seen either with a slow i.v. infusion of up to 10 mg/kg in anesthetized dogs or in a 1 year toxicity study in dogs with a maximum daily dose of 150 mg/kg p.o. However, comparison drugs were not used in these studies; a more informative study would have used other antidepressants, and pushed up doses until adverse EKG/cardiovascular effects were seen so that the relative potency of B could be estimated. (In in vitro studies, B was approximately 5-15 x less potent than imipramine or amitriptyline regarding cardiodepressant effects but this cannot be readily extrapolated to in vivo conditions). The sponsor points out that doses and concentrations causing cardiovascular effects in the above studies were [illegible] x greater than clinically therapeutic plasma levels (and plasma levels in mice after administration of the "antidepressant" ED 50); however this does not address the question of possible overdose effects.

Pharmacokinetic studies showed a sex difference in rats, i.e. higher blood and tissue levels were found in females. (The acute toxicity of B in rats is greater in F than M, although this did not appear to be true regarding chronic toxicity). The drug appears to undergo extensive first-pass

metabolism in animals and has a short T 1/2 (1-4 hr., but much longer for metabolites), however human studies have shown a longer T 1/2 of 14 hr. B was shown to induce its own metabolism, presumably VIA an effect on liver microsomal enzymes, in rat, mouse, and dog.

Segment II reproduction studies, performed in rats and rabbits, showed a tendency toward delayed ossifications and supernumerary ribs, findings which are relatively common in drug studies and are thought to result from maternal stress/toxicity and/or fetal immaturity (although it should be noted that some of these skeletal findings were seen at the lower doses which did not clearly induce other overt toxic effects). In the rabbit studies overall gross and visceral abnormalities were increased at all doses, although the percent of fetuses affected was relatively low and no increase in any specific type of abnormality was seen. A consultant report by Dr. James G. Wilson, an acknowledged expert in teratology, concluded that there were "no major indications of embryo-fetotoxicity observed ... at any dosage."

Carcinogenesis studies in rats (23-24 months) and mice (21-22 months) did not reveal any increase in neoplasia (maximum daily dose = 300 and 150 mg/kg, resp.), despite the fact that B was weakly positive in some strains in the Ames Test and at 300 mg/kg in a rat bone marrow chromosome study.

The major toxicological findings having possible implication for man were the following:

1) Convulsions - seen in rat, mouse, dog, and rabbit, primarily at the higher doses. Studies in rats suggested that chlordiazepoxide was the most effective antagonist of B-induced seizures. (Other benzodiazepines were not tested).

2) Hyperplastic nodules in liver

These were seen in the 2 yr rat (but not mouse) study. (In the 1 year dog study, "ground glass" and vacuolated cytoplasm were seen but it is not clear if these were similar to "foci of cellular alteration" which have been described in rats and have been considered to be related to [possible precursors of ?] hyperplastic nodules). Nodules were seen at all doses (100, 200, 300 mg/kg) in the 2 year rat study, and thus no "no-effect" dose was established. (Nodules were not seen at 25, 50, or 100 mg/kg in the 55 week rat study; however, they did not appear until around 90 weeks in the 2 year study, and thus might have possibly developed at these lower doses had the rats lived long enough). (For comparison, acute ED 50% for antidepressant activity was approximately 10 mg/kg i.p. in rats, and 12.5 mg/kg i.p. and 32 mg/kg p.o. in mice). The toxicological implications of hyperplastic nodules are not clear. The sponsor suggests that they may represent either (1) a reflection of liver microsomal enzyme induction or (2) an adaptive response to hepatic injury. Regarding the former, B has been shown to induce its own metabolism although the ability of B to induce the metabolism of other compounds was not clearly demonstrated. Regarding the latter, no other indication of hepatic damage (including blood chemistry) was seen in rats, although some indications of liver damage were obtained in dogs. There has been much controversy in recent years concerning the possible role of hyperplastic nodules in the development of hepatocarcinomas. Several years ago some pathologists suggested that such lesions should be considered "pre-neoplastic" or "neoplastic" in that it was hypothesized that they could progress to malignant tumors (Squire and Levitt, Cancer Res. 35: 3214, 1975; Williams, Biochem. et Biophys. Acta 605: 167, 1980). These pathologists thus suggested replacing the term "hyperplastic nodule" with "neoplastic nodule". (It has also been suggested that "foci of cellular alteration" are also "pre-neoplastic" in the sense that they might progress to neoplastic nodules or possibly directly to malignant tumors). However, this area was recently the subject of a symposium (Rodent Liver Nodules - Significance to Human Cancer Risk?, Int'l Symposium of the Society of Toxicologic Pathologists, May 10-12, 1982, Reston, VA; proceedings to be published) at which these

earlier hypotheses were challenged. Data was presented showing that in several cases nodules and foci of cellular alteration regressed after cessation of treatment, suggesting that they are not necessarily on an irreversible pathway to malignancy. It has also been shown that nodules are not necessarily transplantable. Based on these observations of a lack of autonomy of these proliferative lesions, an informal consensus was reached agreeing with the proposition that the term "neoplastic nodule" was a misnomer and that such lesions do not necessarily progress irretrievably to malignancy. However, even though these proliferative lesions may not be autonomous and do not necessarily progress irretrievably to malignancy, it is possible that they would progress under the influence of continued drug administration, or alternatively they may simply be "markers" for malignancy (i.e. if a drug produces such lesions it is an indication that the drug is also likely to produce malignancies). Again, based on an informal vote a majority of pathologists present at this symposium believed that the production of nodules or foci of cellular alteration in liver by a chemical was not sufficient evidence to establish that chemical as a hepatocarcinogen. Although several potent hepatocarcinogens have been shown to produce nodules and foci of cellular alteration, several examples were given of chemicals, d' tary regimens, and surgical manipulations which produced
ules or foci but did not produce malignancies despite
. longed treatment. (B would also be an example of this). In summary, I believe that given the state of the art in this area, there is not enough evidence at this time to label B a hepatocarcinogen. It is not known if the proliferative lesions produced by B were autonomous since no studies on reversibility or transplantability were performed. However, these lesions did not progress to malignancy despite continued drug administration in a lifetime rat study. In addition, the nodules were very late appearing (most seen at terminal sacrifice; almost all after 90 weeks), in contrast to the effects of established hepatocarcinogens. On the other hand, in view of the still lingering uncertainty in this area (as well as the weakly positive mutagenicity results), I believe that the findings of an increase in proliferative lesions in liver should be mentioned prominently in the labeling, at least until the issue of the carcinogenic significance of these lesions is resolved.

3) A marked toxic interaction between B and phenelzine was demonstrated in rats (although no pharmacodynamic interactions were seen in several tests at lower doses). Thus, as with classical tricyclic antidepressants, the combined use of B and MAO inhibitors in man should proceed cautiously if at all.

Other findings of more questionable or unknown significance to man were the following:

1) Increased hemosiderosis in several organs in the 55 week and 2 year rat studies, primarily at the higher doses. No other pathological findings were present to explain this; RBC, Hct, and Hb were decreased in 2 of 20 HD rats in the 55 week study but no effect seen in the 2 year study; a slight decrease in Hb and Hct was seen in the 3 month study but no hemosiderosis was reported. (A dark brown pigment was seen in liver and kidney in the 1 year dog study and in kidney in the 2 year mouse study; the pigment was not characterized; decreases in RBC, Hct, and Hb were seen in dogs).

2) Increased incidence of extremely dilated uterine blood vessels with thrombus, uterine bleeding, and acute metritis/pyometritis seen at all doses in the 2 year mouse study. It was considered to be an accentuation of a spontaneous lesion; time of onset was not affected. Similar findings were not seen in other species.

3) Some evidence of liver toxicity was seen at all doses in the 1 year dog study, including elevated AP, SGOT, SGPT, and BSP retention. Liver histopathology included findings of pigment, vacuolation, "ground glass" cytoplasm, and bile duct proliferation; necrosis was not reported. Most of these changes were reversible upon cessation of treatment.

RECOMMENDATIONS:

This NDA is approvable based on the preclinical data submitted, with the following recommendations:

1) Regarding the 2 year rat and mouse carcinogenicity studies, the sponsor should indicate how often the drug solutions for dosing were prepared, and what the drug stability was under these conditions, in order to assure that the actual doses administered were what they were stated to have been.

2) The findings in uterus in the 2 year mouse study (extremely dilated blood vessels with thrombus, bleeding, metritis/pyometritis) should be brought to the attention of the clinical reviewer. The relevance of this finding, seen only in mouse, to man is not clear; a review of adverse reactions in this area would be helpful. Post-marketing monitoring as well as inclusion of the mouse results in the labeling should also be considered.

3) The clinical reviewer should consider making combined use of Wellbutrin and monoamine oxidase inhibitors a contraindication (as with other antidepressants) in view of the toxic potentiation noted in rats. (The sponsor mentions this finding in the "Drug Interactions" section of the labeling).

4) The following recommendations concern the proposed labeling:

a) Carcinogenesis section

The word "small" in the sentence "In rats there was a small increase in nodular proliferative lesions of the liver..." should be eliminated. The incidence of this finding in the drug groups was several times that in controls.

b) Mutagenesis section

The weakly positive effects noted in the Ames Test should be mentioned.

c) Pregnancy section

The findings of an increase in fetal anomalies (aside from supernumerary ribs and delayed ossifications) in the rabbit studies should be mentioned. Although there was no strong evidence that the drug was teratogenic (i.e. there was no increase in any specific type of anomaly and the number of fetuses affected was relatively small), the data do raise a suspicion which should be mentioned.

EICON 301 MADE IN JA

APR 21 1982

Review and Evaluation of the Pharmacology & Toxicology Data of NDA 18-644 New NDA of 12/23/81 Drug Abuse Staff Consult

Background:

Wellbutrin (Bupropion) is an antidepressant drug which Burroughs-Welcome has submitted for marketing approval (NDA 18-644). The drug differs from a classic phenethylamine structure in three ways: it has a meta-chloro substituent on the phenyl ring, a B-keto group on the ethyl side chain, and a t-butyl substitution on the nitrogen atom. The similarity of bupropion to amphetamine and diethylpropion was recognized during the drug's development and, consequently, a battery of neuropharmacologic and behavorial tests were performed to address issues relating to abuse potential.

Preclinical pharmacology:

Bupropion lacks the peripheral sympathomimetic effects of amphetamine. Large i.v. and oral doses were without sustained cardiovascular effects in dogs and had only weak transient effects on the pressor response to exogenous norepinephrine and tyramine. Doses of 25 or 50 mg/kg, p.o. did not affect systolic blood pressure or heart rate. No significant effects were observed on α or β-adrenergic mediated responses. Further, in isolated tissue preparations, buoropion did not release catecholamines.

Bupropion was compared to amphetamine in terms of appetite suppression, CNS stimulation and stereotypy responses. The drug produced a mild decrease in food consumption in food-deprived mice. Milk consumption in mice was disrupted but the confounding effect of increased motor activity makes it difficult to determine the specificity of the anorectic response. In terms of increased locomotor activity, bupropion was approximately 1/10 as potent as amphetamine. The effects of either compound could be blocked by prior destruction of central catecholamine neurons, lesioned by 6-hydroxydopamine.

Buproprion's and amphetamine's actions on locomotor activity could be differentiated by pretreatment with reserpine or α-methyl paratyrosine (α-MPT). While reserpine blocked the locomotor activity of bupropion, amphetamine's actions were unaffected. Conversely, while the stimulant activity of amphetamine was antagonized by α-MPT treatment, the action of bupropion was unchanged.

High doses of amphetamines produce a well defined stereotypy response consisting of intense sniffing, licking and chewing movements. Bupropion (25 mg/kg, i.p.) produced a partial replication of amphetamine stereotypy in that sniffing movements were observed but licking and chewing movements were absent.

The ability of a compound to reverse tetrabenazine-induced sedation is a preclinical screening test for antidepressant activity. Both bupropion and amphetamine pretreatment prevented tetrabenazine-induced sedation but only amphetamine reversed the sedation when given after tetrabenazine.

Amphetamine and bupropion were tested for effects on schedule controlled behavior in rodents. The effects of bupropion were qualitatively similar to amphetamine; i.e., bupropion increased low rates of responding and decreased high rate of responding in a number of operant tasks.

In another series of behavioral experiments, animals were trained to discriminate bupropion from saline. Several psychomotor stimulants, including caffeine and amphetamine, and the antidepressant viloxazine cross-generalized to the discriminative stimulus of bupropion. In animals trained to discriminate amphetamine from saline, bupropion generalized to amphetamine whereas viloxazine did not.

In a study conducted in codeine lever-trained rhesus monkeys, parenteral administration of bupropion at the unit doses of 0.3 and 1.0 mg/kg produced response rates which exceeded those maintained by codeine and approached those maintained by the optimal unit dose of amphetamine.

Bupropion differed from amphetamine in <u>in vitro</u> synaptosomal preparations in the following ways: (1) it did not release catecholamines; and (2) the action to block accumulation of catecholamines was unaffected by prior reserpinization (amphetamine was enhanced.)

Clinical studies:

Psychomotor stimulation, or lack thereof, can be inferred from symptom checklists used in placebo controlled studies. Four studies were identified in which patients received treatment for 4-6 weeks: <u>06</u>, 100-200 mg, t.i.d.; <u>08</u>, 100-250, t.i.d.; <u>09</u>, 50-150 mg, t.i.d.; and <u>14</u>, 100-200 mg, t.i.d. Consistent measures in these studies included the symptoms of agitation/excitement, increased motor activity, decreased appetite, insomnia, drowsiness/sleepiness and hallucinations. In study 06, bupropion increased scores on the agitation/excitement parameter. In study 08, bupropion increased agitation/excitement and increased motor activity relative to the placebo scores. No definite trends were observed for insomnia, decreased appetite and drowsiness. Additionally, there were no reports of anti-fatigue effects, abnormal elation, racing thoughts, heightened sensory perception or hallucinations.

In two studies (#09 and #14), a weight loss of about two pounds occurred in the bupropion groups. This difference was statistically significant from placebo at $p < 0.05$. In another clinical study (#17), longer treatment (6 months) with bupropion produced a slight weight gain.

Bupropion (100, 200 and 400 mg) was tested against amphetamine (15 and 30 mg) for anorectic activity in a double-blind, placebo controlled fashion. Bupropion had no anoretic effect, nor did it produce a decrease in caloric intake.

Analysis of post-treatment (withdrawal) periods failed to note any systematic changes in symptoms associated with amphetamine withdrawal.

Behavioral, physiological and subjective effects of bupropion were compared to amphetamine in three placebo controlled, double-blind studies. In the first two studies (11 UK and 37 UK) d-amphetamine (10 mg) and placebo were compared to 100 or 200 mg doses of bupropion. Amphetamine increased auditory vigilance, decreased reaction time, increased heart rate and systolic blood pressure, increased pupil diameter, increased attention and subjective measures of alertness, elation and energy in normal volunteers. Bupropion at doses up to 200 mg did not affect any of the behavioral or subjective measures. A 12% increase in heart rate was observed with the 200 mg bupropion dose.

The third study (#24) evaluated the effects of single dose of bupropion (100, 200 or 400 mg) or amphetamine (15 or 30 mg) on a number of behavioral, physiological and subjective rating scales in multiple drug abusers. The study design was placebo-controlled, double-blind crossover type with a latin square to correct for order effects. Subjective effects were measured on the Addiction Research Center Inventory (ARCI) and the Amphetamine Self-Rating Scale (ASRS). Subjects were also administered a single dose questionnaire and the Liking Scale (a rating of degree of preference).

Behavioral measures rated were appetite, caloric intake at lunch and supper and an estimate of quality and duration of sleep.

Physiological indeces obtained were pulse rate, blood pressure, and body temperature, respiratory rate and pupillary diameter.

Thirteen subjects completed the crossover design. Measurements were obtained at 0.5, 1, 2, 3, 4, 5, 12, and 24 hours following each dose.

Amphetamine produced dose-related effects on the amphetamine, benzedrine and morphine benzedrine group scales. Bupropion could not be differentiated from placebo on the amphetamine or benzedrine subscales; the 400 mg bupropion dose registered above placebo values on the morphine benzedrine group scale. On the Single Dose Questionnaire, bupropion was identified more often as a placebo. Further, the identifications of bupropion as benzedrine occurred no more often than placebo was identified as benzedrine. On the Liking Scale, amphetamine was clearly differentiated from placebo and bupropion. The 400 mg dose produced a slight elevation of the liking score relative to the placebo response.

On the behavioral measure, amphetamine reduced appetite and caloric intake whereas bupropion could not be differentiated from placebo. Further, amphetamine decreased total sleep time, quality of sleep and feelings of freshness in the morning and increased feelings of tiredness during the day. Bupropion did not affect sleep indeces.

Amphetamine increased systolic and diastolic blood pressure in a dose-related fashion. The 30 mg dose of amphetamine increased pulse rates at a number of time points. There was a trend for amphetamine to increase body temperature. Bupropion had no significant effect on the physiological parameters.

Evaluation:

The sponsor has submitted preclinical and clinical data which address the relative stimulant effects of bupropion vs. amphetamine. Preclinical data in rodents suggest some weak amphetamine-like effects wth respect to locomotor activity, effects on schedule controlled behavior and cross-generalization to amphetamine in a discriminative stimulus paradigm. Further, self-administration data in the rhesus monkey suggest that intravenous administration of bupropion at unit doses of 0.3 and 1.0 mg/kg maintains response rates equivalent to amphetamine.

Neurochemistry and pharmacology data suggest that amphetamine and bupropion act on catecholaminergic neurons but the two substances act on different pools of norepinephrine. Amphetamine appears to interact with a reserpine-insensitive (newly synthesized?) pool whereas bupropion may interact with a reserpine sensitive (granule storage?) pool.

Data obtained from clinical efficacy studies suggest mild amphetamine-like activity with respect to increased motor activity. However, no anorectic effect of note was observed with bupropion. Further, no peripheral sympathomimetic activity was consistently observed with bupropion.

On the behavioral and subjective rating scales, doses of 10 to 30 mg of amphetamine had their expected effects of increased vigilance, decreased fatigue, elation, insomnia, etc. On the ARCI subscales, amphetamine scored highly on the amphetamine, benzedrine, and morphine benzedrine subscales whereas the 400 mg dose of bupropion produced only a modest elevation over placebo responses on the morphine benzedrine group scale. On the Liking Scale, amphetamine produced significant elevations whereas the 400 mg doses of bupropion produced a score intermediate to amphetamine and placebo.

There is an apparent discrepancy between the preclinical and clinical data with respect to the amphetamine-like activity of bupropion. Several explanations are conceivable. It may be that bupropion would have more amphetamine-like activity if higher oral doses or parenteral doses were administered. For ethical reasons, neither of these possibilities was

investigated. It appears that 400 mg of orally administered bupropion may have some threshold amphetamine-like activity. Higher doses may produce a more reliable, intensive amphetamine-like effect. The sponsor's argument is that 800 mg of bupropion may produce seizures, thus limiting the abusable dose range of the compound from a threshold dose of 400 mg to the toxic single dose of 800 mg.

Conclusion:

The abuse potential of bupropion by the oral route appears to be minimal. Therapeutic doses lack subjective amphetamine-like activity and higher doses appear to have weak amphetamine-like activity. The abusable dose range appears to be between 400 and 800 mg, p.o.

The abuse potential of bupropion by the parenteral route appears to be greater than that observed with the oral route. The animal data do not permit a conclusion with respect to reinforcement efficacy vis a vis amphetamine. No human parenteral experience has been documented with this substance. However, given the animal data, it is tempting to speculate that bupropion may be amphetamine-like in man if administered intravenously.

The issue now becomes what to do with the available data on bupropion's abuse potential. I do not believe that bupropion warrants scheduling under the Controlled Substances Act. Rather, I believe the available data should be incorporated into a Drug Abuse and Dependence Section in the labeling.

Recommendation:

1. The sponsor should incorporate a Drug Abuse and Dependence Section into the labeling which incorporates the following data:

[redacted]

(2) In operant behavioral paradigms, bupropion has effects on behavior similar to those observed with psychomotor stimulants;

(3) In animals trained to discriminate amphetamine from placebo, bupropion was identified as amphetamine-like;

(4) In rhesus monkeys, bupropion was self-administered at rates above those maintained by codeine and approximating rates maintained by amphetamine.

b. Clinical studies

(1) In clinical trials, oral doses of up to 250 mg t.i.d. had mild effects on an agitation/excitement parameter in a symptom checklist. No reports of amphetamine-like effects were observed at these doses;

(2) In psychopharmacology studies, single oral doses of up to 200 mg of bupropion were indistinguishable from placebo. Amphetamine had its usual effects of increased vigilance, elation and increased sociability. Single oral doses of 400 mg bupropion had mild amphetamine-like activity as measured by the morphine-benzedrine scale of the Addiction Research Center Inventory and Liking Scores. Higher doses were not tested as 800 mg may produce seizures;

(3) tolerance did not develop to the antidepressant effect of bupropion;

(4) the bupropion post-treatment period was not associated with rebound phenomena thought to constitute an amphetamine withdrawal syndrome; e.g., somnolence, hyperphasia, depression.

Frank T. Vocci Jr, Ph.D.
Frank J. Vocci, Jr., Ph.D.

cc:
NDA Orig
HFD-180
HFD-120
HFD-120/FVocci/3/25/82
FT:dcm/3/26/82
DOC #1806B

Filed 4-26-82

Product Name(s):
Proprietary: Wellbutrin (USA) Amfebutamone (INN, MFN)
Non-proprietary: bupropion hydrochloride
Compendium:
USAN: bupropion hydrochloride
Code name/number: [redacted]
Drug Classification: 1C

Dosage Form(s) and Route(s) of Administration: Tablets - oral

Pharmacological Category and/or Principal Indication: Antidepressant

Structural Formula & Chemical Name:

Initial Submission: December 28, 1981
Amendment(s): 5/21/85 (Rec'd. in HFN-120 5/21/85 and for Rev. 5/23.85) (see Chem. Rev. dated 6/9/83 for amend
Related Documents: See prior Chem. Rev. for related docs.

Conclusions and Recommendations:

The application remains approvable pending receipt of FPL and concurrence with the Division of Biopharmaceutics regarding the dissolution specifications and test as cited above.

Francis A. Zinsitz 5/24/85
Chemist

cc: IND/NDA Original
HFD-120/Kumkumian (only Chemist's Review #1)
HFD-Division File
HFD- Div./drafter/date/typist/date

R/D Initialed by:

Omit entire Page

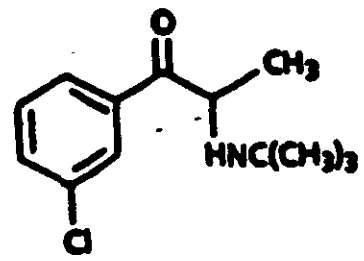
BURROUGHS WELLCOME CO. ANALYTICAL STANDARD

NAME: Bupropion Hydrochloride				ITEM NO. or STOCK NO. [redacted]
PAGE 1 OF 3	DATE ISSUED: [redacted] DATE EFFECTIVE: [redacted]	SUPERSEDES [redacted]	MFD. BY: CDL	APPROVED BY: J.B. Gillikin

COPY TO: Distribution List

OFFICIAL IN: [redacted]

SPECIFICATIONS



• HCl

$C_{13}H_{18}ClNO \cdot HCl$ Mol. Wt. 276.21

PHYSICAL EXAMINATION: [redacted] White powder with a slight characteristic odor.

COLOR AND CLARITY:

A. [redacted] A 2 percent aqueous solution has [redacted]

B. [redacted] A 2 percent aqueous solution has [redacted] than the Reference Standard.

IDENTIFICATION:

A. Infrared: [redacted] The infrared absorption spectrum of a potassium bromide dispersion of the sample exhibits maxima and minima only at the same wavelengths with the same relative intensities, as that of the Reference Standard similarly run.

For revision refer to [redacted]

1

CONFIDENTIAL - NOT TO BE COPIED

[redacted]

NAME: Bupropion Hydrochloride | DATE ISSUED [redacted]

B. HPLC: [redacted] The retention time for the bupropion peak in the sample chromatogram agrees with that of the Reference Standard.

RELATED SUBSTANCES:

I) TLC:

[redacted] Not more than [redacted]

[redacted] Not more than [redacted]

[redacted] Not more than [redacted]

[redacted] Not more than [redacted]

II) HPLC:

[redacted] Not more than [redacted]

[redacted] Not more than [redacted]

III) [redacted] The total related substances found is not more [redacted]

LOSS ON DRYING: [redacted] Not more th[redacted]

WATER: [redacted] Not more than [redacted]

CONFIDENTIAL - NOT TO BE COPIED

[redacted]

BURROUGHS WELLCOME CO. ANALYTICAL STANDARD [redacted] PAGE [redacted]

NAME: Bupropion Hydrochloride	DATE [redacted]

CHLORIDE: [redacted] Not less th[redacted] and not more than [redacted]

ASSAY: [redacted] (HPLC) Between [redacted] and [redacted]

CONFIDENTIAL - NOT TO BE COPIED

LION 301 MADE IN

BURROUGHS WELLCOME CO. ANALYTICAL STANDARD

NAME: Bupropion Hydrochloride				ITEM NO. or STOCK NO. [redacted]
PAGE 1 OF 7	DATE ISSUED: [redacted] DATE EFFECTIVE:	SUPERSEDES [redacted]	MFD. BY: CDL	APPROVED BY: Jesse Gillikin
COPY TO: Distribution List				OFFICIAL IN: [redacted]

TESTING INSTRUCTIONS

PHYSICAL EXAMINATION: Examine a portion of sample on a clean sheet of white paper, report the color, odor and form.

COLOR AND CLARITY:

Sample Preparation: Transfer 1.0 g of sample into a 50-ml color comparison tube, dissolve in and dilute to volume with water, and mix.

A. Color - Proceed as directed in the General Method entitled "APHA Color of Solutions[redacted], comparing the sample to APHA Standard 20.
[redacted]

B. Clarity - Compare the sample with the Reference Suspension, 5 minutes after preparation, in matched 50-ml color comparison tubes in diffused daylight, viewing vertically against a black background. The diffusion of light must be such that the Reference Suspension can readily be distinguished from water. [redacted]

Reagents:

Hydrazine Sulfate Solution - Dissolve 1.0 g of hydrazine sulfate (ACS reagent grade) in water and dilute to 100.0 ml with the same solvent. Allow to stand 4 to 6 hours.

Hexamethylenetetramine Solution - Dissolve 2.5 g of hexamethylenetetramine (ACS reagent grade) in 25.0 ml water in a 100-ml glass-stoppered flask.

Primary Opalescent Suspension - Add to the Hexamethylenetetramine Solution in the flask 25.0 ml of Hydrazine Sulfate Solution. Mix and allow to stand for 24 hours. This solution [redacted] provided it is stored in a glass container free from surface defects.

For revision refer to [redacted]

C O N F I D E N T I A L - N O T T O B E C O P I E D

[redacted]

The suspension must not adhere to the glass and must be well mixed before use.

Standard of Opalescence - Dilute 15.0 ml of the Primary Opalescent Suspension to 1000.0 ml with water. This suspension must be [redacted]

Reference Suspension - Add 5.0 ml of Standard of Opalescence to a 100-ml volumetric flask and bring to volume with water. Mix thoroughly and transfer 50 ml into a 50-ml color comparison tube.

IDENTIFICATION:

A) Infrared - Determine the infrared absorption spectrum of a potassium bromide dispersion of a portion of sample using a suitable infrared spectrophotometer and compare it to the Reference Standard similarly run. Use a vibrating ball mill to grind the sample and standard with the potassium bromide prior to pressing it into a disk.

B) HPLC- Obtain the chromatograms of the Standard and Sample Preparations in the ASSAY below, and compare the retention times for the bupropion peak in each. Report the results.

RELATED SUBSTANCES:

I. TLC

Standard Preparation:

Stock Solutions:

CAUTION: 2-bromo-3'-chloropropiophenone is a pungent lachrymator. Handle with gloves and goggles. Use in a fume hood whenever possible.

(A) Transfer 25 mg of 2-bromo-3'-chloropropiophenone, accurately weighed, into a 25-ml volumetric flask, dissolve in and dilute to volume with methanol.

(B) Transfer 25 mg of 3'-chloropropiophenone and 25 mg of Bupropion Hydrochloride Reference Standard, accurately weighed, into a 5-ml volumetric flask, dissolve in and dilute to volume with methanol.

NAME: Bupropion Hydrochloride	DATE ISSUED [redacted]

(C) Transfer [redacted] of 3-chlorobenzoic acid, accurately weighed, into a [redacted] volumetric flask, dissolve in and dilute to volume with methanol.

Standard 1 Preparation: Pipet [redacted] of the Stock Solutions B and C into separate [redacted] volumetric flasks, dilute to volume with methanol and label B' and C'. Into a 10-ml volumetric flask, pipet [redacted] of Stock Solution A, [redacted] of diluted Solution B', and [redacted] of diluted Solution C'. Dilute to volume with methanol and mix. This solution represents the following concentrations [redacted] bupropion sample concentration:

[redacted]
2-bromo-3'chloropropiophenone
3'-chloropropiophenone
3-chlorobenzoic acid
bupropion hydrochloride

Standa: 2 Preparation: Into a [redacted] volumetric flask, pipet [redacted] each of [redacted] Stock Solutions A, B, and C, dilute to volume with methanol, and mix. This solution represents the following concentrations relative to a [redacted] bupropion sample concentration:

[redacted]
2-bromo-3'-chloropropiophenone
3'-chloropropiophenone
3-chlorobenzoic acid
bupropion hydrochloride

Sample Preparation: Transfer 500 mg of sample, accurately weighed, into a [redacted] volumetric flask, dissolve in and dilute to volume with methanol.

Analysis: Spot 5 µl of the Sample and Standard Preparations, separately, about 1 cm from the bottom of a Silica Gel with fluorescent indicator TLC plate which has been washed with the mobile phase and dried in an oven. Develop the chromatogram in a chamber previously equilibrated for 30 minutes, using a solvent system of toluene:cyclohexane:acetic acid [redacted] until the solvent front has traveled about [redacted] above the origin. Remove the plate, air dry, and locate the spots under both long and short wavelength ultraviolet light. Plates should be viewed immediately since the spots can evaporate with time.

NOTES: 1. Camag Nanomat® used for spotting, spot diameter [redacted]
2. Merck Silica Gel 60 F-254 plates were employed.

CONFIDENTIAL - NOT TO BE COPIED

NAME: Bupropion Hydrochloride | DATE ISSUED: [redacted]

Approximate R_f Values

Compound	Approximate R_f Value

II) HPLC - See ASSAY

LOSS ON DRYING:

Dry about 1.0 g of sample, accurately weighed, for [redacted] and calculate as follows:

$$\text{Percent Loss on Drying} = \frac{\text{Net Loss in Weight}}{\text{Initial Sample Weight}} \times 100$$

WATER:

Proceed as directed in the General Method entitled "Moisture Determination by Karl Fischer" [redacted]

CHLORIDE:

NOTE: Use water from the same container to prepare the Standard and Sample Preparations and for the blank.

Standard Preparation: Transfer approximately [redacted] accurately weighed, of dry sodium chloride into a [redacted] volumetric flask. Dissolve in and dilute to volume with water and mix. This solution contains [redacted] of chloride per ml.

Sample Preparation: Transfer approximately [redacted] of sample, accurately weighed, into a [redacted] volumetric flask. Dissolve in and dilute to volume with water and mix.

Acid Reagent: Carefully transfer [redacted] of nitric acid and [redacted] of glacial acetic acid into a [redacted] volumetric flask containing [redacted] of water and mix.

C O N F I D E N T I A L - N O T T O B E C O P I E D
[redacted]

NAME: Bupropion Hydrochloride	DATE ISSUED [redacted]

Gelatin Reagent: Transfer 1.24 g of a dry mixture containing gelatin [redacted] soluble thymol blue 1 part; and thymol 1 part; by weight into a 500-ml beaker. Add 200 ml of water and heat on a steam bath with stirring until the solution is clear. Pour about 10-ml portions into small glass vials, stopper [redacted]

Procedure: Proceed as directed in the [redacted] titled [redacted], employing [redacted] of the Standard and Sample Preparations, 2.0 ml of the Acid Reagent and [redacted] Run a blank determination using [redacted] of water instead of the sample or standard.

[redacted]

Run blanks, samples, and standards in duplicate. Correct for the blank and determine the percent chloride as follows: [redacted]

% Chloride =

$$\frac{\text{Sec SPL-Sec blank}}{\text{Sec STD-Sec blank}} \times \frac{\text{Conc STD* mg/ml} \times \text{ml STD} \times 100 \text{ ml} \times 100}{\text{Wt SPL(mg)} \times 2.0 \text{ ml}}$$

* [redacted] $\times \frac{\text{Wt Sodium Chloride (mg)}}{500 \text{ ml}}$

[redacted]

NOTE: Care must be taken that all transfers and dilutions are done quantitatively.

ASSAY:

Related Substances Standard Preparation: Transfer [redacted] accurately weighed, of each of the following into [redacted] volumetric flask: 2-(tert-butylamino)propiophenone hydrochloride, 2-(tert-butylamino)-2'-chloropropiophenone hydrochloride, and 3-chlorobenzoic acid. Add a mixture of methanol:water [redacted] and bring to volume with mixing.

Standard Preparation: Transfer approximately 60 mg of Bupropion Hydrochloride Reference Standard, accurately weighed, into a 100-ml volumetric flask. Transfer 1.0 ml of the Related Substances Standard Preparation to the flask and add a mixture of methanol:water [redacted] to volume with mixing to dissolve the bupropion hydrochloride. [redacted]

CONFIDENTIAL - NOT TO BE COPIED

[redacted]

Instrumental Conditions+:

Instrument:
Column:

Mobile Phase:

Flow Rate:
Detection:
Retention Times:

+Instrumental Conditions may be varied so that the requirements of the System Suitability Test (below) are met.

++pH 7 Phosphate Buffer Preparation: Transfer 27.22 g of monobasic potassium phosphate (KH_2PO_4) into a 1000-ml volumetric flask, dissolve in and dilute to volume with water and mix. Prepare fresh every two days. Then transfer 250.0 ml of this solution and 100.0 ml of 0.291N sodium hydroxide into a 1000-ml volumetric flask, dilute to volume with water, and mix. [redacted]

[redacted]

CONFIDENTIAL - NOT TO BE COPIED

[redacted]

NAME: Bupropion Hydrochloride	DATE ISSUED [redacted]

Calculations: (weights in mg)

a) percent 2-(tert-butylamino)propiophenone hydrochloride =

$$\frac{\text{SPL Pk Ht or Area}}{\text{Avg}^{**}\text{ STD Pk Ht or Area}} \times \frac{\text{STD Wt}}{100} \times \frac{1}{100} \times \frac{100}{\text{SPL Wt}} \times \frac{100}{(100-\%\text{LOD})} \times 100$$

b) percent 2-(tert-butylamino)-2'-chloropropiophenone hydrochloride =

$$\frac{\text{SPL Pk Ht or Area}}{\text{Avg}^{**}\text{ Std Pk Ht or Area}} \times \frac{\text{STD Wt}}{100} \times \frac{1}{100} \times \frac{100}{\text{SPL Wt}} \times \frac{100}{(100-\%\text{LOD})} \times 100$$

c) percent bupropion hydrochloride (dry basis) =

$$\frac{\text{SPL Pk Ht or Area}}{\text{Avg}^{**}\text{ STD Pk Ht or Area}} \times \frac{\text{STD Wt}}{100} \times \frac{100}{\text{SPL Wt}} \times \frac{100}{(100-\%\text{LOD})} \times 100$$

[redacted]

System Suitability Test:

Six replicate injections of the Standard Preparation give relative standard deviations of [redacted] and peak retention times of the bupropion peaks. The resolution (R_s) of the bupropion peak from the 2-(tert-butylamino)-2'-chloropropiophenone peak in the Standard Preparation chromatogram [redacted] The retention time for bupropion [redacted]

[redacted]

[redacted]

CONFIDENTIAL - NOT TO BE COPIED

[redacted]

MDR 1866 Pg 310

AL, Sign, LA,

NDA 18-644

DEC 30 1985

Burroughs Wellcome Company
Attention: Donald A. Knight
3030 Cornwallis Road
Research Triangle Park, North Carolina 27709

Dear Mr. Knight:

Please refer to your new drug application dated December 28, 1981, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation Wellbutrin (bupropion hydrochloride) Tablets, NDA 18-644.

We also acknowledge receipt of your additional communications dated:

March 14, 1985	June 21, 1985
March 19, 1985	August 9, 1985
March 21, 1985	September 20, 1985
April 9, 1985	September 26, 1985
May 1, 1985	September 30, 1985
May 21, 1985	November 20, 1985
June 11, 1985	November 26, 1985

We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that bupropion is safe and effective for use as recommended in the revised labeling that was developed at our meeting on December 20, 1985. Accordingly, the application is approved, effective on the date of this letter, provided that the precise text of the labeling to be employed is that incorporated in the body of this letter.

Twelve copies of the final printed version of the revised labeling (including container and package labeling) must be submitted to FDA prior to marketing. Marketing of the drug before the changes specified above are made and submitted to FDA renders the product misbranded under 21 U.S.C. 352.

In addition to the submission of revised labeling, the approval of the application is conditioned upon your commitment, made earlier, to undertake the program of post-marketing studies enumerated in our December 31, 1984 approvable letter. Also, as agreed at our December 20, 1985 meeting, you will modify your plans for the post-marketing chronic, repeated dose, dose proportionality 'bio' study to evaluate not only bupropion but its major, active metabolites. As agreed December 30, 1985, by telephone conversation between Richard Kiernan and Dr. Stanley Blum, the Dissolution Specification will be: Q=80% at 45 minutes, using the paddle method (50 rpm) in 900 mL water at 37°C. Finally, you must also submit, within a reasonable interval, the laboratory test results and cross-tabulations requested earlier.

The approved labeling of Wellbutrin follows:

NDA 18-644/S-001
/S-002

Burroughs Wellcome Co.
Attention: Donald A. Knight
Drug Regulatory Affairs
3030 Cornwallis Road
Research Triangle Park, N.C. 27709

Dear Mr. Knight:

We acknowledge the receipt on January 14, 1986 of your supplemental new drug applications (S-001, S-002) dated January 14, 1986 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Wellbutrin^{R} (bupropion hydrochloride).

The first submission (S-001) provides for final printed labeling agreed upon in the meeting of December 20, 1985, between Burroughs Wellcome and this Agency. In addition, your second submission (S-002) contains a change in this labeling which was discussed in a January 9, 1986 teleconference between Dr. Allen Cato of Burroughs Wellcome and Dr. Paul Leber of this Agency. The change provides for the removal from the Dosage and Administration section of the statement, "While no systematic study of withdrawal has been conducted, it seems prudent to recommend gradual tapering of drug over a period of a week".

We have completed the review of these supplemental applications (S-001, S-002) and they are approved. Our letter of December 30, 1985 detailed the conditions relating to the approval of this application.

Should you have any questions please contact Mr. Tony DeCicco, Consumer Safety Officer at (301) 443-4020.

Sincerely yours,

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

cc:
Orig NDA
HFN-120
HFN-120/TLaughren/PLeber
TDeCicco
ad/1/17/86/1/23/86
DOC 1466x

Summary for Basis of Approval

NDA 18-644

Drug Generic Name:
bupropion hydrochloride

Applicant:
Burroughs Wellcome Company
Research Triangle Park, NC 27709

Brand Name:
Wellbutrin

I. Indications for Use:

WELLBUTRIN[R] is indicated for the treatment of depression in patients who fail to respond adequately to or who cannot tolerate alternative antidepressant treatments. Wellbutrin is not recommended as an antidepressant of first choice for most patients because its use at doses approximately one and one third times greater than the usually required daily dose (450 mg) is associated with a high risk of seizure (see Warnings).

The efficacy of WELLBUTRIN was demonstrated in placebo controlled clinical trials which enrolled principally hospitalized patients with diagnoses of depressive neurosis or manic-depressive (depressed type) disorder. The depressive illness of the patients studied most closely corresponds 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.

Evidence to demonstrate the sustained effectiveness of WELLBUTRIN after three weeks of use in placebo controlled investigations is not presently available.

II. Dosage form, route of administration and recommended dosage:

At doses that are one and one-third times the usually required dose (450 mg/day), (See Warnings), the observed incidence of seizure increases by as much as ten fold. This predicts a relatively narrow therapeutic ratio for the safe use of bupropion, especially as there is considerable inter-individual variability in the capacity of patients to metabolize drugs.

Consequently, it is particularly important to administer bupropion in a manner that is most likely to minimize the risk of seizure. Retrospective analysis of clinical experience gained during its premarketing development 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 in divided doses to avoid high peak concentrations of bupropion and/or its metabolites, and 3) the rate of incrementation of dose is very gradual.

WELLBUTRIN should therefore be given t.i.d., preferably with intervals of at least 6 hours between successive doses. Besides its apparent value in lowering the risk of seizure, gradual dose escalation is important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these side effects may be managed by temporary reduction of dose or the transitory administration of a sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment.

The following suggested dosing regimen incorporates the principles described above.

Usual Adult Dosage:

A starting dose of 225 mg/day given as 75 mg t.i.d. is recommended. Based on clinical response this dose may be increased by 75 mg/day no sooner than every three days according to the following schedule up to a total maximum daily dose of 450 mg/day. Of course, if distressing untoward effects supervene, dose escalation should be stopped.

Dosing Schedule

Treatment Day	75 mg Tablets			Total Daily Dose
	Morning	Midday	Evening	
1	1	1	1	225 mg
4	2	1	1	300 mg
7	2	2	1	375 mg
10	2	2	2	450 mg

In patients who do not demonstrate an adequate response after an appropriate period of treatment at 450 mg/day, drug should be discontinued.

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. The maximum recommended maintenance dose is 450 mg/day. While it is generally recommended that a course of antidepressant drug treatment should continue for several months and many patients have been treated with WELLBUTRIN in long-term clinical trials of up to 2 years duration, there has been no systematic placebo-controlled evaluation of the efficacy of WELLBUTRIN for a period beyond three to four weeks.

III. Chemistry:

A. Manufacturing and Controls: The description of the synthesis included in the application provides additional details not completely covered by the referenced U.S. Patent 3,819,706 which permits evaluation of the specifications and tests including those limits on impurities detected by the use of TLC and HPLC.

B. Stability Studies: Stability data has been included for all proposed marketed dosage strengths which support the recommended 18 month expiration dating for the drug product stored within the label stated limits.

C. Methods Validation: The analytical methods were validated by both the New York District and the Division of Drug Chemistry Laboratories and found satisfactory for regulatory purposes.

D. Labeling: The draft labels for 50 mg, 75 mg and 100 mg strengths include the required statements; however, those labels used for containers of 100's of the tablet strengths require repositioning of the Caution statement from the vertical side panel to the horizontal center panel.

E. Establishment Inspection: Evaluation of establishment inspection reports on January 18, 1983 by HFN-320 indicate the referenced facilities are in conformance with CGMP's.

F. Environmental Impact Analysis Report: A statement on EIAR has been provided in accordance with 21 CFR, Part 25(g). This statement has been reviewed and found to be acceptable.

IV. Biopharmaceutics:

Using normal healthy volunteers, five full-scale bupropion HCl bioavailability/pharmacokinetic type studies were conducted along with several in-vitro dissolution studies.

1. In study No. 27, seven fasting male volunteers received 200 mg of an aqueous solution of ^{14}C-bupropion HCl orally. Blood, urine and fecal samples were collected for 96 hours.

   Study results indicated that over 96 hours, approximately 87% of the administered radiolabeled dose was excreted in urine, and approximately 10% was excreted in the feces. For those two routes of elimination, only a negligible amount of the parent drug, i.e., less than 1%, was recovered by each route. From the results of this study and from animal data, it appears that bupropion undergoes significant first-pass metabolism.

III. Chemistry:

A. Manufacturing and Controls: The description of the synthesis included in the application provides additional details not completely covered by the referenced U.S. Patent 3,819,706 which permits evaluation of the specifications and tests including those limits on impurities detected by the use of TLC and HPLC.

B. Stability Studies: Stability data has been included for all proposed marketed dosage strengths which support the recommended 18 month expiration dating for the drug product stored within the label stated limits.

C. Methods Validation: The analytical methods were validated by both the New York District and the Division of Drug Chemistry Laboratories and found satisfactory for regulatory purposes.

D. Labeling: The draft labels for 50 mg, 75 mg and 100 mg strengths include the required statements; however, those labels used for containers of 100's of the tablet strengths require repositioning of the Caution statement from the vertical side panel to the horizontal center panel.

E. Establishment Inspection: Evaluation of establishment inspection reports on January 18, 1983 by HFN-320 indicate the referenced facilities are in conformance with CGMP's.

F. Environmental Impact Analysis Report: A statement on EIAR has been provided in accordance with 21 CFR, Part 25(g). This statement has been reviewed and found to be acceptable.

IV. Biopharmaceutics:

Using normal healthy volunteers, five full-scale bupropion HCl bioavailability/pharmacokinetic type studies were conducted along with several in-vitro dissolution studies.

1. In study No. 27, seven fasting male volunteers received 200 mg of an aqueous solution of ^{14}C-bupropion HCl orally. Blood, urine and fecal samples were collected for 96 hours.

   Study results indicated that over 96 hours, approximately 87% of the administered radiolabeled dose was excreted in urine, and approximately 10% was excreted in the feces. For those two routes of elimination, only a negligible amount of the parent drug, i.e., less than 1%, was recovered by each route. From the results of this study and from animal data, it appears that bupropion undergoes significant first-pass metabolism.

Nine metabolites were identified in urine; four were shown to have some pharmacologic activity in mice. For this study, the mean elimination (beta phase) half-lives were about 21 and 32 hours for bupropion and total plasma radioactivity, respectively.

2. In study No. 30, eighteen fasting male volunteers received single oral doses of 2 x 50 mg WELLBUTRIN tablets, and 100 mg and 250 mg of bupropion in an aqueous solution of bupropion HCl in a three period crossover study. Plasma samples were collected for 60 hours following administration. The 50 mg tablet lot tested was used in four clinical trials, including one that was positive; it was made on production-size equipment using the same procedures as those for the marketed drug.

   This study demonstrated that a single dose of two 50 mg tablets is equivalent in its absorption to the 100 mg aqueous solution, and that bupropion plasma concentrations are dose proportional following the 100 and 250 mg doses which are the lowest and highest (t.i.d.) doses recommended in the labeling.

3. Study No. 07A was a crossover bioequivalence study in which 16 fasting male volunteers received single doses of 4 x 50 mg capsules, 2 x 100 mg capsules, 4 x 50 mg tablets and 2 x 100 mg tablets. Plasma samples were collected for 24 hours following each dose. Calculated area under the plasma level vs. time curves (AUC) for this interval (0-24 hours) accounted for about 88% of AUC, calculated from time zero to time infinity.

   The tested batches of capsules were used in early clinical trials and it was necessary to compare them to the final marketed product. The batches of tablets in this study, however, were made by procedures different from those used for making the final marketed product. Although this study demonstrated that the different treatments are bioequivalent in absorption, other data are needed to conclude that capsules are equivalent to the marketed product (see study 07D).

4. Study No. 07B was a crossover in which 12 females and 12 males received 1 x 50 mg tablet, 1 x 100 mg tablet, and 2 x 100 mg tablets while fasting. Plasma samples were collected over 24 hours, and calculated AUC_{0-24} values accounted for about 88% of $AUC_{0-infinity}$ values. The tablet batches in this study were the same batches tested in Study No. 07A.

   This study demonstrated bupropion to be dose proportional over a dosing range of 50 to 200 mg.

5. Study No. 07D was an additional study period (fourth) added to Study No. 07B. Eleven male volunteers received 1 x 50 mg modified tablet and 11 female volunteers received 1 x 100 mg modified tablet. The modified tablets were from pilot batches that were made by the same procedures used for the final marketed tablets and were used in clinical trials.

This study demonstrated the 50 mg modified tablet to be similar in its extent of drug absorption to the 50 mg reference tablet. The 100 mg modified tablet, which had poorer in vitro dissolution, was shown to be marginally equivalent in its extent of drug absorption to the 100 mg reference tablet.

Using an in vitro dissolution test method (USP XX, Apparatus 1, 500 ml of 0.6% HCl, 100 rpm, 37°C) that tended to reflect in vivo drug absorption, three production size batches each of the 75 mg and 100 mg tablets, formulations proportionally similar in their active and inactive ingredients to the 50 mg tablet, were shown to have in vitro dissolution characteristics similar to the 50 mg tablet batch tested in Study No. 30.

Other general pharmacokinetic information from bio-studies included the following:

1. Bupropion plasma concentration-time data following single oral doses are described by a two-compartment open model with first-order absorption.

2. The half-life for the initial disposition phase (alpha phase) for the drug's biexponential decay curve is approximately 1-2 hours. The decay curve's second phase half-life (beta phase) is approximately 14 hours, with a range of about 8 to 24 hours.

3. Peak bupropion plasma concentrations occur within two hours following oral administration.

4. Bupropion is approximately 80% bound to human serum albumin.

As a condition of approval the Applicant is required to conduct as Phase IV studies 1) a multiple-dose dose proportionality study that covers the drug's recommended dosing range and 2) a multiple-dose study in geriatric patients.

The basis for requiring the Phase IV studies are the following:

1. The Applicant has conducted only single dose bioavailability/pharmacokinetic studies. From animal studies in the mouse, rat, and dog, bupropion has been shown to induce its own metabolism. For example, mouse whole body bupropion levels were reduced 58% following subchronic treatment for 10 days; dog plasma levels declined by 76% and 90% for two different dose levels following chronic treatment for 366 days).

2. Bupropion is extensively metabolized. Only a small fraction of the absorbed dose reaches the systemic circulation intact. Bupropion has at least two metabolites with significant pharmacologic activity. Because of their longer elimination half-lives, these metabolites, are likely to accumulate when bupropion is administered repeatedly.

This study demonstrated the 50 mg modified tablet to be similar in its extent of drug absorption to the 50 mg reference tablet. The 100 mg modified tablet, which had poorer in vitro dissolution, was shown to be marginally equivalent in its extent of drug absorption to the 100 mg reference tablet.

Using an in vitro dissolution test method (USP XX, Apparatus 1, 500 ml of 0.6% HCl, 100 rpm, 37°C) that tended to reflect in vivo drug absorption, three production size batches each of the 75 mg and 100 mg tablets, formulations proportionally similar in their active and inactive ingredients to the 50 mg tablet, were shown to have in vitro dissolution characteristics similar to the 50 mg tablet batch tested in Study No. 30.

Other general pharmacokinetic information from bio-studies included the following:

1. Bupropion plasma concentration-time data following single oral doses are described by a two-compartment open model with first-order absorption.

2. The half-life for the initial disposition phase (alpha phase) for the drug's biexponential decay curve is approximately 1-2 hours. The decay curve's second phase half-life (beta phase) is approximately 14 hours, with a range of about 8 to 24 hours.

3. Peak bupropion plasma concentrations occur within two hours following oral administration.

4. Bupropion is approximately 80% bound to human serum albumin.

As a condition of approval the Applicant is required to conduct as Phase IV studies 1) a multiple-dose dose proportionality study that covers the drug's recommended dosing range and 2) a multiple-dose study in geriatric patients.

The basis for requiring the Phase IV studies are the following:

1. The Applicant has conducted only single dose bioavailability/pharmacokinetic studies. From animal studies in the mouse, rat, and dog, bupropion has been shown to induce its own metabolism. For example, mouse whole body bupropion levels were reduced 58% following subchronic treatment for 10 days; dog plasma levels declined by 76% and 90% for two different dose levels following chronic treatment for 366 days).

2. Bupropion is extensively metabolized. Only a small fraction of the absorbed dose reaches the systemic circulation intact. Bupropion has at least two metabolites with significant pharmacologic activity. Because of their longer elimination half-lives, these metabolites, are likely to accumulate when bupropion is administered repeatedly.

For both reasons, well-controlled multiple dose bioavailability/pharmacokinetic studies are needed. In addition all bioavailability/pharmacokinetic studies have been carried out in normal healthy young volunteers. Although no differences in the drug's clinical behavior have yet been seen in different age groups, there should be a specific evaluation of metabolism and kinetics in the elderly who may have altered hepatic metabolism of drugs.

IV. Pharmacology:

A. Survey of Effects: Bupropion (BUP) is structurally similar to amphetamine, fenfluramine, diethylpropion, and other phenethylamine derivatives. Its pharmacological profile is that of a CNS stimulant with several similarities to amphetamine.

BUP was active in three types of tests predictive of antidepressant activity: prevention or reversal of tetrabenazine/reserpine effects in mouse, decreased immobility in the Porsolt behavioral despair test in rats, and potentiation of the behavioral effects of pargyline plus DOPA in mice.

BUP was shown to be a relatively weak blocker of the uptake of NE (norepinephrine) and 5-hydroxytryptamine (5-HT) into brain and peripheral nerve compared with classical tricyclics. It was somewhat more potent in blocking dopamine (DA) uptake, although the dose in rat (40 mg/kg i.p.) needed to produce serum levels high enough to cause 50% inhibition of DA (or NE) uptake into brain synaptosomes was 4x greater than the ED_{50}% in the Porsolt test. (The reverse holds true for imipramine regarding the potency ratio for "antidepressant effect" and NE uptake blockade.) The relationship between the blockade of DA (or NE) uptake and the "antidepressant" effect of BUP, therefore, is problematic. However, destruction of dopaminergic neurons with 6-hydroxydopamine + DMI blocked [illegible] in the Porsolt test in rats, suggesting that DA neurons [illegible] in some way. BUP did not inhibit MAO or elevate brain NE or DA at relatively high doses.

B. Comparison with Amphetamine and other CNS Stimulants: Many similarities between the pharmacological profiles of BUP and amphetamine (and other CNS stimulants) were noted, along with some differences, as follows:

1. BUP, amphetamine, and methylphenidate all produce dose-related antitetrabenazine effects and cause dose-related increases in locomotor activity in mice. However, the ratio of the i.p. ED_{50}% values for these two effects was approximately 1:2 for BUP, compared with 2:1 for amphetamine or methylphenidate. (In contrast, classical tricyclics cause decreased locomotor activity above "antidepressant" doses.)

2. Amphetamine and methylphenidate reversed tetrabenazine-induced sedation in mice whether given before or after the tetrabenazine; BUP was active only when given before.

3. Selective depletion of brain DA blocked the locomotor effects of both BUP and amphetamine; selective depletion of NE had no effect on either drug.

4. The locomotor effect of BUP and methylphenidate depends primarily on a storage (reserpine-sensitive) pool of catecholamines, whereas that of amphetamine depends primarily on newly synthesized (alpha-methyltyrosine sensitive) catecholamines.

5. BUP caused an increase in stereotyped behavior in rats; no direct comparison to amphetamine was made.

6. Several behavioral (operant) tests showed the profile of BUP to be more similar to amphetamine than to classical tricyclics.

7. BUP had an anorexic effect in mice. (Oral potency was at least 2x less than that of fenfluramine and diethylpropion; amphetamine was not tested.)

8. Drug discrimination studies in rats showed similarities between BUP and several CNS stimulants (e.g., amphetamine, methylphenidate, caffeine, cocaine) as well as the newer antidepressants viloxazine and nomifensine.

9. At high doses BUP caused hypothermia in mice, whereas amphetamine caused hyperthermia.

10. Grouping of mice caused an increase in the i.p. lethality of amphetamine but had no effect on that of BUP; BUP decreased the lethality of amphetamine in grouped mice.

C. Cardiac Effects: Cardiovascular studies showed rather large but generally transient decreases in cardiac output and right ventricular contractile force, and both increases and decreases in heart rate (HR) and blood pressure (BP), at i.v. doses of 1-20 mg/kg in anesthetized dogs and cats. (It is not clear if these results were corrected for vehicle effects). In conscious dogs, 20 mg/kg p.o. caused slight increases in HR and BP lasting at least 6 hrs.; in conscious rats 50 mg/kg caused a slight increase in HR lasting 3 hrs. Comparison drugs were not used in these studies so that the relative potency of BUP in causing these changes is not known. No effect on EKG (aside from increased HR) was seen in dogs at 10 mg/kg i.v. (2 mg/kg/min). In dogs, 5-10 mg/kg i.v. caused rather large increases in respiratory rate and smaller increases in minute volume. A relatively weak depressant effect on cardiac tissue in various in vitro preparations was noted which may have been due to the local anesthetic properties of BUP (equipotent with cocaine in guinea pig cornea); the potency of BUP was generally 5-15x less than that of imipramine and amitriptyline.

D. Receptor Agonist/Antagonist Effects: Several studies were performed to assess the anticholinergic effects of BUP, and such effects were generally weak or absent. Antagonist actions at other receptors (adrenergic, serotonergic, and histaminergic) were also generally weak or absent, although reference drugs which could have validated the systems and formed a basis for estimating the relative potency of

BUP were not used. Likewise, binding studies showed little or no interaction of BUP with a variety of receptors, but no reference drugs were used.

E. ADME/Pharmacokinetics: ADME/pharmacokinetic studies were performed in rat, mouse, and dog. After oral dosing, plasma levels of BUP peaked rapidly (within 1/4-1/2 hr.) and declined rapidly with a T 1/2 in the 1-4 hr. range. Over a dosage range of 10-100 mg/kg p.o. in rats, plasma levels increased with increasing dose but slightly less than proportionately at the highest dose. Studies comparing plasma AUC after i.v. and p.o. dosing showed a bioavailability of 8-21% in rats and 4% in dogs; however, excretion studies using labeled drug showed complete absorption in dogs and a high, if not complete, degree of absorption in rats after p.o. dosing. BUP was widely distributed in rat tissues; levels were highest in liver and lung after p.o. and i.p. dosing, respectively; lowest levels were in plasma. BUP was shown to be rapidly and extensively metabolized, in agreement with the low oral bioavailability of the drug. Plasma and tissue levels of metabolites were generally substantially higher than those of unchanged drug, except in the brain. Very little unchanged BUP was found in rat or dog urine; acidic metabolites were predominant; m-chlorohippuric and m-chlorobenzoic acids, and a conjugate of the former were identified, presumably arising from side chain oxidation. In human urine, in contrast, acidic and basic metabolites were present in nearly equal amounts. Plasma and tissue levels of metabolites declined much more slowly than those of unchanged drug; in one study the plasma T 1/2 for metabolites appeared to be about 12 hours, suggesting that whereas the parent drug is unlikely to accumulate with repeated dosing due to its short T 1/2, metabolites may. In one mouse study, however, 10 days dosing did not lead to an accumulation of metabolites; such a tendency may have been counteracted by an enzyme-induction effect, since levels of unchanged BUP were decreased.

The ability of BUP to induce liver microsomal metabolic enzymes was demonstrated in rat, mouse, and dog. In rat, pre-treatment with 15-50 mg/kg/day p.o. for 13 days decreased the rise of BUP in plasma seen after an acute dose of 50 mg/kg i.p., and 50 mg/kg/day p.o. for 4 days decreased the rise of BUP in tissues seen after an acute dose of 50 mg/kg i.p. In mouse, 50 mg/kg i.p. for 8 or 10 days decreased the rise in whole body level of BUP seen after an acute dose of 50 mg/kg. In dog, plasma levels after 1 year treatment at 40 or 80 mg/kg/day p.o. were significantly less than those seen on day 1.

Studies on pentobarbital sleep time in mice showed a decrease after 5-150 mg/kg/day p.o. for 10 days; the effect at HD was slightly less than the effect of phenobarbital pretreatment at 80 mg/kg/day; in rats a slight decrease was seen at high doses (100-150 mg/kg/day) only. It is possible that part or all of these effects on pentobarbital sleep time were due to CNS stimulation by BUP. Thus, although BUP appears to induce its own metabolism, its ability to induce the metabolism of other compounds has not been clearly demonstrated.

Excretion of BUP + metabolites was shown to be primarily via the kidney in rats (78%) and exclusively by this route in dogs.

Over concentration ranges that were stated to be "normally found in animals and during clinical studies in man," BUP was 75-85% bound to plasma proteins from mouse, rat, dog, and man. Binding was generally constant over the concentration ranges used, although it tended to fall off in man at the highest concentration (1000 micromolar).

There appear to be some sex differences in the disposition of BUP, at least in rats. Plasma and tissue levels of unchanged drug, plasma AUC, and oral bioavailability were several-fold greater in F; T 1/2 was greater in F in one rat study, but apparently not in another. There did not appear to be any important sex differences in metabolic pattern or excretion, although data on these points were limited. No sex differences in plasma levels in dogs were apparent, although only two dogs per sex were used. The acute toxicity of BUP in rats was slightly greater in F than M, but the reverse appeared to be true in the chronic rat toxicity studies.

F. Toxicology: The acute oral LD_{50} was 544 (M) and 636 (F) mg/kg in mouse, and 607 (M) and 482 (F) mg/kg in rat. Acute i.p. LD_{50} was 273 and 263 mg/kg in male mice and male rats, respectively. Prominent acute signs in the mouse included: ataxia, convulsions, prostration, ptosis, and compulsive gnawing by both routes, plus labored breathing, decreased respiration, and salivation after i.p. only. Signs in the rat included: ataxia, loss of righting reflex, labored breathing, prostration, salivation, ptosis, arched back, and compulsive gnawing by both routes.

Acute p.o. toxic interaction studies were performed in rats. Phenelzine (at highest no-effect and highest non-lethal doses) caused a marked decrease in the LD_{50} of BUP. (However, no pharmacodynamic interactions were seen in several tests at lower doses). Only a slight potentiation of the lethality of BUP was caused by treatment with ethanol at its highest non-lethal dose; this was seen in F only. Lethal potentiation was noted between BUP and amitriptyline (each given at 1/2 LD_{50}), in F only.

The following oral subacute/chronic toxicity/carcinogenicity studies were performed (daily dose in mg/kg in parentheses):

Rat	(Long Evans)	3 month (150, 300, 450)
Rat	(Charles River CD)	55 week (25, 50, 100)
Rat	(Charles River CD)	2 year (100, 200, 300)
Mouse	(Charles River CD-1)	21-22 month (50, 100, 150)
Dog	(Beagle)	3 month (15, 35, 75 to 150)
Dog	(Beagle)	1 year (40, 80, 150)

The principal findings are as follows:

1. Rat:

a. General: Increased mortality, associated with convulsions, was seen in the 2 year study at all doses (except LD M), and was marked at HD (300 mg/kg). No effect on mortality was seen in the 55 week study (HD = 100 mg/kg); in the 3 month study 2/20 died at 450 mg/kg. Observed signs included urinary incontinence/urine staining (all studies, all doses), dried blood around nose/mouth (55 wk and 2 yr studies, all doses), and convulsions (2 yr study, all doses). Slight decreases in bodyweight gain were seen in all M groups in the 2 yr study. Slight decreases in blood glucose were seen above 100-150 mg/kg.

b. Gross/Histopathology: The most prominent findings were:

(1) Liver: In the two-year study there was an increase in incidence of hyperplastic nodules and hepatocellular hypertrophy at all doses; hyperplasia was increased at LD and MD only. (In a consultant report many of the hyperplastic nodules were reclassified as "foci or areas of altered hepatocytes.") The incidence of these findings is underestimated in the drug groups in a dose-related fashion due to the increased mortality and the late appearance of the lesion. (Most hyperplastic nodules were found at the terminal sacrifice, and almost all were found after 90 weeks). There was no increase in the incidence of hepatocellular carcinoma; the observed incidence 0/147, 3/140, 1/141, and 1/123 in control, LD, MD, and HD, respectively is within the historical control range. Similar findings were not seen in the 55 week study (HD = 100); in the 3 month study a low incidence of hyperplasia and "prominent cellular organelles" was seen at all doses. Increased liver weights were seen in all studies at all doses except LD in the 3 month study. Grossly, in the 2 year study, slight increases in the incidence of masses/nodules/raised area (F only) and dark red/brown/hemorrhagic foci were seen at all doses at termination but not among deaths.

The significance of these proliferative lesions in the liver is not straight-forward. The sponsor suggests they may arise as either (1) a result of microsomal enzyme induction or (2) an adaptive response to hepatic injury. Regarding the former, BUP has been shown to induce its own metabolism (see above). Regarding the latter, no other indication of hepatic damage (including blood chemistry) was obtained in rats, although some indications of liver damage were obtained in dogs.

Nonetheless, there has been controversy concerning the possible role of hyperplastic nodules in the development of hepatocarcinomas in rodents. Several years ago some

pathologists suggested that such lesions should be considered "pre-neoplastic" or "neoplastic" because it was hypothesized that they could progress to malignant tumors (Squire and Levitt, Cancer Res. 35: 3214, 1975; Williams, Biochem. et Biophys. Acta 605: 167, 1980). These pathologists thus suggested replacing the term "hyperplastic nodule" with "neoplastic nodule". (It has also been suggested that "foci of cellular alteration" are also "pre-neoplastic" in the sense that they might progress to neoplastic nodules or even directly to malignant tumors.)

The subject was discussed at a symposium (Rodent Liver Nodules - Significance to Human Cancer Risk?, International Symposium of the Society of Toxicological Pathologists, May 10-12, 1982, Reston, Va.; proceedings published in Toxicologic Pathology, Volume 10, Number 2, 1982). Data was presented to challange the view that proliferative hepatic lesions are progenitors of hepatic malignancy. The outcome of several types of experimentally induced hepatic nodules, including those induced by drugs, was reviewed. In several cases, nodules and foci of cellular alteration regressed after cessation of treatment, documenting that proliferative lesions are not inherently malignant. The fact that proliferative lesions are not necessarily transplantable was considered to add additional support to conclusion that these lesions may be entirely benign. In any event, based on these and related observations, symposium participants reached an informal consensus that the term "neoplastic nodule" was a misnomer and that such lesions do not necessarily progress irretrievably to malignancy. However, while these proliferative lesions may not be autonomous and do not necessarily progress to malignancy, it is possible that they might progress under the influence of continued drug administration or, alternatively, they may simply be "markers" for malignancy, i.e., if a drug produces such lesions it is an indication that the drug is also likely to produce malignancies. Again, based on an informal vote a majority of pathologists present at this symposium appeared to believe that the production of nodules or foci of cellular alteration in the liver by a chemical is not sufficient evidence to establish that chemical as a hepatocarcinogen. Although several potent hepatocarcinogens do produce nodules and foci of cellular alteration, there are several examples of drugs, dietary regimens, and surgical manipulations which produced nodules or foci but did not produce malignancies despite prolonged treatment. Thus, no generalization about the carcinogenicity of agents which cause nodules is possible.

Thus, bupropion's capacity to produce proliferative lesions raises questions that cannot be answered absolutely. It is reassuring, however, that despite continued administration of bupropion in a lifetime rat study, the proliferative

lesions did not progress to malignancy. In addition, the nodules were very late appearing (most seen at terminal sacrifice; almost all after 90 weeks), in contrast to the effects of established hepatocarcinogens. In summary, the evidence at this time does not support identification of BUP as a hepatocarcinogen.

(2) Hemosiderosis: In the 55 week rat study an increase in hemosiderosis (as determined either by H + E stain, iron stain, or presence of pigment-containing macrophages) was seen in spleen, kidney, lung, and liver. This was seen primarily at HD, but lung and liver were not examined at the lower doses. Likewise, in the two year study, evidence of increased hemosiderosis was seen in spleen, lung, and lymph nodes at MD and HD; these organs were not examined in LD animals. No other pathological findings were present to help explain the increased hemosiderosis. Hematology did not reveal any striking abnormalities. (2/20 HD in the 55 week study had low Hb, Hct, and RBC; no effect was seen in the two year study; slight decreases in Hb and Hct were seen in the 3 month study, but no hemosiderosis reported.)

(3) Kidney: Slight increases in the incidence of chronic nephritis were seen in the 55 week study (HD only) and in the MD and HD groups in the two-year study in which LD was not examined. (There were no consistent effects on lab tests indicative of renal function; in the 55 week study there were elevations of BUN in 3/40 rats at MD and HD.) Kidney weights were elevated in all studies at all doses.

c. Neoplasia: There were no drug-related increases.

2. Mouse:

a. General: In the 22 month study, mortality was increased in all M groups and HD F. There was no effect on weight gain. As in rats, convulsions were seen (MD and HD). Laboratory studies were not performed.

b. Gross/Histopathology: In the 22 month study most prominent postmortem findings were in the uterus, consisting of a dose-related increased incidence of extremely dilated blood vessels, with thrombus, in all F groups; this increase was seen both among mice which died and those which survived to termination, suggesting it is not associated with lethality. On gross examination, there was an increased incidence of uterine nodules/masses; according to the histopathologic report, these were extremely dilated veins with thrombosis. The antemortem urogenital staining noted was probably also related to these changes.

An increased (dose-related) incidence of acute metritis and/or pyometritis in the uterus was also seen in all drug groups, along with a slight increase in the incidence of uterine hemorrhage in all drug groups (not dose-related). Splenomegaly and hematopoiesis in spleen and liver were also seen in F; the pathology report considered these to be secondary to the uterine blood loss, although an independent analysis by the sponsor did not show a good correlation between the uterine and spleen/liver changes. Changes similar to those in uterus were not clearly seen in other organs, although a low frequency of hemorrhage and ulcer in stomach and small intestine was noted, primarily at HD. The incidence of thrombus in heart was increased in HD among deaths but not at termination, and the incidence of congestion and/or hemorrhage in lung was increased in HD M. An increased incidence of atrophic tubules in testes at HD was also seen in this study, although there was no effect on the incidence of aspermatogenesis.

c. Neoplasia: There was no drug-related effect on the incidence of neoplastic changes.

3. Dog:

a. General: No significant toxic effects were seen in the 90 day study (HD = 75 to 150), a slight increase in liver weight was seen with no associated pathology. In the one year study, the HD (150 mg/kg) produced 3/16 deaths; this dose also produced convulsions in one dog and body trembling in several others. Emesis and ptyalism were seen at both MD and HD. Bodyweight gain was decreased at HD. There was a dose-related elevation of serum alkaline phosphatase in all groups at all months measured, and the magnitude increased over time; no elevations were seen in recovery dogs. Elevations of SGOT and SGPT were also seen mainly at the higher doses, starting at three months but not clearly progressive over time. Some recovery dogs still had elevated SGPT after the recovery period, but of smaller magnitude. Slight increases in BSP retention were seen at MD and HD. Liver weights were increased in all groups (dose-related) at both six and 12 months but not at recovery.

b. Gross/Histopathology: In the 1 year study microscopic exam of liver showed several drug-related changes including finely granular "ground glass" cytoplasm (MD and HD, seen at 12 months but not at six months or after recovery period), dark brown pigment in hepatocytes and phagocytic cells (MD and HD, seen at 12 but not at six months, and seen at all doses after recovery period), slight coarse vacuolation of hepatocytes (seen in HD at 12 months and in LD and MD at six months and in the one MD which died; not seen after recovery period), and bile duct proliferation (very slight to slight, seen at MD and HD at 6 months and at HD at 12 months, also seen after recovery period in 2/4 LD and 2/3 HD and in 1/4 control but absent in three at MD). Kidney weight was elevated in all groups at 6 months; at 12 months an increased relative weight only was seen at MD and

HD. Histologically, the incidence and severity of brown pigment in tubular epithelium was increased in all groups at termination. The incidence of this finding among recovery dogs was similar across groups although severity was greater at MD and HD. No clear abnormalities of renal function were noted.

G. Mutagenicity: BUP was weakly positive in some Salmonella strains in the Ames Test. (TA 100, both with and without metabolic activation, and TA 1535, with activation only.) Greatest effects were 2-3 X control revertant count; positive controls caused 6-10 X increases. In a rat bone marrow chromosome study, an increase in aberrations was seen at 300 but not 100-200 mg/kg p.o., given for 5 days; the increase was 2-3 X control compared to 6-19 X for the positive control. In a study of binding to rat liver DNA after oral administration, it was found that the binding of BUP (+ metabolites) was much lower than that of known hepatocarcinogens; it was concluded that the effect is nonspecific.

H. Reproduction: A two generation reproduction and fertility study was performed in rats. Both M and F (of the F 0 generation only) were drug treated at dosages of 100, 200, and 300 mg/kg/day. Except for wobbly gait in one MD and one HD, no drug-related signs were observed. Bodyweight gain was slightly increased in all treated groups, but was not dose-related. There was no drug-related increase in mortality. No drug effects on M or F mating performance, on F fertility or reproductive parameters, or on pup (F 1 generation) survival and body weight were seen. There were no significant effects on mating or reproductive performance of the F 1 generation. Pup survival (F 2 generation) was not affected by treatment, although F 2 pups in all drug groups had slightly increased body weight.

Segment II reproduction studies were performed in rats and rabbits. In rats (dosages = 150, 300, and 450 mg/kg/day), signs including ataxia, urinary incontinence, and gnawing were seen primarily in HD dams. Mortality was increased at HD (24/53 = 45%). Bodyweights were transiently decreased in all drug groups after the first dose. There was a slight decrease in fetal weight and length in all drug groups, not dose-related. There were no drug-related effects on gross or visceral fetal abnormalities. A slightly increased incidence of reduced or absent ossification of some bones was seen at MD and HD and to a smaller extent at LD; this was reflected in a slight increase in total skeletal findings in all drug groups.

Two segment II reproduction studies were performed in rabbits, one within the sponsor's lab and the other by International Research and Development Corporation. Dosages were 25 (latter study only), 50, 100, and 150 mg/kg/day. Does displayed slight hypoactivity at 100 and 150 mg/kg, and convulsions, ataxia, tremors, and hyperpnea were seen in some does at 150; convulsions were also seen in one doe at 100 mg/kg. In one study, decreased doe food consumption on individual days was seen in all drug groups, but no overall effects on body weight were seen; however, the other study showed reduced weight gain at 100 and 150 mg/kg. There was no drug-related increase

HD. Histologically, the incidence and severity of brown pigment in tubular epithelium was increased in all groups at termination. The incidence of this finding among recovery dogs was similar across groups although severity was greater at MD and HD. No clear abnormalities of renal function were noted.

G. Mutagenicity: BUP was weakly positive in some Salmonella strains in the Ames Test. (TA 100, both with and without metabolic activation, and TA 1535, with activation only.) Greatest effects were 2-3 X control revertant count; positive controls caused 6-10 X increases. In a rat bone marrow chromosome study, an increase in aberrations was seen at 300 but not 100-200 mg/kg p.o., given for 5 days; the increase was 2-3 X control compared to 6-19 X for the positive control. In a study of binding to rat liver DNA after oral administration, it was found that the binding of BUP (+ metabolites) was much lower than that of known hepatocarcinogens; it was concluded that the effect is nonspecific.

H. Reproduction: A two generation reproduction and fertility study was performed in rats. Both M and F (of the F 0 generation only) were drug treated at dosages of 100, 200, and 300 mg/kg/day. Except for wobbly gait in one MD and one HD, no drug-related signs were observed. Bodyweight gain was slightly increased in all treated groups, but was not dose-related. There was no drug-related increase in mortality. No drug effects on M or F mating performance, on F fertility or reproductive parameters, or on pup (F 1 generation) survival and body weight were seen. There were no significant effects on mating or reproductive performance of the F 1 generation. Pup survival (F 2 generation) was not affected by treatment, although F 2 pups in all drug groups had slightly increased body weight.

Segment II reproduction studies were performed in rats and rabbits. In rats (dosages = 150, 300, and 450 mg/kg/day), signs including ataxia, urinary incontinence, and gnawing were seen primarily in HD dams. Mortality was increased at HD (24/53 = 45%). Bodyweights were transiently decreased in all drug groups after the first dose. There was a slight decrease in fetal weight and length in all drug groups, not dose-related. There were no drug-related effects on gross or visceral fetal abnormalities. A slightly increased incidence of reduced or absent ossification of some bones was seen at MD and HD and to a smaller extent at LD; this was reflected in a slight increase in total skeletal findings in all drug groups.

Two segment II reproduction studies were performed in rabbits, one within the sponsor's lab and the other by International Research and Development Corporation. Dosages were 25 (latter study only), 50, 100, and 150 mg/kg/day. Does displayed slight hypoactivity at 100 and 150 mg/kg, and convulsions, ataxia, tremors, and hyperpnea were seen in some does at 150; convulsions were also seen in one doe at 100 mg/kg. In one study, decreased doe food consumption on individual days was seen in all drug groups, but no overall effects on body weight were seen; however, the other study showed reduced weight gain at 100 and 150 mg/kg. There was no drug-related increase

in mortality in either study. Fetal weight was slightly reduced in all drug groups at 50 mg/kg and above, and these reductions were dose-related. Fetal length (reported in one study) was slightly reduced at 150 mg/kg. There was a trend toward an increase in gross, visceral, and skeletal abnormalities in fetuses of all drug groups, which was partly dose-related. The increase in gross and visceral abnormalities does not appear to be biologically significant in that no pattern of abnormalities was seen, i.e. there was no significant increase in any particular type of abnormality, and the overall percent of fetuses affected was relatively low. Regarding skeletal abnormalities, a significant increase in supernumerary ribs occurred in all drug groups which was dose-related in one study but not in another. In addition, one study showed an increase in reduced ossification of the palate (all drug groups, not dose-related), and the other study showed an increase in delayed ossification of the fifth phalanx of the forelimb at HD only as well as a low incidence of barbell-shaped thoracic centra in all drug groups. Reduced ossification (also seen in rat study) and supernumerary ribs are considered to be normal variations, and it is concluded that the above skeletal findings, as well as the findings of decreased fetal weight and length, were secondary consequences of maternal toxicity.

V. Clinical Evidence:

This section presents 1) a brief overview, 2) a description of the adequate and well-controlled clinical trials which provided evidence of efficacy, 3) a brief review of other adequate and well controlled controlled trials which failed to support the efficacy claim, and 4) two sections listing general and special safety considerations pertinent to this drug product.

A. General: The approval decision is based on clinical studies enrolling a total of approximately 2400 patients. The original NDA provided reports on clinical trials involving 1300 patients and volunteers. Prior to final approval, however, data and information from experience with an additional 1000 or so individuals was submitted and reviewed.

The agency relied solely upon the results of placebo controlled investigations to reach its conclusion that bupropion is an effective antidepressant. The amended application provided full reports on 5 investigations that employed placebo controls: numbers 06, 08, 09, 14 and 25. The agency also evaluated the results of all active control investigations. Only one of the latter, study 15, demonstrated consistent, statistically significant differences among treatments.

Among the placebo controlled trials, only 06 and 25 provide clear support for the antidepressant efficacy of bupropion under the conditions of use recommended in its approved labeling. Study 14 is a strongly positive study, but a substantial proportion of the individuals who participated in it were treated with bupropion at

doses exceeding the maximum recommended daily dose (450 mg/day). Study 0f was equivocal in its results, showing significant treatment by investigator interactions between its two major components (08-01 and 08-02).

B. Studies demonstrating or supporting efficacy for this indication:

Two placebo controlled inpatient studies of similar parallel design provide persuasive evidence of bupropion's efficacy as an antidepressant.

1. Study 06 (K. Brodie, W. Zung, L. Fabre, and D. Garver)

a. Design: The study was planned as a 28-day trial comparing titrated doses of bupropion with placebo. Because of its design, which allowed withdrawals at day 21, many patients failed to complete the full 28 days and 21 days is a more accurate description of the study's duration.

The inclusion criteria in this and other inpatient studies required that patients be non-psychotic and exhibit a depressed mood (characterized as sad, blue, low, despondent, hopeless, or gloomy) plus at least four of these symptoms:

anhedonia
poor appetite
sleep difficulty (insomnia or hypersomnia)
loss of energy, fatigue, lethargy
agitation
retardation
decrease in libido
loss of interest in work or usual activities
feelings of self-reproach or guilt
diminished ability to think or concentrate
thoughts of death and/or suicide attempts
feelings of helplessness and hopelessness
anxiety or tension
bodily complaints

Exclusion criteria for this and other studies were as follows:

actively suicidal ideation
schizophrenia
organic CNS disease
severe dementia
incapable of spontaneous conversation or behavior
seizure disorders
alcoholism
glaucoma
prostatic hypertrophy
abnormal laboratory or ECG values

women of childbearing potential who were not willing to sign an intent to avoid pregnancy form lactating women, if breastfeeding

Patients were randomly assigned to either BUP or PBO. Drug was administered according to a titration schedule that allowed for individual dose adjustment. In the first week, patients received BUP in a dose of 300 to 400 mg (divided t.i.d.). From day 8 to the end of the study, the dosage could be increased to 600 mg/day. Psychoactive drugs were interdicted, except chloral hydrate for sleep.

Weekly assessments included the Hamilton Depression (HAM-D), Hamilton Anxiety (HAM-A), Self-Rating Depression (Zung-D), Self-Rating Anxiety Scale (Zung-A), Clinical Global Impressions (CGI), Dosage Records and Treatment Emergent Symptoms (DOTES) Scales and the Patient Termination Record. The protocol permitted replacement of any subject who dropped from the study before 21 days and interdicted use of psychoactive drugs.

b. Conduct and Execution: A total of 85 adult inpatients were enrolled. The principal diagnoses (DSM-II classification) were:

manic-depressive (depressed)	55%
depressive neurosis	35%
involutional melancholia	8%
manic-depressive (circular)	2%

Over the evaluable course of the study (days 1-21), the dose of BUP for the vast majority of patients was 450 mg or less. At day 7, all participants were on 450 mg or less. At day 14, 42 of 50 participants were receiving 450 mg or less. At day 21, 38/49 patients were receiving 450 mg or less. Ten patients (BUP x 7, PBO x 3) received hypnotic drugs at some time during the study, usually flurazepam. Dropouts occurred for:

ineffectiveness or deterioration	2 PBO
adverse reactions	1 BUP, 1 PBO
intercurrent illness	1 BUP
did not return or refused treatment	4 BUP
administrative or uncooperative	1 BUP, 2 PBO

The number of patients participating after day 21 was markedly reduced from the original number.

c. Results: Because a substantial number of patients dropped out before the day 28 ratings, analyses were performed on the combined data from all three sites using the day 21 ratings or the last observation carried forward (LOCF) for those who dropped out earlier. Four combined study analyses were performed by weighting centers equally as well as proportionally to sample size and by subtracting as well as not subtracting baseline scores. These analyses all provided consistent statistical evidence of effectiveness which is provided in the following table:

Protocol 06

LOCF (21) Analyses of Wellbutrin Minus Placebo
Change from Baseline Score for
All Patients Randomized
Investigators Weighted Proportionally to Sample Size

Scale	# of Patients	Wellb. Minus Pbo Change from Baseline	2-tail p-value
HAMD Total	81	3.82	.05
CGI-SI	81	.631	.04
Depr. Item* of HAMD	79**	NA*	.01

* Based on Blocked Wilcoxon Rank Sum test of LOCF(21) value blocked on baseline value

** Two observations fell into blocks with no other data.

2. Study 25: (Investigators: G. Chouinard, A. Halaris, O. Karabanow and M. Mandel/C.Welch).

a. Design: The study was planned as a four site, multicenter parallel comparison of two levels of bupropion (300 mg and 450 mg a day) with placebo. The original goal of the study was to evaluate the "efficacy and chronic dose tolerance of low doses of [bupropion] in ...hospitialized depressed patients." The study called for each site to contribute 30 patients, 10 assigned to each of the three treatment arms.

Inclusion and exclusion criteria were essentially identical to those employed in study 6 described above. Patients recruited were overtly depressed, non-psychotic, without evidence of severe dementia or a recent history of alcohol or substance abuse. The current depressive episode had to have been present at least 4 weeks and not longer than 2 years. A minimum total score of 18 on the 21 item version of the Hamilton Depression Scale and at least a moderate rating on the Global Severity Scale were required for admission.

Schizoaffective and schizophrenic patients were to be excluded. Patients could also be excluded for medical reasons if it was thought necessary by investigators or monitors.

Concomitant medications: Washout of active psychotropic medications was required before the start of active medication: one month for fluphenazine esters, two weeks for MAOIs and

phenothiazines, and one week for benzodiazepines. During the trial, the protocol disallowed the use of all psychotropic medications save chloral hydrate for sleep.

Rating instruments for assessment of outcome included the Hamilton Depression and Anxiety Scales, the patient rated Zung Depression and Anxiety Scales, Clinical Global Impressions, and the SCL 90. Laboratory tests and side effect assessment was carried out predrug and throughout the trial.

The protocol allowed replacement of patients who terminated prior to day 21.

b. Conduct and Execution:

One hundred and twenty eight patients were randomized to treatment. Eighteen patients did not have a rating obtained on drug treatment. Because of the protocol design which allowed withdrawals at day 21, many patients did not complete the full 28 days of the study. Indeed, 24/43 placebo, 22/45 bupropion 300 mg and 24/40 bupropion 450 mg patients did not complete the study. The causes of premature termination, however varied with treatment assignment. Among the 43 placebo patients, 16 discontinued because of deterioration or lack of efficacy. Among the 85 treated with bupropion only 14 terminated for similar reasons. In contrast, no placebo patient was terminated because of an adverse effect, but 4/45 bupropion 300 mg and 7/40 bupropion 450 mg patients were.

c. Analysis of Results:

The study was analysed by 1) an intent to treat analysis employing a last observation carried forward (LOCF) methodology and 2) an observed cases (i.e., those patients actually observed at a particular time) analysis. 109 patients were evaluated in the LOCF analysis; 19 patients who had been randomized to treatment were excluded due to the absence of efficacy assessments during double-blind treatment.

The results of the LOCF analysis at day 21 are generally more favorable than those obtained with the observed cases method. The differences between the results of the two analyses are related to the fact that both the timing of withdrawals and the scores of the patients at the time of their withdrawal differ as a function of treatment assignment. In particular, there are more dropouts before day 21 among placebo patients (6) than among bupropion 300 mg (4) and bupropion 450 mg (4). Furthermore, as the causes for dropout would predict (see above), the status of bupropion assigned patients at the time of their withdrawal was generally better those assigned to placebo. For dropouts on bupropion 300 mg, the average improvement in the Ham D total score was 16 points. For dropouts from the bupropion

450 mg group, the average improvement was 20 points. In contrast, the average improvement among placebo dropouts was only 6.5 points.

In summary, the missing data brought forward in the LOCF is generally more favorable to drug and less favorable to placebo. In contrast, the observed cases analysis is strongly biased against bupropion because prematurely terminating bupropion patients who were doing comparatively well and prematurely terminati g placebo patients who were doing comparatively poorly were excluded from it.

In its assessment of study 25, the agency relied primarily upon the results of the LOCF analysis evaluated at day 21. Day 21 was selected because of the large number of dropouts that occurred in all groups following that study day. The results of the LOCF analysis are presented below for the HAM D total score.

Hamilton Depression Total Score: Study 25
LOCF data: Mean decrease from baseline

Day	Placebo	Bupropion 300mg	Bupropion 450mg	PBO vs. 300mg*	PBO vs. 450mg*
7	9.6	8.8	10.4	.64	.65
14	13.1	13.2	17.0	.95	.06
21	13.3	16.1	17.7	.21	.06

*(2-tail 'p' values)

By day 21 (LOCF analysis) patients assigned to 450 mg of bupropion improved to a statistically significant greater extent (or nearly so) than those on placebo on other standard measures of efficacy (i.e., Ham-D retardation factor (p=0.03), Clincal Global improvement rating (p=0.06) and Clinical Global Severity of Illness (p=0.014)). The LOCF analysis, however, failed to detect statistically significant differences between bupropion and placebo on the HAM-D depression item (i.e., at day 21, p=0.26 and p=0.87 respectively for the 300 mg and 450 mg groups). This failing may reflect the early timepoint employed for trial assessment. If the depression item reflects primarily verbal reports of patients, it is likely to lag behind other measures of improvement, much as improvement judged by self-report scales lags behind improvement judged by observer scales in depressed patients.

d. Conclusion:

Despite the relatively high drop-out rate, analysis of the drop-out pattern and use of scores at the time patients left the study show a clear improvement in the treated group on the Hamilton Total Score and the Clinical Global Items providing evidence of bupropion's antidepressant efficacy. The study does not, however, demonstrate the efficacy of a 300 mg dose.

The following study supports the efficacy of bupropion at doses between 450 and 600 mg. Because a substantial proportion of patient were treated at doses outside the recommended dose range, the study cannot be considered a persuasive source of evidence of efficacy for the drug's approval under the proposed labeling. However, given the wide variability in the capacity of individuals to metabolize drugs, and the variability of the pharmcodynamic response, the study does lend additional support to the conclusion that bupropion is effective as an antidepressant.

3. .Study 14 (J. Feighner and J. Cohn)

a. Design: This was a five week (four weeks of treatment, one week of follow-up) randomized comparison of titrated bupropion and placebo at two centers.

b. Conduct and Execution: There were 117 patients enrolled and 86 included in the efficacy analysis (60 BUP, mean age = 45.9 yr; 26 PBO, mean age = 48.2 yr; 50 M, 36 F). The sponsor's analyses excluded five patients (BUP x 2, PBO x 3) who received psychoactive concomitant medications for eight or more days for anxiety or agitation, 25 who were treated (BUP x 14, PBO x 11) for less than 14 days, and one who received less than the minimum dose of BUP for 27 days. Principal diagnoses were:

depressive neurosis	50%
manic depressive (depressed)	40%

Dosage of BUP was 300 mg for days 1-4, 400 mg for days 5-7, and 600 mg up to day 28. Mean dose at days 22-28 was about 470 mg (546 at center 02 vs 392 at center 01); 13 patients (BUP x 8, PBO x 5) received flurazepam or diphenhydramine concurrently for sleep. Patients who failed to complete the study included:

ineffective or deterioration	(22)	10 BUP, 12 PBO
adverse effects	(8)	6 BUP, 2 PBO
intercurrent illness	(4)	3 BUP, 1 PBO
did not return or refused treatment	(12)	7 BUP, 5 PBO
administrative reasons		1 BUP

Medication was discontinued in 16 BUP and five PBO patients for clinically significant adverse experiences. Adverse reactions to BUP included seizure (1), agitation/excitement (3), increased insomnia and anxiety (1), and total body rash (1).

c. Results: There were quantitative but no qualitative center by treatment interactions, with marked BUP/PBO differences at center 01 with 49 patients (34 BUP, 15 PBO), and minimal differences at center 02. Additional analyses, with techniques similar to those described above for study 06, disclosed the following two-tailed p-values:

Protocol 14

LOCF (21) Differences in Change from Baseline between Wellbutrin and Placebo Groups

All Patients Randomized
Investigators Weighted Proportionally to Sample Size

Scale	# of Patients	Differences for Change from Baseline Scores	2-tail p-value
HAMD Total	114	6.94	.01
CGI	114	.594	.01
Depr. Item of HAMD	113**	NA*	.01

* Based on Blocked Wilcoxon Rank Sum test of LOCF(21) value blocked on baseline value.

** One Wellbrutrin observation fell into a block with no other data.

C. Studies of adequate design that failed to provide support for the indication:

1. Study 08 (A. Halaris and W. Fann)

a. Design: This was a five week (four weeks of treatment, one week of followup) study. Data from three centers following a single protocol were submitted. Inclusion criteria were identical to those for Study 06, above.

b. Conduct and Execution: Sixty-eight patients were enrolled and 59 were included in the analysis (34 with mean age of 42.8 yr on BUP, 25 with mean age of 40.8 yr on PBO; 40 M, 26 F, and two unlisted). Principal diagnoses were:

depressive neurosis	60%
manic-depressive (depressed)	30%
other diagnoses	10%

Dosage started at 300 mg/day and was increased to 750 mg/day by day 11 if lower doses were well-tolerated. Mean daily dose of BUP for weeks 2-4 was about 725 mg. Thirty patients received either chloral hydrate or flurazepam for sleep at some time during the study. In addition to measures listed above, this study employed the BPRS, and the POMS at center 01. Dropouts were attributed to:

ineffectiveness	1 BUP
adverse reactions	3 BUP
intercurrent illness	2 BUP

After inspections disclosed that one investigator had violated regulations pertaining to the conduct of clinical studies, the investigator was disqualified from handling investigational drugs, and results from all 16 patients at that site were excluded from subsequent consideration for efficacy.

c. Results: A strong qualitative treatment by center interaction was found; center 02 was essentially negative while the results at center 01 supported the efficacy of bupropion. Because it had been designed as a multicenter trial, the agency examined only the combined results of these two centers; a subset analysis of each subcenter was conducted but was not relied upon.

Because of the strong qualitative treatment by investigator interaction, no combined data analysis of Study 08 could be considered reliable.

2. Study 09 (L. Fabre and J. Mendels)

a. Design: This was an eight week study with one week of PBO washout, six weeks of treatment, and one week of followup comparing two dose ranges of BUP to PBO at two centers. The low dose (LD) group started at 150 mg and was increased to 400 mg/day at day 15; the high dose (HD) group received double these amounts. Inclusion and exclusion criteria were similar to those listed above. After approximately one-fourth of the patients were completed, the study was amended to delete the HD group because one patient had a seizure at 900 mg/day.

b. Conduct and Execution: A total of 160 outpatients were entered; 29 were removed during the initial PBO week, and 131 were admitted to the randomized treatment period. Mean daily doses ranged from 137 to 331 mg in the LD and from 287 to 687 mg in the HD group. Patients were excluded from the sponsor's efficacy analysis if they either failed to complete two weeks of randomized treatment or required unacceptably large doses of anxiolytic drugs; 97 were included on this basis; 66 F & 31 M, 40 LD, 42 PBO, and 15 HD. Principal diagnoses were:

manic depressive (depressed)	60%
depressive neurosis	35%

Dropouts were attributed to:	LD	HD	PBO	Total
did not return or refused treatment	9	4	6	19
did not meed study criteria	1			1
ineffectiveness/deterioration		1		1
adverse reactions	6	4	1	11
Totals	16	9	7	32

c. Results: With data combined across centers, neither dose range was significantly more effective than PBO at any period on the rating scales employed. Patients rated much or very much improved at termination included 62% on LD, 60% on HD, and 43% on PBO.

D. Active control studies bearing on the relative efficacy of bupropion:

Active control trials are generally poor sources of information about the efficacy of antidepressant drugs. In the typical case, the study results in a finding of no difference between the treatments compared. However, even if there is adequate statistical power, such a result cannot be accepted uncritically as evidence of drug effect. A finding of no difference may occur for many reasons other than that both drugs were effective; for example, neither drug may have worked in the population studied. Consequently, the finding that six of the seven active control studies submitted in the NDA failed to distinguish between bupropion and an active control was not considered evidence of bupropion's antidepressant efficacy.

However, when one active treatment betters another in an adequate and well controlled investigation, the difference can generally be attributed to a drug effect of the superior drug, unless the inferior drug had been used in a manner that actually made patients worse than they would have been had they received no drug at all. Of course, such a finding does not speak to the question of whether the poorer performing drug is effective, a point that should be born in mind when considering the results of study 15 described below. The study suggests that in some settings, bupropion may not be as effective as traditional antidepressant drugs.

1. Study 15 (R. Remick, A. Cooper, J. Mendels, A. Singh, M. Amin, and G. Chouinard)

a. Design: This was a 92 day comparison to amitriptyline (AMI), with an initial week of PBO washout, at six centers. After the first week, patients received either 300 mg BUP or 75 mg AMI for one week; BUP could then be increased to 450 mg and AMI dosage doubled.

b. Conduct and Execution: A total of 196 outpatients were enrolled, and 190 continued after the PBO week. Five patients randomized but treated for one day or less were excluded from efficacy analyses as well as two who had no evaluations after treatment was instituted. Prescription of concomitant drugs was more frequent in BUP patients; twenty such patients and six randomized to AMI were excluded at FDA request because they received antihistamines or psychoactive drugs concomitantly. After four weeks on active drugs, at least 70% of randomized

patients remained under treatment at all six centers; at center 02, 70% were retained through six weeks.

c. Results: For the combined centers, results favored AMI numerically on the Ham-D total score and change from baseline, Ham-D retardation factor, Ham-D depression item score and change from baseline, CGI Severity and change from baseline, and CGI Improvement. These differences achieved statistical significance for AMI over BUP on all except the retardation factor change item at most observation points in both weighted and unweighted analyses.

E. Limits on Evidence of Efficacy and Duration of Effect: On the basis of the evidence available it is not known whether bupropion maintains its therapeutic effect for more than three weeks. The number of patients remaining in placebo controlled trials after that point does not permit any conclusions for a longer duration. BUP failed to do better than the control treatment in both outpatient studies, in one compared to PBO and, in the other, to amitriptyline.

F. Safety Data from Clinical Studies: More than 2400 patients participated in clincal studies of bupropion during its premarketing testing and evaluation. The original NDA reported on data involving approximately 1300 individuals. In subsequent amendments, including the 'safety update,' the sponsor provided additional reports and summaries of experience with an additional thousand or so patients.

The safety review focused primarily upon events that led to the discontinuation or death of patients. The safety review also considered the pattern and relative incidence of abnormalities in vital signs, laboratory and special tests, and reports of adverse events. Of particular importance for comparative and relative event incidence assessment are data submitted to the original NDA from four double-blind, PBO-controlled studies involving over 300 patients; two double-blind studies controlled with amitriptyline (AMI) in which over 100 patients received BUP, including about 25 who received the drug for up to three months. All information concerning more chronic experience with bupropion, however, is derived from open clinical trials.

1. Effects on Vital Signs and Physical Measurements:

a. Heart Rate: Doses of BUP up to 800 mg in volunteers did not cause significant changes in heart rate. In Study 08, mean supine heart rates on BUP rose gradually from 80.9 to 87.6/minute; rates on PBO varied from 84.1 at baseline to 82.4 at 21 days and declined to 77.7 at 28 days, a statistically significant difference at that point. In other studies, there was no consistent pattern of BUP effect on heart rate.

b. Blood Pressure: In Study 08, statistically significant differences were found in within-treatment comparisons to baseline on BUP in standing blood pressure, with decreases of 4-9 mm Hg for systolic readings, compared with 1-5 mm on PBO; supine readings were not consistently affected, and diastolic measurements indicated no trend. No consistent changes in supine or erect blood pressure were seen in other studies. Long-term treatment with BUP was associated with either small decreases or no change.

Among patients with a history of clinically significant orthostatic hypotension on tricyclic antidepressants (TCA) who were enrolled and showed no blood pressure effects on PBO, none of 12 who had received ascending doses of BUP (at the time of data cutoff) showed significant changes between PBO and BUP periods. In 86 hypertensive patients, vital signs did not differ significantly from baseline during BUP treatment. Among 156 patients with cardiac disease, symptoms and complaints did not increase during BUP treatment.

c. Respiration: No clinically important increases or decreases in respiratory rate were seen.

d. Temperature: In those instances in which body temperature was measured, no consistent changes were found on BUP.

e. Body Weight: Weight loss of five or more pounds was noted in more BUP patients than PBO patients (23% vs 11%). Weight gain of five or more pounds was only about one-third as likely on BUP as on AMI and only 40% as likely on placebo. Patients whose weights were measured and who gained or lost at least five pounds were as follows:

	BUP			PBO			TCA		
Studies	n	+5	-5	n	+5	-5	n	+5	-5
08, 09, 14	130	6%	23%	81	14%	11%			
15, 21	91	13%	34%				67	39%	9%
35	298	3%	15%						
Total	519	5.7%	20.2%	81	14%	11%	67	39%	9%

2. Adverse Effects on Laboratory Evaluations:

a. EKGs and Cardiac Conduction: 4/304 patients developed abnormalities during BUP treatment. One was noted to have a single premature ventricular contraction (PVC) during BUP; another had abnormal ST-T wave recordings at baseline that

worsened during treatment; the third was a woman aged 61 who had APC and PVC at 5, 12, and 21 days which were still present two weeks after discontinuance; the fourth, a woman aged 58, had newly observed junctional or nodal premature beats.

The overall effect of treatments on ECG recordings is as follows:

	BUP	PBO	TCA
n =	304	123	72
Baseline - Treatment	Percent of Patients		
Normal - Normal	69.7	79.7	65.2
Normal - Abnormal	8.6	3.2	15.3
Abnormal - Normal	5.6	3.2	6.9
Abnormal - Abnormal	16.1	13.8	12.5

One study center provided lead II rhythm strips of 15 seconds taken at double paper speed and voltage for 62 patients; these were to be scored on a blinded basis by the sponsor for the duration of the QRS, P-R, R-R, and the corrected QT intervals (QTc) and the amplitude of the QRS complex; tracings taken on days 14, 21, and 42 were found scorable for 23 BUP and 23 TCA patients. For BUP, there was no statistically significant difference in the length of QRS or P-R intervals developing during treatment; for TCA, these were significantly longer, but the between-treatment comparisons did not show significance.

Overall, there appeared to be no consistent or clearly drug-related on ECG effects of bupropion.

b. Clinical Hematology Evaluations: Decreased hematocrit following a normal baseline value occurred more frequently with BUP than with PBO or TCA treatment. One BUP patient was recorded as having a WBC value of 2300 one day post-treatment in a 42 day study; the result was within the normal range when repeated one week later. BUP was associated with decreases in mean values for hemoglobin (in study 08 at day 14, in study 21 at termination, and in study 26 at 3-8 weeks), hematocrit (in study 21 at termination, and in study 26 at 3-8 weeks), WBC (in study 15 at day 29 and day 92, and in study 17 at 1-2 months and over 6 months), lymphocytes (in study 17 at 1-2 months, in study 08 at day 14, and in study 15 at day 92), monocytes (in study 17 at 3-6 months), and RBC (in study 15 at day 29), and with increased neutrophils (in study 08 at day 14). PBO was associated with increased WBC in one study at termination and with increased neutrophils in another at day 14. TCA was associated with decreased hemoglobin and decreased hematocrit in discrete studies at one point each, and with increased blood glucose (in study 17 at over 6 months, and in study 21 at termination), and increased monocytes (in study 17 at 3-6 months).

Overall, there were no consistent effect of bupropion on hematologic measurements.

c. Clinical Chemistry Evaluations: For liver enzyme values, the pattern of results was similar. Overall, liver enzyme values showed no consistent change during BUP treatment.

BUP was associated with altered mean values for other chemistry examinations at 14 time points during these studies, but the changes appear to occur in a random fashion. PBO was associated with significantly altered mean values in three instances, and AMI in four.

3. Observed Adverse Reactions: The Standard Adverse Experience Listing or the Dosage Record and Treatment Emergent Symptoms (DOTES) Scale was administered at baseline and at intervals during the studies. In listing the data derived from these questionnaires, neither the severity of the reported reaction nor the investigator's judgment of the probability that the event was drug-related has been taken into account.

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 incidence figures cited in the following discussion must be accepted as rather imprecise estimates. They cannot be used to predict 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 calculated incidence estimates cannot reflect the relative severity and/or clinical importance of events. Whether or not an event was severe enough to cause discontinuation of a drug's use is one guide to its importance.

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 the product's premarketing clinical trials. 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, primarily rashes (1.4%). It is important to note, however, that many of these events occurred at doses that exceed the recommended daily dose.

Because the design and duration of a study can influence both the calculated incidence of adverse events and the inferences subsequently drawn, the following discussion provides a separate assessment for each related group of clincal studies.

a. During PBO-Controlled Studies: Data from 222 BUP and 138 PBO patients in studies 06, 08, 09, and 14 were initially combined. Subsequently, the results of another placebo controlled study were added. These results are shown in the attached labeling. The excess of adverse effects in patients on BUP (compared to PBO) was largest for agitation, dry mouth, sweating, and tremor. Other adverse experiences reported more frequently by BUP patients than those on PBO included insomnia, constipation, syncope/dizziness/fainting, weight loss and confusion.

b. During TCA-Controlled Studies: Data from 120 BUP and 83 AMI patients in studies 15 and 21 were combined. There was a notable excess of complaints of increased salivation, nausea/vomiting, headache, and decreased appetite/anorexia in BUP patients, and a numerical excess for complaints of euphoria, numbness, dystonic symptoms, paresthesia, chills, diarrhea, urinary frequency, increased libido, decreased libido/impotence, edema, and dermatologic symptoms compared to AMI patients.

c. During Long-Term Studies: The percent of 60 patients receiving BUP in studies 17 and 26 who developed symptoms not present at baseline was as follows:

Dry Mouth	28%
Tremor	15%
Menstrual Disturbance	13%
Increased Appetite	13%
Nausea/Vomiting	13%
Syncope/Dizzy/Fainting	13%
Headache	12%
Blurred Vision	12%
Pruritis	11%
Skin Lesion	10%
Agitation/Excitement	10%
Decr Libido/Impotence	8%
Ataxia	6%
Swelling (Testis/Breast)	6%
Peculiar Taste in Mouth	6%

In comparison with the 19 AMI patients in study 17, there was a notable excess of complaints of agitation/excitement, insomnia, and tiredness/fatigue on BUP. (AMI patients had notably more complaints of dry mouth, drowsiness or sleepiness, and constipation than those treated with BUP.)

d. Associated with Discontinuance: Adverse reactions caused discontinuation of BUP treatment in 177 instances. Three patients receiving both BUP and a neuroleptic under

circumstances in which attribution of the event to either drug is problematic; 6/40 patients in one protocol received doses of more than 750 mg/day, a dose larger than that recommended in the originally proposed labeling, and 2/157 normal volunteers were discontinued after receiving doses larger than those anticipated in the t.i.d. schedule adopted. Excluding these 11 cases, the rates are:

Drug	# Treated	# Discontinued	Percent
BUP	1153	166	14.4
PBO	177	10	5.6
AMI	196	33	16.8

Among subjective, behavioral, or psychological adverse reactions, the one most frequently associated with discontinuance of BUP was excitement/agitation in 9.1%, compared with 6.8% on PBO and 9.2% on AMI. In the nonsubjective, nonbehavioral, or nonpsychological category, the reaction most frequently associated with discontinuance of BUP was dermatologic (usually urticarial or pruritic skin rashes).

e. Post-NDA Exposures: As noted earlier, experience with approximately 1000 additional patients and volunteers was included in the sponsor's final cumulative safety review. In general, no new events or findings that might affect either the approval decision or product labeling were identified that had not been detected in the data submitted with the original NDA.

However, the added experience did affect the precise incidence figures calculated for adverse events and for discontinuations. The revised estimates of incidence are not tabulated herein, but may be found in the attached final product labeling. The safety update, however, did provide greater detail about certain events, especially those that had been described ambiguously. In general, however, the safety update did not substantively alter any conclusion about the safety or relative risk and benefit of bupropion as an antidepressant.

F. Special Safety Considerations:

1. Seizures:

Seizures were first seen in volunteers participating in Phase I studies and the relatively high risk of seizure associated with the use of bupropion is an important determinant of dosing recommendations. The data suggest that high daily dose dose and/or rapid escalation of dose are strong predictors of seizure risk. Prior history of seizures and primary structural brain disease also appear to increase the risk of seizure.

The table below illustrates the relationship between dose, predisposing factors and seizure risk:

INCIDENCE OF SEIZURES IN PATIENTS RECEIVING BUPROPION

BUPROPION Dose mg/day	Total Seizure Incidence (%)	Seizure Incidence in Patients Without Seizure Predisposition (%)
less than 450mg	0.2%	0.0%
450mg	0.3%	0.2%
600mg*	2.3%	1.3%
600mg-900mg*	2.8%	1.9%

*: symbol indicates a dosage exceeding the maximum recommended daily dose.

2. Overdoses, Suicides and Deaths:

In the original NDA, reports described five outpatients who ingested single overdoses in amounts of 900 to 3000 mg BUP during clinical trials. Several vomited, and all recovered without sequellae following hospital admission. (OD-5 ingested an overdose of diphenhydramine 11 days after being restarted on BUP and was terminated from the study at that point.) Three other patients receiving BUP in clinical trials ingested overdoses of other drugs, and one attempted suicide by cutting his wrists.

The safety update included 8 more overdoses, for a total of 13. None had proven fatal, although seizures occurred definitely in one and probably in another. All these patients recovered without "residual impairments."

Fatalities in temporal association with the use of bupropion were reported in 14 patients prior to approval. None are known or believed to be a consequence of treatment with bupropion. Nine deaths were self-inflicted. Three deaths occurred in elderly and/or seriously ill patients.

3. Evaluation of Abuse Potential:

Preclinical studies in rodents suggest weak amphetamine-like effects with respect to locomotor activity and effects on schedule controlled behavior; in animals trained to discriminate amphetamine from PBO, BUP was identified as amphetamine-like.

Data obtained from clinical efficacy studies suggest mild amphetamine-like effects, with increased motor activity. Neither notable anorectic effect nor peripheral sympathomimetic activity was consistently observed with BUP; although, in regard to the former, weight loss in patients was more common than in TCA treated patients.. A dose of 400 mg produced a modest elevation over PBO responses on the morphine benzedrine group subscale of the Addiction Research Center Index (ARCI), and a score intermediate between amphetamine and PBO on the Liking Scale of the ARCI.

VI. Advisory Committee and Foreign Regulatory Agency Actions:

Psychopharmacologic Drugs Advisory Committee (PDAC):

Wellbutrin was presented to the Committee on June 10, 1982, prior to the assessment of the data and reports bearing on its safety. The application was presented to the Committee in an attempt to gain their views about the adequacy of the three week long efficacy trials. The Committee, however, elected to consider the issue of approval.

The Committee reviewer noted that all four PBO-controlled studies showed the common problem of an inordinate drop-out rate at day 21, due to a feature which allowed patients to be removed from the study at that point if favorable therapeutic effects were not apparent.

It was noted that results in study 15 favored AMI over BUP, significantly in some instances. The reviewer concluded that BUP was associated with greater improvement than PBO in the three inpatient studies, based on Ham-D and Clinical Global Severity of Illness scores at day 21.

The Committee recommended approval of bupropion for the treatment of depression, but conditioned their recommendation upon acceptable findings in the then incomplete safety review. The Committee was not aware of the inordinately high risk of seizure at the time its recommendation was made.

VII. Conditions for Approval:

Performance of (1) a multiple-dose dose proportionality study covering the drug's recommended dosage range which is to evaluate bupropion and its active metabolites, (2) a multiple-dose pharmacokinetic study in geriatric patients, (3) clinical studies to determine whether or not the antidepressant effect persists beyond three weeks, (4) a program to determine the potential of bupropion to cause seizures, (5) an investigation for an extended period to determine the extent of abuse and diversion of the drug in comparison to other antidepressants will be required after marketing is approved, and (6) the submission of laboratory data collected in the period following the submission of the original NDA.

VIII. Approved Package Insert:

The approved package insert is attached.

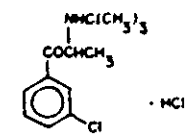
WELLBUTRIN® TABLETS - PACKAGE INSERT

646430
Special Fold 646436

Wellcome

WELLBUTRIN® (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 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 50 mg (white), 75 mg (yellow-gold), and 100 mg (red) film-coated tablets.

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 twice 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 20% 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 (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 in patients who fail to respond adequately to or who cannot tolerate alternative antidepressant treatments. Wellbutrin is not recommended as an antidepressant of first choice for most patients because its use at doses approximately one and one-third times greater than the usually required daily dose (450 mg) is associated with a high risk of seizure (see WARNINGS).*

The efficacy of Wellbutrin was demonstrated in placebo-controlled clinical trials which enrolled principally hospitalized patients with diagnoses of depressive neurosis or manic-depressive (depressed type) disorder. The depressive illness of the patients studied most closely corresponds 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.

Evidence to demonstrate the sustained effectiveness of Wellbutrin after three weeks of use in placebo-controlled investigations is not presently available.

CONTRAINDICATIONS: Because of its potential to induce seizures, Wellbutrin should not be used in patients with a convulsive disorder.

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:

CONVULSIONS: Wellbutrin appears to possess a greater epileptogenic potential than other marketed antidepressants. While the estimated risk of seizure at doses of 450 mg and below does not appear excessive in comparison to the risk reported for other antidepressant drug products, the estimated risk increases almost tenfold between a dose of 450 and 600 mg a day. Given the wide variability among individuals in their capacity to metabolize and eliminate drugs, this disproportionate increase in seizure incidence with dose incrementation is a cause for concern.

WELLBUTRIN® (BUPROPION HYDROCHLORIDE) Tablets

Bring the period of premarketing evaluation. 25 among approximately 2400 patients treated with Wellbutrin exr /reated seizures. At the time of seizure, seven (7) patients were receiving daily doses of Wellbutrin at or below the lowest recommended effective daily dose of 450 mg. Twelve (12) patients experienced seizures at daily doses of 500 mg: six (6) additional patients had seizures at daily doses between 600 and 900 mg. The risk of seizure appears to be strongly associated with dose and may be increased by predisposing factors (e.g., head trauma, CNS tumor, etc.) or a history of prior seizure. In addition, sudden and large increments in dose may contribute to an increased risk. While many seizures occurred early in the course of treatment, some seizures did occur after several months of use at fixed dose.

INCIDENCE OF SEIZURES IN PATIENTS RECEIVING WELLBUTRIN

	Wellbutrin Dose mg/day	Total Seizure Incidence (%)	Seizure Incidence in Patients Without Seizure Predisposition (%)
Within Recommended Dose	<450	0.2%	0.0%
	450	0.3%	0.2%
Above Recommended Dose	600	2.3%	1.3%
	600-900	2.8%	1.9%

DOSAGE AND ADMINISTRATION RECOMMENDATIONS SHOULD BE STRICTLY FOLLOWED TO MINIMIZE THE RISK OF SEIZURE (see DOSAGE AND ADMINISTRATION). Extreme caution should be used when combining Wellbutrin with other agents which lower seizure threshold or when administering Wellbutrin to patients with a history of seizure disorder or cranial trauma.

Potential for hepatotoxicity: In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatocellular neoplasms 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 hostility: *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 delirium. Because of the uncommon reported 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.*

Alcoholism and/or Mania: *Antidepressants can precipitate manic episodes in bipolar depressive patients during the depressive phase of their illness and may activate latent psychosis in other susceptible patients. Wellbutrin is expected to pose similar risks.*

Impaired Hepatic and Renal: *A weight loss of greater than 5 pounds occurred in 25% of Wellbutrin patients. This incidence is approximately twice that seen in comparable patients treated with placebo or diazepam. Additionally, lowering maximum daily dose in patients with severe hepatic cirrhosis may be advisable. Wellbutrin did not significantly affect liver performance in patients with renal impairment. Since the metabolites are excreted by the kidneys, it would be prudent to use lower doses in patients with severe renal impairment.*

Weight Loss: *Approximately 30% of patients treated with Wellbutrin experience weight loss, usually during the first month of therapy. Weight loss was significantly greater than placebo in controlled clinical trials. Consideration should be given to discontinuing Wellbutrin in patients who lose a significant amount of weight.*

Seizure: *The possibility of a seizure attends the administration of any psychotropic medication. The risk of seizure is dose related. Wellbutrin should not be given to patients with a current or prior diagnosis of bulimia or anorexia nervosa because these patients are at an increased risk of seizure.*

Use in Patients with Concomitant Illness: *Clinical experience gained with Wellbutrin in patients with concomitant diseases is limited. Wellbutrin has been used in patients with stable cardiovascular disease who have been carefully monitored during treatment. No clinically significant changes in blood pressure, pulse, or ECG were observed in controlled studies. Wellbutrin should be used with extreme caution 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*

WELLBUTRIN® TABLETS - PACKAGE INSERT

WELLBUTRIN® (BUPROPION HYDROCHLORIDE) Tablets

Nursing Mothers: It is not known whether Wellbutrin is excreted in the milk of lactating women. Because many drugs are excreted in human milk, caution should be exercised when Wellbutrin is administered to women who are nursing.

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 the product's premarketing clinical trials. 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	10.6	3.6
DERMATOLOGIC		
Pruritus	2.2	0.0
Rash	8.0	6.5
GASTROINTESTINAL		
Anorexia	16.3	18.4
Appetite Increase	3.7	2.2
Constipation	25.0	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	9.0	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	19.5	15.7
Muscle Spasms	4.3	3.2
Pseudoparkinsonism	1.5	1.6
Sedation	19.6	19.5
Sensory Disturbance	4.3	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	3.2
NONSPECIFIC		
Fatigue	5.0	3.6
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 entire premarketing evaluation of Wellbutrin: During its premarketing assessment, Wellbutrin was evaluated in almost 2400 subjects. 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; and rare were pallor and phlebitis.

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

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, and intestinal perforation.

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 was lymphadenopathy.

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

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 and rate or rhythm disorder.

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.

WELLBUTRIN® (BUPROPION HYDROCHLORIDE) Tablets

DRUG ABUSE AND DEPENDENCE:

Animals: 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-Centering 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 features 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 similar generalization between bupropion and amphetamine and other psychostimulants. Rhesus monkeys have been shown to self-administer bupropion intravenously.

OVERDOSAGE:

Lethal dosage 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 536 mg/kg. Signs of acute toxicity included labored breathing, salivation, tremor, dark diarrhea, 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.

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.

Whether dialysis, 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 marginal 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 overdosages may be available from a poison control center.

DOSAGE AND ADMINISTRATION: At doses that are one and one-third times the usually required dose (450 mg/day) (see WARNINGS), the observed incidence of seizure increases by as much as tenfold. *This predicts a relatively narrow therapeutic ratio for the safe use of bupropion.* especially as there is considerable inter-individual variability in the capacity of patients to metabolize drugs.

Consequently, it is *necessary prudent* to administer bupropion in a manner that is most likely to minimize the risk of seizure. Therefore analysis of clinical experience gained during its premarketing development suggests that the risk of seizure may be minimized *. The total* daily dose of Wellbutrin does *not* exceed 450 mg. The daily dose is administered in divided doses to avoid high peak concentrations of bupropion and/or its metabolites, and it the rate of intermittent dose is very gradual.

Wellbutrin should be given to patients at least 6 hours between successive doses. Besides its apparent value in decreasing the risk of seizure, gradual dose escalation is important *Note:* noticeable. often seen during the initial days of treatment. are to be minimized. If necessary, these side effects may be managed by temporary reduction of dose or the transient administration of a sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment.

The following suggested dosing regimen accommodates the principles described above

Usual Adult Dosage: A starting dose of 225 mg/day given as 75 mg t.i.d. is recommended. Based on clinical response, this dose may be increased by 75 mg/day no sooner than every three days according to the following schedule, up to a total maximum daily dose of 450 mg/day. If convenient, uniformly divided doses should be stopped.

Dosing Schedule 75 mg Tablets				
Treatment Day	Morning	Midday	Evening	Total Daily Dose
1	1	1	1	225 mg
4	2	1	1	300 mg
7	2	2	1	375 mg
10	2	2	2	450 mg

In patients who do not demonstrate an adequate response after an appropriate period of treatment at 450 mg/day, drug should be discontinued.

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 which maintains remission is recommended. The maximum recommended maintenance dose is 450 mg/day. While it is generally recommended that a course of antidepressant drug treatment should continue for several months and many patients have been *treated* with Wellbutrin in long-term clinical trials of up to 2 years duration, there has been no systematic placebo-controlled evaluation of the efficacy of Wellbutrin for a period beyond three to four weeks

HOW SUPPLIED: Wellbutrin (bupropion hydrochloride) Tablets are supplied as 50 mg (white) round, biconvex tablets printed "WELLBUTRIN" and "50" bottles of 100 (NDC 0081-0176-55). 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°-25°C (59°-77°F)

U.S. Patent No. 3819706
U.S. Patent No. 3885046 (use patent)

BURROUGHS WELLCOME CO
Research Triangle Park, NC 27709
Printed in U.S.A.

January 1986

546430
Docket Rev 646436

Department of Health and Human Services
Public Health Service
Food and Drug Administration

Memorandum

Date:

To: File NDA 18-644

Director
Office of Drug Research and Review, HFN-100

From: Director
Division of Neuropharmacological Drug Products, HFN-120

Subject: Approval Package

Introduction:

Almost a year ago, an approvable letter for NDA 18-644, Wellbutrin, issued to Burroughs-Wellcome. The letter conditioned the agency's final approval of the NDA upon the firm's agreement to:

1) revise, as directed, the product's proposed labeling,

2) submit a comprehensive safety update on adverse reactions and laboratory findings. (An especially elaborate update effort was required because the firm's previous tabulations of adverse events employed idiosyncratic rules [e.g., events recorded before drug administration began were included in the list of possible ADRs], entailed repeated categorizations of events, and employed redundant terminology making it difficult to obtain reliable estimates of the incidence of various untoward events associated with the product's use. Thus, before final labeling could be drafted, a systematic re-analysis of ADR incidence was needed. Incidentally, the Division went to considerable lengths to provide the sponsor with concrete examples of an adverse event enumeration strategy, including the creation, de novo, of a glossary of terms organized by body system.),

3) commit to conduct, after approval, a series of clinical studies including:

   a) a study to assess the sustained antidepressant efficacy of bupropion at intervals beyond three weeks. (Three weeks was the maximum effective duration of any clinical trial providing persuasive evidence of antidepressant efficacy.)

   b) a study or studies to assess the efficacy of bupropion in the outpatient population. (Bupropion's efficacy was not demonstrated in adequate and well-controlled investigations employing outpatients; only the inpatient trials provided persuasive evidence of efficacy).

c) studies to characterize more precisely the relationship between dose and ADR profile under conditions of actual use. In particular, a program to assess the risk of seizures was of interest.

d) post-marketing studies to assess the risk of diversion and abuse of bupropion

e) studies required to meet biopharmaceutic requirements. (Bupropion undergoes extensive pre-systemic clearance, can induce its own metabolism, at least in animals, and has several active, long lived, metabolites. The degree of accumulation of bupropion and its active metabolites in chronic use is, therefore, of potential clinical importance.

Comments on the May 1, 1985 submission:

In their first formal reply to the approvable action letter (May 1, 1985), the firm 1) agreed in principle to carry out the requested post-marketing investigations, 2) provided a safety update, and 3) presented a new labeling proposal that differed from the one outlined in the approvable letter.

a) Post-marketing studies:

Given the firm's agreement to conduct them, the subject of post-marketing studies requires little further comment. It is important, however, to ensure, and the approval letter makes this point, that the 'bio' studies will assess, at sufficiently long periods of exposure, the proportionality between dose and plasma concentrations of bupropion and its active metabolites.

b) Safety update:

The total number of patients reported upon in the update was 2,398; the original submission was based on 1315 patients. The increase reflected subjects exposed in formal clinical investigations and in open use antidepressant 'treatment' settings (protocol extensions and compassionate use).

On the positive side, the May 1, 1985 Safety Update did not identify any new risk not previously appreciated. The deaths reported in association with the use of bupropion could not reasonably be attributed to it. Furthermore, the calculated incidence of untoward events reported in the update did not vary significantly from earlier incidence estimates. To be clear, the incidence of some events increased, but others decreased. In any case, no new substantive risk was identified.

On the negative side, however, the update was poorly organized and did not provide a clear accounting of many items. Staff was concerned about 1) the accuracy and the manner in which the ADR incidence figures were calculated, tabulated and presented, and 2) the firm's failure to comply with several of our requests.

Dr. Lee (June 25, 1985), under the supervision of Dr. Hayes and with some input from me, reviewed the May 1, 1985 safety update.

For the administrative record, I would like to document several of the obstacles we encountered in attempting to conduct a fair and impartial review of the May 1, 1985 submission.

The firm's May submission was plagued by inaccuracies and inconsistencies. For example, the sponsor's table comparing the incidence of ADRs in the original and the expanded data base (Lee's 6/25/85 review as table 8, [sponsor's table 10]) is not always consistant with the remainder of the May submission. In particular, the incidence of convulsions is given as 0.53% in the table, but using other data in the report, the incidence is about double (see also discussion above): 15/1315 (1.1%) in the original data base or 26/2313 (1.1%) in the expanded data base. This sort of discrepancy hardly creates great confidence.

There are other examples. The sponsor was asked, as we usually do, for a listing of all patients who terminated while on Bupropion. The tabulation provided, however, was said to be restricted to terminations from among 1734 patients in "all clinical trials" and to terminations for 'toxicity' only from among the patients in 'long term continuation and humanitarian' protocols. The sponsor's approach presents review staff with an unresolvable problem. What are the real rules used to enumerate cases and what is the real size of the data base?

First, consider the question of rules for event enumeration. Under the firm's apparent rules, whether or not a discontinuation is counted among patients in the compassionate program is determined by a judgment made about the root cause of an untoward event. In actuality, whether or not an event is spontaneous or caused by drug is not readily determined. The sponsor's approach allows for selective and potentially biased reporting.

Second, what is the real size of the data base being used for the denominator of incidence estimates. The problem is illustrated by the table of discontinuations (see Lee's 6/25 review-table 7 [sponsor's table 16]). One may infer from the figures presented in the table that the denominator used to calculate the percentage of dropouts was approximately 2672, that is, 264 discontinuations/0.0988 percent = 2672 total bupropion patients. This number exceeds by approximately 270 the number (2398) said to be included in the data base used for the Safety Update. In the text of the submission, the firm (p. 9, Vol 10.2) acknowledges that the number they used, 2642, reflects 'exposures', and not unique patients. Again, this is not an especially critical fault, but, again, it is the sort of fault that tends to undermine the review team's confidence in the consistency and reliability of the firm's presentation.

Furthermore, there are instances where less than careful selection of numerators and denominators can dramatically influence incidence estimates. Consider, again, the matter of seizures. Table 7 in the May 1, 1985 submission (see Dr. Lee's (6/25/85) review) included only 14 of the 26 known seizures. In a footnote, the firm noted that 12 seizures were not included because they occurred beyond the cut-off time for the Safety Update data base. This is not an especially credible explanation because according to the firm's own count there are a minimum of 2672 patients allegedly at risk and reported upon in the update. If the 12 patients, not enumerated in Table 7, did not come from among these 2672 or so patients, where did they come from? If the 14 seizures came from only the original data base, why were they used as the numerator in an incidence fraction employing the entire expanded data base as a denominator? Finding the answers to these questions takes time and slows the review process.

More subtle problems were also identified in the submission. The firm's display of the relationship between seizure incidence and dose illustrates the problem. In generating a table of seizure incidence and dose, a single patient who experienced seizures following an OD with 9000 mg of bupropion was included in a group with six other patients who experienced seizures using the product with therapeutic intent at doses in the 600 to 900 mg range. While it is certainly important to convey that the risk of seizure is dose related, it is not appropriate to imply the existence of a large margin of safety when one does not exist. Specifically, the risk of seizure is very high (i.e., at least 3%) among patients exposed to 600-900 mg and 600 mg is less than one and one-third times the minimum established effective dose of bupropion, 450 mg.

The firm proposed to present an abbreviated version of this 'table' in the Warning Section of Wellbutrin's labeling, an action that would make the labeling misleading. We, of course, have insisted that the firm 'correct' this presentation, but this sort of 'activity' simply complicates the review process and compounds its difficulty.

Another problem with the safety update was the terminology employed and specific examples of questionable untoward event classification. For example, in study 25-04, a patient is described as being discontinued for an intercurrent illness; a more detailed review of the individual case, however, reveals that the patient had an epidural hematoma, a type of intracranial bleed that might well occur as a consequence of a fall which in turn might have been caused by a seizure. Was the firm's decision to classify the event as an intercurrent illness reasonable? Perhaps, but it might just as reasonably be considered drug related.

The selection of terminology can also influence the impression one has about the type of risks associated with the use of a drug. Our experience with psychosis is an illustration of the problem. In May 1985, we were not especially concerned about "psychotic" induction as a risk associated with the use of bupropion. The firm's tabulation of the reason's for discontinuation did not even mention 'psychosis'. To be fair, 79 patients were said to have discontinued

because of 'Neurospychiatric' reasons. Among the terms in this category, abnormal mental status (12 cases) and delirium (11 cases) might well have included patients who had psychotic episodes. (See section on psychosis below).

In any event, at the completion of our review of the firm's May 1, 1985 submission, staff was not fully confident that it clearly understood the full panoply of risks that might be associated with the use of bupropion.

Also important was the firm's failure to honor our request, made in January 1985 and acknowledged by the firm in their March 4, 1985 letter, for an expanded cross-tabulation of laboratory test results. The firm had provided a review of laboratory test results in the original NDA, but the limits for declaring results abnormal were rather broad.

c) May 1985 counter proposal for Labeling:

The firm objected to our proposed labeling for bupropion and proposed alternative labeling. Uncertainty about the risks and the factors mitigating the risks associated with the use of bupropion, however, made it difficult to respond intelligently to the firm's counter-proposals. The two more important issues in dispute involved the Indications section and the directions for the product's use.

First, the firm objected to our proposal that the Indication section carry the statement that bupropion not be used as the 'antidepressant of first choice for most depressed patients'. The firm argued that the risk of seizure was dose related, and, consequently, that 1) if the maximum daily dose were limited to 600 mg (inpatients) and 450 mg (outpatients) and 2) if drug was introduced slowly, Bupropion could be used with reasonable safety in any depressed patient.

We were not convinced, however, that the evidence upon which we based our conclusion tnat bupropion was effective would support a claim that it would be effective if administered at 450 mg. In particular, the original studies providing 'persuasive' evidence of efficacy were conducted at doses above 450 mg. The 06 trial, as planned, allowed a maximum dose of 450 mg; as conducted, even higher doses were employed. The 08 trial allowed doses as high as 750 mg and 14-01 employed doses in the range of 300 to 600 mg.

Furthermore, the amount of drug that would be taken under the firm's revised dosing recommendations was not substantially different from doses known to be associated with a high risk of seizure (i.e., more than two percent of those exposed at doses of 600 or more). Indeed, available data allows construction of a dose response curve for seizure that predicts almost a ten fold increment in risk for less than a doubling of dose over the 300 to 600 mg dose interval. This observation, coupled with the knowledge that variation in drug metabolism capacity among individuals is often measured on a log scale, gives little reassurance about the freedom from risk of doses in the 450 mg range.

Consequently, we found the firm's labeling proposal unacceptable and informed them of our views.

Interim divisional communications with the firm:

In the interest of quickly resolving the status of the bupropion NDA, the division's staff initiated a series of continuing contacts with the firm during 1985. As noted, even before the firm's first official response (May 1, 1985) to the approvable letter of 12/31/84, the division had been in repeated contact with the firm working on an ADR glossary.

Within two weeks of our receipt of the firm's May 1, 1985 submission, I spoke with Dr. Cuatrecasas (Telcon of 5/16/85) and informed him of some of the problems we had with the firm's submission. A day later, I spoke to Dr. Lineberry and I reiterated what I had told Dr. Cuatrecasas about the lack of evidence to support the effectiveness of bupropion at lower doses and the problems with the ADR enumeration and tabulations. We discussed several approaches that might be used to document the efficacy of bupropion at lower doses, but none seemed especially useful. Nonetheless, Dr. Lineberry agreed to attempt to document the drug's efficacy at lower doses with the goal of allowing the drug to be marketed at recommended doses where the risk of seizure would be lowered to a level that would not require a restricted indication.

On June 7, 1985, a more detailed explanation of the problems with the firm's May 1, 1985 submission was provided during a telconference. In addition, specific questions were asked for the first time about several terms used in the ADR enumeration (psychosis, confusion [? we did not understand the latter term]). We also reiterated our request for a cross-tabulation of laboratory test results, noting that the firm had <u>not</u> provided one as we had requested in our January meeting.

On June 17, 1985, Dr. Lineberry called to complain about the difficulty and burden of our many requests. I listened, but did not agree to rescind any that had been made.

On June 19, 1985, the firm formally submitted data to support its argument that bupropion was effective in patients receiving doses below 450 mg in studies 06 and 14-01. The firm's argument, of course, required an analysis of a subset of patients randomized to treatment in a flexible dose study. Unfortunately, patients requiring less drug in a flexible dose investigation may simply be less ill or spontaneously responding individuals. Consequently, the firm's comparison of patient's receiving less than 450 mg of Wellbutrin with all placebo patients is a biased analysis. <u>Dr. Nevius' memo of June 20, 1985 makes this point for the official record.</u>

The firm was informed of our view that the re-analysis could not support the efficacy at a lower dose. Sometime later, we learned that the firm had a study allegedly documenting the efficacy of bupropion at 450 mg/day. The study had evidently been completed after the filing of the NDA and had not been submitted. On July 12, 1985, shortly after learning of the existence of the study, I asked Dr. Cato to submit it.

August 9, 1985 and September 20, 1985 submissions:

The August 9, 1985 submission contained the results of 1) Study 25 (intended to support the efficacy of 300 and/or 450 mg of burpropion in depression), 2) information requested about EKGs, 3) ADR event re-tabulations carried out in a manner that BW staff believed repaired faults we had identified in earlier ADR tabulations, and 4) newly revised labeling.

The original report on Study 25 was difficult to review. It lacked a protocol and a means to identify who was excluded from the efficacy analysis and why. Further, it contained confusing tables about concomitant medication and reported ADRs using a definition that we had asked the firm to discard in the approvable letter. Thus, Dr. Lineberry was asked on 9/4/85 to submit additional data and reports; he reluctantly agreed. His response was received on 9/20/85.

I (this memorandum), Dr. Lee (11/9/85 review)) and Dr. Marticello (November 26, 1985) have each, independently reviewed Study 25. There are some minor disagreements among us, but I believe that we now agree, in particular, after our own 'in house' re-analysis of the data, that it provides support for the conclusion that bupropion, administered at a daily dose of 450 mg, is more effective than placebo. My comments about the the study are as follows:

Study 25:

This multicenter (4 sites), prospectively randomized, double-blind and controlled trial, compared the antidepressant efficacy of placebo with 300 and 450 mg of bupropion in 128 hospitalized depressed patients. The study was analysed by both an intent to treat LOCF and an observed cases analysis. One hundred and nine patients were eligible for the intent to treat LOCF analysis; eighteen of the nineteen patients excluded from the intent to Rx analysis had no efficacy evaluation on drug. In a true intent to treat analysis, these 18 patients would have been included as well by assigning them their entry scores at all subsequent ratings; in our modification of the intent to treat analysis, however, they are not.

It is worth noting that at least three of the patients assigned to bupropion and excluded from the efficacy analysis in study 25 (subject 14 [300 mg group] and subject 104 [450 mg group] at site 25-02, and subject 3 [450 mg group] at site 25-04) were withdrawn for ADRs that are commonly considered signs of psychosis: hallucinations and formal thought disorder.

The results of the LOCF analysis are generally more favorable than those obtained with the observed cases method. In part, this is explained by the large number of placebo non-responders who were dropped after week 3, effectively enriching the residual placebo group with spontaneous responders. The LOCF analysis is also marred by a differential cause of dropout among treatments. Among those in the efficacy analysis, there are more dropouts before day 21 among placebo patients (6) than among bupropion 300 mg (4) and bupropion 450 mg (4). Among the dropouts,

however, those on bupropion 300 mg had an average improvement of 16 points on their HAMD, those on bupropion 450 mg, an average of 20 points, while those on placebo, 6.5 points.

What does this mean? Well, the missing data brought forward in the LOCF is generally favorable to drug and unfavorable to placebo. Is this a bias? Perhaps, but it is impossible to assess reliably. If the early results reflect final results, the LOCF analysis is fair. However, if placebo patients would have eventually improved spontaneously, and the early improvement seen on drug assigned patients was merely a transient effect, the LOCF method would be biased in favor of drug. The evaluation of the dropout scores, however, does illustrate why the observed cases analysis is less favorable to drug than the LOCF analysis.

Bearing in mind the generally more favorable impression conveyed by the LOCF analysis, what are its actual findings? Patients assigned to 450 mg of bupropion did improve to a statistically significant greater extent than those on placebo as measured by several standard measures of antidepressant efficacy (Ham-D total, Ham-D retardation factor and the Clincal Global improvement rating; see tables 1 to 3 in Dr. Marticello's review). The LOCF analysis, however, fails to show statistically significant differences between bupropion and placebo on the HAM-D depression item, an item we usually consider essential to the declaration that a drug is an effective antidepressant.

Interestingly, the firm did not analyze the depression item in their report of Study 25. Dr. Marticello did the item analysis at my request. For the contrasts between the 300 and 450 doses and placebo, the observed differences between LOCF item scores at day 21 may have easily occurred by chance ($p=0.26$ and $p=0.87$ respectively).

Bottom line on Study 25:

After considering all the issues, it is my conclusion that Study 25 documents that a 450 mg daily dose of Wellbutrin is effective. The study does <u>not</u> demonstrate the efficacy of a 300 mg dose.

The changed status of our views on the clinical trials (06, 08-01, and 14-01):

The results of study 25, however, provide only one source of support of bupropion's efficacy at a daily dose of 450 mg. We, therefore, conducted a reanlysis of the doses employed in the studies that we had relied upon for evidence of efficacy in 1984 (i.e., 06, 08-01, and 14-01).

In the course of the reanalysis, I recognized that 08-01 and 14-01 were merely subparts of larger multicenter trials. Why we had agreed to analyze only the most positive subparts of studies 8 and 14 is not made clear in the administrative record. I can only guess that when the original statistical review was initiated, divisional policy was directed at finding "positive" trials.

In recent times, however, I have adopted a very tough policy on data-conditioned selection of positive subparts of multicenter trials. Indeed, recent NDA disapprovals have been based upon our refusal to

recognize fragments of multicenter studies as independent positive trials.

Thus, as part of our reanalysis, I asked our statistical consultants to evaluate studies 6, 8 and 14 as they were planned by the sponsor, that is, as multicenter pooled studies. The results of the analysis are presented in Dr. Stein's November 15, 1985 review.

> 06: This study, conducted at three sites, concinues to provide persuasive evidence of bupropion s antidepressnt efficacy when analysed as a multicenter pooling. Furthermore, a review of the daily administered dosages (see Lee tabulation of December 19, 1985) reveals that the vast majority of patients received a daily dose of bupropion that did not exceed 450 mg. Thus, I am prepared to accept this study as a confirmatory source of evidence of bupropion's efficacy at 450 mg.
>
> 08: This study, conducted at three sites, is no longer acceptable as a major source of evidence of efficacy. First, one site, 8-03 which provided the smallest number of patients was dropped at the agency's request because of unacceptable findings in a DSI inspection. More critical, the combined results from the two remaining sites do not support a conclusion that bupropion is an effective antidepressant. Indeed, the trends at site 8-02 favor placebo.
>
> 14: This study was conducted at two sites. The combined pooling remains positive, but the daily dose received by a significant proportion of treated patients was 600 mg. Consequently, the study cannot support the dosing recommendation in the proposed labeling.

The bottom line on Efficacy at a daily dose of 450 mg:

Studies 25 and 6 serve as independent sources of evidence supporting bupropion's antidepressant efficacy at a daily dose of 450 mg. However, as a result of our reanalysis (study 8) and and the firm's revised marketing plans (study 14), two studies identified as pivotal in our 1984 approval decision can no longer be relied upon.

Further safety considerations:

However, while the issues of minimum effective dose were being assessed, we became concerned about psychosis as a risk of bupropion's use.

The Psychosis issue:

> Antidepressant drugs have been reported to cause psychosis in some small proportion of patients exposed. The mechanism(s) underlying the psychotic induction is not understood. Various arguments and explanations have been advanced. Perhaps the patients who develop psychosis are especially vulnerable in the sense that for any provocative stimulus they are more likely to become psychotic than other individuals. Alternatively, they may suffer from a disease that in one state exhibits psychotic phenomena. For example, if patients are manic-depressives being treated during the depressed phase of their Bipolar Affective illness, treatment with an antidepressant may activate their mania. (Mania can be hard to differentiate from schizophreniform psychotic phenomena). Still other

patients may simply become spontaneously psychotic while under antidepressant treatment; presumably this may be more likely if the patient has schizophrenia and has been misdiagnosed.

In any case, reports of a few cases of psychosis among depressed patients, especially hospitalized patients, would not be unexpected. Indeed, some psychotic signs and symptoms may occur as part of the phenomenology of depression; hallucinations and delusions, for example, are acceptable signs of depression if mood congruent.

As noted earlier, the record of ADRs initially reported with bupropion suggested a low incidence of psychosis and the firm's May 1985 safety update tabulation (Lee's June 25, 1985 review) did not attribute the discontinuation of any patient to psychosis, per se.

Actually, because of my contacts with NIMH staff, I had been aware of the possibility that bupropion might cause psychosis. Indeed, in January of 1985, after a chat with Dr. William Potter about his experiences, I was provided with a draft copy of an article reporting on four patients who had developed short term psychotic episodes while on bupropion.

However, being suspicious of the generalizability of isolated reports, I had elected to await the firm's Safety Update to assess the risk in context of the overall data base experience. I mentioned the problem to the firm in June 1985, but they did not clarify the matter. In early September 1985, before we had received any further clarification from the firm, I attended a scientific meeting at the NIMH during which I heard additional presentations about the possible potential of bupropion to cause elevations of homovanillic acid (HVA) and, more critically, presentations describing a linkage between plasma HVA and the level of psychopathology among schizophrenics. Homovanillic acid is a metabolite of dopamine, the primary neurotransmitter in the neuronal system believed to be deranged in schizophrenia. The discussion at the meeting suggested a possible explanation for the induction of psychosis that Dr. Potter's group had observed in 4 of 11 depressed patients treated with bupropion. In any case, mechanisms aside, Dr. Potter's findings did not seem compatible with the firm's failure to identify psychosis as a cause of discontinuation of treatment with the drug. In fact, drug was discontinued in 3 of the 4 patient's described by Dr. Potter's group. Where in the data base were these patients enumerated?

As a matter of interest, I arranged for Dr. Potter and his associate, Dr. Rudorfer to present their findings to a group at ODDR. The meeting (10/3/85) was attended by the firm and their guest 'experts' who sought to explain away the findings of psychosis. Unfortunately, at the time of the meeting, there was little agreement about case definitions and the firm had not done a systematic analysis of the problem. It was agreed, however, that several phenomena might explain the 'unusual' experience of Dr. Potter's group. On the other hand, we emphasized that the discrepancy might in part be due to under-ascertainment of cases. Indeed, the failure to identify the three cases in Study 25 supported this possibility.

Following further discussion, the firm submitted a report on psychosis (Novmeber 26, 1985). In the report, Psychosis appears to be given as an explanation for discontinuation of 9 patients (see Lee reveiw of

11/27/85). Unfortunately, the nature of the records, and the firm's method of recording adverse events makes it virtually impossible to ascertain clearly why patients were actually discontinued. Clearly, the possibility exists that some patients were psychotic when withdrawn from drug, but the withdrawal was attributed to some other cause.

In any event, there is little doubt in my mind that psychosis is a risk of treatment with bupropion. Unfortunately, I have no sense of the absolute incidence of the risk. Even more important, the relative potential of bupropion and other antidepressants to cause psychosis is not discoverable from the data available. Perhaps, post-marketing experience will provide some insight into the problem, perhaps not. Given the circumstances, however, I believe we must prominently identify neuropsychiatric disturbances, including psychosis, in Wellbutrin's labeling as risks associated with its use.

The missing safety update on laboratory data:

As noted earlier, we had asked for, but not received, a re-expression of laboratory test results using a cross-tabulation method preferred by the division. The original submission of the NDA disregarded requests made by the division at a pre-NDA meeting. The request for such an expanded cross-tabulation of lab results, first made in January 1985, was initially ignored, and then, upon our repeated insistence, promised for delivery in September 1985. At this time (circa December 18, 1985), it has not yet been received.

I am at somewhat of a loss to deal with this matter. The firm warrants that there are no abnormal laboratory results of concern. My perusal of the summary data for the original NDA suggests that they are correct, but we have not had a direct 'hands on' look at the data in the presentation format we prefer, nor have we received any update on laboratory findings in the expanded data base.

The orignal submission, Volume 1.3, does present (p. 93-143) statistical summaries of means and statistically significant within group differences for placebo and bupropion for the original placebo controlled studies (i.e., 06,08,09, and 14) for those patients who had both a baseline and at least one subsequent lab test result. There were 107 treatment vs baseline mean comparisons for bupropion and 86 for placebo. The means compared, however, frequently involve groups of different size; in short, patients were lost and the means compared represent groups composed of different individuals. Thus, the results do not provide a 'worst case' analysis because a patient suffering a bad result and leaving the trial might be 'missed.' As the firm points out, however, none of the mean changes are of substantive size or clinical importance. Indeed, none of the baseline and 'on treatment' means fell outside the normal range.

The firm also points out that the 3 statistically significant between group contrasts (bupropion vs. placebo) were unimportant and I agree. Finally, lab data from several active control trials is also unalarming.

Thus, by and large, the data provided on lab results in the original NDA does not raise any substantive concerns. However, means, for larger groups especially, may be insensitive to one or two abnormal outliers that might

2) the labeling warns fully of the risks, and 3) the labeling provides adequate guidance on ways to minimize the risks (e.g., limit the use of the drug to a narrow population, contraindicate its use in specific populations, etc.). In applying the policy, consideration is given to the potential advantages of the drug relative to available alternative therapeutic regimens in the treatment of all patients and in the treatment of special populations of patients (e.g., patients unresponsive to other treatments, the elderly, those with complicating conditions like heart disease, etc.).

To begin, does bupropion offer any specific advantages? As a 'clinician,' I am persuaded that some documented properties of bupropion (its relative lack of anticholinergic activity and its apparent lack of potential to cause orthostatic hypotension) would make it a valuable drug for some depressed patients.

Has bupropion been shown to be especially useful in any special population? To be clear, the firm has not provided evidence from adequate and well-controlled investigations to support its implied claim that bupropion is effective in patients who fail to respond to other antidepressant therapies. On the other hand, they have 'testimonials' from open clinical practice settings arguing this advantage. I am not personally persuaded by testimonals, but some experts may find the evidence fairly persuasive. The question, therefore, is what level of documentation of special benefit is necessary to justify approval of bupropion given its clear risk of seizure?

Are clinical trials documenting any or all of bupropion's alleged advantages essential to its approval? We took such a position in dealing with the NDA for clozapine, an effective antipsychotic with a high risk of agranulocytosis. In anticipation of questions about the applicability of this precedent, I would point out that clozapine induced agranulocytosisis occurs in as many as one percent of patients exposed for six months and is associated with a case fatality rate of 20 to 50%. I believe that this is a substantially more serious risk than seizure. Furthermore, the data presented by the firm suggests that limiting the maximum dose of bupropion and slowing the rate at which the daily dose is escalated will probably reduce the risk of seizure. In contrast, no known maneuver alters the risk of agranulocytosis with clozapine. Thus, I find the two cases sufficiently different to recommend approval of the NDA without requiring proof from controlled clinical trials of bupropion's advantage over standard antidepressants in the treatment of recidivistic depressed patients.

In summary, my recommendation is to approve bupropion, but for a restricted population, with very cautionary labeling that identifies its ususual propensity to cause seizures and its more troublesome side-effects.

Labeling issues and the conditions of approval:

My recommendation to approve the NDA for bupropion is conditioned upon the requirement that its labeling 1) state that bupropion is not the drug of first choice for most depressed patients, and 2) carry a prominent warning about its risk of seizure. Of course, the remaining sections of the labeling must be consistant with the Indications and Warnings Sections. The labeling must provide instructions for use that emphasize how the risk of seizure can be minimized (i.e., limitation in maximum dose to 450 mg, slow incrementation of dosing, contraindication of use in patients with seizure disorder, etc.).

Specific labeling recommendations:

The labeling upon which this approval recommendation is conditioned is presented in toto in the attached labeling draft (December 18, 1985). The labeling, with possible minor modifications, should be made a condition of approval and should become a part of the approval letter, either as an attachment or in the body of the letter, whichever is easiest to accomplish.

Post-marketing requirements:

All post-marketing requirements enumerated in our December 1984 approvable letter remain in force. The following additional demands are made:

1) In view of new information about bupropion's several active metabolites, the post-marketing chronic dose proportionality studies must be modified to include assessments of metabolites as well as parent drug after many weeks of use. If possible, using an approach similar to the 'pharmacokinetic screen,' I would also ask for the sampling of blood levels of drug and metabolites in patients taking drug for very long periods.

2) In view of the time elapsed and my opinion that they will primarily be used to modify labeling, I would agree to make the submission of the lab data safety update and the previously requested lab data cross-tabulations a post-marketing requirement.

Paul Leber, M.D.

12/19/85

NDA 18-644
doc # 3709p/3739p

Bupropion HCl
Wellbutrin
75, 100 mg Tablets
NDA 18-644
Wang [redacted]
1-D

Burroughs Wellcome Co.
Research Triangle Park, NC
Submission Dated:
September 26, 1985

DEC 1 2 1985

Review of Dissolution Data

The firm has submitted dissolution data (attached) pursuant to Dr. Karin Kook's review of the firm's May 21, 1985 submission where she requested the raw dissolution data used in the firm's basket vs. paddle method comparison. Dr. Kook's request that interim (i.e. prior to 45 minutes) dissolution data be submitted if available could not be complied with due to such data's lack of availablility.

Recommendation:

Dr. Kook's provisions for setting a dissolution specification of Q=80% at 45 minutes using the paddle method (50 rpm) in 900 ml water at 37°C have been met. This recommendation should be forwarded to the firm.

Paul L. Hepp, Pharm.D.
Pharmacokinetics Evaluation Branch

RD Initialed by C.T. Viswanathan, Ph.D.
FT Initialed by C.T. Viswanathan, Ph.D. 12/12/85

cc: NDA 18-644 orig., HFN-120, HFN-226(Hepp), Chron, Drug, and FOI files.

PLH:smj:kek [redacted] (12-06-85)

DISSOLUTION OF WELLBUTRIN® Tablets

% l.s. Bupropion Hydrochloride Dissolved

Batch	Basket Method	Paddle Method
2E2791 (75 mg)	45 min.	45 min.
		
Mean	96.9	96.5
Std. Dev.	1.1	1.9

Batch	Basket Method	Paddle Method
2I6030 (75 mg)	45 min.	45 min.
		
Mean	94.0	91.2
Std. Dev.	0.3	4.0

Batch	Basket Method	Paddle Method
2I6031 (75 mg)	45 min.	45 min.
		
Mean	93.2	90.5
Std. Dev.	1.6	1.8

DISSOLUTION OF WELLBUTRIN® Tablets

% l.s. Bupropion Hydrochloride Dissolved

Batch	Basket Method	Paddle Method
2I6032 (100 mg)	45 min.	45 min.
		
Mean	93.7	87.8
Std. Dev.	1.8	4.1

Batch	Basket Method	Paddle Method
2I6033 (100 mg)	45 min.	45 min.
		
Mean	94.1	90.9
Std. Dev.	1.4	4.3

Batch	Basket Method	Paddle Method
2D6011 (100 mg)	45 min.	45 min.
		
Mean	96.7	84.3
Std. Dev.	1.1	3.8

DAK/mg/LD
TRZO/85/0629-4

Bupropion HCl
75, 100 mg Tablets
NDA 18-644
Reviewer: Karin A. Kook, Pharm.D.
1-D
Wang [redacted]

Burroughs Wellcome Co.
Research Triangle Park, NC 27709
Date of Submission:
May 21, 1985

SEP 25 1985

Review of In Vitro Dissolution Data

In the early development of bupropion, a non-standard basket method (100rpm, 500ml of 0.6% HCl at 37°C) was used; the sampling times were twenty minutes or, more often, thirty minutes. As a result of an FOA Review Chemist suggestion, the procedure was changed on June 10, 1982 to a paddle method (50 rpm, 900ml water at 37°C) with a 45 minute sampling time. During the review of the NDA submission, one lot of 100mg Tablets [redacted] was found to have poor in vivo absorption relative to another lot (7J2700). These lots were tested in vitro with the basket method and poorer dissolution was also noted (60% at 20 minutes versus 104%); lot 8A2704 was 102.5% dissolved after 30 minutes. Thus, the Division of Biopharmaceutics recommended the basket method with a specification of not less than [redacted] percent (Q) drug dissolution in 20 minutes.

The firm has responded to the proposed specification. They indicate that the baskets will ultimately be corroded by the acidic medium and, thus, could give erratic results. They furthermore state that the paddle method is easier to automate. They claim limited experience with a 20 minute sampling time using a basket method. They propose the dissolution specifications to be not less than [redacted] dissolved in 45 minutes using the paddle method at 50 rpm in 900 ml water at 37°C. In support, they provide summary comparative dissolution on three batches of their 75 mg and 100mg tablets (Table 1). Further comparative data was provided in the previcusly reviewed NDA submission and is summarized on Table 2. Finally, they indicate that they "will further evaluate the possibility of reducing the time specification below 45 minutes if warrented, as data and experience is accumulated with production batches."

Table 1

	Basket Data, 45 Minutes		Paddle Data, 45 Minutes	
Batch	Mean	Std. Dev.	Mean	Std. Dev.
75 mg				
2E2791	96.9	1.1	96.5	1.9
216030	94.0	0.3	91.2	4.0
216031	93.2	1.6	90.5	1.8
100 mg				
2D6011	96.7	1.0	84.3	3.8
216032	93.7	1.8	87.8	4.1
216033	94.1	1.4	90.9	4.3

Table 2

Batch	$\bar{X}$ Paddle @ 45 Min[1]	S.D	$\bar{X}$ Basket @ 20 min[2]	S.D.
2J3145	103.8	1.7	96.0	3.87
3A2716	100.7	1.0	91.0	21.76
3A2717	100.7	1.0	99.3	2.38
3A2718	100.2	3.5	98.3	2.20
3A2719	101.6	3.7	95.9	14.62
3A2720	102.6	3.4	100.5	2.92

[1] n=6
[2] n=12

Recommendation

The Division of Biopharmaceutics agrees to dissolution testing with the paddle method. However, the firm is requested to supply the raw dissolution data used in making the basket versus paddle methods comparisons. This has been communicated by telephone. They were also asked to provide interim (i.e. 30 minute) results, if available. Provided the data are in support, a dissolution specification of Q=[redacted] at 45 minutes using the paddle method in 900 ml water at 37°C could be set.

Karin A. Kook, Pharm.D.
Pharmacokinetic Evaluation Branch

RD Initialed by Paul L. Hepp, Pharm.D.
FT Initialed by C.T. Viswanathan, Ph.D. CTV 9/25/85

cc: NDA 18-644 orig., HFN-120, HFN-226(Kook), Chron, Drug. and FOI Files

KAK:tw:kek:smj:(5004x) 9/16/85