CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-584

Approval Letter

ANDA 75-584

FEB 7 2000

Invamed Inc.
Attention: Mahendra Patel, Ph.D.
2400 Route 130
Dayton, NJ 08810

Dear Sir:

This is in reference to your abbreviated new drug application dated February 16, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Bupropion Hydrochloride Tablets, 75 mg and 100 mg.

Reference is also made to your amendments dated February 26, April 9, September 1, and December 8, 1999.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Bupropion Hydrochloride Tablets, 75 mg and 100 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Wellbutrin® Tablets, 75 mg and 100 mg, respectively, of Glaxo Wellcome, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the

proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies which may be identified.

Sincerely yours,

/S/ 2/7/00

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-584

FINAL PRINTED LABELING

NDC 52189-362-30

invamed inc.

Bupropion Hydrochloride Tablets

100 mg

WARNING: Do not use in combination with ZYBAN™, or any other medicines that contain bupropion hydrochloride.

Rx only

1000 TABLETS

EACH TABLET CONTAINS:
Bupropion Hydrochloride ..... 100 mg

USUAL DOSAGE: See accompanying prescribing information for complete details.

Keep this and all drugs out of the reach of children.

Dispense in a tight, light-resistant container as defined in the USP.

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

Zyban™ is a registered trademark of Glaxo Wellcome.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

52189-362-30

FEB -7 2000

Lot No.:
Exp. Date:

MF # 1495-02

NDC 52189-362-24

invamed inc.

Bupropion Hydrochloride Tablets

100 mg

WARNING: Do not use in combination with ZYBAN™, or any other medicines that contain bupropion hydrochloride.

Rx only

100 TABLETS

EACH TABLET CONTAINS:
Bupropion Hydrochloride ..... 100 mg

USUAL DOSAGE: See accompanying prescribing information for complete details.

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Dispense in a tight, light-resistant container as defined in the USP.

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

Zyban™ is a registered trademark of Glaxo Wellcome.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

52189-362-24

FEB -7 2000

Lot No.:
Exp. Date:

MF # 1494-02

NDC 52189-361-30

invamed inc.

Bupropion Hydrochloride Tablets

75 mg

WARNING: Do not use in combination with ZYBAN™, or any other medicines that contain bupropion hydrochloride.

Rx only

1000 TABLETS

EACH TABLET CONTAINS:
Bupropion Hydrochloride ..... 75 mg

USUAL DOSAGE: See accompanying prescribing information for complete details.

Keep this and all drugs out of the reach of children.

Dispense in a tight, light-resistant container as defined in the USP.

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

Zyban™ is a registered trademark of Glaxo Wellcome.

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

52189-361-30

FEB -7 2000

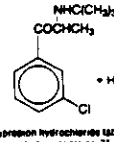
Lot No.:
Exp. Date:

MF # 1493-02

BUPROPION HYDROCHLORIDE TABLETS

Rx Only

DESCRIPTION: Bupropion hydrochloride, an antidepressant of the aminoketone class, is chemically unrelated to tricyclic, tetracyclic, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.21. The molecular formula is $C_{13}H_{18}ClNO \cdot HCl$. Bupropion hydrochloride powder is white, crystalline and highly soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa. It has the structural formula:



Each bupropion hydrochloride tablet intended for oral administration contains 75 mg or 100 mg bupropion hydrochloride. In addition, each bupropion hydrochloride tablet contains the following inactive ingredients: FD&C Blue No. 2 aluminum lake, FD&C Red No. 40 aluminum lake, hydroxypropyl methylcellulose, microcrystalline cellulose, potassium chloride, pregelatinized starch, stearic acid, titanium dioxide, and triethyl citrate.

CLINICAL PHARMACOLOGY: **Pharmacodynamics and Pharmacological Actions:** The neurochemical mechanism of the antidepressant effect of bupropion is not known. Bupropion does not inhibit monoamine uptake. Compared to classical tricyclic antidepressants, it is a weak blocker of the neuronal uptake of serotonin and norepinephrine and does not inhibit 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 fivefold the dose recommended as the human antidepressant dose.

Absorption, Distribution, Pharmacokinetics, Metabolism, and Elimination:

Oral bioavailability and single-dose pharmacokinetics: In humans, following oral administration of bupropion, 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 bupropion hydrochloride tablets in humans has not been determined because an intravenous formulation for human use is not available.

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

Metabolism: Following oral administration of 200 mg of ^{14}C-bupropion, 87% and 10% of the radioactive dose were recovered in the urine and feces, respectively. However, the fraction of the oral dose of bupropion 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

hours, followed by a biphasic decline. The average half-life of the plasma (post-distribution) phase is approximately 14 hours, with a range of 8 to 24 hours. The urinary 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 200 mg; however, it is not known if dose proportionality between dose and plasma level is maintained at chronic use.

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

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

Metabolism: Following oral administration of 200 mg of ^{14}C-bupropion, 87% and 10% of the radioactive dose were recovered in the urine and feces, respectively. However, the fraction of the oral dose of bupropion 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. Thus it 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 bupropion may be changed in chronic use.

Plasma and urinary metabolites so far identified include biotransformation products formed via reduction of the carbonyl group and/or hydroxylation of the *tert*-butyl group of bupropion. Four basic metabolites have been identified.

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

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

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

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 to 100 times the steady-state concentrations of the parent drug.

The effect of other disease states and altered organ function on the metabolism and/or elimination of bupropion has not been studied in detail. However, the elimination of the major metabolites of bupropion may be affected by reduced renal or hepatic function because they are moderately polar compounds and are likely to undergo conjugation in the liver prior to urinary excretion. The preliminary results of a comparative single-dose pharmacokinetic study in normals 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 85% or more bound to human albumin at plasma concentrations up to 800 micromolar (200 mcg/mL).

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

The efficacy of bupropion has been established in three placebo-controlled trials, including two of approximately 3 weeks duration in depressed inpatients, and one of approximately 5 weeks duration in depressed outpatients. The depressive disorder of the patients studied corresponds most closely to the Major Depression Category of the APA Diagnostic and Statistical Manual III.

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

Effectiveness of bupropion in long-term use, that is, for more than 5 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use bupropion for extended periods should periodically re-evaluate the long-term usefulness of drug for the individual patient.

CONTRAINDICATIONS: Bupropion hydrochloride tablets are contraindicated in patients with a seizure disorder. Bupropion hydrochloride tablets are contraindicated in patients treated with ZYBAN™ (bupropion hydrochloride) Sustained-release Tablets, or any other medications that co-rain bupropion because the incidence of seizure is dose dependent. Bupropion hydrochloride tablets are also contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa because of a higher incidence of seizures noted in such patients treated with bupropion hydrochloride tablets. The concurrent administration of bupropion hydrochloride tablets and a monoamine oxidase (MAO) inhibitor is contraindicated. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with bupropion hydrochloride tablets. Bupropion hydrochlo-

clearly 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 decline in sexual drive, increased fatigability, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and recurrent ideation or attempts.

Effectiveness of bupropion 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 bupropion for extended periods should periodically re-evaluate the long-term usefulness of drug for the individual patient.

CONTRAINDICATIONS: Bupropion hydrochloride tablets are contraindicated in patients with a seizure disorder. Bupropion hydrochloride tablets are contraindicated in patients treated with ZYBAN™ (bupropion hydrochloride) Sustained-release Tablets, or any other medications that contain bupropion because the incidence of seizure is dose dependent. Bupropion hydrochloride tablets are also contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa because a higher incidence of seizures noted in such patients treated with bupropion hydrochloride tablets. The concurrent administration of bupropion hydrochloride tablets and a monoamine oxidase (MAO) inhibitor is contraindicated. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with bupropion hydrochloride tablets. Bupropion hydrochloride tablets are contraindicated in patients who have shown an allergic response to it.

WARNINGS: Patients should be made aware that bupropion hydrochloride tablets contain the same active ingredient found in ZYBAN™, used as an aid to smoking cessation treatment, and that bupropion hydrochloride tablets should not be used in combination with bupropion hydrochloride sustained-release tablets, or any other medications that contain bupropion.

Seizures: Bupropion is associated with seizures in approximately 0.4% (4/1000) of patients treated at doses up to 450 mg/day. This incidence of seizures may exceed that of other marketed antidepressants by an order of magnitude. The relative risk is only an approximate estimate because no direct comparative studies have been conducted. The estimated seizure incidence for bupropion increases almost tenfold between 450 and 600 mg/day, which is below the maximum recommended 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 underscores the importance of adherence to dosing recommendations.

During the initial development, 25 among approximately 3,600 patients treated with bupropion hydrochloride tablets experienced seizures. At the time of seizure, seven patients were receiving daily doses of 450 mg or below for an incidence of 0.33% (3/1000) within the recommended dose range. Twelve patients experienced seizures at 600 mg per day (2.3% incidence); six additional patients had seizures at daily doses between 450 and 600 mg (2.5% incidence).

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

The risk of seizure appears to be strongly associated with dose and the presence of predisposing factors. A significant predisposing factor (e.g., history of head trauma or prior seizure, CNS tumor, concomitant medications that lower seizure threshold, etc.) was present in approximately one-half of the patients experiencing a seizure. Sudden and large increases in dose may contribute to increased risk. While many seizures occurred early in the course of treatment, some seizures did occur after several weeks of fixed dose.

Recommendations for reducing the risk of seizure: Retrospective analysis of clinical experience gained during the development of bupropion suggest that the risk of seizure may be minimized if (1) the total daily dose of bupropion hydrochloride tablet does not exceed 450 mg, (2) the daily dose is administered t.i.d., with each single dose not to exceed 150 mg to avoid high peak concentrations of bupropion (adjust the dose in individuals), and (3) the rate of incrementation of dose is very gradual. Extreme caution should be used when bupropion hydrochloride tablets are (1) administered to patients with a history of seizure, special trauma, or other predisposing factor(s) toward seizure, or (2) prescribed with other agents (e.g., antipsychotics, other antidepressants, etc.) or treatment regimens (e.g., abrupt discontinuation of a benzodiazepine) that lower seizure threshold.

Potential for Hepatotoxicity: In rats receiving large doses of bupropion chronically, there was an increased incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in 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 bupropion experience some degree of increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment. In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs. In approximately 2% of patients, symptoms were sufficiently severe to require discontinuation of treatment with bupropion.

Psychosis, Confusion, and Other Neuropsychiatric Phenomena: Patients treated with bupropion 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 bupropion. 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. Bupropion is expected to pose similar risks.

Altered Appetite and Weight: A weight loss of greater than 5 pounds occurred in 25% of patients receiving bupropion. This incidence is approximately double that seen in comparable patients treated with fluoxetine or placebo

tion occasionally, various biochemical changes were seen in liver, and laboratory tests suggesting mild bronchoconstrictor injury were noted. Although mentioned 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.

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General:

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

Psychosis, Confusion, and Other Neuropsychiatric Phenomena: Patients treated with bupropion 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 associated by treatment with bupropion. 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. Bupropion is expected to pose similar risks.

Altered Appetite and Weight: A weight loss of greater than 5 pounds occurred in 16% of patients receiving bupropion. 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 bupropion did. Consequently, a weight loss is a major potential sign of a patient's depressive illness, the anorectic and/or weight reducing potential of bupropion should be considered.

Seizure: The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Accordingly, prescriptions for bupropion hydrochloride tablets 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 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. Bupropion was well tolerated in patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants.

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

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

Physicians are advised to discuss the following issues with patients:

Patients should be instructed to take bupropion hydrochloride tablet 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 bupropion may impair their ability to perform tasks requiring judgment or motor and cognitive skills. Consequently, until they are reasonably certain that bupropion 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 bupropion 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 systemic data have been collected on the consequences of the concomitant administration of bupropion and other drugs.

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

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

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

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

Concurrent administration of bupropion 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 to 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

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in carcinogenicity assessment. Salmonella mutations 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 to 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 to 45 times the human daily dose and have revealed no definitive evidence of impaired fertility or harm to the fetus due to bupropion. (In rabbits, a slightly increased incidence of fetal abnormalities was seen in two studies, but there was no increase in any specific abnormality.) There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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

Nursing Mothers: Because of the potential for serious adverse reactions in nursing infants from bupropion, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and effectiveness of bupropion in pediatric patients under 18 years old have not been established.

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

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

Adverse events were sufficiently troublesome

to cause discontinuation of treatment with bupropion in approximately ten percent of the 2400 patients and volunteers who participated in clinical trials during the product's clinical development. The more common events causing discontinuation included 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 dosing range.

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 judgements, 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 bupropion under relatively similar conditions of dose/dosage (300 to 600 mg), setting, and duration (3 to 4 weeks). The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors must differ from those which prevailed in the clinical trials. These incidence figures also cannot be compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions.

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

TREATMENT EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS*

Adverse Experience	Bupropion Patients (n=323)	Placebo Patients (n=185)
(Percent of Patients Reporting)		
CARDIOVASCULAR		
Cardiac Arrhythmias	5.3	4.3
Dizziness	22.3	16.2
Hypertension	4.3	1.6
Hypotension	2.5	2.7
Palpitations	3.7	2.2
Syncope	1.2	0.5
Tachycardia	10.8	8.6
DERMATOLOGIC		
Pruritis	2.2	0.0
Rash	8.0	6.5
GASTROINTESTINAL		
Anorexia	18.3	10.4
Appetite Increase	3.7	2.2
Constipation	26.0	17.3
Diarrhea	9.5	8.6
Dyspepsia	3.1	2.2
Nausea/Vomiting	22.9	19.9
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
Amnesia/ 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	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	8.8
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 patients receiving bupropion are included.

Other Events Observed During the Development of Bupropion: The conditions and duration of exposure to bupropion 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 bupropion. 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 section 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 patients; rare events are those occurring in less than 1/1000 patients.

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

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

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

Gastrointestinal: Infrequent were dysphagia, thirst disturbance, and liver damage [illegible]

...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 bupropion. 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 section of the labeling.

The following definitions of frequency are used: Frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; while rare events are those occurring in less than 1/1000 patients.

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

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

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

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

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

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

Musculoskeletal: Rare was musculoskeletal chest pain.

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

Neuropsychiatric: (see PRECAUTIONS) Frequent were mania/hypomania, increased libido, hallucinations, decrease in sexual function, and depression; infrequent were memory impairment, depersonalization, psychosis, dysphoria, mood instability, paranoia, formal thought disorder, and agitation; 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, rales or rhythm disorder, pneumonia, and pulmonary embolism.

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

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

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

Cardiovascular: orthostatic hypotension, third degree heart block.

Endocrine: syndrome of inappropriate antidiuretic hormone secretion.

Gastrointestinal: esophagitis, hepatitis.

Hemic and Lymphatic: ecchymosis, leukocytosis, leukopenia.

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

Nervous: coma, delirium, dream abnormalities, paresthesia, unmasking of tardive dyskinesia.

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

Special Senses: tinnitus.

DRUG ABUSE AND DEPENDENCE:

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

In a population of individuals experienced with drugs of abuse, a single dose of 400 mg bupropion hydrochloride tablets 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 users. 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 535 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 bupropion hydrochloride tablets. Thirteen overdoses occurred during clinical trials. Twelve patients ingested 850 to 4200 mg and recovered without significant sequelae. Another patient who ingested 9000 mg of bupropion hydrochloride and 300 mg of tranylcypromine experienced a grand mal seizure and recovered without further sequelae.

Since introduction, overdoses of bupropion up to 17,300 mg have been reported. Seizure was reported in approximately one-third of all cases. Other serious reactions reported with overdoses of bupropion alone included hallucinations, loss of consciousness, and tachycardia. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported when bupropion was part of multiple drug overdoses.

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

bupropion exhibits some pharmacologic actions common to psychostimulants, including increases in locomotor activity and the production of a mildly 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 psychostimulants and other psychostimulants. However, studies have shown no self-administration bupropion intravenously.

OVERDOSAGE:

Lethal Dose in Animals: In rats, the acute oral LD_{50} values were 807 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, arched back, ptosis, ataxia, and convulsions.

Human Overdose Experience: There has been limited clinical experience with overdosage of bupropion hydrochloride tablets. Thirteen overdoses occurred during clinical trials. Twelve patients ingested 850 to 4200 mg and recovered without significant sequelae. Another patient who ingested 9000 mg of bupropion hydrochloride and 300 mg of tranylcypromine experienced a grand mal seizure and recovered without further sequelae.

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

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

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

If the patient is stuporous, comatose, or convulsing, airway intubation is recommended prior to undertaking gastric lavage. Although there is little clinical experience with lavage following an overdose of bupropion, 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 overdoses of bupropion. 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:

General Dosing Considerations: It is particularly important to administer bupropion hydrochloride tablet in a manner most likely to minimize the risk of seizure (see WARNINGS). Increases in dose should not exceed 100 mg/day in a 3-day period. Gradual escalation in dosage is also important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these effects may be managed by temporary reduction of dose or the short-term administration of an intermediate to long-acting sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment. Insomnia may also be minimized by avoiding bedtime doses. If distressing, untoward effects supervene, dose escalation should be stopped.

No single dose of bupropion hydrochloride tablet should exceed 150 mg. Bupropion hydrochloride tablet should be administered t.i.d., preferably with at least 6 hours between successive doses.

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

Treatment Day	Total Daily Dose	Dosing Regimen			
		Tablet Strength	Number of Tablets		
			Morning	Midday	Evening
1	200 mg	100 mg	1	0	1
2	300 mg	100 mg	1	1	1

Increasing the Dosage Above 300 mg/Day: As with other antidepressants, the full antidepressant effect of bupropion may not be evident until 4 weeks of treatment or longer. An increase in dosage, up to a maximum of 450 mg/day, given in divided doses of not more than 150 mg each, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day. Dosing above 300 mg/day may be accomplished using the 75 or 100 mg tablets. The 100 mg tablet must be administered q.i.d. with at least 4 hours between successive doses, in order not to exceed the limit of 150 mg in a single dose. Bupropion hydrochloride tablet should be discontinued in patients who do not demonstrate an adequate response after an appropriate period of treatment at 450 mg/day.

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

Maintenance: The lowest dose that maintains

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 conditioned/reinforced behavioral paradigms. Drug discrimination studies in rats showed stimulus generalization between bupropion and amphetamine and other psychostimulants. Recent research have been shown to self-administer bupropion intravenously.

OVERDOSAGE:

Lethal Doses in Animals: In rats, the acute oral LD_{50} values were 807 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 laboured breathing, salivation, arched back, ptosis, ataxia, and convulsions.

Human Overdose Experience: There has been limited clinical experience with overdosage of bupropion hydrochloride tablets. Thirteen overdoses occurred during clinical trials. Twelve patients ingested 250 to 4200 mg and recovered without significant sequelae. Another patient who ingested 9000 mg of bupropion hydrochloride and 300 mg of tranylcypromine experienced a grand mal seizure and recovered without further sequelae.

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

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

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

If the patient is stuporous, comatose, or convulsing, airway intubation is recommended prior to undertaking gastric lavage. Although there is little clinical experience with lavage following an overdose of bupropion, 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 overdoses of bupropion. 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:

General Dosing Considerations: It is particularly important to administer bupropion hydrochloride tablet in a manner most likely to minimize the risk of seizure (see WARNINGS). Increases in dose should not exceed 100 mg/day in a 3-day period. Gradual escalation in dosage is also important if agitation, motor restlessness, and insomnia (often seen during the initial days of treatment) are to be minimized. If necessary, these effects may be managed by temporary reduction of dose or the short-term administration of an intermediate to long-acting sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment. Insomnia may also be minimized by avoiding bedtime doses. If distressing, unmasked effects supervene, dose escalation should be stopped.

No single dose of bupropion hydrochloride tablet should exceed 150 mg. Bupropion hydrochloride tablet should be administered t.i.d., preferably with at least 6 hours between successive doses.

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

Treatment Day	Dosing Regimen				
	Number of Tablets			Tablet Strength	Total Daily Dose
	Morning	Midday	Evening		
1–3	1	0	1	100 mg	200 mg
4	1	1	1	100 mg	300 mg

Increasing the Dosage Above 300 mg/Day: As with other antidepressants, the full antidepressant effect of bupropion may not be evident within 4 weeks of treatment or longer. An increase in dosage, up to a maximum of 450 mg/day, given in divided doses of not more than 150 mg each, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day. Dosing above 300 mg/day may be accomplished using the 75 or 100 mg tablets. The 100 mg tablet must be administered q.i.d. with at least 4 hours between successive doses in order not to exceed the limit of 150 mg in a single dose. Bupropion hydrochloride tablet should be discontinued in patients who do not demonstrate an adequate response after an appropriate period of treatment at 450 mg/day.

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

Maintenance: The lowest dose that maintains

Increasing the Dosage Above 300 mg/Day: As with other antidepressants, the full antidepressant effect of bupropion may not be evident until 4 weeks of treatment or longer. An increase in dosage, up to a maximum of 450 mg/day, given in divided doses of not more than 150 mg each, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day. Dosing above 300 mg/day may be accomplished using the 75 or 100 mg tablets. The 100 mg tablet must be administered q.i.d. with at least 4 hours between successive doses, in order not to exceed the limit of 150 mg in a single dose. Bupropion hydrochloride tablet should be discontinued in patients who do not demonstrate an adequate response after an appropriate period of treatment at 450 mg/day.

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

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

HOW SUPPLIED

Bupropion hydrochloride tablets 75 mg are lavender, round, film-coated tablets engraved WV over 361 on one side and plain on opposite side, and are supplied as follows:

NDC 52189-361-24 in bottles of 100 tablets
NDC 52189-361-30 in bottles of 1000 tablets

Bupropion hydrochloride tablets 100 mg are lavender, round, film-coated tablets engraved WV over 362 on one side and plain on opposite side, and are supplied as follows:

NDC 52189-362-24 in bottles of 100 tablets
NDC 52189-362-30 in bottles of 1000 tablets

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

Dispense in a tight, light-resistant container as defined in the USP.

ZYBAN™ is a registered trademark of Glaxo Wellcome.

Manufactured by:
INVAMED INC
2400 Route 130
Dayton, NJ 08810, USA

Date of Revision: August 1999
L-1498, MF# 1498-02

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-584

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMISTRY REVIEW NO.#** 3

2. **ANDA #** 75-584

3. **NAME AND ADDRESS OF APPLICANT:**
Invamed Inc.
Attention: Mahendra Patel, Ph.D.
2400 Route 130
Dayton, NJ 08810

4. **LEGAL BASIS FOR SUBMISSION:**
Reference listed drug:
Wellbutrin Tablets, 75 mg & 100 mg
NDA No: N18644 002 and 003 (Dec 30, 1985)

Manufacturer: Glaxo Wellcome

The firm certifies that, in its opinion and to the best of its knowledge, there are no patents that claim the listed drug product and there are no exclusivity provisions.

5. **SUPPLEMENT(s):** N/A

6. **PROPRIETARY NAME:** N/A

7. **NONPROPRIETARY NAME:** Bupropion Hydrochloride

8. **SUPPLEMENT(s) PROVIDE(s) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

02-16-1999	Original submission
02-26-1999	Telecon and new correspondence (Patent Certification)
03-16-1999	ANDA Acceptance letter
08-16-1999	Deficiency letter - Major Amendment
09-01-1999	Response to Deficiency letter dated 8/16/99
12-07-1999	Deficiency letter - Facsimile
12-29-1999	Response to Deficiency letter dated 12/07/99

10. **PHARMACOLOGICAL CATEGORY:** Anti-depressant

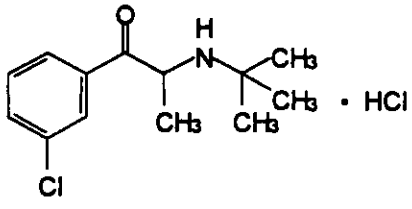
11. **Rx or OTC:** Rx

12. **RELATED IND/NDA/DMF(s):**

13. **DOSAGE FORM**: Tablets

14. **POTENCY**: 75 mg and 100 mg

15. **CHEMICAL NAME AND STRUCTURE**:
Bupropion Hydrochloride. 1-Propanone, 1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-, hydrochloride (±)-.$C_{18}H_{18}ClNO \cdot HCl$. 276.21. 31677-93-7. Antidepressant.



16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS**: N/A

18. **CONCLUSIONS AND RECOMMENDATIONS**: The application is Approvable.

19. **REVIEWER:** Neeru B. Takiar
Endorsed by D. Gill, Ph.D.

DATE COMPLETED: 12/29/99

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Commercial/Confidential

Information and are not

releasable.

12/29/99.

Chemistry Review #3

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12/7/94

Chemistry Comments

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5/16/99

Chemistry Comment

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releasable.

Chemistry Comments

12/7/99

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-584

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY COMMENTS

ANDA: 75-584 APPLICANT: Invamed, Inc.

DRUG PRODUCT: Bupropion HCl Tablets, 100 mg and 75 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of water at 37°C using USP Apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 75-584 **SPONSOR:** Invamed, Inc.

DRUG & DOSAGE FORM: Bupropion HCl Tablets

STRENGTH: 75 mg and 100 mg

TYPE OF STUDY: **Fasting Bioequivalence Study and Dissolution**

STUDY SITES:
CLINICAL:

ANALYTICAL:

STUDY SUMMARY:
Acceptable (See Review)

DISSOLUTION :
Acceptable (See Review)

PRIMARY REVIEWER: James E. Chaney, Ph.D. **BRANCH:** I
INITIAL: /S/ **DATE:** 4/15/99

BRANCH CHIEF: Yih Chain Huang, Ph.D. **BRANCH:** I
INITIAL: /S/ **DATE:** 4/15/99

DIRECTOR
DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.
INITIAL: /S/ **DATE:** 4/30/99

DIRECTOR, OFFICE OF GENERIC DRUGS:
INITIAL: _____ **DATE:** _____

Bupropion HCl Tablets	Invamed, Inc.
75 mg and 100 mg	Dayton, NJ
ANDA #75-584	Submission Date:
Reviewer: James Chaney	February 16, 1999
	April 12, 1999

V:\FIRMSAM\INVAMED\LTRS&REV\75584sdw.299

REVIEW OF SINGLE DOSE BIOEQUIVALENCE STUDY, UNDER FASTING FASTING CONDITIONS, *IN VITRO* DISSOLUTION TESTING DATA AND A WAIVER REQUEST

I. OBJECTIVE:

The objective of this study is to compare the relative bioavailability of 100 mg bupropion HCl tablets (Invamed) with that of WELLBUTRIN 100 mg tablets (Glaxo-Wellcome) in healthy adult male subjects under fasting conditions.

II. BACKGROUND:

Indication: Depression.

Metabolites:

Bupropion undergoes extensive metabolism. Several of the known metabolites are pharmacologically active and have long elimination half-lives. Four basic metabolites have been identified: erythro- and threo-amino alcohols of bupropion, the erythro-amino diol of bupropion, and hydroxybupropion.

Half Life:

The average half-life bupropion is about 14 hours.

Absorption:

Following oral administration, peak plasma bupropion concentrations are achieved within 2 hours. Plasma bupropion concentrations are dose-proportional following single doses of 100 to 250 mg.

III. STUDY FACILITIES

Clinical Facility:

Analytical Facility:

IV. STUDY DATES

Period I ran from October 2-8, 1998, and period II from October 23-29, 1998. The study samples were analyzed between December 04, 1998 to January 17, 1999. (The maximum storage time was 107 days.)

V. STUDY DESIGN

Open-label, randomized, single-dose 2-way crossover bioequivalence study.

VI. TREATMENTS

Treatment A: 1 X 100 mg of Invamed's Bupropion HCl Tablets, Lot # D980805, Batch size tablets, Content Uniformity, 100.1% (0.8%CV, 99.0-101.2%); Assay, 100.6%; manufacturing date: August 98

Treatment B: 1 X 100 mg of Glaxo Wellcome's WELLBUTRIN 100 mg tablets, Lot # 23923, Content Uniformity, 100.8% (1.5%CV, 99.1-103.2%); Assay, 100.3%; expiration date: 11/99.

VII. STUDY SCHEDULES:

Blood samples, (2 x 7 mL each) were obtained by direct venipuncture using pre-coded Vacutainers that contained EDTA according to the following schedule: 0, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 14.0 24.0, 36.0, 48.0, 60.0, 96, and 120 hours post-drug administration. The blood samples were collected, cooled in ice baths and centrifuged under refrigeration within 15 minutes after collection. After mixing, the plasma was stored frozen at -20°±5°C until assay.

VIII. ANALYTICAL

PRESTUDY VALIDATION

The analytical method employed detection and as the internal standard (IS).

Table 1. Pre-Study Assay Validation For Bupropion		
Parameter	**Q. C. Samples**	**Standard Curve Samples**
QC or Std. Curve Conc. (ng/mL)	2.00, 15.0 and 150	1.00, 2.00, 5.00, 10.0, 20.0, 50.0, 125 and 250
Intra-day Precision (%CV)	2.3 to 12.1	
Intra-day Accuracy (%)	98.0 to 109	
Inter-day Precision (%CV)	5.3-9.0	1.4-7.3
Inter-day Accuracy (%)	100-104	98.2-102
Mean % Recovery	Analyte, 86.7; IS, 101	
Linearity	Correlation Coefficient ≥ 0.999190	
Linear Range	1.00 to 250 ng/mL	
Sensitivity/LOQ	1.00 ng/mL	
Stability in Plasma a) Hr @ Room Temp. b) Freeze-Thaw c) Long-Term Frozen	a) Stable at room temperature 4 hours. b) Stable after 3 cycles at -20°C c) 109 days	
d) Reconstituted Stability	d) Reconstituted Extracts are stable 72 hours at room temperature.	
Specificity	No significant interference at the retention time of bupropion, or internal standard,	

Table 2. Pre-Study Assay Validation For Hydroxybupropion		
Parameter	**Q. C. Samples**	**Standard Curve Samples**
QC or Std. Curve Conc. (ng/mL)	4.00, 30.0 and 300	2.00, 4.00, 10.0, 20.0, 40.0, 100, 250 and 500
Intra-day Precision (%CV)	1.5 to 3.5	
Intra-day Accuracy (%)	98.7 to 104	
Inter-day Precision (%CV)	2.6-3.2	1.0-6.2
Inter-day Accuracy (%)	100-104	95.7-110
Mean % Recovery	Analyte, 85.6; IS, 101	
Linearity	Correlation Coefficient ≥ 0.999644	
Linear Range	2.00 to 500 ng/mL	
Sensitivity/LOQ	2.00 ng/mL	
Stability in Plasma a) Hr @ Room Temp. b) Freeze-Thaw c) Long-Term Frozen	a) Stable at room temperature for 4 hours. b) Stable after 3 cycles at -20°C c) 109 days	
d) Reconstituted Stability	d) Reconstituted Extracts are stable 72 hours at room temperature.	
Specificity	No significant interference at the retention time of hyroxybupropion, or internal standard.	

Table 3. Pre-Study Assay Validation - Threo/erythroamino-alcohol Bupropion		
Parameter	**Q. C. Samples**	**Standard Curve Samples**
QC or Std. Curve Conc. (ng/mL)	2.00, 15.0 and 150	1.00, 2.00, 5.00, 10.0, 20.0, 50.0, 125 and 250
Intra-day Precision (%CV)	1.5 to 11.0	
Intra-day Accuracy (%)	101 to 111	
Inter-day Precision (%CV)	2.2-8.4	0.7-7.7
Inter-day Accuracy (%)	102-109	96.0-103
Mean % Recovery	Analyte, 90.1; IS, 101	
Linearity	Correlation Coefficient ≥ 0.99977	
Linear Range	1.00 to 250 ng/mL	
Sensitivity/LOQ	1.00 ng/mL	
Stability in Plasma a) Hr @ Room Temp. b) Freeze-Thaw c) Long-Term Frozen	a) Stable at room temperature for 4 hours. b) Stable after 3 cycles at -20°C c) 109 days	
Reconstituted Stability	Reconstituted Extracts are stable 72 hours at room temperature.	
Specificity	No significant interference at the retention time of threo/erythroamino-alcohol bupropion or internal standard.	

DURING STUDY ANALYTICAL

Table 4. During Study Analytical For Bupropion		
Parameter	**Q.C. Samples**	**Std. Curve Samples**
QC or Std. Curve Conc. (ng/mL)	Same as for pre-study validation	Same as for pre-study validation
Interday Precision (%CV)	7.4	8.3
Interday Accuracy %	99.0-103	97.1-102
Linearity	Correlation Coefficient ≥ 0.998180	
Sensitivity/LOQ (ng/mL)	1.00	

Table 5. During Study Analytical For Hydroxybupropion		
Parameter	**Q.C. Samples**	**Std. Curve Samples**
QC or Std. Curve Conc. (ng/mL)	Same as for pre-study validation	Same as for pre-study validation
Interday Precision (%CV)	6.2	7.6
Interday Accuracy %	98.7-101	97.5-104
Linearity	Correlation Coefficient ≥ 0.999133	
Sensitivity/LOQ (ng/mL)	2.00	

Table 6. During Study Analytical For Threo/Erythroamino-Alcohol Bupropion		
Parameter	**Q.C. Samples**	**Std. Curve Samples**
QC or Std. Curve Conc. (ng/mL)	Same as for pre-study validation	Same as for pre-study validation
Interday Precision (%CV)	9.4	9.3
Interday Accuracy %	97,3-101	96.6-103
Linearity	Correlation Coefficient ≥ 0.998365	
Sensitivity/LOQ (ng/mL)	1.00	

The specificity of the assay was documented during sample analysis by assaying predose samples. No significant

interference was observed at the retention time of either of the three analytes or the internal standard.

Chromatograms and associated data sheets from 20% of the subjects, representative of the chromatograms in the study, were submitted.

IX. STATISTICAL ANALYSIS:

ANOVA was performed on each of the pharmacokinetic parameters using SAS® software. The ANOVA model contained factors for sequence, subjects within sequence, periods and products.

X. CLINICAL NOTES:

The study protocol was approved by the Ethics Review Board,

All subjects selected for the study met the inclusion and exclusion criteria described in the study protocol (Appendix 1 of the report) and signed a Written Informed Consent Form. All subjects underwent pre-study examinations that included a physical examination, and laboratory tests.

Thirty (36) healthy male subjects between the ages of 18 to 45 were dosed and 28 subjects completed the clinical portion of the study. Subject #4 withdrew from the study due to difficulty in obtaining blood samples. Subjects #7, #9, #18, #29 and #33 withdrew from the study due to personal reasons. Subject #3 was dismissed from the study prior to dosing due to a positive drug screen. Subject #35 failed to report to the clinic for Period II. The plasma samples from 28 subjects were assayed for bupropion and the metabolites.

The subjects were monitored throughout the confinement portion of the study. Only one adverse event was observed - mild nausea which was possibly drug related.

XI. RESULTS OF FASTING BIOEQUIVALENCE STUDY:

The mean plasma concentrations of bupropion at each time point for each product and the arithmetic means of the pharmacokinetic parameters are shown in Table 7. A linear plot of the mean plasma concentration for bupropion as a function of time is shown in Figure 1. The two curves are very similar.

Table 7. Mean Plasma Bupropion Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 100 mg (1x100 mg Tablet) Bupropion HCl Under Fasting Conditions (N=28)

Mean Plasma Levels (ng/mL)

TIME (HRS)	TEST		REFERENCE		T/R
	MEAN	%CV	MEAN	%CV	
0	0	--	0	--	.
0.5	12.38	134	4.77	214	2.60
0.75	55.51	70	31.74	116	1.75
1	83.55	42	67.95	69	1.23
1.5	95.31	30	99.48	42	0.96
2	89.21	33	94.18	35	0.95
2.5	72.73	27	82.21	27	0.88
3	63.89	28	72.25	28	0.88
4	45.47	28	51.96	28	0.88
5	32.39	35	35.37	30	0.92
6	23.48	34	25.58	30	0.92
8	13.99	33	15.55	32	0.90
10	9.12	35	10.07	34	0.91
14	5.64	34	6.20	34	0.91
24	2.56	30	2.74	32	0.94
36	0.98	91	1.14	77	0.86
48	0.39	162	0.42	157	0.91
60	0.13	285	0.13	285	0.98
72	0.04	525	0	--	.
96	0	--	0	--	.
120	0	--	0	--	.

Pharmacokinetic Parameters

PARAMETER	TEST		REFERENCE		T/R
	MEAN	%CV	MEAN	%CV	
AUCI	495.18	29	523.04	29	0.95
AUCT	471.82	29	498.89	29	0.95
CMAX	103.19	32	109.82	35	0.94
THALF	11.32	46	11.50	45	0.98
TMAX	1.54	37	1.77	26	0.87

Units: AUC, ng*hr/mL; CMAX, ng/mL; TMAX, hr

The comparison of LSmeans, geometric LSmeans and 90% confidence intervals for the pharmacokinetic parameters of bupropion are shown in Table 8.

Table 8. LSMeans, Geometric LSMeans, T/R Ratios, 90% Confidence Intervals (C.I.) and Intrasubject Variability (%CV) For Bupropion Pharmacokinetic Parameters in a Fasting Single-Dose Study

PARAMETER	TEST LSMEANS	REF LSMEANS	T/R	90% C.I.	%CV
AUCI	497.65	523.13	0.95	---	---
AUCT	474.13	498.96	0.95	---	---
CMAX	103.81	109.76	0.95	---	---
LAUCI**	479.35	500.86	0.96	90.52-101.19	---
LAUCT**	455.75	476.75	0.96	90.39-101.1	12.2
LCMAX**	99.35	103.55	0.96	89.45-102.91	15.3

Units: AUC, ng*hr/mL; CMAX, ng/mL. **Geometric Means

A summary of individual test/reference ratios of the pharmacokinetic parameters AUCL, AUCI, and Cmax, and individual AUCL/AUCI ratios for bupropion are shown in Table 9.

Table 9. Statistics on Individual Bupropion Test/Reference Ratios and Individual AUCT/AUCI Ratios in Fasting Study

PARAMETER	N	MEAN	S.D.	MINIMUM	MAXIMUM
AUCT T/R	28	0.97	0.17	0.58	1.26
AUCI T/R	28	0.97	0.17	0.57	1.29
CMAX T/R	28	0.98	0.22	0.57	1.41
AUCT/AUCI TEST	28	0.95	0.02	0.91	0.97
AUCT/AUCI REF	28	0.95	0.02	0.92	0.98

The mean plasma concentrations of hydroxybupropion at each time point for each product and the arithmetic means of the pharmacokinetic parameters are shown in Table 10. A linear plot of the mean plasma concentration for hydroxybupropion as a function of time is shown in Figure 2. The two curves are very similar.

Table 10. Mean Plasma Hydroxybupropion Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 100 mg (1x100 mg Tablet) Bupropion HCl Under Fasting Conditions (N=28)

Mean Plasma Levels (ng/mL)

TIME (HRS)	TEST		REFERENCE		T/R
	MEAN	%CV	MEAN	%CV	
0	0	--	0	--	.
0.5	33.19	109	11.88	130	2.79
0.75	90.68	69	52.27	76	1.73
1	128.43	51	98.90	56	1.30
1.5	170.25	42	154.59	48	1.10
2	189.44	40	178.46	43	1.06
2.5	191.30	38	185.51	42	1.03
3	202.11	39	196.55	41	1.03
4	200.96	37	197.40	38	1.02
5	193.14	38	190.06	40	1.02
6	185.93	43	179.95	34	1.03
8	166.65	39	168.89	37	0.99
10	155.86	38	158.92	36	0.98
14	143.54	36	146.15	40	0.98
24	109.20	38	111.60	41	0.98
36	69.02	47	69.04	46	1.00
48	46.06	50	48.63	49	0.95
60	30.41	58	31.13	57	0.98
72	21.13	70	22.83	70	0.93
96	9.58	79	10.90	80	0.88
120	5.04	103	5.80	97	0.87

Pharmacokinetic Parameters

PARAMETER	TEST		REFERENCE		T/R
	MEAN	%CV	MEAN	%CV	
AUCI	6798.88	42	6937.5	43	0.98
AUCT	6603.04	42	6706.46	42	0.98
CMAX	211.08	38	206.02	38	1.02
THALF	20.84	20	21.94	22	0.95
TMAX	3.55	29	4	34	0.89

Units: AUC, ng*hr/mL; CMAX, ng/mL; TMAX, hr

The comparison of LSmeans, geometric LSmeans and 90% confidence intervals for the pharmacokinetic parameters of hydroxybupropion are shown in Table 11.

Table 13. Mean Plasma Threo/erythroamino-alcohol Bupropion Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 100 mg (1x100 mg Tablet) Bupropion HCl Under Fasting Conditions (N=28)

Mean Plasma Levels (ng/mL)					
TIME (HRS)	TEST		REFERENCE		T/R
	MEAN	%CV	MEAN	%CV	
0	0	--	0	--	.
0.5	1.81	145	0.56	286	3.22
0.75	16.40	93	6.93	145	2.37
1	35.78	63	22.44	94	1.59
1.5	62.06	38	57.27	58	1.08
2	78.33	32	74.47	46	1.05
2.5	80.95	30	80.18	37	1.01
3	85.65	30	86.46	35	0.99
4	83.91	31	86.31	35	0.97
5	82.55	38	84.26	35	0.98
6	77.58	36	78.60	35	0.99
8	69.10	36	73.10	38	0.95
10	61.87	39	65.73	41	0.94
14	55.40	39	58.27	40	0.95
24	40.26	42	41.51	38	0.97
36	29.29	34	30.49	45	0.96
48	23.11	38	24.16	35	0.96
60	18.76	38	19.94	47	0.94
72	15.28	40	16.9	37	0.90
96	10.78	45	12.21	39	0.88
120	8.05	52	8.93	44	0.90

Pharmacokinetic Parameters					
PARAMETER	TEST		REFERENCE		T/R
	MEAN	%CV	MEAN	%CV	
AUCI	3731.75	38	3975.96	36	0.94
AUCT	3117.32	35	3278.93	36	0.95
CMAX	91.96	33	93.36	34	0.98
THALF	48.01	30	51.24	28	0.94
TMAX	3.43	35	3.70	45	0.93

Units: AUC, ng*hr/mL; CMAX, ng/mL; TMAX, hr

The comparison of LSmeans, geometric LSmeans and 90% confidence intervals for the pharmacokinetic parameters of Threo/erythroamino-alcohol Bupropion are shown in Table 14.

Table 14. LSMeans, Geometric LSMeans, T/R Ratios, 90% Confidence Intervals (C.I.) and Intrasubject Variability (%CV) For Threo/erythroamino-alcohol Bupropion Pharmacokinetic Parameters in a Fasting Single-Dose Study					
PARAMETER	**TEST LSMEANS**	**REF LSMEANS**	**T/R**	**90% C.I.**	**%CV**
AUCI	3756.25	3996.44	0.94	---	---
AUCT	3139.32	3290.92	0.95	---	---
CMAX	92.44	93.36	0.99	---	---
LAUCI**	3524.10	3741.22	0.94	88.0-100.8	---
LAUCT**	2979.37	3091.64	0.96	91.5-101.5	11.3
LCMAX**	87.56	87.45	1.00	94.6-105.9	12.3

Units: AUC, ng*hr/mL; CMAX, ng/mL. **Geometric Means

A summary of individual test/reference ratios of the pharmacokinetic parameters AUCL, AUCI, and Cmax, and individual AUCL/AUCI ratios for of threo/erythroamino-alcohol bupropion are shown in Table 15.

Table 15. Statistics on Individual Test/Reference Ratios and Individual AUCT/AUCI Ratios in Fasting Study					
PARAMETER	N	MEAN	S.D.	MINIMUM	MAXIMUM
AUCT T/R	28	0.97	0.17	0.75	1.42
AUCI T/R	28	0.96	0.21	0.66	1.46
CMAX T/R	28	1.01	0.19	0.66	1.46
AUCT/AUCI TEST	28	0.85	0.07	0.63	0.97
AUCT/AUCI REF	28	0.83	0.07	0.70	0.97

XII. DISSOLUTION

The reported methodology and results from the original submission (2/99) and the 4/12/99 amendment are shown in Table 16.

Table 16. In Vitro Dissolution Testing

Drug (Generic Name): Bupropion HCl Tablets
Dose Strength: 100 mg and 75 mg
ANDA No.: 75-584
Firm: Invamed
Submission Date: February 16, 1999
File Name: 75584SDW.299

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 900 mL 0.01 N HCl
Specifications:
Reference Drug: Wellbutrin^{R}
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Times	Test, Lot D980805, 100 mg			Reference, Lot # 7I1736		
	Mean %	Range	%CV	Mean %	Range	%CV
15 min	90.5		8	85.9		11
30 min	93.9		6	97.4		4
45 min	96.1		4	98.7		3
60 min	97.6		3	99.3	94.[illegible]	3
	Test, D981006, 75 mg			Reference, Lot 7I1771, 75 mg		
15 min	95.5		6	77.7		11
30 min	98.0		4	92.6		6
45 min	99.7		3	97.0		22
60 min	100.3	[illegible]	3	97.9		2

Amended Dissolution Testing Submitted April 9, 1999 Using Water As Solvent (See Reviewer Comment # 12)

Times	Test, Lot D980805, 100 mg			Reference, Lot 7I1736, 100 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
15 min	89.9		4	88.1		9
30 min	93.2		3	97.6		4
45 min	95.4		2	99.7		3
60 min	96.6	94.	1	100.6		2
	Test, D981006, 75 mg			Reference, Lot 7I1771, 75 mg		
15 min	91.7		6	85.6		10
30 min	94.7		4	93.8		5
45 min	96.6		3	96.7		3
60 min	97.8		2	98.0		2

XIII. PRODUCT FORMULATION

Table 17. Composition of Bupropion Hydrochloride Tablets

COMPONENT	75 mg Strength (mg)	100 mg Strength (mg)	Percent per Unit

see package insert

XV. COMMENTS

1. The dissolution testing should be conducted in 900 mL of water at 37°C using USP Apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

The firm conducted the dissolution testing in 900 mL of 0.01N HCl at 37°C using USP Apparatus II (paddle) at 50 rpm. The firm's specifications were that not less than

On 4/6/99 the firm was requested by telephone to submit its dissolution data obtained from using the appropriate

solvent. This data was faxed and received on April 12, 1999. This dissolution testing by the firm on its Bupropion HCl Tablets, 100 mg and 75 mg, lot numbers D980805 and D981006, respectively, is acceptable (Table 16).

The Simiarity Factors (f_2) were calculated by the reviewer on the amended data and the following results were obtained: 84.3 for 100 mg test vs 75 mg test; 68.3 for 100 mg test vs 100 mg reference; and 74.7 for 75 mg test vs 75 mg reference.

2. The firm's single-dose bioequivalence study under fasting conditions, conducted on its 100 mg bupropion hydrochloride tablet is acceptable.

3. The formulation for Bupropion HCl 75 mg tablet is proportionally similar to the 100 mg strength of the test product.

4. The calculations on the pharmacokinetic parameters and statistical analysis for the fasting study were spot-checked by the reviewer using SAS and the results were in agreement with what the firm reported.

5. The assayed potency and the content uniformity of the test and reference products are satisfactory.

6. The analytical data is acceptable.

7. The test product used for the biostudies and dissolution studies were from the same batch.

XV1. RECOMMENDATIONS

1. The bioequivalence study under fasting conditions conducted by Invamed, Inc. on its Bupropion HCl, 100 mg Tablet, lot D980805, comparing it to Glaxo Wellcome's Wellbutrin® 100 mg Tablet has been found acceptable by the Division of Bioequivalence. The study demonstrates that Invamed's Bupropion HCl Tablet, 100 mg, is bioequivalent to the reference product, Wellbutrin®, 100 mg Tablet, manufactured by Glaxo Wellcome.

2. The dissolution testing used by the firm on its Bupropion HCl Tablets, 100 mg and 75 mg, lot numbers D980805 and D981006, respectively, is acceptable. The formulation for the 75 mg is proportionally similar to the 100 mg strength of the test product which underwent acceptable bioequivalence testing. Waiver of *in vivo* bioequivalence study requirements for the 75 mg tablets of the test products may be granted. The Division of Bioequivalence deems Bupropion HCl 75 mg Tablets manufactured by Invamed, Inc. to be bioequivalent to Wellbutrin[R] Tablets, 75 mg manufactured by Glaxo Wellcome.
3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

4. From the bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing and the application is acceptable.

The firm should be informed of the above recommendations.

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

/S/

RD INITIALED YCHuang
FT INITIALED YCHuang

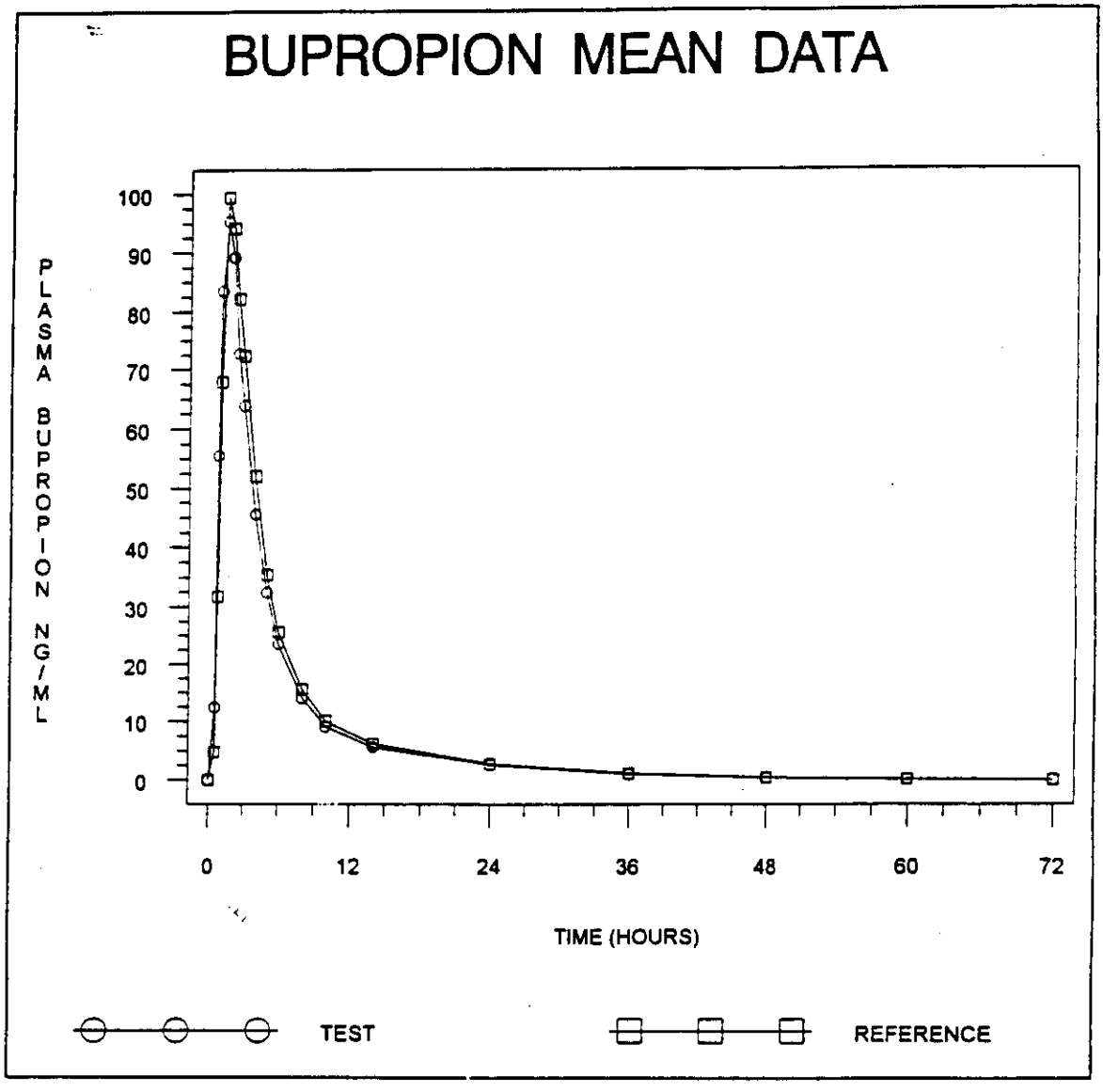
Date 4/15/99

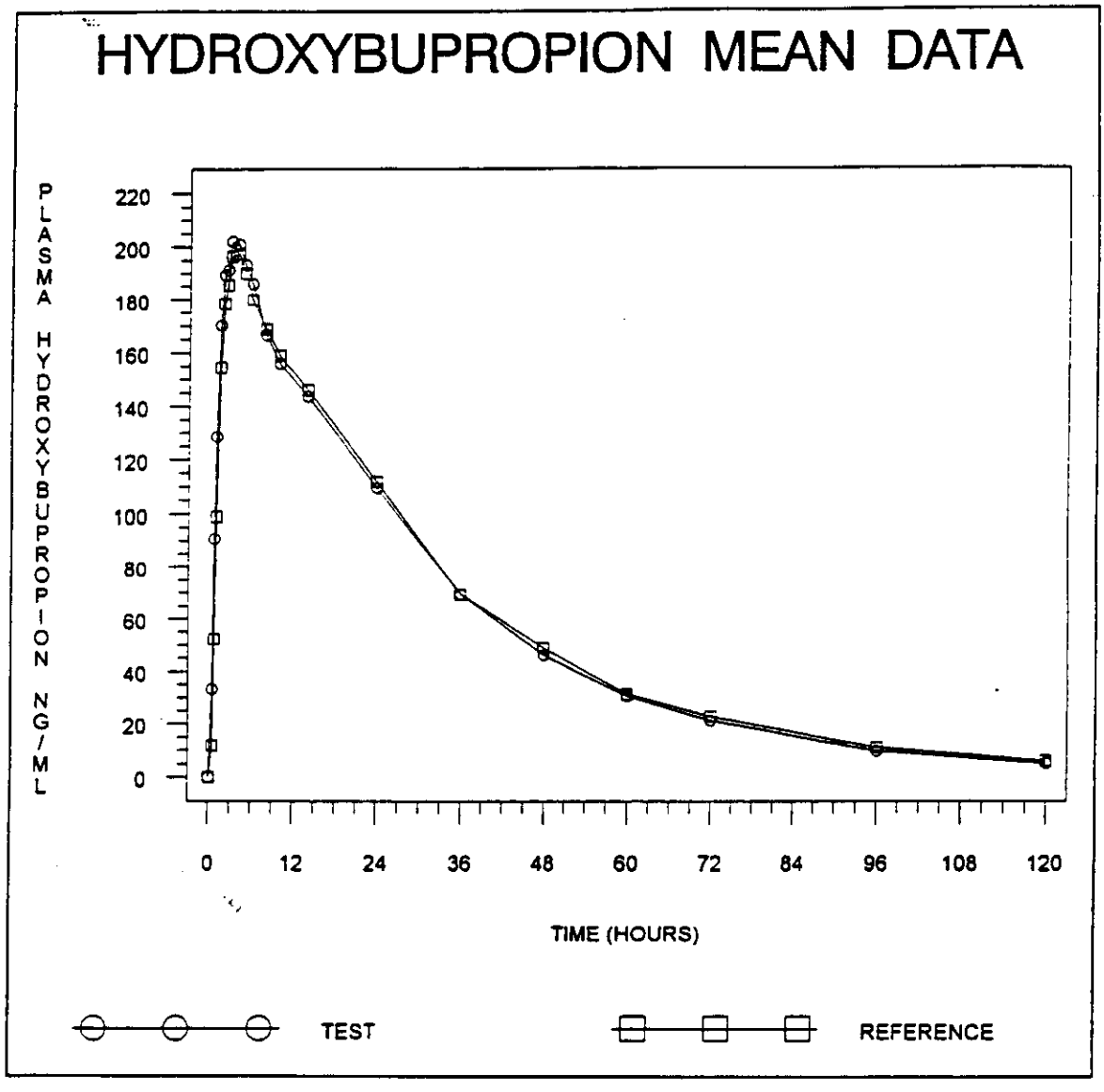
Concur /S/

Date 4/30/99

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

BUPROPION HC1 100 MG TABLET FASTING STUDY
INVAMED B-09018

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PLASMA HYDROXYBUPROPION NG/ML
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180
160
140
120
100
80
60
40
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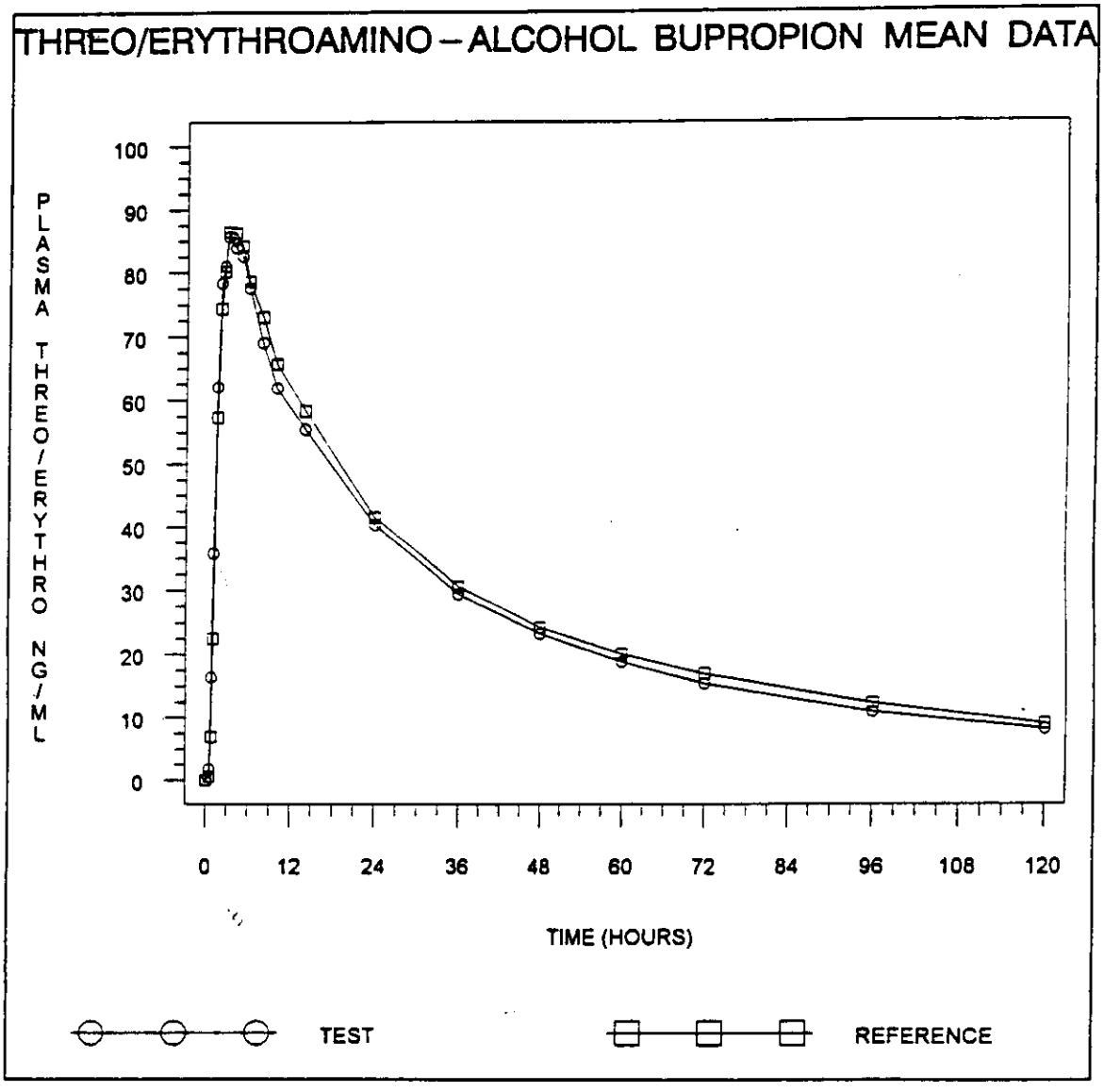
0
0
12
24
36
48
60
72
84
96
108
120
TIME (HOURS)
TEST
REFERENCE


THREO/ERYTHROAMINO – ALCOHOL BUPROPION MEAN DATA
PLASMA THREO/ERYTHRO NG/ML
100
90
80
70
60
50
40
30
20
10
0
0
12
24
36
48
60
72
84
96
108
120
TIME (HOURS)
TEST
REFERENCE

BIOEQUIVALENCY COMMENTS

ANDA: 75-584 APPLICANT: Invamed, Inc.

DRUG PRODUCT: Bupropion HCl Tablets, 100 mg and 75 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of water at 37°C using USP Apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-584

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA: 75-584	CHEMIST: Neeru B. Takiar	DATE: December 29, 1999
DRUG PRODUCT: Bupropion Hydrochloride Tablets		
FIRM: Invamed Inc.		
DOSAGE FORM: Tablets	**STRENGTH:** 75 mg and 100 mg	
cGMP: The facilities were acceptable on 05/21/99.		
BIO: Satisfactory dated 4/30/99.		
VALIDATION - *(Description of dosage form same as firm's):* The DS and DP are not covered by monographs in the USP. Test data submitted by the firm is satisfactory and meet all the specifications. Method Validation from the FDA District Laboratory has been requested. *Pending Results.*		
STABILITY: The containers in the stability studies are identical to those in the container section. The firm has provided satisfactory accelerated stability data for 3 months and room temperature stability data for 3 months so far to support an expiration period of 24 months.		
LABELING: Labeling was acceptable on 9/20/99.		
STERILIZATION VALIDATION *(If applicable)*: N/A		
SIZE OF BIO BATCH *(Firm's source of NDS ok?)*:		
SIZE OF STABILITY BATCHES *(If different from bio batch, were they Manufactured via the same process?)*: 100 mg).		
PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME?: The proposed production batch size is 1,000,000 tablets for both strengths (75 mg and 100 mg). The manufacturing process is identical to the exhibit batch.		
Signature of chemist: /S/ 1/10/00 Neeru B. Takiar	**Signature of supervisor:** DSG 1/11/2000 Dave Gill, Ph.D.	

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-584

CORRESPONDENCE

invamed inc.
732-274-2400 Fax: 732-274-8989
2400 Rt. 130 North, Dayton, New Jersey 08810

September 1, 1999

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

MAJOR AMENDMENT

Labeling review
drafted 9/17/99
AVegga

Re: **BUPROPION HYDROCHLORIDE TABLETS, 75 mg and 100 mg**
ANDA # 75-584
MAJOR AMENDMENT

Dear Sirs:

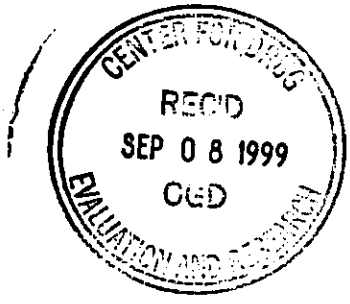
I have herewith enclosed a "*MAJOR AMENDMENT*" document submitted in duplicate for our pending application for **BUPROPION HYDROCHLORIDE TABLETS, 75 mg and 100 mg (ANDA # 75-584)** as required under 21 CFR 314.120.

The firm has submitted an additional copy of this major amendment to the U.S. Food and Drug Administration, New Jersey District Office. We hereby certify that this additional copy (field copy) is a true copy of the Archival and Review copies of the Major Amendment.

Sincerely,

M. R. Patel

Mahendra Patel, Ph.D.
Vice President



ANDA 75-584

Invamed Inc.
Attention: Mahendra Patel, Ph.D.
2400 Rt. 130 North
Dayton, NJ 08810

MAR 16 1999

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated February 26, 1999 and your correspondence dated February 26, 1999.

NAME OF DRUG: Bupropion Hydrochloride Tablets, 75 mg and 100 mg

DATE OF APPLICATION: February 16, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 17, 1999

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 827-5849

Sincerely yours,

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

invamed inc.
732-274-2400 Fax: 732-274-8989
2400 Rt. 130 North, Dayton, New Jersey 08810

February 26, 1999

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP

Re: **BUPROPION HYDROCHLORIDE TABLETS,**
75 mg and 100 mg strengths
ANDA # 75-584
New Information

Dear Sirs:

I have herewith enclosed the ***New Information*** document for our Abbreviated New Drug Application (ANDA # 75-584) for ***BUPROPION HYDROCHLORIDE TABLETS, 75 mg and 100 mg strengths.***

Reference is made here to a telephonic conversation on February 26, 1999, between Mr. Gregory S. Davis, Project Manager, OGD and Dr. Dave of Invamed. As recommended by Mr. Davis, I am herewith submitting following documents (in duplicate):

1. An amended "Patent Certification" (based on the information published in the electronic orange book, a copy attached). Mr. Davis indicated in his telephone call that "FDA has removed patents relevant to the listed drug, WELLBUTRIN TABLETS 75 mg and 100 mg, NDA # 18-644. In light of this fact, there is no need to provide a Paragraph IV Certification and accordingly the firm should submit an amendment to the Patent Certification".

2. An amended copy of Page 3721 and 3737 of the original ANDA submission. This amendment reflects a typographical correction.

The firm has submitted an additional copy of this submission [as required under 314.50 (d) (1)] to the U.S. Food & Drug Administration, New Jersey District Office. We hereby certify that this additional copy (field copy) is a true copy of the New Information document as described in § 314.94 (a) (9) contained in the Archival and Review copies of the abbreviated application.

RECEIVED

MAR 0 1 1999

GENERIC DRUGS

Sincerely,

M. Patel

Mahendra Patel, Ph.D.
Vice President

invamed inc.
732-274-2400 Fax: 732-274-8989
2400 Rt. 130 North, Dayton, New Jersey 08810

February 16, 1999

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

505(j)(2)(A) OK
3/1/99
Gregory S. Davis

Re: **Original ANDA Submission for**
BUPROPION HYDROCHLORIDE TABLETS
75 mg and 100 mg strengths

Dear Sirs:

I have herewith enclosed the original Abbreviated New Drug Application (ANDA) document for ***BUPROPION HYDROCHLORIDE TABLETS, 75 mg and 100 mg strengths.*** The ANDA application contains the following documents:

1.	Archival Copy	8 volumes
2.	Review Copy Chemistry, Manufacturing and Controls	4 volumes
3.	Review Copy Bioavailability/Bioequivalence (Hard copy of Raw Data with a copy of raw data on 3½" disk, attached to the inner cover)	4 volumes

4. Two additional separately bound copies of **Section 15 (Controls for the Finished Dosage Form)** and **Section 16 (Analytical Methods); Page(s) 2645 through 3692** as the drug substance and drug product are not compendial articles.

The firm has submitted an additional copy of the Technical Section [as required under 314.50 (d) (1)] to the U.S. Food & Drug Administration, New Jersey District Office. We hereby certify that this additional copy (field copy) is a true copy of the Technical Section as described in § 314.94 (a) (9) contained in the Archival and Review copies of the abbreviated application.

Sincerely,

M. Patel

Mahendra Patel, Ph.D.
Vice President

RECEIVED
FEB 17 1999
GENERIC DRUGS

invamed inc.
732-274-2400 Fax: 732-274-8989
2400 Rt. 130 North, Dayton, New Jersey 08810

AC

September 1, 1999

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

MAJOR AMENDMENT

Labeling review
drafted 9/17/99
aVegga

Re: **BUPROPION HYDROCHLORIDE TABLETS, 75 mg and 100 mg**
ANDA # 75-584
MAJOR AMENDMENT

Dear Sirs:

I have herewith enclosed a "*MAJOR AMENDMENT*" document submitted in duplicate for our pending application for **BUPROPION HYDROCHLORIDE TABLETS, 75 mg and 100 mg (ANDA # 75-584)** as required under 21 CFR 314.120.

The firm has submitted an additional copy of this major amendment to the U.S. Food and Drug Administration, New Jersey District Office. We hereby certify that this additional copy (field copy) is a true copy of the Archival and Review copies of the Major Amendment.

Sincerely,

M. R. Patel

Mahendra Patel, Ph.D.
Vice President