CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-613

APPROVAL LETTER

ANDA 75-613

OCT 10 2000

Eon Labs Manufacturing, Inc.
Attention: Sadie M. Ciganek
227-15 North Conduit Avenue
Laurelton, NY 11413

Dear Madam:

This is in reference to your abbreviated new drug application dated April 1, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Bupropion Hydrochloride Tablets, 75 and 100 mg.

Reference is also made to your amendments dated September 8, and November 15, 1999; May 19, June 16, August 1 and August 29, 2000.

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 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.

Sincerely yours,

Gary Buehler 10/10/00
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVED DRAFT LABELING

Levodopa: Limited clinical data suggest a higher incidence of adverse experience 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.

Drugs That Lower Seizure Threshold: Concurrent administration of bupropion and agents (e.g., antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) or treatment regimens (e.g., abrupt discontinuation of benzodiazepines) that lower seizure threshold should be undertaken only with extreme caution (see WARNINGS). Low initial dosing and small gradual dose increases should be employed.

Nicotine Transdermal System: (see PRECAUTIONS, Cardiovascular Effects)

Carcinogenesis, Mutagenesis, Impairment of Fertility: Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg/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 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: Like many other drugs, bupropion and its metabolites are secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from 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. The immediate-release formulation of bupropion was studied in 104 pediatric patients (age range, 6 to 16) in clinical trials of the drug for other indications. Although generally well tolerated, the limited exposure is insufficient to assess the safety of bupropion in pediatric patients.

Geriatric Use: Of the approximately 6000 patients who participated in clinical trials with bupropion sustained-release tablets (depression and smoking cessation studies), 275 were 65 and over and 47 were 75 and over. In addition, several hundred patients 65 and over participated in clinical trials using the immediate-release formulation of bupropion (depression studies). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects; however, another pharmacokinetic study, single and multiple dose, has suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites (see CLINICAL PHARMACOLOGY).

Bupropion hydrochloride and its metabolites are almost completely excreted through the kidney and metabolites are likely to undergo conjugation in the liver prior to urinary excretion. The risk of toxic reaction to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see Use in Patients with Systemic Illness).

ADVERSE REACTIONS: (see also WARNINGS and PRECAUTIONS) Adverse events commonly encountered in patients treated with 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 10% of the 2400 patients and volunteers who participated in clinical trials during the product's initial development. The more common events causing discontinuation include neuropsychiatric disturbances (3.0%), primarily agitation and abnormalities in mental status; gastrointestinal disturbances (2.1 %), primarily nausea and vomiting; neurological disturbances (1.7%), primarily seizures, headaches, and sleep disturbances; and dermatologic problems (1.4%), primarily rashes. It is important to note, however, that many of these events occurred at doses that exceed the recommended daily dose.

Accurate estimates of the incidence of adverse events associated with the use of any drug are difficult to obtain. Estimates are influenced by drug dose, detection technique, setting, physician judgments, etc. Consequently, the table below is presented solely to indicate the relative frequency of adverse events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of bupropion hydrochloride under relatively similar conditions of daily dosage (300 to 600 mg), setting, and duration (3 to 4 weeks). The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors must differ from those which prevailed in the clinical trials. These incidence figures also cannot be compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions.

Finally, it is important to emphasize that the tabulation does not 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 is provided in WARNINGS and PRECAUTIONS.

TREATMENT EMERGENT ADVERSE EXPERIENCE
INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS*
(Percent of Patients Reporting)

Adverse Experience	Bupropion Hydrochloride Patients (n = 323)	Placebo Patients (n =185)
CARDIOVASCULAR		
Cardiac Arrhythmias	5.3	4.3
Dizziness	22.3	16.2
Hypertension	4.3	1.6
Hypotension	2.5	2.2
Palpitations	3.7	2.2
Syncope	1.2	0.5
Tachycardia	10.8	8.6
DERMATOLOGIC		
Pruritus	2.2	0.0
Rash	8.0	6.5
GASTROINTESTINAL		
Anorexia	18.3	18.4
Appetite Increase	3.7	2.2
Constipation	26.0	17.3
Diarrhea	6.8	8.6
Dyspepsia	3.1	2.2
Nausea/Vomiting	22.9	18.9
Weight Gain	13.6	22.7
Weight Loss	23.2	23.2
GENITOURINARY		
Impotence	3.4	3.1
Menstrual Complaints	4.7	1.1
Urinary Frequency	2.5	2.2
Urinary Retention	1.9	2.2
MUSCULOSKELETAL		
Arthritis	3.1	2.7
NEUROLOGICAL		
Akathisia	1.5	1.1
Akinesia/Bradykinesia	8.0	8.6
Cutaneous Temperature Disturbance	1.9	1.6
Dry Mouth	27.6	18.4
Excessive Sweating	22.3	14.6
Headache/Migraine	25.7	22.2
Impaired Sleep Quality	4.0	1.6
Increased Salivary Flow	3.4	3.8
Insomnia	18.6	15.7
Muscle Spasms	1.9	3.2
Pseudoparkinsonism	1.5	1.6
Sedation	19.8	19.5
Sensory Disturbance	4.0	3.2
Tremor	21.1	7.6
NEUROPSYCHIATRIC		
Agitation	31.9	22.2
Anxiety	3.1	1.1
Confusion	8.4	4.9
Decreased Libido	3.1	1.6
Delusions	1.2	1.1
Disturbed Concentration	3.1	3.8
Euphoria	1.2	0.5
Hostility	5.6	3.8
NONSPECIFIC		
Fatigue	5.0	8.6
Fever/Chills	1.2	0.5
RESPIRATORY		
Upper Respiratory Complaints	5.0	11.4
SPECIAL SENSES		
Auditory Disturbance	5.3	3.2
Blurred Vision	14.8	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 WARNINGS and PRECAUTIONS.

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

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

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

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

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

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

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

Musculoskeletal: Rare was musculoskeletal chest pain.

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

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

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

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

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

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

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

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

Cardiovascular: hypertension (in some cases severe; see PRECAUTIONS); orthostatic hypotension; third degree heart block

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

Gastrointestinal: esophagitis; hepatitis; liver damage

Hemic and Lymphatic: ecchymosis; leukocytosis; leukopenia; thrombocytopenia

Musculoskeletal: arthralgia; myalgia; muscle rigidity/fever/rhabdomyolysis; muscle weakness

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:

Human: 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 produced mild amphetamine-like activity as compared to placebo on the Morphine-Benzedrine Subscale of the Addiction Research Center Index (ARCI) and a score intermediate between placebo and amphetamine on the Liking Scale of the ARCI. These scales measure general feelings of euphoria and drug desirability.

Findings in clinical trials, however, are not known to predict the abuse potential of drugs reliably. Nonetheless, evidence from single-dose studies does suggest that the recommended daily dosage of bupropion when administered in divided doses is not likely to be especially reinforcing to amphetamine or stimulant abusers. However, higher doses, which could not be tested because of the risk of seizure, might be modestly attractive to those who abuse stimulant drugs.

Animals: Studies in rodents have shown that bupropion exhibits some pharmacologic actions common to psychostimulants, including increases in locomotor activity and the production of a mild stereotyped behavior and increases in rates of responding in several schedule-controlled behavior paradigms. Drug discrimination studies in rats showed stimulus generalization between bupropion and amphetamine and other psychostimulants. Rhesus monkeys have been shown to self-administer bupropion intravenously.

OVERDOSAGE:

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

Since introduction, overdoses of bupropion tablets up to 17,500 mg have been reported. Seizure was reported in approximately one-third of all cases. Other serious reactions reported with overdoses of bupropion tablets alone included hallucinations, loss of consciousness, and sinus 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 tablets alone have been reported rarely in patients ingesting massive doses of bupropion tablets. Multiple uncontrolled seizures, bradycardia, cardiac failure, and cardiac arrest prior to death were reported in these patients.

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

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

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

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

DOSAGE AND ADMINISTRATION:

General Dosing Considerations: It is particularly important to administer bupropion hydrochloride 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 should be administered three times a day, preferably with at least 6 hours between successive doses.

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

Dosing Regimen

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

Increasing the Dosage Above 300 mg/Day: As with other antidepressants, the full antidepressant effect of bupropion hydrochloride 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 should be discontinued in patients who do not demonstrate an adequate response after an appropriate period of treatment at 450 mg/day.

Maintenance: The lowest dose that maintains remission is recommended. Although it is not known how long the patient should remain on 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 round, biconvex tablets, film-coated orange, imprinted "GX 175" on one side and plain on the other, supplied in bottles of 100.

Bupropion Hydrochloride Tablets, 100 mg are round, biconvex tablets, film-coated red, imprinted "GX 176" on one side and plain on the other, supplied in bottles of 100.

Store at controlled room temperature 15° to 30°C (59° to 86°F). (See USP). Protect from light and moisture.

ZYBAN™ is a registered trademark of GlaxoWellcome.

Manufactured by:
Eon Labs Manufacturing, Inc
Laurelton, NY 11413

Issued 08/00
MR0175ISS08/00
OS7617

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F). (See USP). **Store in a dry place. Keep tightly closed. Protect from light and moisture.**

Dispense contents in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Issued 10/99

NDC 0185-0176-01

Bupropion Hydrochloride Tablets

100 mg

Rx only

100 Tablets

Eon Labs

APPROVED

Each tablet contains:
Bupropion Hydrochloride.....100 mg

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

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

ZYBAN™ is a registered trademark of GlaxoWellcome.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

3 0185-0176-01 4

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F). (See USP). **Store in a dry place. Keep tightly closed. Protect from light and moisture.**

Dispense contents in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Issued 10/99

NDC 0185-0175-01

Bupropion Hydrochloride Tablets

75 mg

Rx only

100 Tablets

Eon Labs

APPROVED

Each tablet contains:
Bupropion Hydrochloride.....75 mg

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

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

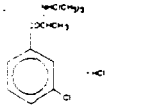
ZYBAN™ is a registered trademark of GlaxoWellcome.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

3 0185-0175-01 7

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 276.2. The molecular formula is $C_{13}H_{18}ClNO \cdot HCl$. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa. The structural formula is:



$C_{13}H_{18}ClNO \cdot HCl$ MW 276.2

Bupropion hydrochloride is supplied for oral administration as 75 mg (orange) and 100 mg (red) film-coated tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients: 75 mg tablet - FD&C Yellow No. 6 Aluminum Lake, Hydroxypropyl Cellulose, Hydroxypropyl Methylcellulose, Microcrystalline Cellulose, Polyethylene Glycol, Talc and Titanium Dioxide; 100 mg tablet - Hydroxypropyl Methylcellulose, Microcrystalline Cellulose, Polyethylene Glycol, Polysorbate 80, Synthetic Red Iron Oxide, Talc and Titanium Dioxide.

CLINICAL PHARMACOLOGY:

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

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

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

Absorption, Distribution, Pharmacokinetics, Metabolism, and Elimination: Oral bioavailability and single-dose pharmacokinetics: In 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 not been fully characterized. However, because of their longer elimination half-lives, the plasma concentrations of at least two of the known metabolites can be expected, especially in chronic use, to be very much higher than the plasma concentration of bupropion. This is of potential clinical importance because factors or conditions altering metabolic capacity (e.g., liver disease, congestive heart failure, age, concomitant medications, etc.) or elimination may be expected to influence the degree and extent of accumulation of these active metabolites.

Furthermore, bupropion has been shown to induce its own metabolism in three animal species (mice, rats, and dogs) following subchronic administration. If induction also occurs in humans, the relative contribution of bupropion and its metabolites to the clinical effects of 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.

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

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

During a chronic dosing study in 14 depressed patients with left ventricular dysfunction, it was found that there was substantial interpatient variability (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 normal versus cirrhotic patients indicated that half-lives of the metabolites were prolonged by cirrhosis and that the metabolites accumulated to levels two to three times those in normals.

The effects of age on the pharmacokinetics of bupropion and its metabolites have not been fully characterized, but an exploration of steady-state bupropion concentrations from several depression efficacy studies involving patients dosed in a range of 300 to 750 mg/day, on a three times daily schedule, revealed no relationship between age (18 to 83 years) and plasma concentration of bupropion. A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects. These data suggest there is no prominent effect of age on bupropion concentration; however, another pharmacokinetic study, single and multiple dose, has suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites (see PRECAUTIONS: Geriatric Use).

In vitro tests show that bupropion is 90% 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 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 four-fold. 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 6 weeks' duration in depressed outpatients. The depressive disorder of the patients studied corresponds most closely to the Major Depression category of the APA Diagnostic and Statistical Manual 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 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use bupropion for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

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

Bupropion is contraindicated in patients treated with ZYBAN™ (bupropion hydrochloride) Sustained Release Tablets, or any other medications that contain bupropion because the incidence of seizure is dose dependent. Bupropion is also contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa because of a higher incidence of seizures noted in such patients treated with bupropion.

The concurrent administration of bupropion 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.

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

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

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

During the initial development, 25 among approximately 2400 patients treated with bupropion hydrochloride experienced seizures. At the time of seizure, seven patients were receiving daily doses at 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 800 and 900 mg (2.5% incidence).

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

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

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

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

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

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

PRECAUTIONS:

General: Agitation and Insomnia: A substantial proportion of patients treated with 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 psychoses 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 28% of patients receiving bupropion. This incidence is approximately double that seen in comparable patients treated with tricyclics or placebo. Furthermore, while 24.5% of patients receiving tricyclic antidepressants gained weight, only 9.4% of patients treated with bupropion did. Consequently, if weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight reducing potential of bupropion should be considered.

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

Allergic Reactions: Anaphylactoid/anaphylactic reactions characterized by symptoms such as pruritus, urticaria, angioedema, and dyspnea requiring medical treatment have been reported in clinical trials with bupropion. In addition, there have been rare spontaneous postmarketing reports of erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated with bupropion. A patient should stop taking bupropion and consult a doctor if experiencing allergic or anaphylactoid/anaphylactic reactions (e.g., skin rash, pruritus, hives, chest pain, edema, and shortness of breath) during treatment.

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

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

Data from a comparative study of the sustained-release formulation of bupropion (ZYBAN™ Sustained-Release Tablets), nicotine transdermal system (NTS), the combination of sustained-release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher incidence of treatment-emergent hypertension in patients treated with the combination of sustained-release bupropion and NTS. In this study, 6.1% of patients treated with the combination of sustained-release bupropion and NTS had treatment-emergent hypertension compared to 2.6%, 1.6%, and 3.1% of patients treated with sustained-release bupropion, NTS, and placebo, respectively.

The majority of these patients had evidence of preexisting hypertension. Three patients (1.2%) treated with the combination of ZYBAN™ and NTS and one patient (0.4%) treated with NTS had study medication discontinued due to hypertension; no patients treated with ZYBAN™ or placebo discontinued. Monitoring of blood pressure is recommended in patients who receive the combination of bupropion and nicotine replacement.

There is no clinical experience establishing the safety of 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 depressed patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants and was also generally well tolerated in a group of 36 depressed inpatients with stable congestive heart failure who received bupropion in a controlled trial. There was a risk in supine blood pressure in the study of patients with CHF, resulting in discontinuation of treatment in two patients for exacerbation of baseline hypertension.

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

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

Physicians are advised to discuss the following issues with patients:

Patients should be instructed to take bupropion 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.

Laboratory Tests: There are no specific laboratory tests recommended.

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

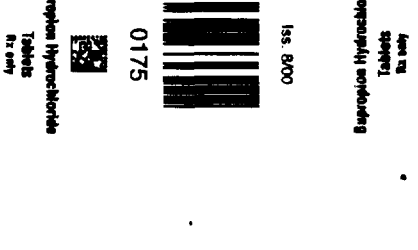
However, animal data suggest that bupropion may be an inducer of drug metabolizing enzymes. This may be of potential clinical importance because the blood levels of coadministered drugs may be altered.

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

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

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

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



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-613

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS

DIVISION OF CHEMISTRY II

ANDA REVIEW

1. CHEMISTRY REVIEW NO.4

2. ANDA #

75-613

3. NAME AND ADDRESS OF APPLICANT

Eon Labs Manufacturing, Inc.
Attention: Sadie M Ciganek
227-15 North Conduit Avenue
Laurelton, NY 11413

4. LEGAL BASIS FOR SUBMISSION

Wellbutrin® Burroughs Wellcome Co. (Glaxo Wellcome), NDA 18-644; Section 505(j) of the Act and 21 CFR 314.94 and 314.95.

Patent No.	Expiration Date:
4,507,323	Jul 25, 2004
4,438,138	Dec 06, 2002
4,435,449	May 14, 2001
4,425,363	May 14, 2001
4,393,078	Mar 15, 2002
4,347,257	Oct 09, 1999

There is no exclusivity for the referenced drug product.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME

Bupropion Hydrochloride Tablets, 75 mg and 100 mg

8. SUPPLEMENT(s) PROVIDE(s) FOR

N/A

9. AMENDMENTS AND OTHER DATES

Firm:

4-1-99: Original submission.
11-15-99: Amendment
5-19-2000: Amendment
8-1-2000: Amendmment

FDA:

4-30-99: Acknowledgement.
10-15-99: 1st NA letter
5-6-2000: 2nd NA letter
7-28-2000: Bio NA letter

10. PHARMACOLOGICAL CATEGORY

Antidepressant

11. R_x or OTC

R_x

12. RELATED IND/NDA/DMF(s)

NDA 18-644 Wellbutrin® (Burroughs Wellcome)

13. DOSAGE FORM

Film-coated Tablets

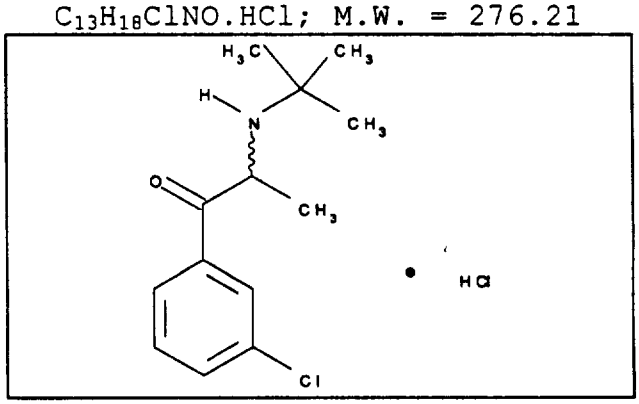
14. POTENCIES

75 mg and 100 mg

15. CHEMICAL NAME AND STRUCTURE

Bupropion Hydrochloride

$C_{13}H_{18}ClNO.HCl$; M.W. = 276.21



(±)-2-(*tert*-Butylamino)-3'-chloropropiophenone hydrochloride.
CAS [31677-93-7]; [34911-55-2] (bupropion)

16. RECORDS AND REPORTS

N/A

17. COMMENTS

Q: The alternate dissolution method, and the comparison between paddles vs baskets and water vs hydrochloride has been sent to our Division of Bioequivalence for evaluation. We will correspond with you when the results become available.

A: OK (see Bio reviewed per J Fan on 9-1-2000 memo).

Status:

a. EER status: Satisfactory

EER was requested for and Eon Laboratories by Tim Ames on April 30, 1999 and found acceptable on June 28, 1999.

b. Method Validation status:

Satisfactory, however, the dissolution test was done using the method in the applications instead of the method suggested by the FDA Division of Bioequivalence.

Not compendial.

Method validation for samples of the active ingredient and finished product were sent to Northeast Regional Laboratory on October 8, 1999 and found acceptable on January 19, 2000.

c. Bio-review status: Satisfactory,

Satisfactory per P. Nwakama & J. Fan (see Emmail) reviewed on 9-1-2000.

d. Labeling review status: Satisfactory

Satisfactory per A. Vezza reviewed on 9-7-2000.

e. DMF Satisfactory

Satisfactory per L. Tang reviewed on 9-28-2000.

18. CONCLUSIONS AND RECOMMENDATIONS

This application is approval

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 9-8-2000

Page(s) 18

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

Chem Rev 4
9/8/2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-613

BIOEQUIVALENCE

Bupropion HCl Tablets
75 and 100 mg
ANDA #: 75613
Reviewer: Patrick Nwakama
File Name: 75-613A.800

EON LABS Manufacturing, Inc.
Laurelton, NY 11413
Submission Date:
~~May 19, 2000 (Amendment)~~
August 1, 2000 (Amendment)

Review Of A Study Amendment

History of Submissions

April 1, 1999 - EON Laboratories submitted original ANDA (75-613) on its Bupropion HCl Tablets, 75mg and 100 mg.

August 16, 1999- The Division of Bioequivalence (DBE) sent a deficiency letter to the firm which included a request to the firm to use the interim FDA dissolution method in lieu of the firm's own method.

September 8, 1999-As an Amendment, the firm responded to the deficiency letter. The firm submitted a new set of dissolution data based on the recommended interim FDA method [900mL Water, Paddle, 50 rpm, (Q) in 45 minutes] which DBE found acceptable. However, in responding to the dissolution deficiency, the firm still insisted on maintaining their original method. In DBE's tentative approval letter on ANDA #75-613, the firm was informed that its own dissolution method could be use for inhouse quality controls while the interim FDA method should remain the official method.

May 8, 2000- In the Division of Chemistry's deficiency letter, EON Labs was requested to conduct dissolution testing based on the method recommended by DBE to meet dissolution specifications at release and stability for its Bupropion HCl Tablets, 75 mg and 100 mg.

May 18, 2000- At the request of the firm, a teleconference call was held between EON Labs and DBE's representatives (Tran, Nwakama and Nguyen). The firm still insisted on keeping their current dissolution method and specification as filed in the original ANDA (submitted 4/1/99) because of the problem of sticking and heap formation of the tablets to the dissolution vessel when Water and Paddle are used as the dissolution medium and apparatus, respectively. According to the firm, its current and preferred dissolution method was obtained from the summary basis of approval (SOA) of the original NDA for Wellbutrin^{R}, the innovator drug. Dr. Tran read to the firm a

sentence in the second paragraph of the SOA(dated 9/25/85) that stated "baskets will ultimately be corroded by the acidic medium and, thus, could give erratic results and that the paddle method is easier to automate". He also informed the firm that the method described in the SOA is no longer employed by the innovator. As a result of the firm's unrelenting insistence on maintaining their current method, Dr. Tran suggested another dissolution method [900 mL Water using Apparatus I (Basket) at 100 rpm] and requested the firm to submit a complete dissolution data to DBE for review.

August 20 - December 14, 1998

-The reviewer went through all approved ANDA submissions on Bupropion and discovered that all were approved on the basis of the interim FDA dissolution method with no reports of tablet sticking or heaping.

May 19, 2000- As an amendment, the firm submitted a set of dissolution data based on a new proposed dissolution method [500 mL 0.6% HCl, using USP Apparatus I (Basket) at 100 rpm with specifications of NLT at 30 minutes)].

July 28, 2000- The DBE sent a deficiency letter to the firm requesting the firm, for the second time, to incorporate the dissolution method [900 mL Water, at 37°C using Apparatus II (Paddle) at 50 rpm with specifications of of the labeled amount of the drug in the dosage form is dissolved in 45 minutes].

In the form of an Amendment to the bioequivalence studies, the firm is now informing the Division of Bioequivalence that they have amended their dissolution test parameters and specification in line with those recommended by the DBE and all master records affected by this change have been revised accordingly. In this submission, the firm also included a set of documents showing that the FDA-recommended dissolution method and specification have already been incorporated into their stability and quality control programs.

Recommendations:

I. The *in vivo* bioequivalence study conducted under fasting conditions by EON LABS, on its Bupropion HCl tablets, 100mg, lot # 981101, comparing it to the reference product, Wellbutrin^{R} tablets, 100 mg, lot # 7G1296, by Glaxo, is now

acceptable to the Division of Bioequivalence. The study demonstrates that Eon's Bupropion HCl tablet, 100 mg, is bioequivalent to the reference product, Wellbutrin[R] Tablets, 100 mg, manufactured by Glaxo.

II. The *in vitro* dissolution testing submitted by the firm on its Bupropion HCl (75 and 100 mg) tablets is acceptable. The formulation for 75 mg is proportionally similar to the 100mg strength of the test product that underwent bioequivalence testing. The waiver of the *in vivo* bioequivalence study requirements for 75 mg tablets, of the test product can be granted under 21 CFR 320.22(d)(2). The 75 mg test tablets are, therefore, deemed bioequivalent to 75 mg Wellbutrin[R] Tablets, manufactured by Glaxo.

III. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution should be conducted in 900 mL Water, at 37°C using USP Apparatus 2 (paddle) at 50 rpm with the following specifications:

Not less than __ of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

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

8/23/2000

Patrick Nwakama,Pharm.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR _____ Date 8/24/2000

Concur: _____ Date 8/31/00
for Dale Conner,Pharm.D.
Director, Division of Bioequivalence

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75613 SPONSOR : EON LABS

DRUG AND DOSAGE FORM : Bupropion Hydrochloride

STRENGTH(S) : 75 mg & 100 mg Tablets

TYPES OF STUDIES: Fasting Study

CLINICAL STUDY SITE: NOVUM Pharmaceutical Research

ANALYTICAL SITE:

STUDY SUMMARY : The 90% CIs in the fasting study are within acceptable limits.
DISSOLUTION : Dissolution was conducted according to FDA (interim) method.
WAIVER: Waiver request of *in vivo* bioequivalence study requirements for 75 mg of the test product is granted.

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic _____	Inspection requested:	
New facility _____	Inspection completed: (date)	
For cause _____		
other _____		

PRIMARY REVIEWER : Patrick E. Nwakama, Pharm.D. BRANCH : II

INITIAL : _____ DATE : 8/23/2000

TEAM LEADER : Shriniwas G. Nerurkar, Ph.D. BRANCH : II

INITIAL : _____ DATE : 8/24/2000

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : _____ DATE : 8/31/00

Bupropion HCl Tablets
75 and 100 mg
ANDA #: 75613
Reviewer: Patrick Nwakama
File Name: 75-613A.500

EON LABS Manufacturing, Inc.
Laurelton, NY 11413
Submission Date:
May 19, 2000

Review Of A Dissolution Amendment

History of Submissions

April 1, 1999 - EON Laboratories submitted original ANDA (75-613) on its Bupropion HCl Tablets, 75mg and 100 mg.

August 16, 1999- The Division of Bioequivalence (DBE) sent a deficiency letter to the firm which included a request to the firm to use the interim FDA dissolution method in lieu of the firm's own method.

September 8, 1999-As an Amendment, the firm responded to the deficiency letter. The firm submitted a new set of dissolution data based on the recommended interim FDA method [900mL Water, Paddle, 50 rpm, NLT in 45 minutes] which DBE found acceptable. However, in responding to the dissolution deficiency, the firm still insisted on maintaining their original method. In DBE's tentative approval letter on ANDA #75-613, the firm was informed that its own dissolution method could be used for inhouse quality controls while the interim FDA method should remain the official method.

May 8, 2000- In the Division of Chemistry's deficiency letter, EON Labs was requested to conduct dissolution testing based on the method recommended by DBE to meet dissolution specifications at release and stability for its Bupropion HCl Tablets, 75 mg and 100 mg.

May 18, 2000- At the request of the firm, a teleconference call was held between EON Labs and DBE's representatives (Tran, Nwakama and Nguyen). The firm still insisted on keeping their current dissolution method and specification as filed in the original ANDA (submitted 4/1/99) because of the problem of sticking and heap formation of the tablets to the dissolution vessel when Water and Paddle are used as the dissolution medium and apparatus, respectively. According to the firm, its current and preferred dissolution method was obtained from the summary basis of approval (SOA) of the original NDA for Wellbutrin^{R}, the innovator drug. Dr. Tran read to the firm a

sentence in the second paragraph of the SOA (dated 9/25/85) that stated "baskets will ultimately be corroded by the acidic medium and, thus, could give erratic results and that the paddle method is easier to automate". He also informed the firm that the method described in the SOA is no longer employed by the innovator. As a result of the firm's unrelenting insistence on maintaining their current method, Dr. Tran suggested another dissolution method [900 mL Water using Apparatus I (Basket) at 100 rpm] and requested the firm to submit a complete dissolution data to DBE for review.

August 20 - December 14, 1998

-The reviewer went through all approved ANDA submissions on Bupropion and discovered that all were approved on the basis of the interim FDA dissolution method with no reports of tablet-sticking or heaping.

TABLE I

ANDA	DRUG NAME	SPONSOR	SUBM. DATE /REVIEWER	DISSOLUTION METHOD
#75-310	BUPROPRION 75 & 100 mg	TEVA	8/20/98 [MAKARY]	900 ml Water, Paddle, 50 rpm, NLT n 45 minutes - Specs(not FDA) but accepted in Amendment (3/18/99)
#75-491	BUPROPRION 75 & 100 mg	MYLAN	2/18/2000 [CHAURASIA]	900 ml Water, Paddle, 50 rpm, NLT in 45 minutes
#75-304	BUPROPRION 75 & 100 mg	CHELSEA	3/10/98 [JACKSON]	900 ml Water, Paddle, 50 rpm, I in 45 minutes
#75-584	BUPROPRION 75 & 100 mg	INVAMED	2/16/99 (original ANDA) 4/12/99 (Dissolution Amendment) [CHANEY]	900 ml, 0.01N HCl Paddle, 50 rpm,) in 45 minutes - rejected; later accepted 900 ml Water, Paddle, 50 rpm, NLT in 45 minutes
#75-487	BUPROPRION 75 & 100 mg	ESI Lederle	12/14/98 [KIM]	900 ml Water, Paddle, 50 rpm,) in 45 minutes

As an amendment, the firm has now submitted a set of dissolution data based on a trial method suggested DBE during the teleconference call on May 18, 2000.

TABLE II

Drug: BUPROPION HYDROCHLORIDE Tablets Dose Strength: 75 mg & 100 mg ANDA #: 75-613(Fascimile **Amendment)** Firm: Eon Laboratories, Inc. Submission Date: May 19, 2000 File Name: 75-613A.500						
I. Conditions for Dissolution/Release Testing: DBE Suggested Method						
USP XXIII Apparatus: Type 1 (Basket) RPM: 100 No. Units Tested: 12 Reference Drug: Not Applicable			Media: Water Volume: 900 mL Tolerance: Not Given			
A. Results of In Vitro Dissolution/Release Testing:						
Sampling Times (min)	Test Product: BUPROPION HCl Lot No.: 981105 Strength: 75 mg			Ref. Product: Wellbutrin® Lot No.: Strength:		
	Mean %	Range	CV%	Mean %	Range	CV%
10	-	-	-	-	-	-
20	-	-	-	-	-	-
30	-	-	-	-	-	-
45	102.1	.9	1.7	-	-	-
60	-	-	-	-	-	-
Sampling Times (min)	Test Product: BUPROPION HCl Lot No.: 981101 Strength: 100 mg			Ref. Product: Wellbutrin® Lot No.: Strength:		
	Mean %	Range	CV%	Mean %	Range	CV%
10	-	-	-	-	-	-
20	-	-	-	-	-	-
30	-	-	-	-	-	-
45	101.4		0.9	-	-	-
60	-	-	-	-	-	-

Recommendations:

1. The Agency prefers to maintain a single dissolution method for an immediate release (IR) product.

2. According to our internal dissolution data on Bupropion HCl (IR) Tablets, the dissolution method is 900 mL Water, at 37°C using USP Apparatus 2 (paddle) at 50 rpm with the following specifications:

   Not less than [redacted] of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

3. The dissolution method suggested by you [500 mL 0.6% HCl, using USP I (basket) at 100 rpm with specifications of [redacted] at 30 minutes], is not sufficiently discriminatory.

Patrick Nwakama,Pharm.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR

Date 7/10/2000

Concur:

Date 7/14/2000

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

Bupropion HCl Tablets
75 and 100 mg
ANDA #: 75613
Reviewer: Patrick Nwakama
File Name:75-613A.0999

EON LABS Manufacturing, Inc.
Laurelton, NY 11413
Submission Date:
September 8, 1999

Review of Amendment to Bioequivalence Study, Dissolution Data and Waiver Request

Introduction:
The firm submitted a single-dose fasting study, dissolution data and waiver request on its Bupropion HCl Tablets, 75 mg and 100 mg on April 1, 1999. On August 16, 1999, the Agency sent a deficiency letter to the firm. As a bioequivalence amendment, the firm has subsequently provided its responses to the cited deficiencies and these are summarized below.

Deficiency #1
You did not provide the manufacturing date for the test product biostudy lot.

FIRM'S RESPONSE:
The manufacturing date for the bio/ANDA Lot 981101 is November, 1998(Certificate of Analysis, Volume 1, page 0146 of ANDA)

REVIEWER'S COMMENT:
The firm's response is acceptable.

Deficiency #2
You did not provide long-term stability data for the test drug as required for a complete assay validation.

FIRM'S RESPONSE:
Long-term stability data was filed as an addendum to the biostudy reports providing for 109 days storage. A copy of the relevant page from the addendum is provided (attachment 1). The time frame is sufficient to cover the storage of the plasma samples.

REVIEWER'S COMMENT:
The firm's response is acceptable.

Deficiency #3

You did not use the interim FDA dissolution method which specifies Apparatus II(paddle) at 50 rpm with 900 mL Water as dissolution medium.

FIRM'S RESPONSE:
The firm has submitted a new dissolution profile report using the interim FDA method (Table 1). With the interim FDA dissolution method, the firm claimed to observe the sticking of tablets to the side of the dissolution vessel (particularly with the test product). According to the firm, this problem was not observed when its own dissolution method(based on the method originally recommended to the innovator by the FDA) was used. Because of the sticking problem, the firm still strongly believes that the interim FDA dissolution method does not produce accurate results and it is not optimum method. Consequently, the firm feels that its current dissolution method is more acceptable and, therefore, it will maintain its current dissolution test method originally filed in the original ANDA for testing and releasing Bupropion HCl tablets.

REVIEWER'S COMMENT:
The firm's dissolution results using the interim FDA method are acceptable. The firm can use their own method for only in-house quality control but, officially, they must meet the interim FDA method.

Recommendations:

I. The firm's responses to all deficiencies are acceptable.

II. The *in vivo* bioequivalence study conducted under fasting conditions by EON LABS, on its Bupropion HCl tablets, 100mg, lot # 981101, comparing it to the reference product, Wellbutrin^{R} tablets, 100 mg, lot # 7G1296, by Glaxo, has been found acceptable by the Division of Bioequivalence. The study demonstrates that EON's Bupropion 100 mg tablet is bioequivalent to the reference product, Wellbutrin^{R} 100 mg tablet, manufactured by Glaxo.

III. The *in vitro* dissolution testing submitted by the firm on its Bupropion HCl (75 and 100 mg) tablets (lot# 981105 and 981101, respectively), based on the interim FDA method, is acceptable. The dissolution testing should be conducted in 900 mL Water, Apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than f labeled amount of the drug in the dosage form is dissolved in 45 minutes.

IV. The waiver of the *in vivo* bioequivalence study requirements for 75 mg tablets, of the test product can now be granted under 21 CFR 320.22(d)(2).

V. From the bioequivalence point of view, the firm has met the requirements of in vivo biostudy and in vitro dissolution testing. The ANDA# 75613 is, therefore, acceptable.

Patrick Nwakama, Pharm.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR Date 10/20/99

Concur: Date 11/16/99
for Dale Conner, Pharm.D.
Director, Division of Bioequivalence

Table 1

IN-VITRO DISSOLUTION TESTING

Drug: BUPROPION HYDROCHLORIDE Tablets
Dose Strength: 75 mg & 100 mg
ANDA #: 75-613(**Amendment)**
Firm: Eon Laboratories, Inc.
Submission Date: September 8, 1999
File Name: 75-613A.0999

I. Conditions for Dissolution/Release Testing: **INTERIM FDA METHOD**

USP XXIII Apparatus: Type 2 (Paddle) RPM: 50 No. Units Tested: 12 Reference Drug: Wellbutrin®	Media: Water Volume: 900 mL Tolerance: NLT 80% (Q) in 45 min

A. Results of In Vitro Dissolution/Release Testing:

Sampling Times (min)	Test Product: BUPROPION HCl Lot No.: 981105 Strength: 75 mg			Ref. Product: Wellbutrin® Lot No.: 7K2422 Strength: 75 mg		
	Mean %	Range	CV%	Mean %	Range	CV%
10	72.9		13.8	71.9		22.6
20	86.6		9.1	94.8		5.4
30	92.0		7.8	97.3		3.4
45	97.1		5.0	99.0		2.1
60	100.1	92.9-10[illegible]	3.6	99.5	96.0-[illegible]	1.8
Sampling Times (min)	Test Product: BUPROPION HCl Lot No.: 981101 Strength: 100 mg			Ref. Product: Wellbutrin® Lot No.: 7G1296 Strength: 100 mg		
	Mean %	Range	CV%	Mean %	Range	CV%
10	68.6		20.1	82.7		8.2
20	78.5		15.5	94.2		2.7
30	84.1		13.0	97.0		2.7
45	90.0		10.1	98.6		2.2
60	93.0		7.6	99.3		2.1

F_2 TEST:

	Test 100mg	Test 75 mg	Ref. 100 mg	Ref. 75 mg
Test 100mg	-	58	46	49
Test 75 mg	58	-	61	68
Ref. 100 mg	46	61	-	65
Ref. 75 mg	49	68	65	-

Bupropion HCl Tablets
75 and 100 mg
ANDA #: 75613
Reviewer: Patrick Nwakama
File Name: 75613SDW.499

EON LABS Manufacturing, Inc.
Laurelton, NY 11413
Submission Date:
April 1, 1999

REVIEW OF *IN VIVO* BIOEQUIVALENCE STUDY, DISSOLUTION DATA AND WAIVER REQUEST

The firm has submitted one single-dose fasting *in vivo* bioequivalence study comparing its test product, Bupropion HCl Tablets, 100 mg, to the reference listed drug, Glaxo's Wellbutrin^{R} Tablets, 100 mg. The firm has also submitted *in vitro* dissolution data and one waiver request.

Introduction

Bupropion is a monocyclic antidepressant, unique as a mild dopamine and norepinephrine uptake inhibitor with no direct effect on serotonin receptors. It is devoid of anticholinergic, antihistaminic, and peripheral adrenergic effects. Unlike the heterocyclic antidepressants, it produces no clinically significant effect on cardiac conduction, no orthostatic hypotension, minimal anticholinergic effects, and it is not associated with weight gain. Disadvantages of bupropion include seizures and the need for multiple daily doses. The elimination half-life is 11-14 hours, but an active hydroxy metabolite has a half-life of > 24 hours.

The reference listed drug is Glaxo's Wellbutrin^{R} Tablets, 100 mg.

I. Single-dose Bioequivalence Study Under Fasting Conditions (Protocol B-10018):

A. Study Information:

Protocol #:	B-10018
IRB Approval:	Yes
Consent Form Signed:	Yes
Clinical Site:	NOVUM Pharmaceutical Research
Analytical Site:	
Principal Investigator:	Adelaida M. Miro, M.D.
Study Dates:	Period I December 19, 1998 Period II January 9, 1999
Analysis Dates:	January 21 - February 23, 1999
Study Design:	Randomized, 2-way cross-over design with washout period of 21 days.

Randomization Scheme:

Sequence Number	Subject Numbers	Phase1	Phase 2
- 1	5, 6,7,11,13, 15, 17, 20, 23, 24, 26, 27,28 29, 31, 32,34,35	A	B
2	1, 2,3,4,8,9, 10, 12, 14, 16, 18,19, 21,22, 25, 30, 33, 36	B	A

A = EON Bupropion HCl
B = Wellbutrin®

Treatments: A: Bupropion HCl, 1x100 mg Tablets; EON Labs; Lot # 981101, Lot size: **Manufacturing Date: XXX;** Assay: 101.6%; Content Uniformity:100.5%

B: Wellbutrin®, 1x100 mg Tablets; Glaxo; Lot # 7G1296; Expiry Date: 10/1999; Assay:100.5%; Content Uniformity: 100.1%

Formulation of Test Drug: Table I

Subjects: 36 male subjects were enrolled per protocol.

Housing: From the evening prior to dosing until 24 hours after dosing in both periods.

Dosing: After overnight fast, with 240 ml water. Standard meals given at 4,10,14 and 24 hours after dosing.

Sampling Times Blood samples (1 × 10 mL) collected at 0 h (pre-dose), 0.5, 0.75, 1, 1.5,2,2.5,3,4,5,6,8,10,14,24,36, 48,60,72,96,120 and 168 h.

B. <u>Study Results</u>:

1. CLINICAL:

Drop-outs: Subjects #2 and #5 voluntarily withdrew before Period 2 due to personal reasons. Therefore, only the 34 subjects who completed Periods 1 and 2 had their samples analyzed.

Adverse Events: A total of 8 medical adverse events (toe ecchymosis, sore back, tiredness, dizziness, cold symptoms, headache, leukocytosis, and light-headness) were reported by 7 subjects during the study. Only sore back and dizziness occurred with the test product. The two events, tiredness and headache, believed to be related to treatment, occurred with the reference. All events were mild severity and resolved without any medical intervention.

Protocol Deviations: Subject #34 used cough drops 6 days before entering the study. Subject #36 was 1 pound above the specified weight limit.

2. **ANALYTICAL METHODOLOGY:**

Method:

Internal Standard: Verapamil HCl, Hydroxybupropion-d_4, Threo/ErythroaminoAlcohol Bupropion-d_9

Sensitivity (LOQ): Hydroxybupropion/Bupropion/Threo-Erythroamino-Alcohol Bupropion (2.00/1.00/1.00 ng/ml)

Specificity: No interfering peaks at retention times of Bupropion, Hydroxybupropion, Threo/Erythroamino-Alcohol Bupropion or internal standard.

Linearity: Standard Curve Range:
1.0 - 250 ng/mL (Bupropion)
2.0 - 500 ng/mL(Hydroxybupropion)
1.0 - 250 ng/mL (Threo/Erythroamino-Alcohol Bupropion)

Correlation Coefficients:
Bupropion $\geq$ 0.9981
Hydroxybupropion $\geq$ 0.9987
Threo/Erythroamino-Alcohol Bupropion $\geq$ 0.9981

Quality Control Samples:
Bupropion - 2.0, 15, 150 ng/mL
Hydroxybupropion - 4.0, 30, 300 ng/mL
Threo/Erythroamino-Alcohol Bupropion- 2.0, 15, 150 ng/mL

Regression: linear weighted (1/concentration)

Accuracy:

[Bupropion]
Standard: - 98.4 - 101%
QC Samples: - 94.0 - 98%

[Hydroxybupropion]
Standard: - 98.5 - 105%
QC Samples: - 96.3 - 99%

[Threo/Erythroamino-Alcohol Bupropion]
Standard: - 98.4 - 103%
QC Samples: - 100 - 104%

Precision:

[Bupropion]
Standard: - 1.5 - 6.8%
QC Samples: - 6.7 - 7.5 %

[Hydroxybupropion]
Standard: - 1.4 - 7.1%
QC Samples: - 6.3 - 7.0%

[Threo/Erythroamino-Alcohol Bupropion]
Standard: - 1.7 - 9.5%
QC Samples: - 6.2 - 11.7%

Reassays: A total of 93 samples from 30 subjects were repeated for bupropion and its active metabolites. Assays were repeated because unacceptable chromatography, value above range, instrument malfunction, low internal standard and unknown processing error. The mean or median of the original and repeat values is used when the two values are different. The repeat values are used when the original value is zero.

The firm has provided the following pre-study method validation results:

Linearity:

[Hydroxybupropion]
Standard Curve Range:
2.0 - 500 ng/mL
QC Sample:
4.0, 30.0, 300.0 ng/mL
Correlation Coefficient: $\geq$ 0.9996

[Buproprion]
Standard Curve Range:
1.0 - 250 ng/mL
QC Sample:
2.0, 15.0, 150.0 ng/mL
Correlation Coefficient: $\geq$ 0.9992

[Threo/Erythroamino-Alcohol Bupropion]
Standard Curve Range:
1.0 - 250 ng/mL
QC Sample:
2.00, 15.0, 150.0 ng/mL
Correlation Coefficient: $\geq$ 0.9997

Accuracy:

[Hydroxybupropion]
INTER-DAY
Standard: 95.7 - 110%
QC Samples: 1.0 - 6.2%

INTRA-DAY
QC Samples: 1.5 - 3.5%

[Buproprion]
INTER-DAY
Standard: 98.2 - 102%
QC Samples: 1.4 - 7.3%

INTRA-DAY
QC Samples: 2.3 - 12.1%

[Threo/Erythroamino-Alcohol Bupropion]
INTER-DAY
Standard: 96.0 - 103%
QC Samples: 0.7 - 7.7%

INTRA-DAY
QC Samples: 1.5 - 11%

Precision:

[Hydroxybupropion]
INTER-DAY
Standard: 1.0 - 6.2%
QC Samples: 2.6 - 3.2%

INTRA-DAY
QC Samples: 1.5 - 3.5%

[Buproprion]
INTER-DAY
Standard: 1.4 - 7.3%
QC Samples: 5.3 - 9.0%

INTRA-DAY
QC Samples: 2.3 - 12.1%

[Threo/Erythroamino-Alcohol Bupropion]
INTER-DAY
Standard: 0.7 - 7.7%
QC Samples: 2.2 - 8.4%

INTRA-DAY
QC Samples: 1.5 - 11.0%

Specificity: no interference from endogenous compounds noted in plasma blanks or pre-dose subject plasma samples.

Recovery:

[Hydroxybupropion]

4.00 ng/mL	85.6%
30.00 ng/mL	87.1%
300.00 ng/mL	88.9%

[Buproprion]

2.00 ng/mL	86.7%
15.00 ng/mL	88.9%
150.00 ng/mL	90.4%

[Threo/Erythroamino-Alcohol Bupropion]

2.00 ng/mL	90.1%
15.00 ng/mL	90.3%
150.00 ng/mL	90.0%

[Internal Standard]
101.0%

Stability:

a) **Stored Frozen at - 20°C:** Not available. Firm plans to send long-term stability as an addendum.

b) **Freeze/Thaw:** Stable over 3 cycles.

c) **In-process:** stable for 72 h during sample processing at room temperature.

d) **Room Temperature:** stable at room temperature for 4 hours.

Conclusion: assay validation is incomplete.

3. **PHARMACOKINETIC / STATISTICAL ANALYSES:**

Bupropion:

Mean Plasma Concentrations: Table 2; Figure 1

Pharmacokinetic Parameters: Table 5

90% Confidence Intervals:

$LAUC_{0-168h}$	98.6 - 112%
$LAUC_{0-INF}$	99.4 - 112%
LC_{MAX}	93.9 - 114%

Test/Reference Ratio:

AUC_{0-168h}	1.07(0.65 - 2.02)
AUC_{0-INF}	1.07(0.66 - 1.98)
C_{MAX}	1.08(0.56 - 2.27)

AUC_{0-168h}/AUC_{0-INF} Ratio:

Test	0.95(0.82 - 0.98)
Reference	0.96(0.91 - 0.98)

Hydroxybupropion:

Mean Plasma Concentrations: Table 3; Figure 2

Pharmacokinetic Parameters: Table 6

90% Confidence Intervals:

$LAUC_{0-168h}$	97.5 - 110%
$LAUC_{0-INF}$	97.6 - 110%
LC_{MAX}	94.2 - 103%

Test/Reference Ratio:

AUC_{0-168h}	1.06(0.67 - 1.87)
AUC_{0-INF}	1.06(0.67 - 1.73)
C_{MAX}	0.99(0.77 - 1.47)

AUC_{0-168h}/AUC_{0-INF} Ratio:

Test	0.98(0.92 - 0.99)
Reference	0.98(0.93 - 0.99)

Threo/Erythroamino-Alcohol Bupropion:

Mean Plasma Concentrations: Table 4; Figure 3

Pharmacokinetic Parameters: Table 7

90% Confidence Intervals:

$LAUC_{0-168h}$	99.3 - 112%
$LAUC_{0-INF}$	98.5 - 112%
LC_{MAX}	93.9 - 105%

Test/Reference Ratio:

AUC_{0-168h}	1.08(0.71 - 2.23)
AUC_{0-INF}	1.08(0.71 - 2.16)
C_{MAX}	1.01(0.64 - 1.66)

AUC_{0-168h}/AUC_{0-INF} Ratio:

Test	0.91(0.81 - 0.97)
Reference	0.90(0.72 - 0.99)

Comments:

1. The maximum (mean) plasma concentrations for bupropion, hydroxybupropion and threo/erythroamino alcohol bupropion were attained at 1.5,4.0 and 3 hours, respectively (Tables 2, 3 & 4).

2. No subjects with zero-hour drug level, no subjects with first scheduled post-dose time point as C_{max}, and no subjects with first measurable drug level as C_{max}. The reviewer recalculated the pharmacokinetic parameters and 90% confidence intervals and found them in complete agreement with those obtained by the firm.

3. The % CVs (and log transformed Root MSEs) for AUCT, AUC_{INF}, and C_{max} were 17.3%(0.15), 16.7% (0.14), and 27.0%(0.23), respectively, for bupropion. The % CVs(and Ln RMEs) for AUCT, AUC_{INF}, and C_{max} were 16.8%(0.15), 16.8%(0.15), and 11.2%(0.11), respectively, for hydroxybupropion. The % CVs(and Ln RMEs) for AUCT, AUC_{INF}, and C_{max} were 21.9%(0.15), 21.1%(0.15), and 17.5%(0.13), respectively, for threo/erythroamino-alcohol bupropion.

4. The fasting study is incomplete because of the deficiencies cited.

***In Vitro* Dissolution Testing and Waiver Request:**

The dissolution testing was done on the 75 and 100 mg tablets of the test and reference products, using the firm's own method: 500 mL 0.6% HCl, using apparatus 1(basket) at 100 rpm. The firm is requesting a waiver of the in-vivo bioequivalence study requirements for its 75mg tablet per 21 CFR 320.22 (d)(2), based on an acceptable in-vivo bioequivalence study on the 100 mg strength, similarly proportional formulations as listed in Table 1. The comparative dissolution data and testing conditions are presented in Table 8.

Comments:

1. There is no USP dissolution method for Bupropion tablets. The interim FDA method, recommends 900 mL Water, apparatus 2(paddle) at 50 rpm.

2. The dissolution testing is not acceptable. The firm would be asked to conduct another dissolution testing according to the FDA method: 900 mL Water, apparatus 2 (paddle) at 50 rpm with specifications of 45 minutes.

Deficiencies:

1. The firm did not provide the manufacturing date for the biostudy lot used.

2. The firm did not provide long-term stability data for the test drug as required for complete assay validation. Rather, they intend to provide results, later, in the form of an addendum.

3. The firm did not use the FDA (interim) method in the dissolution testing.

Recommendations:

I. The *in vivo* bioequivalence study conducted under fasting conditions by EON LABS, on its Bupropion HCl tablets, 100mg, lot # 981101, comparing it to the reference product, Wellbutrin^{R} tablets, 100 mg, lot # 7G1296, by Glaxo, is incomplete due to the deficiencies mentioned above.

II. The *in vitro* dissolution testing submitted by the firm on its Bupropion HCl (75 and 100 mg) tablets is not acceptable. The waiver of the *in vivo* bioequivalence study requirements for 75 mg tablets, of the test product cannot be granted under 21 CFR 320.22(d)(2).

III. The firm should be informed of the recommendations and deficiencies.

Patrick Nwakama, Pharm.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR

Date 6/22/99

Concur: Barbara Mayers David for Dale P. Conner, Pharm.D. Date 6/28/99
Director
Division of Bioequivalence

TABLE 1

Quantitative Composition of Bupropion HCl Tablets (75 mg, and 100 mg)[1]

COMPONENT	AMOUNT / TABLET 75 mg	% W/W	AMOUNT / TABLET 100 mg	% W/W
Bupropion HCl	75.0		100.0	
Microcrystalline Cellulose,				
Dilute HCl				
Purified Water,				
Talc,				
CORE				
COATED TABLETS				

[1] The innovator product (Wellbutrin^{R}) have dissimilar type of proportionality within its tablets. Both strengths of the test product, bupropion HCl, are round, biconvex and film-coated tablets. The 75 mg is orange debossed with **"E175"** on one side and plain on the other and the 150 mg is red debossed with **"E176"** on one side and plain on the other. Both strengths of Wellbutrin^{R} are round and biconvex tablets. The 75 mg (yellow-gold) have "Wellbutrin" on one side and "75" on the other while the 100 mg(red) has "Wellbutrin" on one side and "100" on the other.

TABLE 2

ARITHMETIC MEAN PLASMA BUPROPION LEVELS (ng/mL) [100 mg TABLETS]
Vs TIME (HR) IN FASTING STUDY (n = 34 SUBJECTS)

Time	Test Treatment A		Reference Treatment B		Ratio (A/B)
0	0.00	(CV%)	0.00	(CV%)	0.0
0.5	16.19	162.5	8.06	175.6	2.01
0.75	62.88	88.23	44.95	82.94	1.39
1.0	99.39	54.14	88.82	45.89	1.12
1.50	112.68	27.02	110.94	32.82	1.02
2.0	100.09	28.83	101.72	32.01	0.98
2.5	84.82	25.51	88.87	30.96	0.95
3.0	74.60	25.63	75.54	32.51	0.99
4.0	54.01	25.62	53.23	32.34	1.01
5.0	36.60	28.65	35.97	35.80	1.02
6.0	26.52	28.46	26.44	32.66	1.00
8.0	17.45	30.98	16.72	33.57	1.04
10.0	12.14	29.79	11.76	33.17	1.03
14.0	7.15	34.18	6.81	31.46	1.05
24.0	3.31	35.21	3.09	32.64	1.07
36.0	1.61	52.62	1.53	64.02	1.05
48.0	0.85	86.19	0.69	99.20	1.23
60.0	0.37	295.75	0.08	360.36	4.63
72.0	0.00	0.00	0.00	0.00	0.00
96.0	0.00	0.00	0.00	0.00	0.00
120	0.00	0.00	0.00	0.00	0.00
168	0.00	0.00	0.00	0.00	0.00

TABLE 3

ARITHMETIC MEAN PLASMA HYDROXYBUPROPION LEVELS (ng/mL) Vs TIME (HR) IN FASTING STUDY (n = 34 SUBJECTS)

Time	Test Treatment A		Reference Treatment B		Ratio (A/B)
0	0.00	(CV.%)	0.00	(CV.%)	0.0
0.5	27.93	99.23	19.77	100.8	1.4
0.75	86.68	71.67	54.97	72.06	1.58
1.0	137.9	60.9	75.36	56.09	1.83
1.50	183.9	42.74	79.03	42.56	2.33
2.0	204.7	42.86	85.72	40.83	2.39
2.5	220.0	41.39	93.56	40.47	2.35
3.0	232.5	42.49	93.77	39.92	2.48
4.0	239.1	38.71	97.29	40.88	2.46
5.0	222.9	39.29	85.08	38.17	2.62
6.0	211.8	39.76	84.68	39.76	2.50
8.0	203.0	39.97	81.04	40.11	2.50
10.0	198.9	37.97	83.95	41.59	2.37
14.0	171.6	40.87	72.30	41.96	2.37
24.0	140.8	43.29	64.38	46.98	2.19
36.0	86.9	47.45	48.58	52.79	1.79
48.0	66.1	50.47	35.74	57.51	1.85
60.0	44.6	50.92	28.30	66.84	1.58
72.0	31.9	59.52	20.06	63.87	1.59
96.0	15.6	76.94	11.54	79.64	1.35
120	7.11	98.70	6.73	93.98	1.06
168	1.56	165.72	2.13	174.32	0.73

TABLE 4

ARITHMETIC MEAN PLASMA THREO/ERYTHROAMINO-ALCOHOL BUPROPION LEVELS (ng/mL) Vs TIME (HR) IN FASTING STUDY (n = 34 SUBJECTS)

Time	Test Treatment A		Reference Treatment B		Ratio (A/B)
0	0.00	(CV%)	0.00	(CV%)	0.0
0.5	2.45	199.16	1.31	300.6	1.87
0.75	18.55	124.97	11.54	115.9	1.61
1.0	46.79	85.30	37.91	71.4	1.23
1.50	83.99	55.63	76.19	45.78	1.10
2.0	94.85	44.47	92.49	35.59	1.03
2.5	103.36	41.20	104.95	32.91	0.98
3.0	106.29	37.80	108.91	35.88	0.98
4.0	105.97	39.01	101.96	36.32	1.04
5.0	97.98	36.85	95.70	35.40	1.02
6.0	90.43	37.84	86.79	36.50	1.04
8.0	83.64	44.61	80.52	42.72	1.04
10.0	77.46	51.84	74.04	41.71	1.05
14.0	66.10	49.47	63.63	43.89	1.04
24.0	50.90	49.14	46.81	45.49	1.09
36.0	39.27	54.02	37.01	52.16	1.06
48.0	31.53	45.80	29.24	50.97	1.08
60.0	26.12	52.12	25.18	57.58	1.04
72.0	21.72	43.66	20.65	44.17	1.05
96.0	15.16	49.87	13.74	50.97	1.10
120	11.30	58.59	10.16	50.73	1.11
168	5.36	65.22	5.22	70.66	1.03

TABLE 5

ARITHMETIC MEANS (± SD), LEAST-SQUARES MEANS AND 90% CONFIDENCE INTERVALS OF PHARMACOKINETIC PARAMETERS FOR BUPROPION IN FASTING STUDY (n = 34 SUBJECTS)

Parameter	Treatment[2] Mean ± SD		Ratio A/B[1] (90% Confidence Intervals)	
	Test Formulation (A)	Reference Formulation (B)	Untransformed Data	Ln-Transformed Data
$AUC_{0\text{-}168h}$ (ng-hr/mL)	563.4 ± 164.7 LS Mean: 563.4	540.9 ± 163.4 LS Mean: 540.9	1.04	1.01 (98.6 - 112.0)
AUC I (ng-hr/mL)	593.8 ±168.5 LS Mean: 593.8	565.5 ± 164.1 LS Mean: 565.5	1.05	1.01 (99.4 - 112.0)
C_{max} (ng/mL)	122.4 ± 41.9 LS Mean: 122.4	119.1 ± 37.2 LS Mean: 119.1	1.03	1.01 (93.9 - 114.0)
T_{max} (hr)	1.27 ± 0.36 LS Mean: 1.27	1.36 ± 0.53 LS Mean: 1.36	0.93 -	-
K_{el} (1/hr)	0.06 ± 0.03 LS Mean: 0.06	0.06 ± 0.03 LS Mean: 0.06	1.00 -	-
$T_{1/2}$ (hr)	14.4 ± 8.89 LS Mean: 14.4	12.3 ± 4.7 LS Mean: 12.3	1.17 -	-

[1] LS Means are used in computing the ratios and confidence intervals
[2] Results generally rounded to three significant figures

TABLE 6

ARITHMETIC MEANS (± SD), LEAST-SQUARES MEANS AND 90% CONFIDENCE INTERVALS OF PHARMACOKINETIC PARAMETERS FOR HYDROXYBUPROPION IN FASTING STUDY (n = 34 SUBJECTS)

Parameter	Treatment[2] Mean ± SD		Ratio A/B[1] (90% Confidence Intervals)	
	Test Formulation (A)	Reference Formulation (B)	Untransformed Data	Ln-Transformed Data
$AUC_{0\text{-}168h}$ (ng-hr/mL)	8805.7 ±4121.2 LS Mean: 8805.7	8579.8 ± 4218.9 LS Mean: 8579.8	1.03	1.00 (97.5 - 110.0)
AUCI (ng-hr/mL)	8969.1 ± 4155.8 LS Mean: 8969.1	8737.8 ± 4249.5 LS Mean: 8737.8	1.03	1.00 (97.6 - 110.0)
C_{max} (ng/mL)	246.1 ±101.4 LS Mean: 246.1	249.4 ± 97.2 LS Mean: 249.4	0.99	1.00 (94.2 - 103.0)
T_{max} (hr)	4.2 ± 2.5 LS Mean: 4.2	3.8 ± 1.5 LS Mean: 3.8	1.10	-
K_{el} (1/hr)	0.03 ± 0.01 LS Mean: 0.03	0.03 ± 0.01 LS Mean: 0.03	1.00	-
$T_{1/2}$ (hr)	22.2 ± 4.5 LS Mean: 22.2	22.0 ± 3.6 LS Mean: 22.0	1.01	-

[1] LS Means are used in computing the ratios and confidence intervals
[2] Results generally rounded to three significant figures

TABLE 7

ARITHMETIC MEANS (± SD), LEAST-SQUARES MEANS AND 90% CONFIDENCE INTERVALS OF PHARMACOKINETIC PARAMETERS FOR THREO/ERYTHROAMINO-ALCOHOL -BUPROPION IN FASTING STUDY (n = 34 SUBJECTS)

Parameter	Treatment[2] Mean ± SD		Ratio A/B[1] (90% Confidence Intervals)	
	Test Formulation (A)	Reference Formulation (B)	Untransformed Data	Ln-Transformed Data
$AUC_{0\text{-}168h}$ (ng-hr/mL)	4449.8 ± 2002.6 LS Mean: 4449.8	4189.4 ±1801.8 LS Mean: 4189.4	1.06	1.01 (99.3 - 112.0)
AUCI (ng-hr/mL)	4875.1 ± 2166.8 LS Mean: 4875.1	4630.2 ± 2018.2 LS Mean: 4630.2	1.05	1.01 (98.5 - 112.0)
C_{max} (ng/mL)	114.3 ± 43.9 LS Mean: 114.3	115.2 ± 39.9 LS Mean: 115.2	0.99	1.00 (94.0 - 105.0)
T_{max} (hr)	3.1 ± 1.3 LS Mean: 3.1	2.9 ± 1.4 LS Mean: 2.9	1.1	
K_{el} (1/hr)	0.02 ± 0.01 LS Mean: 0.02	0.02 ± 0.01 LS Mean: 0.02	1.00	
$T_{1/2}$ (hr)	46.1 ± 13.3 LS Mean: 46.1	48.2 ± 15.0 LS Mean: 48.2	0.96	-

[1] LS Means are used in computing the ratios and confidence intervals
[2] Results generally rounded to three significant figures

TABLE 8

IN-VITRO DISSOLUTION TESTING

Drug: Bupropion HCl Tablets
Dose Strength(s): 75 and 100 mg
ANDA #: 75-613
Firm: Eon Labs
Submission Date: April 1, 1999
File Name: 75-613SDW.499

I. Conditions for Dissolution/Release Testing: **USP METHOD:** No

USP XXIII Apparatus: Type 1 (Basket) RPM: 100 No. Units Tested: 12 Reference Drug: Wellbutrin®	Media: 0.6% Hydrochloric Acid at 37°C Volume: 500 mL Tolerance: NLT in 30 min Assay Method:

II. Results of In Vitro Dissolution/Release Testing:

Sampling Times (min)	Test Product: Bupropion HCl Tablets Lot No.: 981105 Strength: 75 mg			Reference Product: Wellbutrin® Tablets Lot No.: 7K2422 Strength: 75 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
10	100.9		1.6	94.6		4.1
20	102.9		0.8	101.5		1.2
30	103.2		0.8	101.8		1.3

Sampling Times (min)	Test Product: Bupropion HCl Tablets Lot No.: 981101 Strength: 100 mg			Reference Product: Wellbutrin® Tablets Lot No.: 7G1296 Strength: 100 mg		
	Mean %	Range	CV%	Mean %	Range	CV%
10	101.7		0.7	99.4		2.3
20	102.6		0.4	102.2		1.3
30	102.7		0.4	102.3		1.3

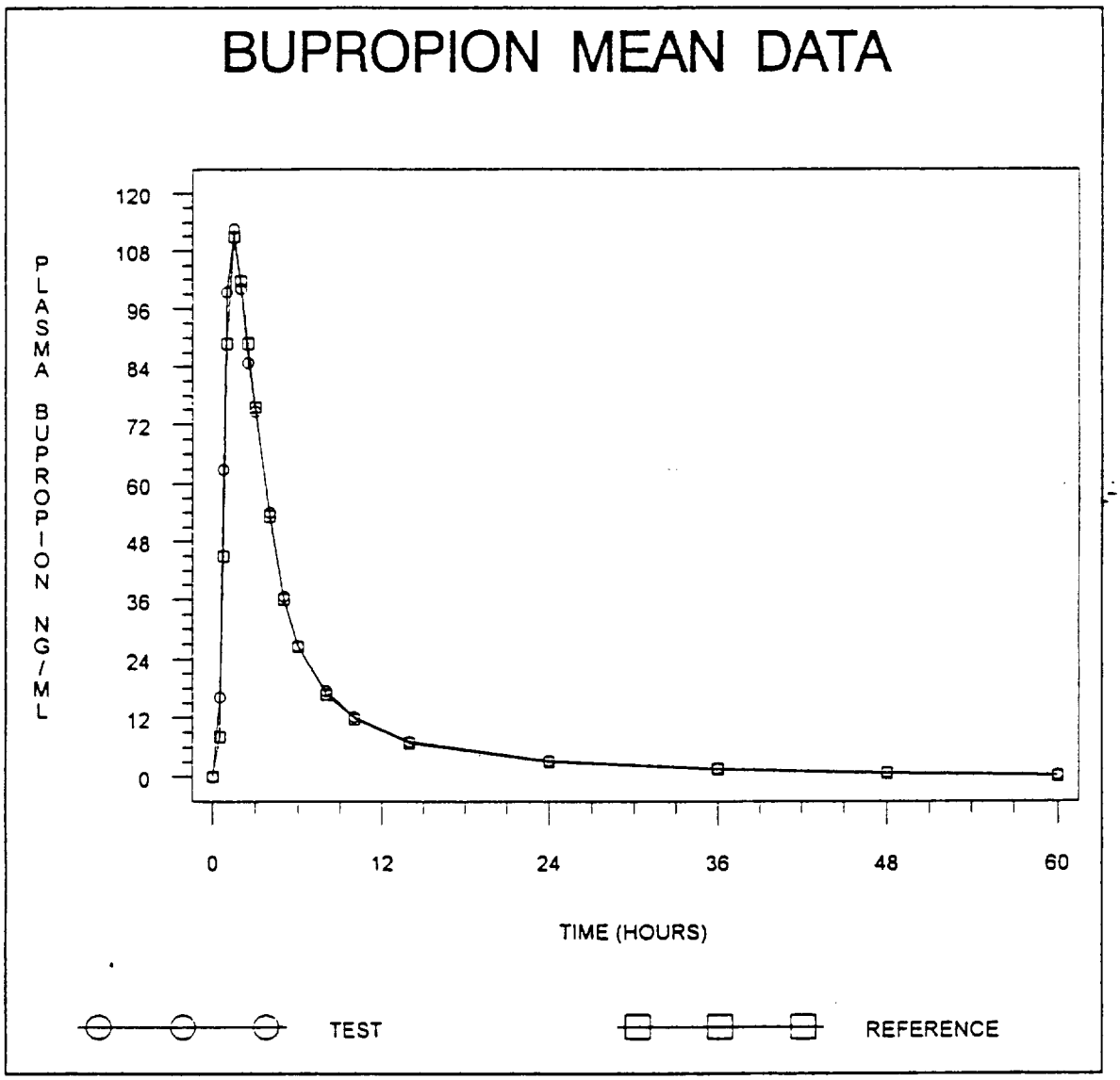
F_2 TEST:

	Test 100mg	Test 75 mg	Ref. 100 mg	Ref. 75 mg
Test 100mg	-	97	85	68
Test 75 mg	97	-	83	68
Ref. 100 mg	85	83	-	80
Ref. 75 mg	68	68	80	-

ANDA# 75-613

Figure 1

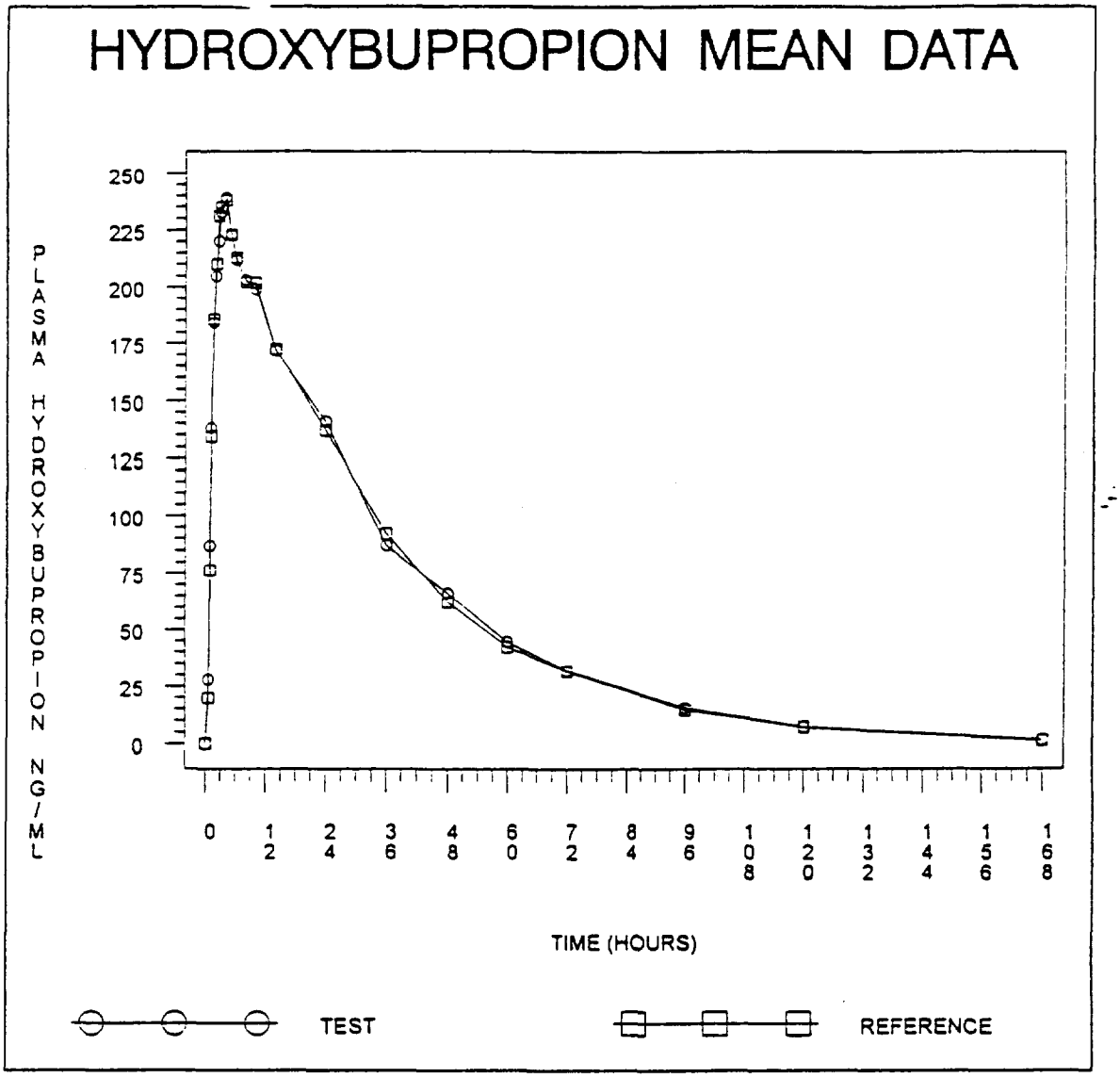
Linear Plot of Mean Plasma Bupropion Concentrations *vs* Time



ANDA# 75-613

Figure 2

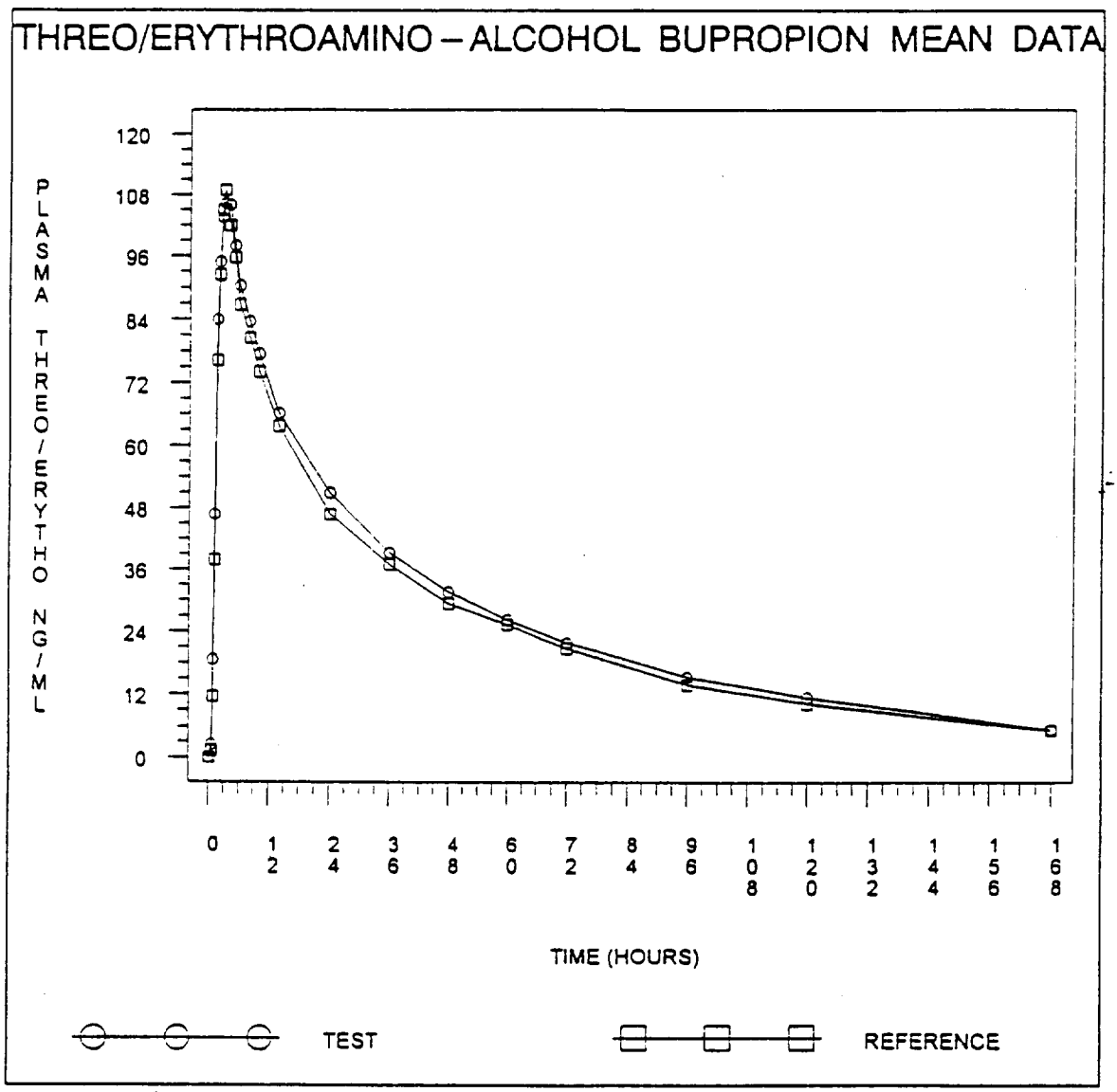
- Linear Plot of Mean Plasma Hydroxybupropion Concentrations *vs* Time



ANDA# 75-613

Figure 3

Linear Plot of Mean Plasma
Threo/erythroamino-alcohol bupropion
Concentrations *vs* Time



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-613

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA # 75-613

DRUG PRODUCT: Bupropion Hydrochloride Tablets, 75 mg and 100 mg.

FIRM: Eon Labs Manufacturing, Inc

DOSAGE FORM: Tablets

STRENGTHS: 75 mg and 100 mg

CGMP STATEMENT/EIR UPDATE STATUS:

Manufacturer-Finished Dosage Form:

Manufacturing, packaging, labeling and testing of the drug products are performed at:

Eon Labs Manufacturing, Inc
227-15 North Conduit Avenue
Laurelton, New York 11413
(OK on June 28, 1999).

Manufacturer-Active Ingredients:

The manufacturer of the drug substance, Bupropion Hydrochloride, is:

Contract Laboratories:

Outside firms including contract testing laboratories were listed as follows:

BIO STUDY:

Satisfactory per P. Nwakama & J. Fan (see Email) reviewed on 9-1-2000.
Lot #981101, 100 mg (Bio-study) and Lot 9811005, 75 mg.

VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Drug substance, Bupropion Hydrochloride and drug product are not compendial.

Method validation for samples of the active ingredient and finished product were sent to Northeast Regional Laboratory on October 8, 1999 and found acceptable on January 19, 2000.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:

Stability protocol: Satisfactory

Expiration date:

2 years expiration date with 1, 2 and 3 month accelerated stability data (40°C/75% R.H.) for 100's (120 cc amber glass) and bulk package sizes for 75 mg (batch #981105) and 100 mg (batch #981101).
Lot #981105, 75 mg
Lot #981101, 100 mg

LABELING:

Satisfactory per A. Vezza reviewed on 9/7/2000.

RILIZATION VALIDATION (IF APPLICABLE):

NA

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

75 mg tablet

Executed batch **Lot #981105** tablets) was granted for the waiver of in-vivo Bio-study and used . as a source of drug substance.

100 mg tablet

Executed batch **Lot #981101** tablets) was used as Bio-study and used '. as a source of drug substance.

was reviewed and found not satisfactory by L. Tang on May 11, 1999. The revised DMF was found satisfactory per L. Tang reviewed on 9-28-2000.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

The stability batch size:

75 mg tablet

Executed batch **Lot #981105** tablets).

100 mg tablet

Executed batch **Lot #981101** lets).

Stability batches were the same as the bio batches as above.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:

The proposed production batch (blank batch):

75 mg tablet

Tablets (blank intended commercial batch record).

100 mg tablet

Tablets (blank intended commercial batch record).

The proposed production batches have the same manufacturing process as the test batches or Bio-batches (see above). Scale-up meets OGD PPG 22-90.

CHEMIST: Lucia C. Tang 9-27-2000 DATE: 9-11-2000

SUPERVISOR: Ubrani Venkataram DATE: 9-14-2000

U.V. Venkataram 9/28/00.

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-613 Date of Submission: April 1, 1999

Applicant's Name: Eon Labs Manufacturing, Inc.

Established Name: Bupropion Hydrochloride Tablets, 75 mg and 100 mg

---

Labeling Deficiencies:

1. GENERAL COMMENT

   Revise your storage temperature recommendations throughout your labels and labeling to be as follows:

   Store at controlled room temperature 15°-30°C (59°-86°F)(see USP).

2. CONTAINER 100s (75 mg and 100 mg)

   a. See GENERAL COMMENT above.

   b. 75 mg - "ZYBAN™" (spelling)

   c. Add the statement: ZYBAN™ is a registered trademark of GlaxoWellcome.

3. INSERT

   a. GENERAL COMMENTS

      i. "ZYBAN™" throughout the text of the insert. (add "TM")

      ii. There is no need to capitalize bupropion unless required by sentence structure.

      iii. Delete the word "hydrochloride" except where indicated below:

         A). DESCRIPTION (4 instances)

         B). INDICATIONS AND USAGE, first sentence ("Bupropion Hydrochloride Tablets are ...)

         C). WARNINGS - Seizures

            1). First paragraph (2 instances)

2). Second paragraph

3). Recommendations for reducing the risk of seizure (first 2 instances)

D). ADVERSE REACTIONS, third paragraph.

E). DRUG ABUSE AND DEPENDENCE, second paragraph.

F). OVERDOSAGE, Human Overdose Experience.

1). First paragraph (2 instances)

2). Second paragraph (first instance)

G). DOSAGE AND ADMINISTRATION

1). General Dosing Considerations

i). First paragraph

ii). Second paragraph (first instance ... bupropion hydrochloride tablet ...)

2). Increasing the Dosage Above 300 mg/Day (2 instances)

H). HOW SUPPLIED (2 instances)

b. DESCRIPTION

i. "molecular" rather than "empirical"

ii. Replace the "I" in the molecular formula with an "l" (two places).

iii. You have indicated in this section that the 75 mg tablet is yellow-gold in color yet the HOW SUPPLIED section states that it is orange. Please revise and/or comment.

iv. There is no need to use "NF" or "USP" when listing the inactive ingredients.

v. Hydroxypropyl Methylcellulose, Polyethylene Glycol, Titanium Dioxide, Hydroxypropyl Cellulose, Polysorbate 80 and Synthetic Red Iron Oxide are all stated in the listing of inactive ingredients but they do not appear in your component and composition statements. Please comment.

vi. We encourage you to alphabetize your listing of inactive ingredients.

c. CLINICAL PHARMACOLOGY

i. Metabolism, first paragraph, first line - "10%" rather than "1 0%" (delete extra space)

ii. Last sentence

A). "*In vitro*" (*italics*)

B). "mcg" rather than "µg"

d. CONTRAINDICATIONS

Second sentence - ... ZYBAN™ (bupropion hydrochloride) Sustained ...

e. WARNINGS

i. Second paragraph - ... day (2.3% incidence); ... (add parenthesis and ";" rather than ":")

ii. Fifth paragraph (The risk of seizure appears ...)

A). First sentence - ... with dose and the presence of predisposing factors.

B). Add the following as the second sentence - ... 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 ...

iii. Sixth paragraph

Delete the text "The risk of seizure is also related ..." to immediately before "Recommendations for reducing the risk of seizure".

iv. Recommendations for reducing the risk of seizure

Third line from the end of the subsection - Delete "theophylline, systemic steroids".

v. Potential for Hepatotoxicity, Add the following as the last sentence:

... 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.

f. PRECAUTIONS

i. General - Delete the "Allergic Reactions" subsection.

ii. Information for Patients, first paragraph - ... an aid to smoking cessation treatment, and that ...

iii. Drug Interactions

A). Fifth paragraph, second line - Realign the word "concurrent" to be flush against the left margin.

B). Revise the last paragraph as follows:

Concurrent administration of bupropion and agents which lower ... be employed.

iv. Nursing Mothers - Delete the first sentence.

g. ADVERSE REACTIONS

i. Fourth paragraph, last sentence - ... in the WARNINGS and PRECAUTIONS sections.

ii. Other Events Observed During the Development of Bupropion

A). First paragraph, last sentence - ... in the WARNINGS and PRECAUTIONS sections of the labeling.

B). Postintroduction Reports, Gastrointestinal - Delete "liver damage".

h. OVERDOSAGE

i. First line - "LD_{50}" rather than "LD^{50}"

ii. Human Overdose Experience, third paragraph, last sentence - ... seizures, bradycardia, cardiac failure ... (commas instead of periods)

i. HOW SUPPLIED

i. See comment 3(b)(iii) above.

ii. We encourage you to include the NDC numbers in this section.

iii. See GENERAL COMMENT 1 above.

iv. Add the statement: ZYBAN™ is a registered trademark of GlaxoWellcome.

Please revise your container labels and insert labeling, as instructed above, and submit in final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-613

CORRESPONDENCE

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-613 APPLICANT: EON LABORATORIES

DRUG PRODUCT: BUPROPION HCL TABLETS 75 mg & 100 mg

The Division of Bioequivalence has completed its review of your submission(s) and has no further questions at this time.

The dissolution testing should be incorporated into the your manufacturing controls and stability program. The dissolution should be conducted in 900 mL Water, at 37°C using USP Apparatus 2 (paddle) at 50 rpm with the following specifications:

Not less than [redacted] of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

Please note that the bioequivalence 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 bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Barbara M Davit

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

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-613(Fax Amendment) APPLICANT: EON LABORATORIES

DRUG PRODUCT: BUPROPION HCL TABLETS 75 mg & 100 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The Agency prefers to maintain a single dissolution method for an immediate release (IR) product.

2. According to our internal dissolution data on Bupropion HCl (IR) Tablets, the dissolution method is 900 mL Water, at 37°C using USP Apparatus 2 (paddle) at 50 rpm with the following specifications:

   Not less than of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

3. The dissolution method suggested by you [500 mL 0.6% HCl, using USP I (basket) at 100 rpm with specifications of NLT at 30 minutes], is not sufficiently discriminatory.

Sincerely yours,

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

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-613(Fax Amendment) APPLICANT: EON LABORATORIES

DRUG PRODUCT: BUPROPION HCL TABLETS 75 mg & 100 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The Agency prefers to maintain a single dissolution method for an immediate release (IR) product.

2. According to our internal dissolution data on Bupropion HCl (IR) Tablets, the dissolution method is 900 mL Water, at 37°C using USP Apparatus 2 (paddle) at 50 rpm with the following specifications:

   Not less than of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

3. The dissolution method suggested by you [500 mL 0.6% HCl, using USP I (basket) at 100 rpm with specifications of at 30 minutes], is not sufficiently discriminatory.

Sincerely yours,

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

MAY 8 2000

38. Chemistry Comments to be provided to the Applicant

ANDA: 75-613 APPLICANT: Eon Labs Manufacturing, Inc

DRUG PRODUCT(s): Bupropion Hydrochloride Tablets, 75 mg and 100 mg.

The deficiencies presented below represent FAX deficiencies.

Chemistry Deficiencies:

1. We note that Ferric Oxide is present in the formulation of the 100 mg strength product. Please provide the amount of iron oxide per tablet for the 100 mg tablet. This is required in order to comply with 21 CFR 1200 which limits the amount of elemental iron to not more than 5 mg per day.

2. Please update your drug substance (DS) OVI specifications to comply with the requirements in USP 24. We note that your DS manufacturer has certified the absence of OVI solvents except for . Revise and resubmit.

3. In response to our comment in the 'Not Approvable' facsimile dated 10-15-1999, you have included a visual test for the Colors Identification (ID) test. This is not acceptable. The ID test should be a chemical test specific to the component. Please revise and resubmit.

4. Your response to our comment regarding the limit for the friability test (page 35 of November 15, 1999) is not acceptable. The proposed limit of is not supported by data and is not justified. Please tighten the limit, revise all appropriate documents (for example the in-process sheets) and resubmit. Note that SOPs are not reviewed in this Office but are reviewed by FDA Inspectors during inspections.

5. We note that your dissolution specifications at release and stability for Bupropion Hydrochloride Tablets, 75 mg and 100 mg do not meet the following recommendations from the Division of Bioequivalence:

> The dissolution testing should be conducted in 900 mL Water at 37°C using USP Apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:
>
> NLT of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

Please revise and resubmit the finished product specifications and stability specifications.

6. Please submit available room temperature stability data. The dissolution test should be conducted using the method recommended by the Division of Bioequivalence and meet the proposed limits.

7. Your proposed limit for individual other related compound of % is high and is not supported by data. Please justify or tighten the limits. Revise and resubmit the drug product release specifications and stability specifications.

Sincerely yours,

for

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Eon Labs
The Pharmacy Drug Company

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 949-3120

Labeling review drafted 11/30/99 A. Vezza

November 15, 1999

ORIG AMENDMENT
N/AC

Florence S. Fang
Director
Office of Generic Drug, HFD-600
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

-MAJOR AMENDMENT-

Re: BUPROPION HYDROCHLORIDE TABLETS, 75 MG AND 100 MG
ANDA 75-613

Dear Fang:

Reference is made to your letter dated October 15, 1999 commenting on our Abbreviated New Drug Application for Bupropion Hydrochloride Tablets, 75 mg and 100 mg, ANDA 75-613. Below are the responses to the deficiencies noted in your letter.

A. Chemistry Deficiencies:

1. The following comment pertains to the components and composition section:

a.

Page(s) 5

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

11/15/99

B. **In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:**

Methods validation will be performed on the drug product by an FDA laboratory.

Response

We acknowledge that methods validation will be performed on the drug product by an FDA laboratory and that approval of our application will depend on a satisfactory evaluation.

Labeling Deficiencies:

1. **GENERAL COMMENT:**

Revise your storage temperature recommendations throughout your labels and labeling to be as follows:

Store at controlled room temperature 15°-30° (59°86°) (see USP).

2. **CONTAINER 100s (75 mg and 100 mg)**

   a. **See GENERAL COMMENT above**

   b. **75 mg - "ZYBAN™" (spelling)**

   c. **Add the statement: ZYBAN™ is a registered trademark of GlaxoWellcome.**

3. **INSERT**

   a. **GENERAL COMMENTS**

      i. **"ZYBAN™" throughout the text of the insert. (add "TM")**

      ii. **There is no need to capitalize bupropion unless required by sentence structure.**

      iii. **Delete the word "hydrochloride"' except where indicated below:**

         A). **DESCRIPTION (4 instances)**

B). INDICATIONS AND USAGE, first sentence ("Bupropion Hydrochloride Tablets are . . .)

C). WARNINGS - Seizures

1). First paragraph (2 instances)

2). Second paragraph

3). Recommendations for reducing the risk of seizure (first 2 instances

D). ADVERSE REACTIONS, third paragraph

E). DRUG ABUSE AND DEPENDENCE, second paragraph.

F). OVERDOSAGE, Human overdose Experience.

1). First paragraph (2 instances)

2). Second paragraph (first instances)

G). DOSAGE AND ADMINISTRATION

1). General Dosing Considerations

i). First paragraph

ii). Second paragraph (first instance . . . bupropion hydrochloride tablet . . .)

2). Increasing the Dosage Above 300 mg/Day (2 instances)

H). HOW SUPPLIED (2 instances)

b. DESCRIPTION

i. "molecular" rather than "empirical"'

ii. Replace the "l" in the molecular formula with an "I" (two places).

iii You have indicated in this section that the 75 mg tablet is yellow-gold in color yet the HOW SUPPLIED section states that it is orange. Please revise and/or comment.

iv There is no need to use "NF" or "USP' when listing the inactive ingredients.

v Hdroxypropyl Methylcellulose, Polyethylene Glycol, Titanium Dioxide, Hydroxypropyl Cellulose, Polysorbate 80 and Synthetic Red Iron Oxide are all stated in the listing of inactive ingredients but they do not appear in your component and composition statements. Please comment.

vi. We encourage you to alphabetize your listing of inactive ingredients.

c. CLINICAL PHARMACOLOGY

i. Metabolism first paragraph, first line -"10%" rather than "1 0%" (delete extra space)

ii. Last sentence

A). *"In vitro" (italics)*

B). "mcg" rather than "μg"

d CONTRAINDICATIONS

Second sentence -. . . ZYBAN™ (bupropion hydrochloride)

e. WARNINGS

i. Second Paragraph - . . . day (2.3% incidence) ;. . . (add parenthesis and rather than "*l*" rather than ":")

ii Fifth Paragraph (The risk of seizure appears . . .)

A). First sentence - . . . with dose and the presence of predisposing factors.

B). Add the following as the second sentence - ... 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 . . .

iii. Sixth paragraph

Delete the text "The risk of seizure is also related . . ." to immediately before Recommendations for reducing the risk of seizure".

iv Recommendations for reducing the risk of seizure

Third line from the end of the subsection - Delete "theophylline, systemic steroids".

v Potential for Hepatotoxicity, Add the following as the last sentence:

. . .noted. Although scattered abnormalities in liver function tests were detected in patients participating in clinical trials, there is not clinical evidence that bupropion acts as a hepatotoxin in humans.

f. PRECAUTIONS

i. General - Delete the "Allergic Reactions" subsection.

ii Information for Patients, first paragraph - . . . an aid to smoking cessation treatment, and that . . .

iii Drug Interactions

A). Fifth paragraph, second line - Realign the word "concurrent" to be flush against the left margin

B). Revise the last paragraph as follows:

Concurrent administration of bupropion and agents which lower . . . be employed.

iv Nursing Mothers - Delete the first sentence

g. ADVERSE REACTIONS

i Fourth paragraph, last sentence - . . . in the WARNINGS and PRECAUTIONS sections.

ii Other Events Observed During the Development of Bupropion

A). First paragraph, last sentence - . . . in the WARNING and PRECAUTIONS sections of the labeling.

B). Postintroduction Reports, Gastrointestinal - Delete "liver damage".

h. OVERDOSAGE

i First line - "LD_{50} " rather than "LD^{50}"

ii Human Overdose Experience, third paragraph, last sentence - . . . seizures, bradycardia, cardiac failure . . (Commas instead of periods).

i. HOW SUPPLIED

i See comment 3(b) (iii) above

ii We encourage you to include the NDC numbers in this sections.

iii See GENERAL COMMENT 1 above.

iv Add the statement: ZYBAN™ is a registered trademark of GlaxoWellcome.

Response:

We acknowledge your comment and revised our labels and labeling. Final Printed container labels and insert are being submitted, **ATTACHMENT 12.** To facilitate review of this submission, included is a side-by-side comparison of the current container labels, insert and the last submission with all differences annotated and explained, **ATTACHMENT 13.**

Please note that we do not include NDC number on our insert. This is due to the fact that the same insert is used by our private customer label distributors and therefore, it would be inappropriate to include NDC numbers.

In addition to addressing the deficiencies noted above, we are also submitting a change to the desiccant component used to package the finished product. The desiccant manufacturer, has changed their name to A letter from the manufacturer to that effect is provided, **ATTACHMENT 14.**

If there are any comments or questions regarding this submission, please contact me at (718) 276-8607, extension 404

Sincerely,
Eon Labs Manufacturing, Inc.

Blessy Johns
Regulatory Affairs Associate

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-613(Amendment) APPLICANT: EON LABORATORIES

DRUG PRODUCT: BUPROPION HCL TABLETS 75 mg & 100 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet 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 Water, at 37°C using USP Apparatus 2(paddle) at 50 rpm. The test product should meet the following specifications:
>
> Not less than of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

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,

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

Eon Labs
The Pharmacy Drug Company

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 949-3120

September 8, 1999

Dale P. Conner, Ph.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FOR ORIG AMENDMENT
AB

-BIOEQUIVALENCY AMENDMENT-

Re: Bupropion Hydrochloride Tablets, 75 mg and 100 mg
ANDA 75-613

Dear Dr. Conner:

In regards to your letter dated August 16, 1999 for Bupropion Hydrochloride Tablets, 75 mg and 100 mg, ANDA 75-613, the following are our responses to the deficiencies in your letter.

1. **You did not provide the manufacturing date for the test product biostudy lot.**

   Response:

   The manufacturing date for the bio/ANDA Lot 981101 is November, 1998. This date appears on the Certificate of Analysis in Volume 1, page 0146 of the original Abbreviated New Drug Application.

2. **You did not provide long-term stability data for the test drug as required for a complete assay validation.**

   Response:

   We refer you to Volume 5, page 2637, of the original Abbreviated New Drug Application. Long term stability data was filed as an addendum to the bio study reports providing for 109 days storage. This time frame is sufficient to cover the storage of the plasma samples. A copy of the relevant page from the addendum is provided, **ATTACHMENT 1.**

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
SEP 09 1999
OGD

3. **You did not use the interim FDA dissolution method which specifies Apparatus II (paddle) at 50 rpm with 900 mL Water as dissolution medium.**

Response:

In accordance with the test requirements for the interim FDA dissolution method, we are submitting a **Dissolution Profile Report** comparing the test product for Bupropion Hydrochloride Tablets, 100 mg and 75 mg, Lots 981101 and 981105 with Wellbutrin, Lots 7G1296 and 7K2422, **ATTACHMENT 2.** These lots are the same as those used in the bioequivalence studies and for which technical information has already been submitted.

Using the interim FDA method, sticking of the tablets to the side of the dissolution vessel was observed by the analyst. The sticking occurred mainly in the test products. This same phenomena was also observed during our earlier laboratory studies when we first began developing a dissolution method. Because of the sticking, an alternate dissolution method was developed to test the finished product. This alternate method was derived from the FIO information and was based on the method originally recommended to the innovator by the Division of Biopharmaceutics, **ATTACHMENT 3.**

Because of the sticking problem, we do not believe that interim FDA dissolution method is the optimum method for our product since it does not produce accurate results. We feel that our current dissolution method, which has been validated, is more acceptable. For that reason, we will maintain our current dissolution test method originally filed in the original Abbreviated New Drug Application for testing and releasing Bupropion Hydrochloride Tablets.

We hope that the responses satisfactorily address your deficiencies. If you need further information or clarification, do not hesitate to call me at (718) 276-8607-330.

Sincerely,
Eon Labs Manufacturing, Inc.

Sadie M. Ciganek
Vice President Regulatory Affairs

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-613 APPLICANT: Eon Labs Manufacturing, Inc

DRUG PRODUCT(s): Bupropion Hydrochloride Tablets, 75 mg and 100 mg.

The deficiencies presented below represent MAJOR deficiencies.

A. Chemistry Deficiencies:

1. Regarding components and composition:

a.

b.

2. There are no specifications for known impurities in drug substance. But one known impurity is listed for drug product. Please explain and provide limits for any known impurities in the drug substance, Bupropion Hydrochloride.

3. The application fails to provide adequate batch records. In this regard:

b.

c.

4. Your application fails to present complete descriptions of the container/closure systems. In that regard:

a.

b.

c.

d

5. Regarding finished product:

a.

b.

6. Your application fails to contain a satisfactory stability protocol and supporting stability data. In this regard:

a. Please include composition of the drug product in stability report.

b.

c.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

Methods validation will be performed on the drug product by an FDA laboratory.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

AUG 16 1999

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-613 APPLICANT: EON LABORATORIES

DRUG PRODUCT: BUPROPION HCL TABLETS 75 mg & 100 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. You did not provide the manufacturing date for the test product biostudy lot.

2. You did not provide long-term stability data for the test drug as required for a complete assay validation.

3. You did not use the interim FDA dissolution method which specifies Apparatus II (paddle) at 50 rpm with 900 mL Water as dissolution medium.

Sincerely yours,

Barbara Myers Saunt

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

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-613 APPLICANT: EON LABORATORIES

DRUG PRODUCT: BUPROPION HCL TABLETS 75 mg & 100 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. You did not provide the manufacturing date for the test product biostudy lot.

2. You did not provide long-term stability data for the test drug as required for a complete assay validation.

3. You did not use the interim FDA dissolution method which specifies Apparatus II (paddle) at 50 rpm with 900 mL Water as dissolution medium.

Sincerely yours,

Barbara Myers Davis

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

ANDA 75-613

Eon Labs Manufacturing, Inc.
Attention: Patricia Kaufold
227-15 North Conduit Avenue
Laurelton, NY 11413

APR 30 1999

Dear Madam:

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 also made to your correspondence dated April 20, 1999.

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

DATE OF APPLICATION: April 1, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: April 2, 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,

Harvey A. Yearley
for

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

Team 8

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75613 SPONSOR : EON LABS, Inc.

DRUG AND DOSAGE FORM : Bupropion Hydrochloride

STRENGTH(S) : 75 mg & 100 mg Tablets

TYPES OF STUDIES : Fasting Study

CLINICAL STUDY SITE : NOVUM Pharmaceutical Research

ANALYTICAL SITE :

STUDY SUMMARY : The 90% CIs in the fasting study are within acceptable limits.
DISSOLUTION : Dissolution was conducted according to acceptable FDA method.
WAIVER: Waiver request of in vivo bioequivalence study requirements for 75 mg tablets of the test product is granted.

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results:
First Generic ____	Inspection requested: N/A	
New facility ____	Inspection completed: (date)	
For cause ____		
other ____		

PRIMARY REVIEWER : Patrick E. Nwakama, Pharm.D. BRANCH : II

INITIAL : PEN DATE : 11/16/99

TEAM LEADER : Shriniwas G. Nerurkar, Ph.D. BRANCH : II

INITIAL : DATE : 11/16/99

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DPC DATE : 11/16/99

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-613(Amendment) APPLICANT: EON LABORATORIES

DRUG PRODUCT: BUPROPION HCL TABLETS 75 mg & 100 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet 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 Water, at 37°C using USP Apparatus 2(paddle) at 50 rpm. The test product should meet the following specifications:
>
> Not less than of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

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,

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

Eon Labs
The Pharmacy Drug Company

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 949-3120

April 1, 1999

labeling review drafted 5/13/99 a Vazquez

Douglas L. Sporn
Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: **Original ANDA**
Bupropion Hydrochloride Tablets, 75 mg and 100 mg

Dear Mr. Sporn:

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act, enclosed is an original Abbreviated New Drug Application for Bupropion Hydrochloride Tablets, 75 mg and 100 mg. This application consists of the following volumes:

Volume 1 Debarment, patent and exclusivity certifications, Section 505(j)(2)(A) information, labeling, dissolution profiles, certificates of analysis, and components and composition statements.

Volume 2 Raw material control data, manufacturing and packaging data including executed batch records.

Volume 3 Container/closure information, finished product controls data, methods validation, stability data, control numbers, and environmental impact statement.

Volume 4 through 7 Biostudy summary and test results including diskettes, which contain electronic biodata.

Eon Labs

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 949-3120

August 1, 2000

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

[illegible] AMENDMENT
AB

-FACSIMILE BIOEQUIVALENCY AMENDMENT-

Re: Bupropion Hydrochloride Tablets, 75 mg and 100 mg
ANDA 75-613

Dear Dr. Conner:

In regards to your facsimile deficiency letter dated July 28, 2000 for Bupropion Hydrochloride Tablets, 75 mg and 100 mg, ANDA 75-613, following is our response to the deficiencies in your letter.

[illegible] AUG 0[illegible] 2000 [illegible]

Deficiencies:

1. **The agency prefers to maintain a single dissolution method for an immediate release (IR) product.**

2. **According to our internal dissolution data on Bupropion HCl (IR) Tablets, the dissolution method is 900 mL Water, at 37°C using Apparatus 2 (paddle) at 50 rpm with the following specifications:**

   Not less than of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

3. **The dissolution method suggested by you [500 mL 0.6 % HCl, using USP I (basket) at 100 rpm with specifications of ... at 30 minutes], is not sufficiently discriminatory.**

A full table of content precedes each appropriately paginated volume.

We have also included an analytical Methods Validation Package in a separate volume.

In addition to the archival and review copies, we are submitting a certified true copy of the chemistry, manufacturing and controls data to the District Field Office, Brooklyn, New York.

Subsequent amendments or supplements containing chemistry, manufacturing and controls data will also be submitted to the District Field Office.

If there are any comments or questions about this application, please contact me at (718) 276-8600, extension 330.

Sincerely,
Eon Labs Manufacturing, Inc.

Patricia Kanfold for
Sadie M. Ciganek
Vice President Regulatory Affairs

Response:

We have amended our dissolution test parameters and specification to that recommended by the Division of Bioequivalence in deficiency 2 above. All master records affected by this change have been revised accordingly **(ATTACHMENT 1)**.

We hope that the responses satisfactorily address your deficiencies. If you need further information or clarification, do not hesitate to call me at (718) 276-8607-330.

Sincerely,
Eon Labs Manufacturing, Inc.

Sadie M. Ciganek
Vice President Regulatory Affairs

5/22/2000
FA sent to CMC
Reviewer for review.

Eon Labs

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 949-3120

May 19, 2000

Florence S. Fang
Director
Office of Generic Drug, HFD-600
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N/FA

-FACSIMILE AMENDMENT-

Re: BUPROPION HYDROCHLORIDE TABLETS, 75 MG AND 100 MG
ANDA 75-613

Dear Fang:

Reference is made to your letter dated October 15, 1999 commenting on our Abbreviated New Drug Application for Bupropion Hydrochloride Tablets, 75 mg and 100 mg, ANDA 75-613. Below are the responses to the deficiencies noted in your letter.

A. Chemistry Deficiencies:

1.

Response:

2.

Response:

Page(s) 1

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

5/19/2000

6.

Response:

7.

resubmit

accelerated

If there are any comments or questions regarding this submission, please contact me at (718) 276-8607, extension 404.

Sincerely,
Eon Labs Manufacturing, Inc.

Sadie M. Ciganek
Vice President Regulatory Affairs